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Synthesis and application of new bipyridine ligands

Syntéza a aplikace nových bipyridinových ligandů

PhD Thesis

Supervisors: Prof. RNDr. Martin Kotora, CSc.
Dr. Frédéric Lamaty

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Synthèse et applications de nouveaux ligands bypiridine

Présentée par Eva BEDNÁŘOVÁ
Le 26 novembre 2018
Sous la direction de Prof. RNDr. Martin KOTORA, CSc.
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INTRODUCTION

Because of the growing demands for enantiomerically pure compounds in pharmaceutical, agrochemical, and other fields of chemical industry, the development of new, more selective, economical, and environmentally friendly methods of asymmetric synthesis are highly sought after. Although there are various possibilities for such transformations, the catalytic approaches still represent the most convenient method. Together with the enzyme-catalyzed and organocatalyzed processes, the methods using chiral metal complexes are the most appealing.

The classical method for the synthesis of enantiomerically pure compounds using catalysis by metal complexes from prochiral precursors is based on the use of chiral ligands. The chiral ligand is able to modulate the reactivity of the metal center in such a way that the prochiral compound is transformed to only one of the two possible enantiomers. Compared to the other frequently used chiral ligands such as chiral phosphines, salens, oxazolines, or tartrate ligands, chiral 2,2'-bipyridines have attracted relatively little attention despite the well-studied coordination abilities of their achiral analogues. This low popularity could stem from the lack of synthetic methods to prepare highly substituted chiral 2,2'-bipyridines. Well-chosen substituents of such bipyridines could improve the activity of the whole metal-ligand complex in various asymmetric reactions, furnishing chiral products in unprecedently high yields and enantiopurities. The development of methods providing such substituted bipyridines is thus desirable.

1. STATE OF THE ART

1.1 Bipyridines

Bipyridines are heterocyclic compounds, which consist of two pyridine rings. There are six types of bipyridines, each differing by the position of the linkage between the two pyridine cores. The most intensively studied is the group of 2,2'-bipyridines, which are joined by the bond between the carbon atoms neighboring with the nitrogen atom of each pyridine (Figure 1).[1]

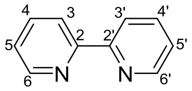


Figure 1. Numbering of atoms in pyridine rings of 2,2'-bipyridine.

1.1.1 Application

These 2,2'-bipyridines have found their application in various fields of chemistry as macromolecular,[2] supramolecular,[3] material chemistry,[4] photochemistry,[5] electrochemistry[6] and due to their extraordinary coordination properties, as ligands in metal-catalyzed reactions.[7] Compared to other commonly used ligands as phosphines and cyclopentadienes, they are remarkably stable towards both air and moisture, which is advantageous during their preparation, handling and storage. The presence of two nitrogen atoms in an almost ideal configuration is a prerequisite to form remarkably stable five-membered chelate ring with a suitable metal sources. In addition, derivatization of one of the other eight carbon atoms enables to achieve the optimal behavior of the whole complex for the appropriate application, thanks to the change of steric and electronical properties.[8]

Among all the possible derivatizations, substitution of hydrogen in position 6 and 6' is causing the most significant change in the coordination abilities of the bipyridine. Bulky substituents are increasing the steric hindrance that makes accessibility of the two nitrogen atoms towards coordination difficult. Nevertheless, a finely tuned substituent with atoms capable of chelation to the metal center can stabilize the whole complex by creation of multidentate complexes (Figure 2). Moreover, the insertion of a side chain bearing the center of chirality allows to control the stereochemistry of the metal center and so widens the application scope to asymmetric catalysis. During the last decades chiral 2,2'-bipyridines have found their application in cyclopropanation of alkenes, alkylation and allylation of aldehydes, hydrogenation and hydrosilylation of carbonyl compounds, alkylation and oxidation of allylic position, aldol type reactions etc.[9]

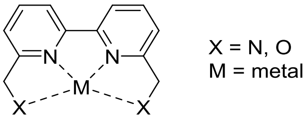
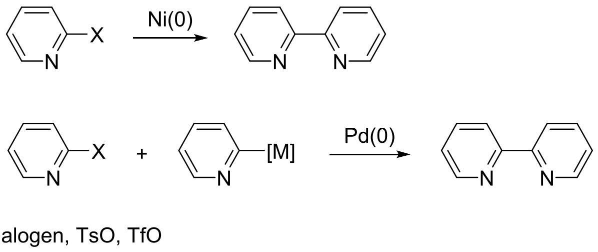


Figure 2. Multidentate chelation of metal center by 6,6'-substituted 2,2'-bipyridine.

Based on the type of symmetry, which they possess, we can divide 2,2'-bipyridines into two groups – C_2-symmetric and C_1-symmetric (asymmetric). Another way of their division is to chiral and achiral, moreover the chiral 2,2'-bipyridines can be sorted into groups based on the element of their chirality, e.g. central, axial, planar, or helical. In addition, one bipyridine can contain more than one type of these elements of chirality. Among all these types of bipyridines, the most significant are C_2-symmetric 2,2'-bipyridines which possess a center of chirality. Because of that and also because of the specialization of this thesis, in the following paragraphs only general methods of the synthesis of these particular bipyridines will be described.

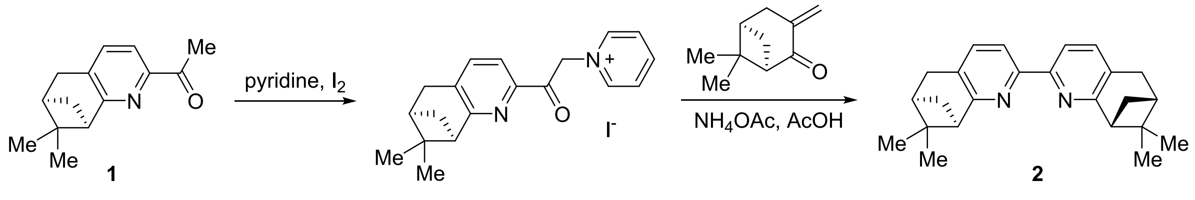
1.1.2 Synthesis

The classical strategy for the synthesis of 2,2'-bipyridines is based on coupling methods (Scheme 1). The starting materials are 2-halopyridines or their sulfonate analogues, which are homocoupled with the second molecule of the same compound yielding the target 2,2'-bipyridine. This coupling is typically performed by Ni(0)-phosphine complex, which is generated *in situ* by reduction of Ni(II) species by zinc. Although some other modifications of the described methodology using e.g. copper[10] or palladium complexes[11] were established, the nickel-mediated dimerization is generally preferred because of the tolerance of wide range of functional groups.[12] Similar strategy based on the ordinary Pd-catalyzed cross-coupling procedures is also applicable. Nevertheless, it requires an extra halogen-metal exchange step for preparation of the organometallic coupling partner.

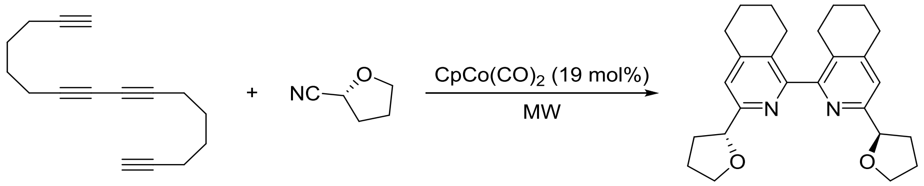


Scheme 1. Coupling methods for the synthesis of 2,2'-bipyridine.

Another possibility of the synthesis of bipyridines is based on the cyclization methods, namely Kröhnke cyclization[13] and [2+2+2] cocyclotrimerization.[14] While the former was used e.g. for the synthesis of bipyridine **2** starting from 2-acetylpyridine **1** (Scheme 2)[15], the latter was used in Kotora's group in the synthesis of bipyridine **5** from tetrayne **3** and nitrile **4** (Scheme 3).[16] This method will be in detail discussed in Chapter 0.



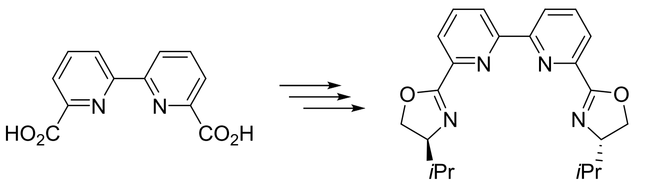
Scheme 2. Synthesis of bipyridine **2** by Kröhnke cyclization method.



3 **4** **5**

Scheme 3. Synthesis of bipyridine **5** by [2+2+2] cyclotrimerization method.

Last but not least, the desired bipyridines can be also prepared from commercially available compounds *via* secondary functionalization as many suppliers have 2,2'-bipyridine derivatives nowadays in their stock. The representative example of this method is a preparation of bis(oxazolinyl)bipyridine (BipyMOX) **7** from commercially available 2,2'-bipyridine-6,6'-dicarboxylic acid **6** (Scheme 4).[17] This particular synthesis will be in detail discussed in Chapter 1.4.



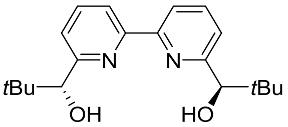
6 **7**

Scheme 4. Synthesis of 2,2'-bipyridine **7** by secondary functionalization of bipyridine **6**.

In general, chiral bipyridines can be obtained (a) by asymmetric synthetic step, (b) by using enantiomerically pure compound from the chiral pool, (c) by separation of racemic mixture using e.g. chromatography with chiral stationary phase, or (d) by derivatization of the racemic mixture with chiral auxiliary followed by separation of diastereoisomers and recovery of the auxiliary after its cleavage.

1.2 Bolm’s ligand

One of the most frequently used chiral 2,2'-bipyridine ligand in metal-catalyzed asymmetric reactions is Bolm’s ligand **8** that is a C_2-symmetric diol (Figure 3) bearing two chiral side chains in positions 6 and 6'.



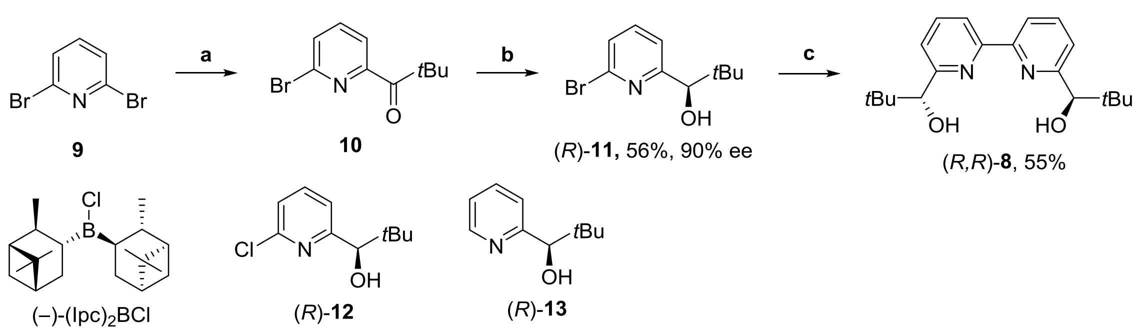
(*R*,*R*)-**8**

Figure 3 . Bolm’s ligand (*R,R*)-**8**.

1.2.1 Synthesis

The chiral bipyridine (*R*,*R*)-**8**, was designed and for the first time synthesized by Bolm *et al.* in 1990 (Scheme 5),[18] a more detailed synthesis was then described in 1992 by the same authors.[19] In the first step of its synthesis, the commercially available 2,6-dibromopyridine **9** was monolithiated using *n*BuLi and reacted with methyl pivalate or pivaloyl cyanide. The resulting ketone **10** was in the next step enantioselectively reduced using (–)-*B*-chlorodiisopinocampheylborane ((–)-$(Ipc)_2BCl$) in 90% ee giving preferentially (*R*)-enantiomer. The optical purity of the chiral alcohol (*R*)-**11** was raised to >99% ee by recrystallization of the corresponding camphanic acid ester following by hydrolysis under basic conditions. Moderate yield of the reaction is caused by complicated separation of product from compounds derived from chiral borane. In addition the product (*R*)-**11** was contaminated by inseparable alcohol (*R*)-**12** containing chlorine instead of bromine in position 6. The origin of this compound is explained by halogen exchange between (*R*)-**11** and (–)-$(Ipc)_2BCl$.

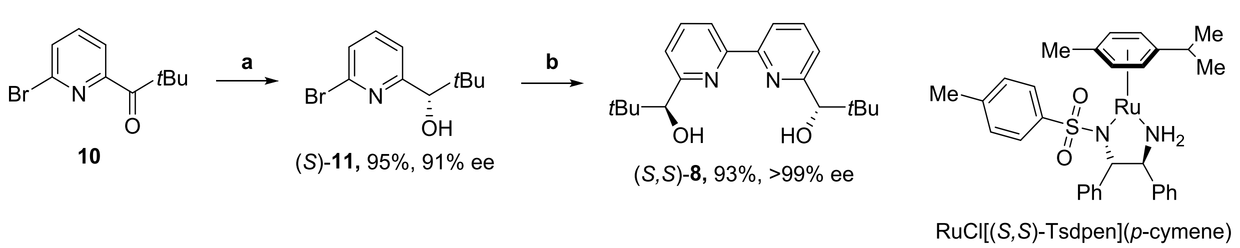
Chiral alcohol (*R*)-**11** was in the last step coupled using *in situ* generated Ni(0)-complex to desired bipyridine (*R,R*)-**8**. The necessity to use more than a stoichiometric amount of coupling nickel agent could be explained by possible complexation of the Ni-catalyst by the bipyridine product. Major side product of the last step is the alcohol (*R*)-**13** formed by reductive dehalogenation under the reaction conditions. The formation of this product can be reduced by using carefully degassed reaction solvent.



a) I) *n*BuLi, Et_2O, -78 °C; II) *t*$BuCO_2Me$ (1.2 eq.), Et_2O, -78 °C to r.t.; III) H^+ work-up (80%)
or I) *n*BuLi, Et_2O, -78 °C; II) *t*BuCN (1.2 eq.), Et_2O, -78 °C to r.t.; III) H_2SO_4, H_2O, reflux (88%)
b) I) (–)-$(Ipc)_2BCl$ (1.2 eq.), THF, r.t.; II) diethanolamine (3.6 eq.), Et_2O, r.t.
c) $NiCl_2{\cdot}6H_2O$ (1.2 eq.), Zn (1.3 eq.), PPh_3 (4.8 eq.), DMF, 70 °C

Scheme 5. Synthesis of (*R*,*R*)-**8** by Bolm.

Low yields and the requirement to use stoichiometric amount of reagents in the last two steps of the preparation of Bolm's ligand (*R*,*R*)-**8** brought Kobayashi *et al.* to the alternative method of synthesis of **8** (Scheme 6).[11] The chiral alcohol (*S*)-**11** was in this case prepared by transfer hydrogenation of the ketone **10** catalyzed by ruthenium complex (RuCl[(*S*,*S*)-Tsdpen](*p*-cymene)) using a mixture of formic acid and triethylamine as a source of hydrogen. The alcohol (*S*)-**11** was obtained in 95% yield with 91% ee, which was further improved by recrystallization from hexane. It should be emphasize that the major enantiomer had in this case (*S*)-configuration on the chiral center in contrast to the abovementioned chiral borane-mediated reduction by (–)-$(Ipc)_2BCl$, which provided (*R*)-enantiomer of alcohol **11**. The homocoupling step was performed using a Pd(0)-catalyst generated *in situ* by reducing Pd(II)-complex with tetrakis(dimethylamino)ethylene (TDAE). The desired bipyridine (*S*,*S*)-**8** was isolated in 93% yield as an optically pure compound.



a) RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) (1 mol%), HCO_2H, Et_3N, r.t.
b) $PdCl_2(PhCN)_2$ (5 mol%), TDAE (2 eq.), DMF, 50 °C

Scheme 6. Synthesis of (*S*,*S*)-**8** by Kobayashi.

1.2.2 Complexes

The NMR studies in the solution as well as a single crystal X-ray analysis in the solid state confirmed *transoid* arrangement of nitrogen atoms in pyridine rings of Bolm's bipyridine **8**. Nevertheless, these nitrogen atoms can adopt, due to the free rotation around C2–C2', also *cisoid* arrangement, which is actually the favorable conformation in its complexes where both nitrogen atoms are coordinated to the same metal center.[19]

Possessing two nitrogens in the pyridine rings and two oxygens in the side chains as possible chelation atoms, Bolm's ligand could theoretically form metal complexes in mono-, bi-, tri- or tetradentate fashion. While monodentate and bidentate coordination of this bipyridine is not known, Bolm's ligand forms tri- and tetradentate complexes with various metal salts.

Tridentate complexes of **8** are formed with zinc(II) bromide as well as with copper(II) bromide. These coordination compounds adopt square-pyramidal structures where both nitrogen and one oxygen atoms of Bolm's ligand **8** are attached to the same metal center (Figure 4).[20,21]

The Fe(II)-,[22–24] Sc(III)-,[25] Bi(III)-,[26] and In(III)-complexes[27] with Bolm's ligand **8** have the pentagonal bipyramidal structure, in which both nitrogen atoms of bipyridine and both oxygen atoms of hydroxy groups coordinate the metal center in the tetradentate manner (Figure 4). The four atoms occupy four out of five equatorial sites of the metal center, which was established by single crystal X-ray analysis. Also with ytterbium(III) triflate the Bolm's ligand is forming tetradentate complex. In this case, the complex occupies dodecahedral conformation, because of the eight-coordination fashion of Y(III) cation. It should be noted that both of the hydroxyl protons are retained in all examples of the metal complexes and that the resting coordination sites are occupied by either anions of the metal salts used for complexation or by molecules of solvents.

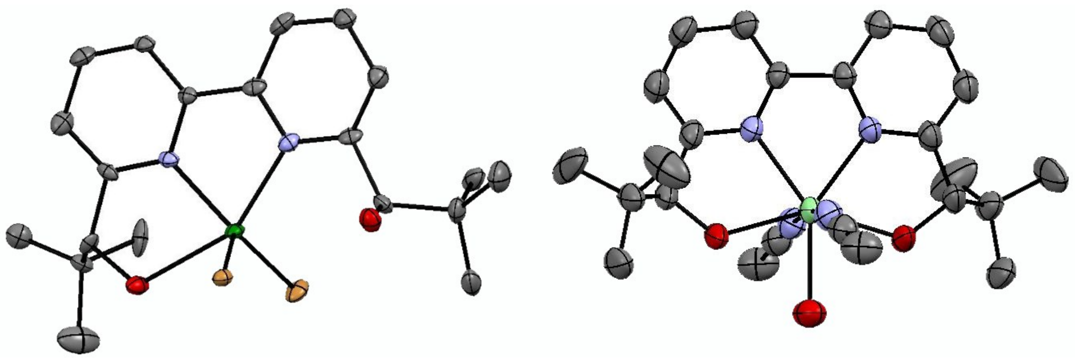


Figure 4. ORTEP drawing of [(*S*,*S*)-**8**·$ZnBr_2$] (left)[20] and [(*S*,*S*)-**8**·Fe·MeCN·H_2O]$^{2+}$·2$(ClO_4)^-$ (right)[24] (grey C, red O, blue N, dark green Zn, light green Fe, orange Br). Hydrogen atoms and ClO_4^- were omitted for clarity.

1.2.3 Application

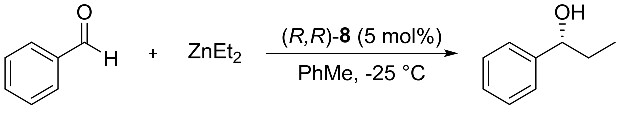
Due to its ability to chelate a number of metals, Bolm's ligand **8** has found application in various types of metal-catalyzed asymmetric reactions. Because of the growing need for more environmentally acceptable processes, some of the applications of Bolm's ligand were also performed in environmentally friendly manner.

In the metal catalysis, these „green processes“ are based on using non-toxic metals, less hazardous chemicals, innocuous solvents, prevention of waste etc.[28] Despite the fact that Ananikov *et al.* recently speculated that light/lighter metals are less toxic compared to heavy metals (palladium, platinum, rhodium, gold),[29] the use of nickel, iron, copper, zinc etc. is still generally assumed to be beneficial from the point of sustainability.

It was estimated that about 80% of the total mass of chemicals and 75% of energy use in pharmaceutical industry accounts for solvents,[30] therefore a special care has to be taken in selection of the appropriate solvent during development of a new green process. Although the popularity of solvent-free reactions is increasing, the need of some diluent is still required in most of the chemical processes. Prat *et al.* divided commonly used organic solvents into four groups (recommended, problematic, hazardous, and highly hazardous).[31] Among recommended he classified alcohols, acetates, anisole, sulfolane and of course water, which is generally the most preferable. Water is non-toxic, non-flammable, abundant and inexpensive. In addition, due to its highly polar character, one can expect the novel reactivities and selectivities in metal-catalyzed reactions compared to reactions performed in common organic solvents.[32] Moreover the use of biphasic systems where the reagents are dissolved in organic phase, while catalyst remains in water phase simplifies product purification and recovery of the catalyst by simple separation of phases.[28] One of the obvious disadvantages of using water is the low solubility of majority of organic compounds. This can be overcome by using mixtures of water with miscible solvents (alcohols, polar ethers etc.), which would increase solubility, or immiscible solvent (chlorinated solvents, hydrocarbons etc.) utilizing the already mentioned biphasic system. Another possibility is an application of surfactants which are in water forming micelles (colloidal particles) with hydrophobic center.[33] The other disadvantage of the use of water is the instability of some compounds in aqueous media. Among others, also most of the Lewis acids are unstable under aqueous conditions.[34] The utilization of ligand, which is able to stabilize Lewis acids in aqueous media, is required. One such compound is also the abovementioned Bolm's ligand **8**.

1.2.3.1 Alkylation and allylation of aldehydes

Straight after its first synthesis, Bolm's ligand was applied in asymmetric alkylation of aldehydes using diethylzinc as alkylating agent.[18] With 5 mol% of (*R*,*R*)-**8** in toluene at -25 °C, the ethylation of benzaldehyde **14** yielded the secondary alcohol **15** in 94% with 97% ee (Scheme 7).



Scheme 7. Alkylation of benzaldehyde **14**.

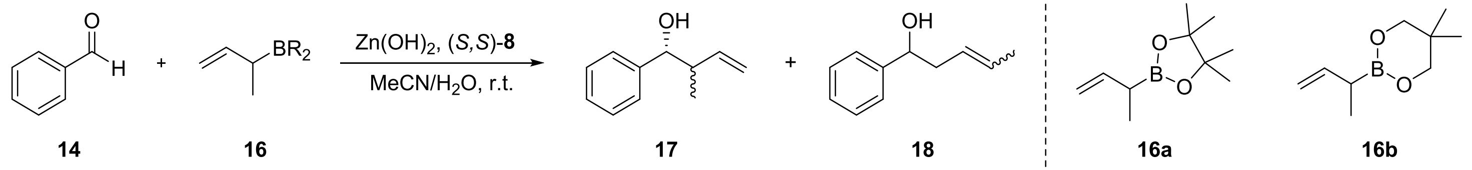
In the following publication Bolm *et al.* treated also other aldehydes under similar reaction conditions.[35] While the aromatic aldehydes provided appropriate products in high yields and enantiomeric purities, the aliphatic aldehydes were alkylated in lower yields and enantioselectivities.

The first examples of allylation of aldehydes by allylboronate catalyzed by zinc(II) hydroxide and Bolm's ligand was described by Kobayashi *et al.* in 2010 and 2011.[36,37] Whereas allylation by pinacol allylboronate **16a** was giving predominantly product of γ-addition **18** in the absence of zinc catalyst and bipyridine (Entry 1, Table 1), the presence of zinc(II) hydroxide shifted the preference towards α-product **17** (Entry 2). The product of α-addition **17** was formed exclusively when boronate **16b** and the chiral bipyridine (*S*,*S*)-**8** was used (Entry 3). In addition, the *syn*-product was obtained predominantly with 71% ee.

The scope of the reaction revealed that also other substrates are forming the α-addition products exclusively (Table 2). 3-Phenylpropanal was α-alkylallylated using various boronates in excellent yields and high to excellent enantioselectivity (Entries 1–3). Also α-chloroallylation proceeded smoothly with 3-phenylpropanal (Entry 4), benzaldehyde (Entry 5), substituted benzaldehydes (Entries 6 and 7), 1-naphthylcarbaldehyde (Entry 8) as well as with undecanal (Entry 9). In all cases, α-chlorohomoallylic alcohols were obtained in higher than 93% selectivity of *syn* product.

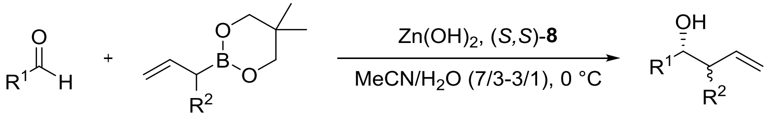
The mechanism of the described allylation has not yet been completely elucidated, but the authors proposed a double γ-addition process where boron is in the first step transmetalated by zinc in γ-addition fashion, while the formed allylzinc species reacts in the next step with aldehyde again by γ-addition. Some of the intermediates of the proposed mechanism were confirmed by mass spectrometry.[20]

Table 1. Allylation of benzaldehyde **14**.



Entry	**16**	Zn(OH)$_2$ (mol%)	(*S*,*S*)-**8** (mol%)	MeCN/H$_2$O	Yield (%)	**17**/**18**	dr (*syn/anti*)	ee (*syn*) (%)
1	**16a**	-	-	4/1	77	5/95	-	-
2	**16a**	10	-	4/1	86	45/55	70/30	-
3	**16b**	10	12	7/3	92	>99/1	91/9	71

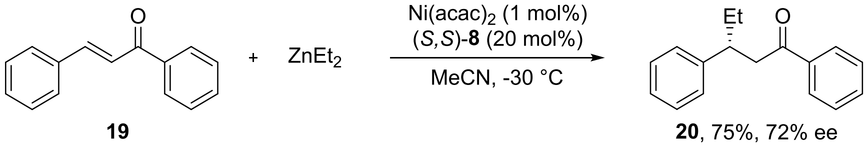
Table 2. Substrate scope of allylation of aldehydes.



Entry	R^1	R^2	Zn(OH)$_2$ (mol%)	(*S*,*S*)-**8** (mol%)	Yield (%)	dr (*syn/anti*)	ee (*syn*) (%)
1	PhCH$_2$CH$_2$	Me	5	6	94	83/17	85
2	PhCH$_2$CH$_2$	Et	5	6	96	75/25	91
3	PhCH$_2$CH$_2$	*i*Bu	5	6	95	75/25	91
4	PhCH$_2$CH$_2$	Cl	3	3.6	92	93/7	95
5	Ph	Cl	5	6	92	96/4	88
6	4-MeC$_6$H$_4$	Cl	3	3.6	91	96/4	87
7	4-BrC$_6$H$_4$	Cl	7.5	9	quant.	95/5	85
8	1-naphthyl	Cl	5	6	94	93/7	85
9	CH$_3$(CH$_2$)$_{10}$	Cl	2	2.4	92	93/7	93

1.2.3.2 Conjugate addition

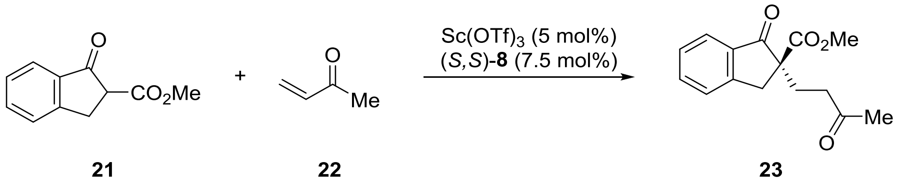
Conjugate addition is one of the most frequently studied reactions utilizing Bolm's ligand. The first reports were published by Bolm *et al.* in 1990 and 1992, respectively, and were dealing with ethylation of chalcone **19** with diethylzinc. The ethylated product **20** was furnished in 75% yield with 72% ee with only 1 mol% of Ni-catalyst, but 20 mol% of bipyridine (*S*,*S*)-**8** was required (Scheme 8).[38,39]



Scheme 8. Alkylation of ketone **19**.

In 2006, Kobayashi *et al.* published an example of Michael addition catalyzed by Sc-bipyridine complex prepared from Sc(OTf)$_3$ and bipyridine (*S*,*S*)-**8**.[40] The study of reaction of β-ketoester **21** with methyl vinyl ketone (MVK) **22** showed the dependence of the results not only on solvent (Entries 3–6, Table 3), but also on concentration of starting material (Entries 6–8). Regarding the temperature, surprisingly the optimal turned out to be 40 °C (Entry 8), while reactions done under lower temperature furnished ester **23** in both lower yields and enantiopurities (Entries 1–3).

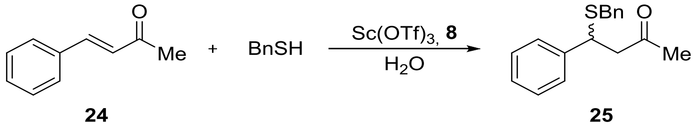
Table 3. Optimization of reaction conditions of Michael addition of β-ketoester **21** to MVK **22**.



Entry	Solvent	*T* (°C)	*c* (M)	Yield (%)	ee (%)
1	DCM	10	0.08	22	53
2	DCM	20	0.08	61	80
3	DCM	30	0.08	98	81
4	PhMe	10	0.08	quant.	5
5	MeCN/DCM	30	0.08	76	8
6	DCE	30	0.08	94	84
7	DCE	30	0.04	96	89
8	DCE	40	0.02	94	92

In 2011, two groups independently published articles dealing with addition of thiols on α,β-unsaturated carbonyl compounds catalyzed by Sc(III) and bipyridine **8** in water.[41,42] Both authors noticed that without using any additive (Entry 1, Table 4), the pH of the reaction is acidic, so they decided to use catalytic amount of base. Albeit Vaccaro *et al.* used NaOH (Entry 2) and Kobayashi *et al.* pyridine (Entry 3); both obtained adduct **25** in comparable yields and ees. In this reaction also demonstrated the recyclability of the Sc(III)-catalyst by simple recovery from water phases after extractions.[41] No decrease in the efficiency of the process (yield, ee) was observed after three subsequent runs.

Table 4. Conjugate addition of benzylthiol on α,β-unsaturated ketone **24**.

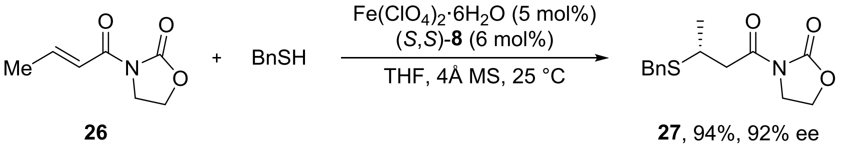


Entry	$Sc(OTf)_3$ (mol%)	**8** (mol%)	Base	mol%	*T* (°C)	Yield (%)	ee (%)
1[41]	2	5 (*R,R*)	-	-	30	46	57 (*R*)
2[41]	1	2 (*R,R*)	NaOH	3	30	95	91 (*R*)
3[42]	1	1.2 (*S,S*)	pyridine	10	r.t.	92	93 (*S*)

The generality of the sulfa-Michael addition was demonstrated by screening various types of substrates as aromatic and aliphatic enones and thiols. In all the examples, the reaction gave products in high to excellent yields (63–100%) and ee (76–97%). The only drop of enantioselectivity was observed while using benzenethiol (44–52% ee) that could be ascribed to its higher acidity.

To get more information about a structure of the catalyst in water, Kobayashi *et al.* conducted experiments on the non-linear effect between ee of bipyridine **8** and ee of product **25**. As positive non-linear effect was observed, the authors are suggesting the formation of dimers or other aggregates of the catalyst in aqueous media.[42]

Sulfa-Michael addition utilizing Fe(II)-(*S*,*S*)-**8** complex has been recently also studied on α,β-unsaturated oxazolidin-2-ones by Ollevier *et al.*, who used iron(II) perchlorate as appropriate Lewis acid.[43] The addition product **27** of benzylthiol to oxazolidin-2-one **26** was isolated in 94% yield with 92% ee (Scheme 9).

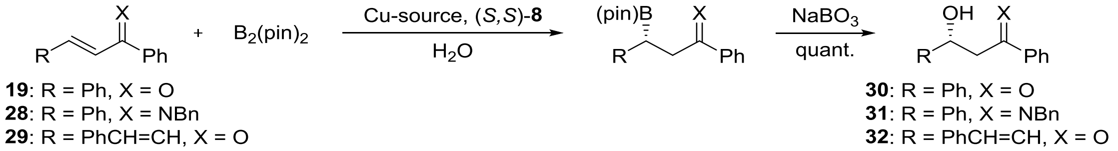


Scheme 9. Sulfa-Michael addition of benzylthiol on α,β-unsaturated oxazolidin-2-one **26**.

Another type of reaction intensively studied in Kobayashi's group was boron 1,4-addition reaction using bis(pinacolato)diboron ($B_2(pin)_2$) as the boron source. The reaction was promoted by either copper(II) salts or copper powder and was applied on various substrates as α,β-unsaturated ketones,[44–46] imines[47] or nitriles.[48] Straight after the reaction, the borylated product was converted to β-hydroxy alcohol (**30**, **31** or **32**) as it was found to be more convenient for determination of ee by HPLC with chiral stationary phase. The representative examples of this reaction are summarized in Table 5.

Interesting results were obtained using α,β,γ,δ-unsaturated dienone **33** (Table 6).[49] The product of 1,6-addition **35** was obtained by using copper(II) hydroxide without an additive (Entry 1). The 1,4-addition product **34** was, on the other hand, obtained either using copper(II) hydroxide with a catalytic amount of acetic acid (Entry 2) or with sole copper(II) acetate (Entry 3) with only small difference in yield and enantiopurity. The authors proposed an explanation of this phenomenon by a difference in the reaction mechanism. In the $Cu(OH)_2$ catalyzed reaction the first copper species activates the carbonyl group, while the second copper-boron species attacks **33** *via* 1,6-addition. The steric hindrance of activating species is probably in this case sterically preventing the attack of the position 4. In the second case, a plausible reaction intermediate in the reactions using $Cu(OAc)_2$ (used as such or formed from $Cu(OH)_2$ and acetic acid) is (pin)B–CuOAc·**8**, which is at the same time activating and reacting agent enabling a smooth 1,4-addition.

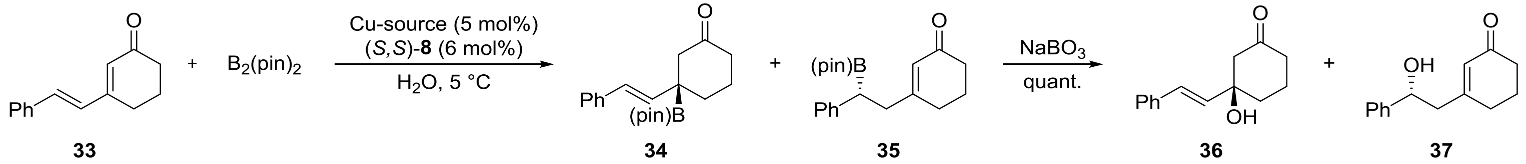
Table 5. Conjugate boron addition on α,β-unsaturated compounds.



Entry	R	X	Cu-source	mol%	(*S*,*S*)-**8** (mol%)	Additive (mol%)	*T* (°C)	Yield (%)	ee (%)
1[44]	Ph	O	$Cu(OH)_2$	5	6	AcOH (6)	5	95	99
2[45,a]	Ph	O	$Cu(OAc)_2$	5	6	MeOH (100)	r.t.	92	92
3[46]	Ph	O	Cu powder	10	12	-	30	92	83
4[47]	Ph	NBn	$Cu(OAc)_2$	5	6	-	r.t.	91	>99
5[49]	PhCH=CH	O	$Cu(OAc)_2$	5	6	-	5	91	91

[a] Et_2O was used instead of H_2O.

Table 6. Boron conjugate addition on cyclic dienone **33**.



Entry	Cu-source	Additive (mol%)	Yield (%)	**36**/**37**	ee (%)
1	$Cu(OH)_2$	-	81	<1/99	76
2	Cu(OH)	AcOH (6 mol%)	92	>99/1	87
3	$Cu(OAc)_2$	-	94	>99/1	91

1.2.3.3 Opening of *meso*-epoxides

The catalytic enantioselective opening of *meso*-epoxides provides a powerful strategy for the formation of enantiomerically enriched product with two contiguous chiral centers in one step from readily available compounds. The reaction can be catalyzed by Lewis acids, thus the applicability of metal-**8** complex in this reaction has been intensively studied by several groups in the last two decades.

The desymmetrization of *meso*-epoxides by amines generally suffers from non-compatibility of Lewis basic amine and Lewis acidic catalyst because of the tendency to irreversibly coordinate to one another. Nevertheless, aminolysis of epoxide ring is providing chiral β-amino alcohols, which can be found in many biologically active compounds and chiral auxiliaries. Hence, development of new highly enantioselective methods is required.[50]

As is shown in Table 7, high activity in this reaction showed combination of Bolm's ligand **8** with Sc(III) triflate in DCM (Entry 1) and Sc(III) dodecyl sulfate (DS, Entry 2) or undecyl sulfonate (UDST, Entry 4) as Lewis acid surfactant catalysts (LASC) in water. In all cases, the β-amino alcohol was isolated in high to excellent yields and enantioselectivities. Unexpectedly, the same reactions utilizing either copper or zinc salts provided the products with opposite configuration (Entries 4–7). Kobayashi *et al.* assumed that this inversion may be caused by different conformation of appropriate metal complexes with bipyridine **8**. Cu(II) and Zn(II) are forming tridentate complexes, which adopt a square-pyramidal structure, while Sc(III) is chelated by ligand **8** in tetradentate manner with pentagonal bipyramidal conformation (*vide supra*).[21] Vaccaro *et al.* showed that the reaction can be also catalyzed by LASC generated *in situ* from Zn(II) triflate or Zr(IV) chloride and sodium dodecyl sulfate (Entries 8 and 9). Last but not least, indium and iron complexes appeared to be also active Lewis acid catalysts for this reaction (Entries 10 and 11).

The study of non-linear effect between the ee of bipyridine **8** and product ee was examined in order to investigate details about the catalyst structure in this reaction.[21] While linearity was observed in the case of a copper catalyst in DCM or in water as well as in the case of a scandium catalyst in water, non-linearity was noticed using the scandium catalyst in DCM.[*] Interestingly, the system again evince the linear relation when the independently pre-prepared complexes Sc-(*S,S*)-**8** and Sc-(*R,R*)-**8** were mixed in DCM with only a small excess of one of them in order to make the catalyst with low enantiopurity. The authors are

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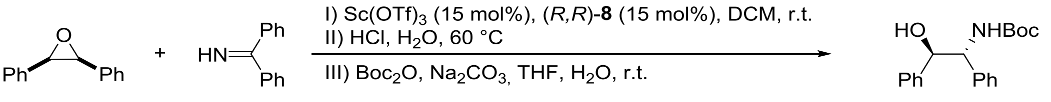
[*] It may seem that the results are in contrast with non-linear effect experiments on conjugate addition with Sc(III) triflate in water where the non-linearity was observed (*vide supra*). On the other hand, Kobayashi *et al.* observed that the presence of additive can influence this effect in Fe(II) catalyzed Mukaiyama aldol reaction.[51] Therefore the presence of pyridine during conjugate addition could clear up this discrepancy of results.

assuming from these experiments that while some aggregates are formed during mixing of bipyridine **8** and Sc(OTf)$_3$ in solution, the Sc-**8** complex is bound irreversibly without any possible dissociation.

Despite indisputable importance of the aminolysis of epoxides, this process under the abovementioned conditions is strictly limited to aromatic amines – anilines. In order to obtain the primary amino alcohols as products, one would need to deprotect the *N*-aryl group and that could be problematic. To overcome this, Schneider *et al.* developed new approach to obtain these compounds based on epoxide ring opening by imines.[52] The products of this reaction were in the next step hydrolyzed and then protected by Boc group, because of the difficulties in separation of highly polar 1,2-amino alcohols. The product **41** was isolated in 51% yield with 80% ee after these three steps using benzophenone imine **40** (Scheme 10).



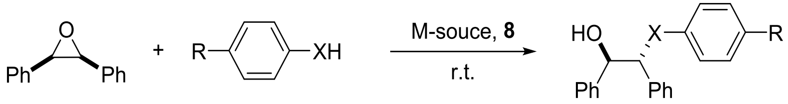
38 **40** **41**, 51%, 80% ee

Scheme 10. Opening of epoxide **38** by benzophenone imine **40**.

Schneider *et al.* and Kobayashi *et al.* also demonstrated the applicability of alcohols (Entries 12 and 13, Table 7), thiols (Entries 14–16) and selenols (Entry 17) in metal-catalyzed opening of epoxide ring. The desired β-hydroxy alcohols, sulfides and selenides were obtained in moderate to high yields and high to excellent enantioselectivities. It should be noted that because of the undesired deselenylation, the selenolyses of *meso*-epoxides needed to be carried out in dark and with degassed solvents.

A great deal of attention was also focused on opening of epoxide ring with indole **42**, because the indole scaffold can be found in many natural products and biologically active compounds.[53] While the reaction utilizing triflates of either scandium (Entry 1, Table 8) or zinc (Entry 6) in DCM provided only traces of the desired product **43**, the reaction with copper(II) triflate yielded **43** in 60% yield with 86% ee (Entry 4). These results were even improved by using LASC based on Sc(III) (Entries 2 and 3), Cu(II) (Entry 5) or Zn(II) (Entry 7). Again the inversion of the absolute stereochemistry of product formed in scandium *vs.* copper or zinc-catalyzed reactions was observed. The best results in terms of yield and enantioselectivity were obtained with Fe(II) perchlorate (Entry 8), the indole derivative **43** was obtained in 90% yield and >99% ee.

Table 7. Opening of epoxide ring of **38** by amine, alcohol, thiol, and selenol.

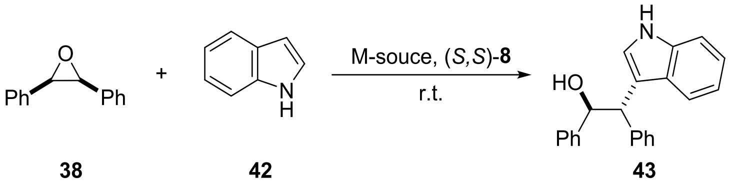


38 **39**

Entry	X	R	**39** (eq.)	M-source[a]	mol%	**8** (mol%)	Additive (mol%)	Solvent	Yield (%)	ee (%)
1[54,55]	NH	H	1	$Sc(OTf)_3$	10	10 (*R,R*)	-	DCM	95	93 (*R,R*)
2[56]	NH	H	1	$Sc(DS)_3$	1	1.2 (*S,S*)	-	H_2O	89	91 (*S,S*)
3[21]	NH	H	1.5	$Sc(UDST)_3$	10	12 (*S,S*)	-	H_2O	87	95 (*S,S*)
4[21]	NH	H	1.5	$Cu(OTf)_2$	10	12 (*S,S*)	-	DCM	18	80 (*R,R*)
5[21]	NH	H	1.5	$Cu(UDST)_2$	10	12 (*S,S*)	-	H_2O	82	80 (*R,R*)
6[21]	NH	H	1.5	$Zn(OTf)_2$	10	12 (*S,S*)	-	DCM	60	90 (*R,R*)
7[21]	NH	H	1.5	$Zn(UDST)_2$	10	12 (*S,S*)	-	H_2O	97	92 (*R,R*)
8[57]	NH	H	1	$Zn(OTf)_2$	5	5 (*R,R*)	NaDS (5 mol%)	H_2O	97	90 (*S,S*)
9[58]	NH	H	1	$ZrCl_4$	5	10 (*R,R*)	NaDS (20 mol%)	H_2O	55	22 (*R,R*)
10[59]	NH	H	2	$In(OTf)_3$	10	10 (*R,R*)	-	DCM	69	89 (*R,R*)
11[24]	NH	H	1	$Fe(ClO_4)_2\cdot 6H_2O$	5	6 (*S,S*)	-	DCM	90	95 (*S,S*)
12[54,60]	CH_2O	MeO	2	$Sc(OTf)_3$	10	10 (*R,R*)	-	DCM	82	97 (*R,R*)
13[61]	CH_2O	Br	1	$Sc(DS)_3$	10	12 (*S,S*)	-	H_2O	34	86 (*S,S*)
14[62]	S	H	3	$Sc(OTf)_3$	10	12 (*S,S*)	-	DCM	84	94 (*S,S*)
15[61]	S	H	3	$Sc(DS)_3$	10	12 (*S,S*)	-	H_2O	73	89 (*S,S*)
16[27]	S	H	1.5	$InBr_3$	10	11 (*R,R*)	-	DCM	81	96 (*R,R*)
17[63]	Se	H	3	$Sc(OTf)_3$	10	10 (*R,R*)	-	DCM	77	93 (*R,R*)

[a] DS – dodecyl sulfate, UDST – undecyl sulfonate.

Table 8. Opening of epoxide ring by indole.



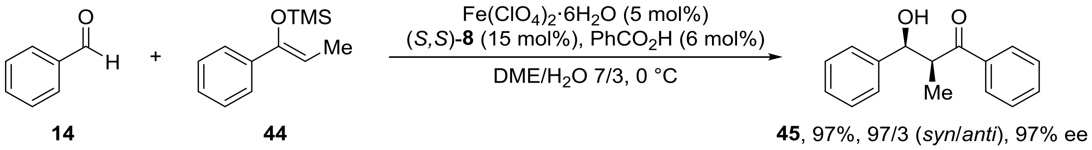
Entry	**42** (eq.)	M-source[a]	mol%	(*S*,*S*)-**8** (mol%)	Additive (mol%)	Solvent	Yield (%)	ee (%)
1[21]	1.2	$Sc(OTf)_3$	10	12	-	DCM	Traces	-
2[61]	1.1	$Sc(DS)_3$	5	6	-	H_2O	85	93 (*R,R*)
3[25]	1.2	$Sc(UDST)_3$	10	12	-	H_2O	69	92 (*R,R*)
4[21]	1.2	$Cu(OTf)_2$	10	12	-	DCM	60	86 (*S,S*)
5[21,25]	1.2	$Cu(UDST)_2$	10	12	-	H_2O	80	96 (*S,S*)
6[21]	1.2	$Zn(OTf)_2$	10	12	-	DCM	Traces	-
7[21]	1.2	$Zn(UDST)_2$	10	12	-	H_2O	8	80 (*S,S*)
8[22]	1.2	$Fe(ClO_4)_2 \cdot 6H_2O$	10	12	4Å MS	DCM	90	>99 (*R,R*)

[a] DS – dodecyl sulfate, UDST – undecyl sulfonate.

1.2.3.4 Mukaiyama aldol reaction

The aldol reaction is well-recognized as one of the most efficient methods for formation of carbon–carbon bond. The classical aldol reaction however suffers from possible formation of several side products, e.g. products of self-condensation, isomerization, or over-reaction. On the other hand, these problems can be overcome by using stable enols (silyl enol ethers). The activation of the carbonyl group is generally done by a Lewis acid. This reaction can proceed enantioselectively if it is carried out in the presence of a chiral ligand.

The highest yields and enantioselectivities were achieved by using 5 mol% of iron(II) perchlorate, 15 mol% of bipyridine (*S*,*S*)-**8** and 6 mol% of benzoic acid in dimethoxyethane (DME) and water mixture by Ollevier *et al.* in 2012 (Scheme 11).[23] Water was found to be essential for this reaction, as the reaction did not result in the formation of the desired product in dry DME.

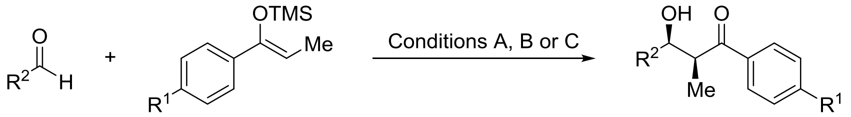


Scheme 11. Mukaiyama aldol reaction catalyzed by Fe(II)-(*S*,*S*)-**8** complex.

In addition, Ollevier showed that this reaction is suitable for various types of substrates including aromatic, aliphatic, heteroaromatic, and unsaturated aldehydes providing products in high yields, diastereoselectivities and enantioselectivities exceeding 91% ee for all substrates.

On the occasion of 40th anniversary of discovery of Mukaiyama aldol reaction Ollevier, Kobayashi *et al.* published a detailed study on utilization of Bolm's ligand **8** in this reaction.[51] They optimized the type of Lewis acid, additive, solvent, ligand and their amounts. They defined three typical conditions (Table 9): conditions A are using iron(II) triflate and pyridine, conditions B iron(II) perchlorate and benzoic acid, while conditions C are based on the use of bismuth(III) triflate and pyridine. Conditions A are suitable for bulky electron-rich aldehydes. On the other hand, bulky electron-poor aldehydes in combination with silyl enol ethers with neutral or electron-withdrawing groups (EWG) are appropriate substrates for conditions B. The bulky, electron-poor aldehydes are reacting well with silyl enol ethers with electron-donating group (EDG) under conditions C, which are also suitable for reaction with non-bulky aldehydes.

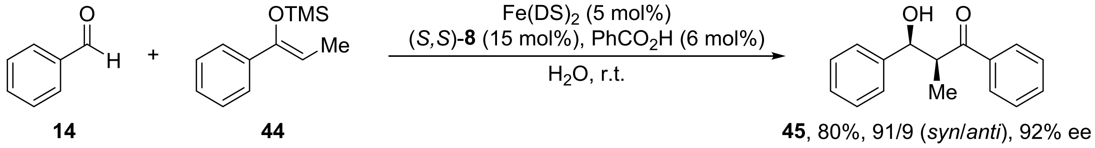
Table 9. Optimized reaction conditions in Mukaiyama aldol reaction.



Silyl enol ether	Aldehyde		
	Bulky		Non-bulky
R^1	Electron-rich	Electron-poor	-
Neutral	A	B	C
EDG	A	C	C
EWG	A	B	C

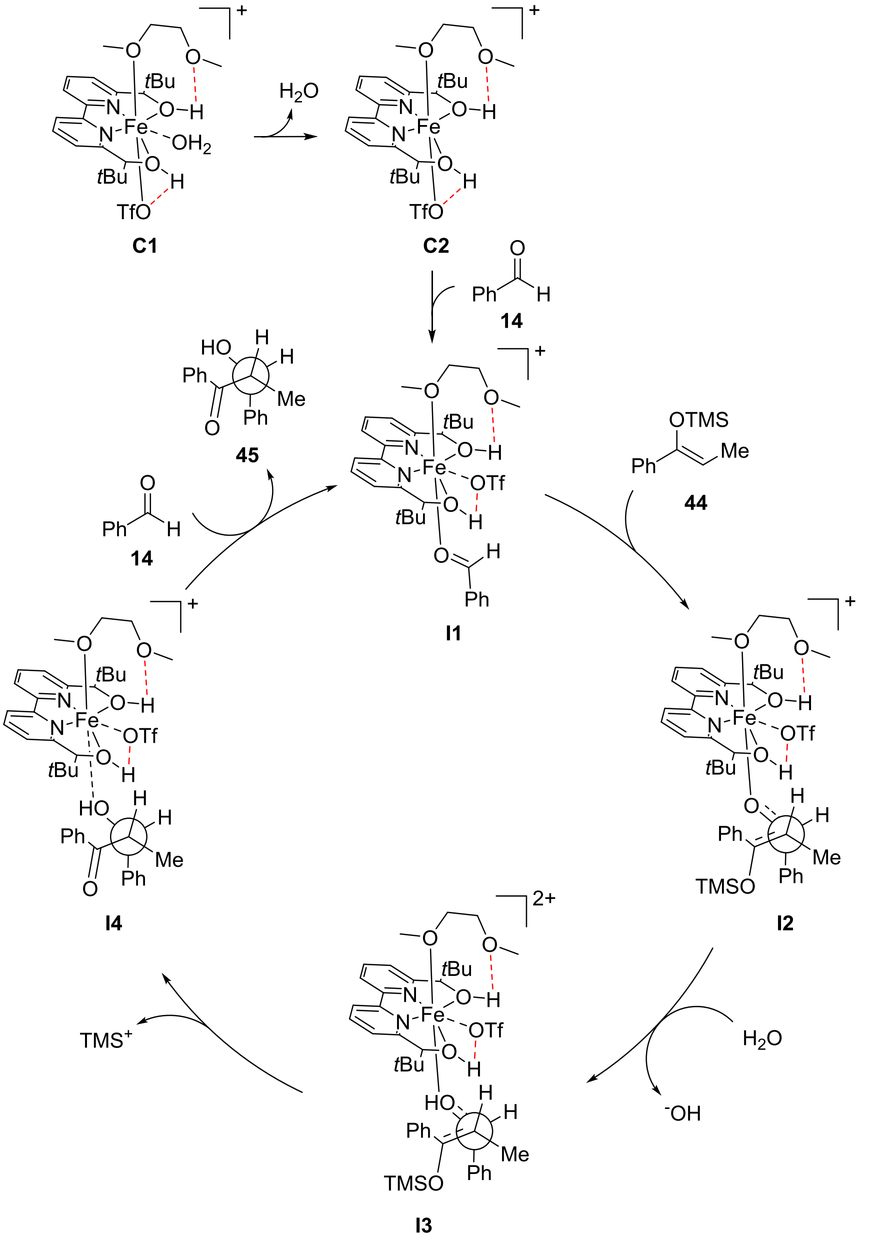
Cond. A: $Fe(OTf)_2$ (3 mol%), (*S,S*)-**8** (3.6 mol%), pyridine (7.2 mol%), DME/H_2O 9/1, 0 °C.
Cond. B: $Fe(ClO_4)_2$ (3 mol%), (*S,S*)-**8** (3.6 mol%), $PhCO_2H$ (3.6 mol%), DME/H_2O 7/3, 0 °C.
Cond. C: $Bi(OTf)_3$ (3 mol%), (*S,S*)-**8** (9 mol%), pyridine (12 mol%), DME/H_2O 9/1, 0 °C.

The sustainability of the Mukaiyama aldol reaction catalyzed by Fe(II)-(*S,S*)-**8** complex was further improved by Ollevier *et al.* in 2014 by using LASC ($Fe(DS)_2$, Scheme 12).[64] The product of the reaction was isolated in 80% yield with 91/9 dr and 92% ee.



Scheme 12. Mukaiyama aldol reaction using LASC.

The mechanism of Mukaiyama aldol reaction is a matter of controversy. To shed some light on it, Morokuma *et al.* performed Density Functional theory (DFT) and Artificial Force-Induced Reaction (AFIR) studies on the system based on iron(II) triflate and (*S,S*)-**8** starting with benzaldehyde **14** and silyl enol ether **44** (Scheme 13).[65] They calculated that high-spin quintet state of Fe(II)-complex is thermodynamically stable, therefore it operates in the whole mechanism. The overall mechanism consists of six steps. The reaction starts with [Fe-(*S,S*)-**8**(OTf)(DME)(H_2O)]$^+$ complex **C1**, which is stabilized by two hydrogen bonds (drawn in red), and is initiated by dissociation of water (**C2**) followed by coordination of aldehyde (**I1**). Then the carbon–carbon bond between aldehyde and silyl enol ether is formed (**I2**). The proton transfer from the molecule of water is then taking place in the next step (**I3**) and the ensuing dissociation of TMS group furnishes the intermediate **I4**. After that, product **45** is discoordinated from the metal sphere, while the next molecule of benzaldehyde is coordinated producing intermediate **I1**, which is entering the next catalytic cycle. It was revealed from the free energy profile of this reaction that, while the formation of carbon–carbon bond is the selectivity-determining step, the rate-determining step of the reaction is the proton transfer from the molecule of water to carbonyl group. Unfortunately the role of additive in this study is fully omitted.



Scheme 13. Proposed mechanism of Mukaiyama aldol reaction catalyzed by Fe(II)-(*S*,*S*)-**8** complex.

1.2.3.5 Hydroxymethylation

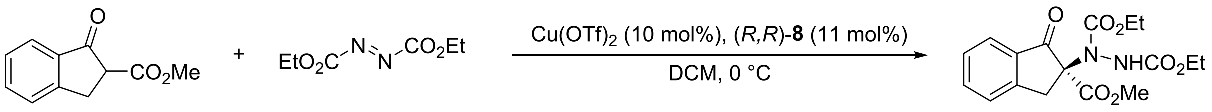
Hydroxymethylation is one of the most useful methods for introduction of one-carbon functional group to the α-position of a carbonyl group by treatment with formaldehyde. It is highly related to aldol reaction and therefore similar catalytic systems can be used.

Kobayashi *et al.* published three studies dealing with Lewis acid catalyzed hydroxymethylation utilizing Bolm's ligand (*S*,*S*)-**8** (Table 10). While they used Sc(III) triflate in DME/water mixture at -20 °C in 2004 (Entry 1), they catalyzed the reaction with Bi(III) triflate in the same type of solvent at 0 °C in the following year. In addition, they revealed the possibility to decrease the amount of catalyst to only 1 mol% by application of 2,2'-bipyridyl as an additive, which further stabilized the Lewis acid in aqueous media (Entry 2). The same authors also developed a method, which did not require any organic cosolvent due to formation of a colloidal system with surfactant-type Lewis acids (Entry 3).

1.2.3.6 α-Amination of β-ketocarbonyl compounds

Synthesis of non-natural α-amino acids attracts the attention of a lot of scientific groups because of their potential application in pharmaceutical industry.[66,67] One of the possible ways for their preparation is α-amination of carbonyl compounds.

Schneider *et al.* were also concerned with this reaction, for which they used diethyl azodicarboxylate (DEAD) as aminating agent and a chiral copper complex derived from Cu(II) triflate and Bolm's ligand (*R*,*R*)-**8** as catalyst.[68] The reaction of cyclic ester **21** under optimized conditions gave product **49** in 81% yield with 97% ee (Scheme 14).



21

49, 81%, 97% ee

Scheme 14. α-Amination of β-ketoester **21** with DEAD by Cu(II)-(*R*,*R*)-**8** complex.

1.2.3.7 C–H activation

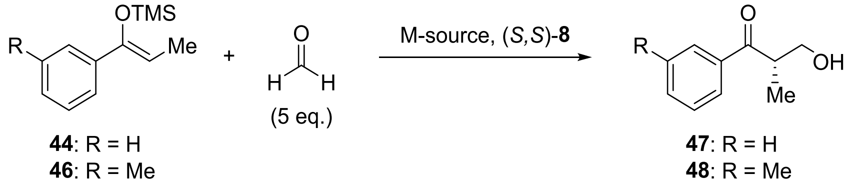
The only application of Bolm's ligand **8** in C–H activation of indoles was published by Kobayashi *et al.* in 2016.[69] The activation of C3–H bonds of indoles was performed by Pd(II) chloride, followed by reaction with α,β-unsaturated ketones. The reaction was carried out in water in the presence of NaDS to stabilize Pd(II)-indolyl intermediate in order to increase the attractiveness of the described process from the point of "green chemistry". In addition, they found that the presence of water is essential for a fruitful course of the reaction, as it did not give any product in a different solvent. They also screened various organic bases and proton scavengers to prevent the undesired Brønsted acid-mediated pathway.[70] The use of either 2,6-di-*tert*-butylpyridine (DTBP) or *N,N*-dimethylaniline turned out to be optimal in terms of yield and enantioselectivity. Starting from unsubstituted indole **42** and ketone **50**, the product **51** was obtained in high yields and enantiopurities 87% ee and 91% ee, respectively (Scheme 15).

1.2.3.8 Diels–Alder reaction

Most recently Ollevier *et al.* also published utilization of Bolm's ligand **8** in the Lewis acid-catalyzed Diels–Alder reaction.[71] In contrast to the already mentioned Mukaiyama aldol reaction, the opening of epoxides, or the Michael addition where iron(II) was compulsory for the activation of substrate, iron(III) is optimal for high yields and selectivities of the desired products in the case of Diels–Alder reaction. The reaction gave **54**, the product of cyclization of cyclopentadiene **52** and α,β-unsaturated oxazolidin-2-one **53**, in quantitative yield with high 92/8 *endo*/*exo* ratio and excellent enantioselectivity of 98% ee using only 2 mol% of the Fe(III)-(*S*,*S*)-**8** catalyst (Scheme 16).

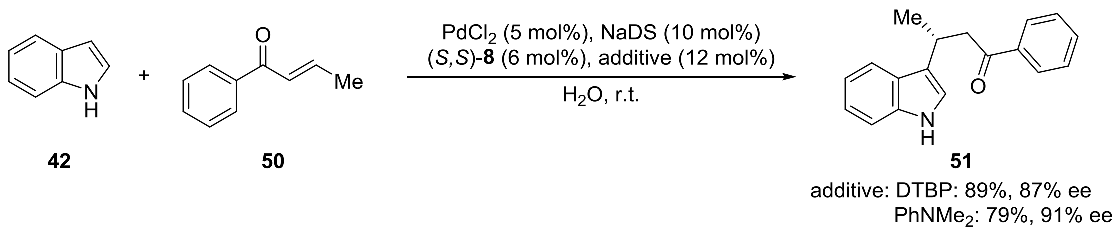
It should be noted that Bolm's ligand **8** was used also in cyclopropanation reaction, however it did not give satisfactory results and so another ligand was used for further studies of this reaction (*vide infra*).[72]

Table 10. Hydroxymethylation of silyl enol ether **44** and **46** by formaldehyde.

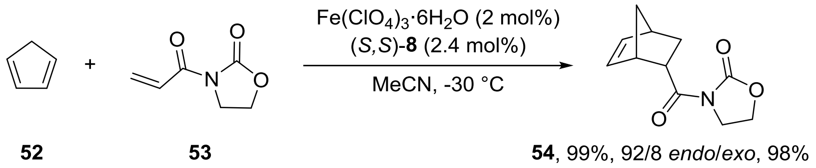


Entry	R	M-source	mol%	(*S*,*S*)-**8** (mol%)	Additive	Solvent	*T* (°C)	Yield (%)	ee (%)
1[73]	H	$Sc(OTf)_3$	10	12	-	DME/H_2O 9/1	-20	80	90
2[26]	H	$Bi(OTf)_3$	1	3	2,2'-bipyridyl (5 mol%)	DME/H_2O 4/1	0	93	91
3[74]	Me	$Sc(DS)_3$[a]	10	12	Triton® X-705	H_2O	r.t.	73	90

[a] DS – dodecyl sulfate.



Scheme 15. C–H activation of indole catalyzed by Pd(II)-(*S*,*S*)-**8** complex.



Scheme 16. Diels–Alder reaction catalyzed by Fe(III)-(*S*,*S*)-**8** complex.

1.3 Analogues of Bolm’s ligand

In this chapter, 2,2'-bipyridines with the substructure depicted in Figure 5 will be discussed. These analogues of Bolm’s ligand **8** include alcohols (R = H) or ethers (R = alkyl, aryl, silyl) with centers of chirality in position 7 and 7' of the side chain connected to the pyridine rings in positions 6 and 6', respectively (Figure 6). All structures are drawn with the same configuration of the chiral center in 7 and 7' position corresponding to Bolm’s ligand with (*S*,*S*)-configuration. If the opposite enantiomer of the depicted bipyridine was used, the compound will be labelled with “*ent*” prefix.

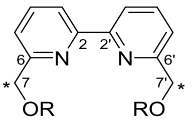


Figure 5. Substructure of defined analogues of Bolm’s ligand **8**.

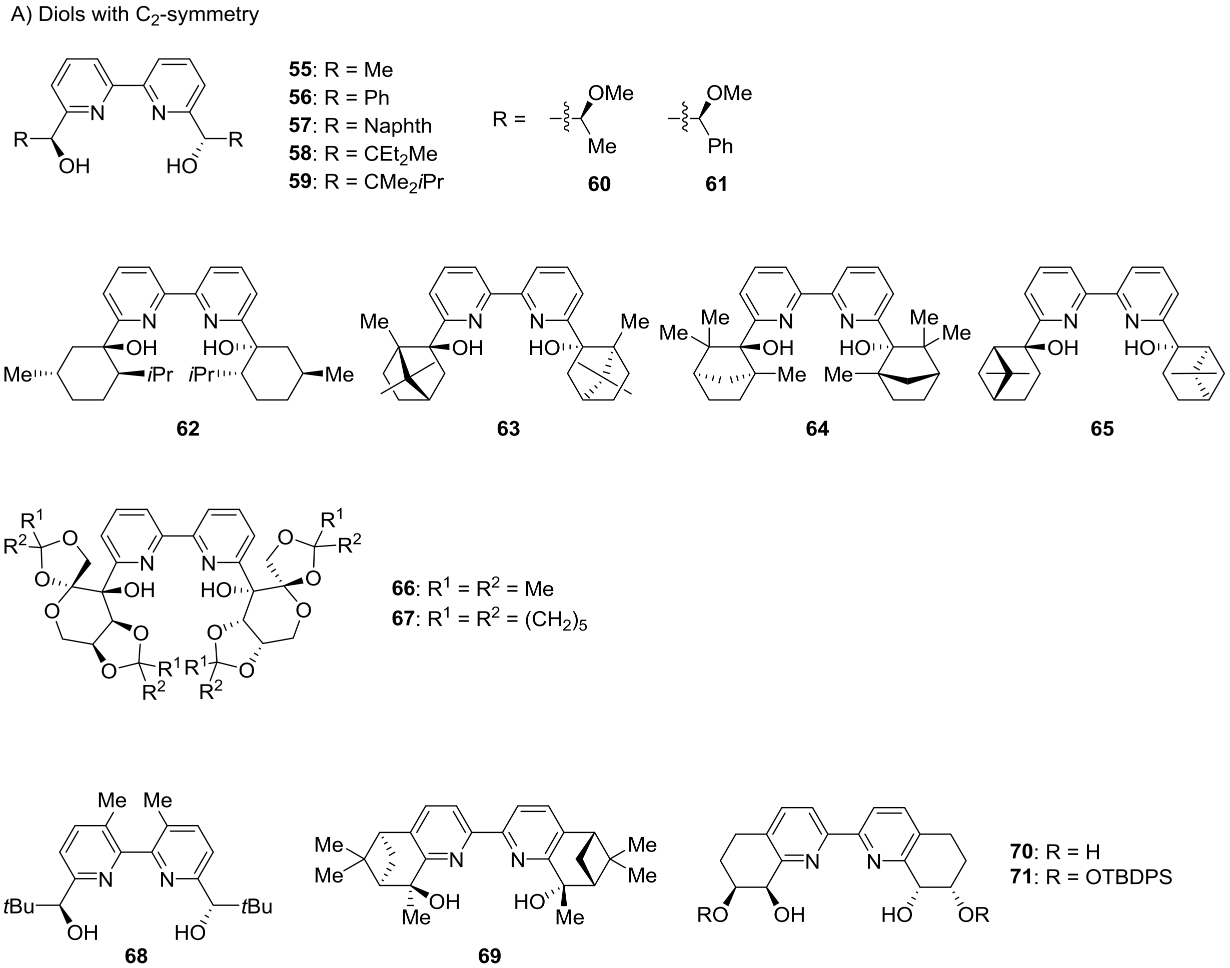
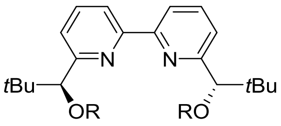
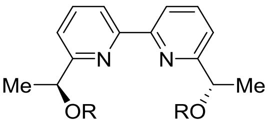


Figure 6. Structures of analogues of Bolm’s ligand **8**.

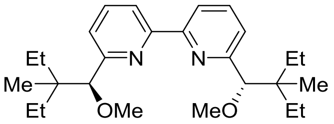
B) Ethers with C_2-symmetry



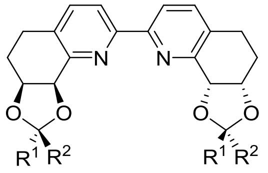
72: R = Me
73: R = Bn



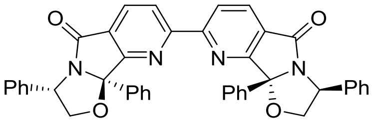
74: R = Me
75: R = Bn



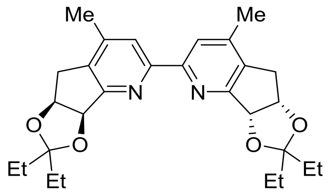
76



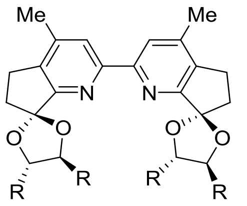
77: $R^1 = R^2 = Me$
78: $R^1 = R^2 = Et$
79: $R^1 = R^2 = Ad$
80: $R^1 = R^2 = (CH_2)_5$
81: $R^1 = Me$, $R^2 = t$Bu



82

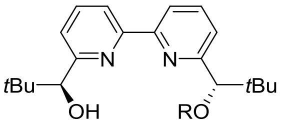


83

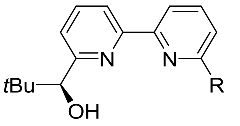


84: R = Me
85: R = *i*Pr
86: R = Ph

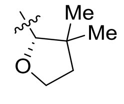
C) 2,2'-bipyridines without C_2-symmetry



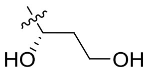
87: R = Me
88: R = Et
89: R = Bn
90: R = TMS
91: R = TBS



R =



92



93

Figure 6. **(continued)** Structures of analogues of Bolm's ligand **8**.

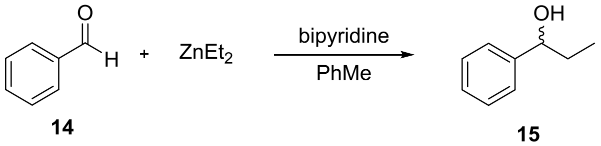
1.3.1 Application

The analogues of bipyridine **8** were also applied as ligands in metal-catalyzed asymmetric reactions. However, in most of these reactions the results in term of yield and enantioselectivity were not better than results obtained in reactions catalyzed by metal complexes of Bolm's ligand **8** without any derivatization.

1.3.1.1 Alkylation and allylation of aldehydes

Simple alkylation of aldehydes was the first application of not only Bolm's ligand itself, but also of its analogues. The alkylation of benzaldehyde **14** by diethyl zinc with bipyridines **60** and **61** (Entries 2 and 3, Table 11) gave the chiral alcohol **15** in high yield in both cases. The enantioselectivity was much higher in the case of using bipyridine **61** bearing sterically more hindered phenyl ring compared to methyl substituent in **60**. Using bipyridines **62**, **63**, **64**, and **65** (Entries 4–7), in which the side chains are derived from terpenoid chiral pool, ethylation of **14** gave alcohol **15** in high yields (74–86%) and high to excellent ee (77–92%). For ethylation of benzaldehyde **14** were also used bipyridines **66** and **67**, which are bearing saccharide moieties (Entries 8 and 9), however, product **15** was obtained only in moderate yields and low enantioselectivities. With bipyridine **69**, the reaction gave only traces of the desired product (Entry 10). Albeit the use of methyl-protected Bolm's ligand **72** gave product **15** in a higher yield (Entry 11) than with Bolm's ligand **8** (Entry 1), the enantiopurity of the alcohol **15** was poor.

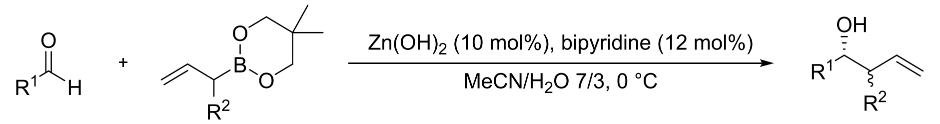
Table 11. Alkylation of benzaldehyde **14** with analogues of Bolm's ligand.



Entry	Bipyridine	mol%	*T* (°C)	Yield (%)	ee (%)
1[35]	(*R,R*)-**8**	5	0	83	93 (*R*)
2[75]	**60**	10	0	88	47 (*S*)
3[75]	**61**	10	0	90	83 (*S*)
4[76]	*ent*-**62**	5	22	74	81 (*S*)
5[76]	*ent*-**63**	5	22	78	92 (*R*)
6[76]	*ent*-**64**	5	22	82	77 (*R*)
7[76]	*ent*-**65**	5	22	86	79 (*R*)
8[77]	*ent*-**66**	5	0	65	15 (*R*)
9[77]	*ent*-**67**	5	0	51	15 (*S*)
10[78]	**69**	5	r.t.	<5	53 (*S*)
11[35]	*ent*-**72**	10	0	93	28 (*R*)

Influence of the bipyridine structure on yields and selectivities of allylation reaction was studied on reaction of benzaldehyde **14** or 3-phenylpropanal **94** by using two different allylating agents, boronates **16b** and **16c**, furnishing α-methyl or α-chlorallyl alcohols **17** and **95**, respectively (Table 12). Using unsymmetrical bipyridines **87**, **88**, **89** and **92** possessing one free hydroxy and one alkyl ether functional group, Kobayashi *et al.* observed only a slight decrease in enantioselectivity, while the diastereoselectivity remained unchanged compared to the use of Bolm's ligand **8** (Entries 1–4 and 7). The α-chlorallylation of **94** with bipyridines **8** and **87** (Entries 10 and 11) also gave similar dependence of the results on the bipyridine structure. On the other hand, when bipyridines bearing sterically hindered silyl ether groups (**90** and **91**) were applied, the selectivities significantly dropped (Entries 5 and 6). Even the presence of the third hydroxyl in **93** did not bring any further advantage (Entry 8). Again dimethyl diether **72** gave in both reactions products with almost no selectivity (Entries 9 and 12).

Table 12. Allylation of aldehydes with different bipyridines.



14: R^1= Ph
94: R^1= PhCH$_2$CH$_2$
16b: R^2 = Me
16c: R^2 = Cl
17: R^1= Ph, R^2 = Me
95: R^1= PhCH$_2$CH$_2$, R^2 = Cl

Entry	R^1	R^2	Bipyridine	Yield (%)	dr *(syn/anti)*	ee (*syn*) (%)
1[20]	Ph	Me	(*S,S*)-**8**	85	91/9	73
2[20]	Ph	Me	**87**	56	91/9	64
3[20]	Ph	Me	**88**	84	92/8	65
4[20]	Ph	Me	**89**	79	89/11	57
5[20]	Ph	Me	**90**	93	80/20	21
6[20]	Ph	Me	**91**	90	80/20	12
7[20]	Ph	Me	**92**	91	90/10	65
8[20]	Ph	Me	**93**	96	75/25	69
9[20]	Ph	Me	**72**	93	45/55	1
10[37]	PhCH$_2$CH$_2$	Cl	(*S,S*)-**8**	85	95/5	97
11[37]	PhCH$_2$CH$_2$	Cl	**87**	91	97/3	95
12[37]	PhCH$_2$CH$_2$	Cl	**72**	93	45/55	1

The results of allylation and alkylation reactions are in good agreement with the theory that the formation of tridentate complex with zinc salts is necessary to obtain product with high level of enantioselectivity. The bipyridine diether **72** is not able to chelate the metal salts with its ethereal oxygen atoms, therefore only bidentate Zn-complex can be formed. The representative example of such complex is depicted in Figure 7.

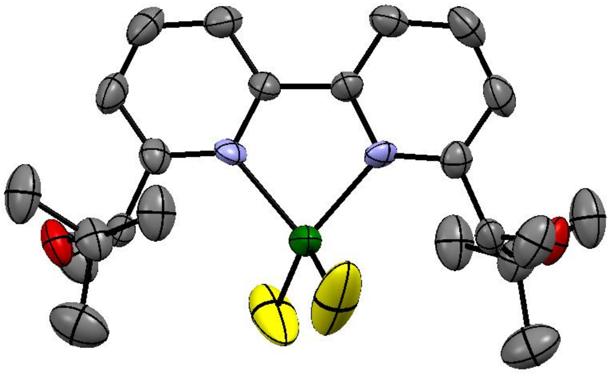
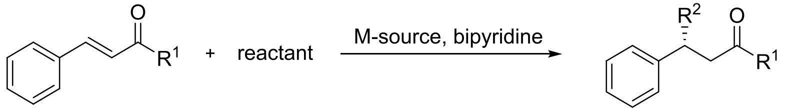


Figure 7. ORTEP drawing of [**72**·ZnCl$_2$] (grey C, red O, blue N, green Zn, yellow Cl).[79] Hydrogen atoms were omitted for clarity.

1.3.1.2 Conjugate addition

A study of metal-catalyzed conjugate addition reaction gave additional information to the already discussed relationships between the types of metal salts and a number of the present free hydroxyls needed to form the active catalytic species. In Sc(III)-catalyzed reaction of α,β-unsaturated ketone **24** with benzyl thiol, the addition of two methyl groups to bipyridine **8** was slowing the reaction down and only traces of the product **25** were isolated when bipyridine **72** was used (Entries 1 and 2, Table 13). In examples of borylations catalyzed by Cu(II) salt, the presence of only one methyl group in bipyridine **87** did not have any influence on either yield or enantioselectivity (Entries 4 and 8), while reaction catalyzed by Cu(II)-**72** with fully protected hydroxy groups proceeded in a low yield of an almost racemic product **97** (Entry 9). When the reaction was catalyzed by copper powder, the results of the reaction were quite different. In that case the single free hydroxy group of bipyridine **87** was not enough to make proper active species and decreased yields and ees were observed (Entries 5 and 6). Wilson *et al.* applied also bipyridine **83** to a similar type of conjugate addition. Although the product of addition (**98**) of indole to α,β-unsaturated ketone **96** was isolated in the quantitative yield (this could be attributed to electron-withdrawing substituent R^1, which is increasing the reactivity of ketone in this reaction), the enantioselectivity reached only moderate level of 59% ee.

Table 13. Conjugate addition with analogues of Bolm's ligand.



24: R^1 = Me
19: R^1 = Ph
96: R^1 = CO_2Me

25: R^1 = Me, R^2 = BnS
97: R^1 = Ph, R^2 = B(pin)
98: R^1 = CO_2Me, R^2 = 3-indolyl

Entry	R^1	Reactant	Product	M-source	mol%	Bipyridine (mol%)	Additive (mol%)	Solvent	*T* (°C)	Yield (%)	ee (%)
1[42]	Me	BnSH	**25**	$Sc(OTf)_3$	10	(*S,S*)-**8** (12)	pyridine (20)	H_2O	r.t.	84	91
2[42]	Me	BnSH	**25**	$Sc(OTf)_3$	10	**72** (12)	pyridine (20)	H_2O	r.t.	2	19
3[46]	Ph	$B_2(pin)_2$	**97**	$Cu(OH)_2$	5	(*S,S*)-**8** (6)	-	H_2O	5	83	81[a]
4[46]	Ph	$B_2(pin)_2$	**97**	$Cu(OH)_2$	5	**87** (6)	-	H_2O	5	82	77[a]
5[46]	Ph	$B_2(pin)_2$	**97**	Cu-powder	10	(*S,S*)-**8** (12)	-	H_2O	30	92	83[a]
6[46]	Ph	$B_2(pin)_2$	**97**	Cu-powder	10	**87** (12)	-	H_2O	30	31	30[a]
7[45]	Ph	$B_2(pin)_2$	**97**	$Cu(OAc)_2$	5	(*S,S*)-**8** (6)	MeOH (100)	Et_2O	r.t.	95	94[a]
8[45]	Ph	$B_2(pin)_2$	**97**	$Cu(OAc)_2$	5	**87** (6)	MeOH (100)	Et_2O	r.t.	92	92[a]
9[45]	Ph	$B_2(pin)_2$	**97**	$Cu(OAc)_2$	5	**72** (6)	MeOH (100)	Et_2O	r.t.	31	4[a]
10[80]	CO_2Me	indol	**98**	$Cu(OTf)_2$	10	**83** (10)	-	Et_2O	-78	97	59[b]

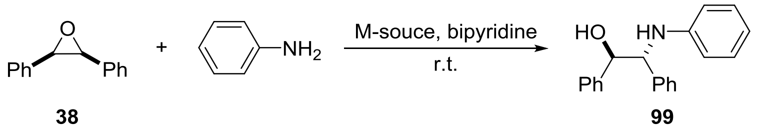
[a] The enantioselectivity was determined after oxidation to alcohol **30** by $NaBO_3$. [b] The product **98** with opposite configuration was isolated.

1.3.1.3 Opening of *meso*-epoxides

Schneider *et al.* studied the possibility to increase the selectivity of desymmetrization of *meso*-epoxides when the *tert*-butyl group of Bolm's ligand was changed to more bulky substituent. Unfortunately, the reactions with bipyridines **58** and **59** did not proceed with higher yields or enantiopurities of the desired product **99** in the scandium-catalyzed reactions (Entries 1–3, Table 14). The results were not further improved even with additional *ortho* methyl substituent on pyridine ring in **68** (Entry 4). On the other hand, the yields and the ees significantly dropped by utilization of tetrahydro-2,2'-biquinolines **70** and **71** in reactions catalyzed by scandium triflate or dodecyl sulfate (Entries 5 and 8). As expected, the reactions catalyzed by scandium (Entry 6), indium (Entry 10) and zinc Lewis acids (Entry 13) gave only racemic amino alcohol **99** (if any) when the diether **72** was used.

One would expect that, as zinc(II) is forming tridentate complex with Bolm's ligand **8** where only one of the two free hydroxy groups is participating in chelation, the reaction with bipyridine **87** will give the product with approximately same yield and selectivity. Indeed, this is not the case and almost racemic product **99** was isolated in only 46% yield (Entry 12). Authors proposed a possible explanation by essentiality of the second hydroxy group for coordination of one of the substrate.

Table 14. Opening of *cis*-stilbene oxide **38** with analogues of Bolm's ligand.

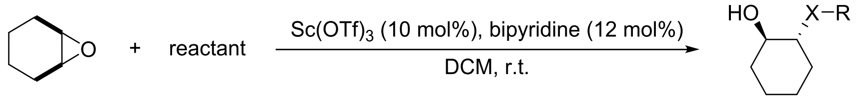


Entry	M-source[a]	mol%	Bipyridine (mol%)	Solvent	Yield (%)	ee (%)
1[55]	Sc(OTf)$_3$	10	(*R,R*)-**8** (12)	DCM	95	93 (*R,R*)
2[55]	Sc(OTf)$_3$	10	*ent*-**58** (12)	DCM	87	92 (*R,R*)
3[55]	Sc(OTf)$_3$	10	*ent*-**59** (12)	DCM	81	89 (*R,R*)
4[55]	Sc(OTf)$_3$	10	*ent*-**68** (12)	DCM	89	86 (*R,R*)
5[81]	Sc(OTf)$_3$	10	**71** (12)	DCM	64	61 (*S,S*)
6[55]	Sc(OTf)$_3$	10	*ent*-**72** (12)	DCM	63	*rac*
7[56]	Sc(DS)$_3$	1	(*S,S*)-**8** (1.2)	H_2O	89	91 (*S,S*)
8[81]	Sc(DS)$_3$	1	**70** (1.2)	H_2O	50	57 (*S,S*)
9[59]	In(OTf)$_3$	10	(*R,R*)-**8** (10)	DCM	69	87 (*R,R*)
10[59]	In(OTf)$_3$	10	*ent*-**72** (10)	DCM	NR	-
11[21]	Zn(UDST)$_2$	10	(*S,S*)-**8** (12)	H_2O	97	92 (*R,R*)
12[21]	Zn(UDST)$_2$	10	**87** (12)	H_2O	46	9 (*R,R*)
13[21]	Zn(UDST)$_2$	10	**72** (12)	H_2O	25	*rac*

[a] DS – dodecyl sulfate, UDST – undecyl sulfonate.

An interesting discrepancy was revealed by comparison of the results reported by Schneider *et al.* dealing with the reaction of cyclohexene oxide **100** and *cis*-stilbene oxide **38** with aniline and allyl alcohol catalyzed by Sc-**68** complex. Both alcoholysis and aminolysis of *cis*-stilbene oxide **38** gave appropriate products in yields and enantioselectivities comparable with the results obtained using bipyridine **8** (aminolysis – Entry 1 and 4, Table 14). Moreover the same observation was made in alcoholysis of cyclohexene oxide **100** (Entries 1 and 2, Table 15). However, when epoxide **100** was treated with aniline, the product **101** was surprisingly isolated as a racemic mixture of both enantiomers albeit in excellent yield (Entry 4). This disagreement in the results has not been elucidated yet.

Table 15. Opening of cyclohexene oxide **100** with allyl alcohol or aniline.



100

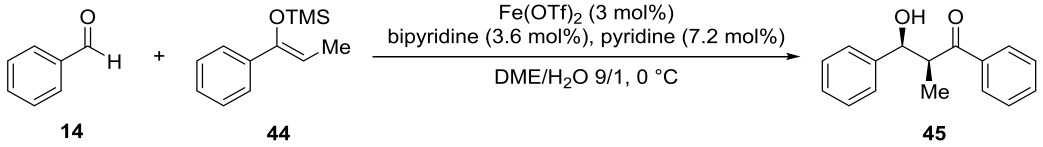
101: X = NH, R = Ph
102: X = O, R = allyl

Entry	reactant	X	R	Bipyridine	Yield (%)	ee (%)
1[60]	allylOH	O	allyl	(*R,R*)-**8**	44	48
2[60]	allylOH	O	allyl	*ent*-**68**	55	43
3[55]	$PhNH_2$	NH	Ph	(*R,R*)-**8**	71	40
4[55]	$PhNH_2$	NH	Ph	*ent*-**68**	93	*rac*

1.3.1.4 Mukaiyama aldol reaction

Kobayashi *et al.* also used some of the analogues of Bolm's ligand in the iron(II)-catalyzed Mukaiyama aldol reaction. Change of the *tert*-butyl group to the less sterically hindered methyl group (**55**) or phenyl (**56**) and naphthyl (**57**) group caused the decrease of both yield and enantioselectivity (Entries 1–4, Table 16). Interestingly, the presence of bipyridine **57** in the reaction gave rise to product **45** with opposite absolute stereochemistry (Entry 4). The utilization of the bipyridine **58** with a bulkier 3-methylpentan-3-yl substituent (compared to *tert*-butyl group in Bolm's ligand) had only marginal if any influence on yield and selectivity of the reaction (Entry 5). Finally, the protection of one (**87**) or both (**76**) hydroxyls with methyl substituent caused the formation of racemic product **45** (Entries 6 and 7). This confirmed the proposed mechanism of the reaction drawn in Scheme 13 where both free hydroxy groups have essential role by making hydrogen bonds with the triflate anion and a molecule of dimethoxyethane.

Table 16. Mukaiyama aldol reaction with analogues of Bolm's ligand.



Entry	Bipyridine	Yield (%)	dr (*syn*/*anti*)	ee (*syn*) (%)
1[51]	(*S*,*S*)-**8**	90	97/3	91
2[51]	**55**	25	97/3	22
3[51]	**56**	21	92/8	39
4[51]	**57**	25	90/10	58[a]
5[51]	**58**	93	93/7	92
6[51]	**87**	49	92/8	*rac*
7[51]	**76**	52	94/6	*rac*

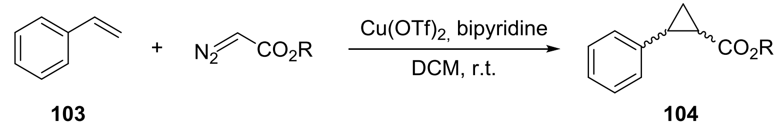
[a] (*R*,*R*)-configuration.

1.3.1.5 Cyclopropanation

Cyclopropanation of alkene by diazoacetates is the only reaction, in which the results obtained with Bolm's ligand **8** were overcome by its analogues (Table 17). The reactions of styrene **103** with ethyl diazoacetate catalyzed by copper(II) triflate complexes with bipyridines **8** and **55** bearing free hydroxyls proceeded in high yields, but with moderate diastereo- and enantioselectivities (Entries 1 and 2). The best selectivities, which reached 80/20 *trans*/*cis* ratio and 90% ee, were observed with the methyl-substituted bipyridine **72** (Entry 3). The use of bulkier benzyl protection of hydroxy groups (**73**) did not improve the selectivities (Entry 4) and unsurprisingly, the switch of *tert*-butyl to simple methyl groups (**74** and **75**) only decreased both selectivities (Entries 5 and 6).

Also copper(I)-complexes were found to be active catalysts for cyclopropanation reactions despite their need to be prepared *in situ* by reduction of copper(II) salt with phenylhydrazine because of their proneness to oxidation. The cyclopropanations catalyzed by copper(I) generally provided products with lower yields, but in some cases much higher *trans*/*cis* ratios and enantioselectivities compared to copper(II) catalyzed reactions. The most effective were bipyridines **78** and **81** with tetrahydro-2,2'-biquinoline core and also bipyridine **83** with similar structure (Entries 7–9). On the other hand, utilization of copper(I) complexes with **82**, **84**, **85**, and **86** gave nearly racemic product **104** (Entries 10–13).

Table 17. Cyclopropanation of styrene **103** with analogues of Bolm's ligand.



Entry	R	$Cu(OTf)_2$ mol%	Bipyridine (mol%)	Additive (mol%)	Yield (%)	*trans*/*cis*	ee (%) (*trans*)[a]
1[72]	Et	2	(*R*,*R*)-**8** (2.2)	-	92	74/26	73 (*R*,*R*)
2[72]	Et	2	**55** (2.2)	-	99	70/30	44 (*S*,*S*)
3[72]	Et	2	*ent*-**72** (2.2)	-	85	80/20	90 (*R*,*R*)
4[72]	Et	2	*ent*-**73** (2.2)	-	86	76/24	83 (*R*,*R*)
5[72]	Et	2	**74** (2.2)	-	88	66/34	30 (*S*,*S*)
6[72]	Et	2	**75** (2.2)	-	92	66/34	43 (*S*,*S*)
7[82]	*t*Bu	1.25	**78** (1.5)	$PhNHNH_2$ (1.5)	55	91/9	88 (*R*,*R*)
8[82]	*t*Bu	1.25	**81** (1.5)	$PhNHNH_2$ (1.5)	58	95/5	90 (*R*,*R*)
9[83]	*t*Bu	1.25	**83** (1.5)	$PhNHNH_2$ (1.5)	67	93/7	92 (*R*,*R*)
10[84]	*t*Bu	1	*ent*-**82** (1.2)	$PhNHNH_2$ (1.2)	65	72/28	15 (ND)
11[85]	Et	1.25	*ent*-**84** (1.25)	$PhNHNH_2$ (1.5)	55	60/40	9 (*R*,*R*)
12[85]	Et	1.25	**85** (1.25)	$PhNHNH_2$ (1.5)	62	70/30	25 (*S*,*S*)
13[85]	Et	1.25	**86** (1.25)	$PhNHNH_2$ (1.5)	58	60/40	*rac*

[a] ND – not determined.

1.3.1.6 Allylic oxidation

One of the applications, in which Bolm's ligand **8** has never been used, is allylic oxidation. The reason for that is obviously the presence of potentially oxidizable hydroxy substituents. On the other hand, bipyridines bearing tertiary alcoholic substituents as well as ethers are compatible with these reaction conditions; therefore they could have been used as ligands in this reaction. Copper(I) salts showed to be suitable Lewis acids for this reaction and they were used either in their stable coordination form or they were generated *in situ* by reduction of copper(II) species.

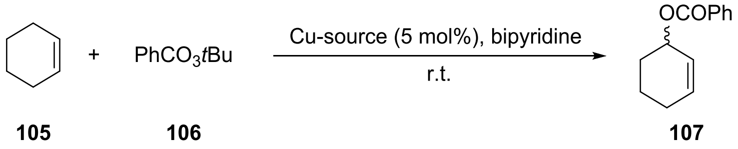
The oxidations of cyclohexene **105** with *tert*-butyl peroxybenzoate **106** catalyzed by copper(I)-complexes with bipyridine diols **62**, **63**, **64**, and **65** gave cyclohex-2-enyl benzoate **107** in moderate yields with low to moderate ees (Entries 1–4, Table 18). The use of Cu(I)-**83** complex furnished the oxidized product **107** in high ee but moderate yield (Entry 5). Finally, Boyd *et al.* synthesized structurally similar tetrahydro-2,2'-biquinolines **77**, **78**, **79**, **80**, and **81** which were also used as ligands in oxidation reaction of allylic position of cyclohexene **105**. The obtained yields and ees highly exceeded results of this reaction catalyzed by bipyridine ligands published so far (Entries 6–10). The best of them, which reached 91% yield and 90% ee, was obtained with bipyridine **81** (Entry 10).

1.3.1.7 Friedel–Crafts alkylation

Wilson *et al.* used one of the analogues of Bolm's ligand in asymmetric Friedel–Crafts reaction.[80] The reaction of indole **42** with derivative of pyruvic acid **109** catalyzed by Cu(II)-**83** complex proceeded in high yield and excellent enantioselectivity (Scheme 17). When they studied the scope of the reaction, they found that the hydrogen atom of the indole nitrogen had the essential role for the reaction. Therefore, when this hydrogen was substituted by methyl group (**108**), the enantioselectivity dramatically dropped.

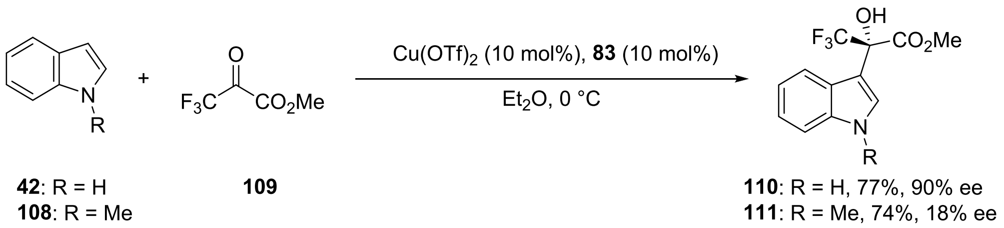
It should be also noted that bipyridine **58** was also used in Nazarov-type reaction[86] and bipyridine **63** in asymmetric polymerization reaction.[87,88] Complexes of both ligands with metal salts gave unfortunately only unsatisfactory results in these reactions.

Table 18. Allylic oxidation of cyclohexene **105** with Bolm's ligand analogue.



Entry	Cu-source	Bipyridine (mol%)	Additive (mol%)	Solvent	Yield (%)[a]	ee (%)
1[89]	$[Cu(MeCN)_4]PF_6$	*ent*-**62** (5)	-	MeCN	79	22 (*R*)
2[89]	$[Cu(MeCN)_4]PF_6$	*ent*-**63** (5)	-	MeCN	57	52 (*R*)
3[89]	$[Cu(MeCN)_4]PF_6$	*ent*-**64** (5)	-	MeCN	44	31 (*R*)
4[89]	$[Cu(MeCN)_4]PF_6$	*ent*-**65** (5)	-	MeCN	47	30 (*R*)
5[90]	$Cu(OTf)_2$	**83** (5.25)	$PhNHNH_2$ (5.25)	MeCN[b]	45	91 (*S*)
6[81]	$Cu(OTf)_2$	**77** (6)	$PhNHNH_2$ (6)	Me_2CO	89	73 (*S*)
7[81]	$Cu(OTf)_2$	**78** (6)	$PhNHNH_2$ (6)	Me_2CO	92	82 (*S*)
8[81]	$Cu(OTf)_2$	**79** (6)	$PhNHNH_2$ (6)	Me_2CO	ND	79 (*S*)
9[81]	$Cu(OTf)_2$	**80** (6)	$PhNHNH_2$ (6)	Me_2CO	55	85 (*S*)
10[81]	$Cu(OTf)_2$	**81** (6)	$PhNHNH_2$ (6)	Me_2CO	91	90 (*S*)

[a] ND – not determined. [b] Reaction proceeded at 0 °C.

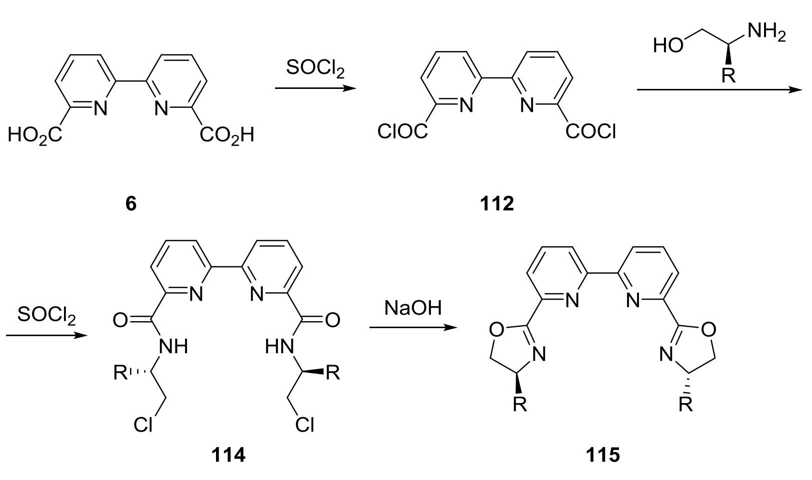


Scheme 17. Friedel-Crafts alkylation catalyzed by Cu(II)-**83** complex.

1.4 Bis(oxazolinyl)bipyridines

From the time of the pioneering work of Masamune *et al.*[91] and later on of Evans *et al.*[92] and Corey *et al.*,[93] compounds bearing oxazoline moiety have become one of the most popular classes of ligands for metal-catalyzed asymmetric catalysis. They are popular because of an easy synthesis of oxazoline ring from readily accessible chiral amino alcohols and their wide applicability in metal-catalyzed transformations. However, while a numerous studies deal with application of bis(oxazoline) (BOX), mono(oxazolinyl)pyridine (PyMOX), and bis(oxazolinyl)pyridine (PyBOX) ligands,[94–96] the reports about bis(oxazolinyl)bipyridine (BipyMOX) are rather scarce.

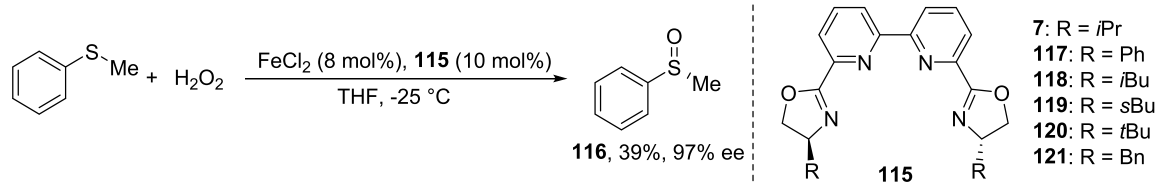
Although few methods of the formation of oxazoline ring in one or two steps have been developed, generally the mostly used is the stepwise method, which in the case of BipyMOX ligands proceeds simultaneously on both pyridine rings (Scheme 18). The synthesis starts from 2,2'-bipyridine-6,6'-dicarboxylic acid **6** by a generation of dicarbonyl dichloride **112** followed by a reaction with two molecules of chiral amino alcohol. The hydroxyl groups of diol **113** are in the next step transformed to chlorides (**114**). In the last step, the oxazoline rings are closed under basic conditions (**115**).



R = *i*Pr, 55% in 4 steps

Scheme 18. General synthesis of BipyMOXes **115**.

The complexes of the known BipyMOXes **7**, **117**–**121** (Scheme 19), which showed either bidentate (two nitrogen of bipyridine scaffold coordinate metal center) or tetradentate (participation of all four nitrogen atoms in coordination) chelation of metal salts, were used by Nishiyama *et al.* as ligands in Ru-catalyzed cyclopropanation and epoxidation of styrenes.[97] However, the formed cyclopropanes and epoxides were isolated as racemic mixtures of both enantiomers or with only slight excess of one of them (<10% ee). Superior results in terms of enantioselectivity were achieved by Rh-catalyzed asymmetric hydrosilylation of ketones reported by the same authors (up to 90% ee)[17] and asymmetric Diels–Alder reaction catalyzed by ytterbium salt (up to 77% ee).[98] The most promising results until now have been obtained by Fe(II)-catalyzed enantioselective oxidation of aromatic sulfides published by Ollevier *et al.* (Scheme 19).[99]



Scheme 19. Asymmetric oxidation of sulfides catalyzed by Fe-**115** complexes.

1.5 2,2'-Bipyridine *N,N'*-dioxides

2,2'-Bipyridine *N,N'*-dioxides are an interesting class of compounds derived from 2,2'-bipyridines, with both nitrogen atoms bearing oxygen atoms (Figure 8). Due to polarization of the N–O bond, they possess unique chemical properties and reactivity. The oxygen of the N–O moiety is Lewis basic and hence able to coordinate to Lewis acidic part of a nucleophilic reagent and thus activate it toward reaction with an electrophile.[100] Therefore *N*-oxides can act as Lewis-base catalysts but also as ligands in metal-catalyzed reactions.[101]

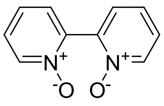
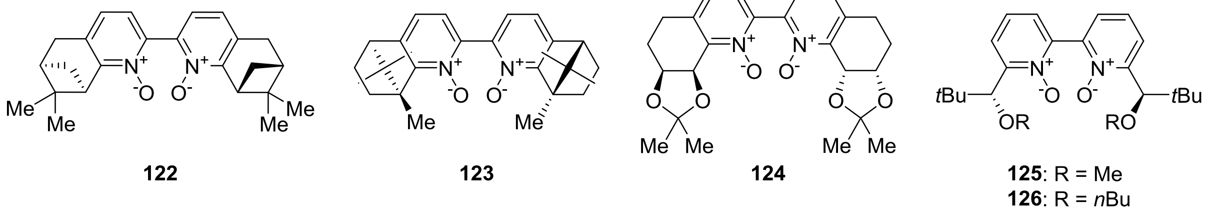

2,2'-bipyridine *N,N'*-dioxide

Figure 8. Structures of 2,2'-bipyridine *N,N'*-dioxide.

As well as bipyridines, 2,2'-bipyridine *N,N'*-dioxides can be divided into achiral and chiral groups and subsequently into groups based on the type of element of chirality, which they possess.[102] Regarding the chiral bipyridine *N,N'*-dioxides, only compounds with central, axial and combination of both elements of chirality were used as Lewis-base catalysts. Syntheses and applications of selected examples of chiral bipyridine *N,N'*-dioxides (Figure 9) will be discussed in the following paragraphs. All catalysts possessing the element of axial chirality are drawn with the same (a*S*)-configuration. For the cases when the opposite enantiomer of the depicted catalyst was used, the compound will be labelled with "*ent*" prefix.

A) Bipyridine *N,N′*-dioxides with elements of central chirality



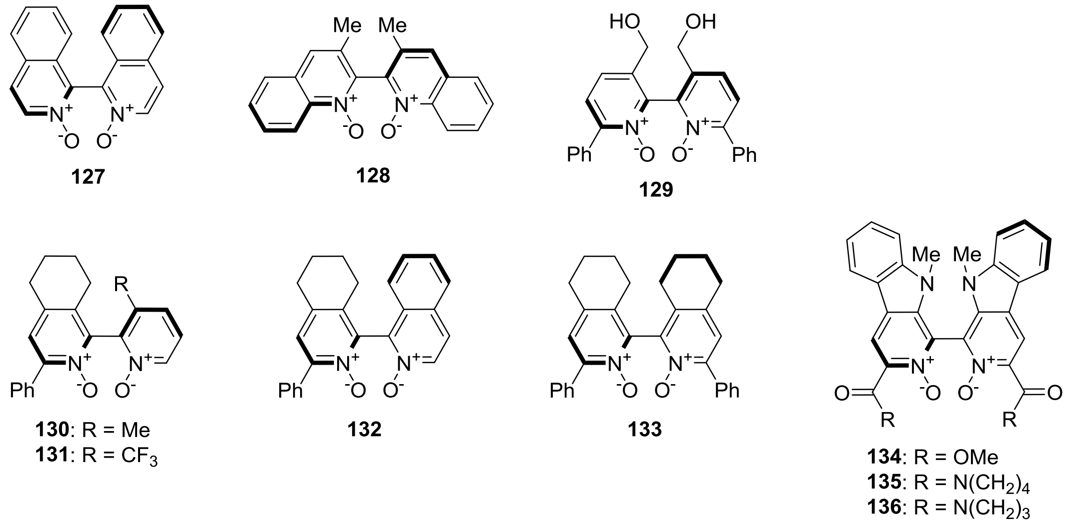
122

123

124

125: R = Me
126: R = *n*Bu

B) Bipyridine *N,N′*-dioxides with an element of axial chirality



127

128

129

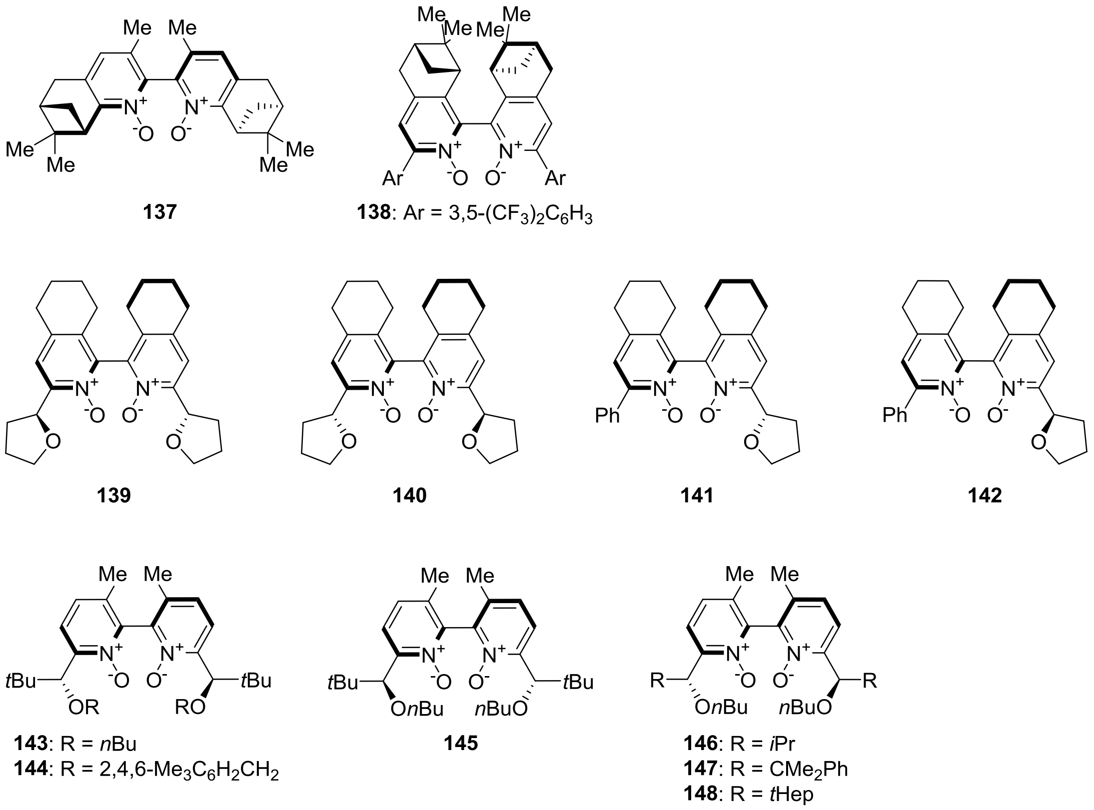
130: R = Me
131: R = CF_3

132

133

134: R = OMe
135: R = $N(CH_2)_4$
136: R = $N(CH_2)_3$

C) Bipyridine *N,N′*-dioxides with elements of central and axial chirality



137

138: Ar = 3,5-$(CF_3)_2C_6H_3$

139

140

141

142

143: R = *n*Bu
144: R = 2,4,6-$Me_3C_6H_2CH_2$

145

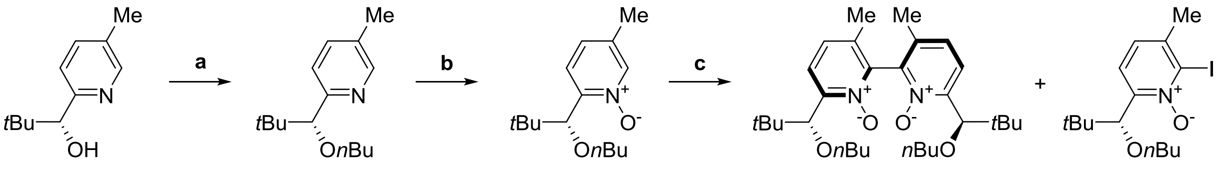
146: R = *i*Pr
147: R = CMe_2Ph
148: R = *t*Hep

Figure 9. Structures of chiral 2,2'-bipyridine *N,N′*-dioxides.

1.5.1 Synthesis

Although the pyridine *N*-oxide moiety can be synthesized by various methods[103] as e.g. radical reactions of esters of *N*-hydroxy-2-thiopyridones with DEAD,[104] base-catalyzed rearrangements of 5-cyanomethyl-2-isoxazolines[105] or cycloaddition reactions of isoxazoles with alkenes,[106] the most convenient method is the simple oxidation of pyridines. Bipyridine *N,N′*-dioxides are easily accessible from appropriate bipyridines (their synthesis was already discussed in Chapter 0) by reaction with *m*-chloroperoxybenzoic acid (MCPBA),[107] which is the first-choice reagent for this reaction, hydrogen peroxide, used, for example, by Fujii in the first synthesis of axially chiral bipyridine *N,N′*-dioxide **127**,[108] or urea hydroperoxide (UHP), used in synthesis of **136**.[109]

Another possibility of preparation of 2,2'-bipyridine *N,N′*-dioxides is *via* an oxidative coupling of the pyridine *N*-oxides after their lithiation in position 2. This method was first used by Denmark *et al.* in synthesis of compound **143** shown in the Scheme 20, but also in synthesis of compounds **144** and **146**–**148** by the same authors.[110] The free hydroxy group of pyridyl alcohol **149**, which was prepared according to Bolm's protocol of synthesis of bipyridine (*R*,*R*)-**8** (Scheme 5), was first protected with *n*-butyl group and the resulted pyridine **150** was oxidized to *N*-oxide **151**. Then it underwent lithiation by lithium tetramethylpiperidide (LiTMP) and the subsequent oxidative coupling by iodine gave selectively (a*S*)-atropoisomer of the *N,N′*-dioxide **143** in 48% yield. The main side product of the dimerization reaction was 2-iodopyridine **152**, which was isolated in 47% yield. In order to obtain the opposite atropoisomer *ent*-**145**, it was necessary to employ the reduction/reoxidation sequence of the *N,N′*-dioxide **143**. The atropoisomers **143** and *ent*-**145** were obtained by this sequence in 67% and 27% yield, respectively.



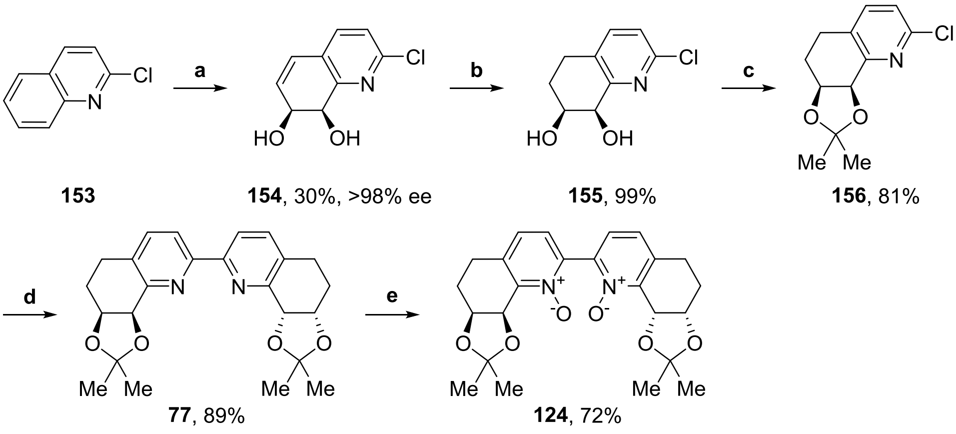
149 **150**, 84% **151**, 84% **143**, 48% **152**, 47%

a) *n*BuBr (5.7 eq.), KOH (6 eq.), 18-cown-6 (0.1 eq.), 3Å MS, DMF, r.t.
b) MCPBA (1.5 eq.), DCM, r.t.
c) I) LiTMP (1 eq.), Et$_2$O, THF, -73 °C; II) I$_2$ (1 eq.), Et$_2$O, THF, -73 °C to r.t.

Scheme 20. Synthesis of *N,N′*-dioxide **143** by oxidative coupling method.

The same method was also recently used in Kotora's group for preparation of dioxide *ent*-**141** and its atropoisomer **142**.[111] Similarly was also prepared *N,N′*-dioxide **138** by Malkov *et al.* using LDA for deprotonation and oxygen gas for the final coupling.[112] The enantiomer with (a*S*)-configuration was the only product of the reaction also in this case.

The chiral *N,N'*-dioxides possessing elements of central chirality were obtained by (a) incorporation of the accessible optically pure compounds from the chiral pool into the *N,N'*-dioxide structure, (b) using enantioselective synthetic step in their preparation, or (c) separation of racemic mixtures of the appropriate enantiomers. The examples of the first method can be found in the preparations of compounds **122**, **123**, *ent*-**137** and **138** with terpene moiety and *ent*-**139**, **140**, *ent*-**141** and **142** derived from (*R*)-tetrahydrofuran-2-carbonitrile. The enantioselective reduction was used in the series of Denmark's *N,N'*-dioxides **125**, **126**, **143**, **144**, *ent*-**145**, and **146**–**148** utilizing chiral borane following the synthesis of Bolm's ligand (*R*,*R*)-**8**. Interestingly, Boyd *et al.* used enzymatically catalyzed dihydroxylation of the quinoline derivative **153** as the key step of the synthesis of compound **124** (Scheme 21).[81,82] After catalytic hydrogenation and protection of the hydroxy groups, 2-halopyridine **156** was homodimerized under classical Ni-mediated conditions. The treatment of the derived bipyridine **77** with MCPBA afforded the desired *N,N'*-dioxide **124**.



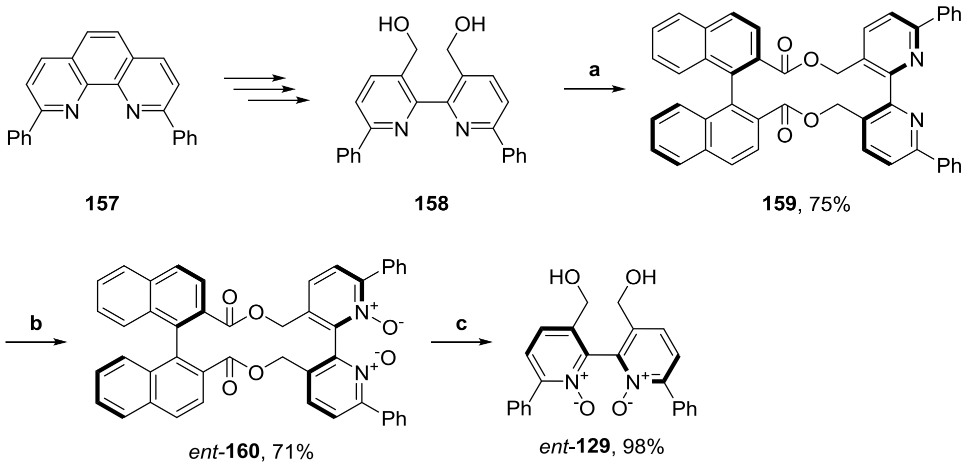
a) *Pseudomonas putida* (UV4), O_2, ms medium 0.05% sodium succinate
b) PtO_2 (8 mol%), H_2, EtOAc (1.5 eq.), r.t.
c) Me_2CO, TFA, DMP, 0 °C to r.t.
d) $NiCl_2{\cdot}6H_2O$ (1.2 eq.), Zn (3.1 eq.), PPh_3 (4.1 eq.), DMF, 60 °C
e) MCPBA (2.5 eq.), DCM, 0 °C to r.t.

Scheme 21. Synthesis of *N,N'*-dioxide **124** with enzymatically catalyzed step.

The enantioselective synthesis of axially chiral *N,N'*-dioxides is more challenging. The *N,N'*-dioxides possessing only the element of axial chirality (B, Figure 9) were mostly synthesized in the racemic manner followed by separation of the enantiomers. The separation was done using liquid chromatography with chiral stationary phase, which was used in the cases of dioxides **130**–**136**, or by cocrystallization technique with chiral 1,1'-binaphtol

(BINOL) or dibenzoyltartaric acid, which was used in majority of axially chiral *N,N'*-dioxides.[113].

The original method was used by Hayashi *et al.* for synthesis of compound *ent*-**129** (Scheme 22).[107] The readily accessible bipyridine **158** (by oxidation of phenantroline **157**) was treated with axially chiral (*R*)-2,2'-bis(chlorocarbonyl)-1,1'-binaphthalene to give the bipyridine diester. In the course of refluxing in toluene, the thermodynamically more stable diastereoisomer **159** with (a*R*)-configuration in bipyridine scaffold was formed. This step introduced chirality into the bipyridine ring and it was fixed in the following step by oxidation to *N,N'*-dioxide *ent*-**160**. The removal of the naphthalene chiral auxiliary furnished the *N,N'*-dioxide *ent*-**129** without any racemization.



a) I) (*R*)-2,2'-bis(chlorocarbonyl)-1,1'-binaphthalene (1.5 eq.), Et_3N (4 eq.), $CHCl_3$, 0 °C to r.t.; II) PhMe, reflux
b) MCPBA (3.1 eq.), DCM, 0 °C to r.t.
c) NaOH (50 eq.), MeOH/H_2O 4/1, r.t.

Scheme 22. Synthesis of axially chiral *N,N'*-dioxide *ent*-**129** using chiral auxiliary.

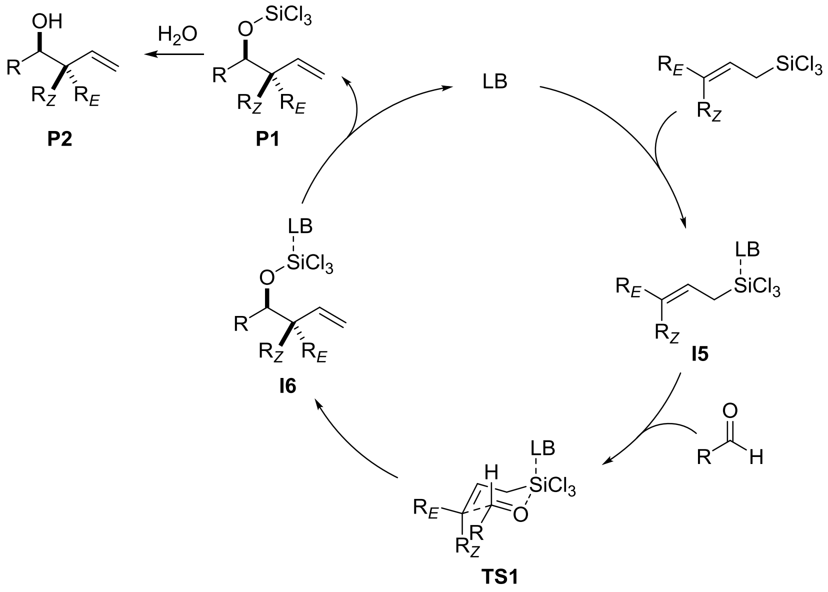
1.5.2 Application

Although *N,N′*-dioxides can be also used as ligands in metal-catalyzed reactions, much more attention was given to their application as organocatalyst.[101] During the last two decades, the chiral *N,N′*-dioxides were used in allylation/propargylation/allenylation reaction with aldehydes, aldol reactions, opening of epoxide rings, cyanosilylation of aldehydes, etc.[102] Most of them take advantage of high affinity of oxygen atom of the *N*-oxide moiety for silicon.[114] Among the abovementioned reactions, the most studied are the allylations of aldehydes.

1.5.2.1 Allylation of aldehydes

Allylation of aldehydes has proven to be a useful method for synthesis of complex molecules of both natural and unnatural origin, because the formed homoallylic function can be easily converted to other functional groups by simple transformations.[115] From the time of pioneering studies of Kobayashi *et al.*[116] and Denmark *et al.*[117], who found out that formamides and phosphoramides can activate allyltrichlorosilane for reaction with aldehydes by noncovalent Lewis acid-base coordination, this reaction has become a testing ground for new Lewis basic catalyst among which the *N*-oxides belong to.[114]

The proposed reaction mechanism is depicted in the Scheme 23. It begins with coordination of a Lewis base (LB) to an electrophilic silicon atom. The silicon atom of the formed complex **I5** becomes more acidic upon coordination of the Lewis base, which facilitates its coordination to the carbonyl group of the reacting aldehyde. It results in the formation of the cyclic chair-like transition state **TS1** with the hexacoordinated silicon atom. The presence of the reactive intermediate **TS1** provides an opportunity for high diastereocontrol of the reaction. Hence, the R_E substituent of the former double bond is situated in the latter products *anti* to the oxygen moiety, while the substituent R_Z of the *trans* double bond is then in *syn* configuration. At the end, the Lewis base is dissociated from the intermediate **I6** forming the product **P1**, which provides the homoallylic alcohol **P2** after hydrolytic work-up, while the Lewis base itself is re-entering the new catalytic cycle. In addition, because of high organizational features of the silicon center in **TS1**, the Lewis base is held in close proximity to the reacting molecules. Thus, if the Lewis base owns the chiral information, it can be transferred to the molecule of product.[115,118]



Scheme 23. Reaction mechanism of the Lewis base-catalyzed allylation of aldehydes with allyltrichlorosilane.

According to the study of Kotora's group, the *N,N′*-dioxides of **133** type can coordinate the silicon atom in both bidentate or monodentate manner depending on the reaction media.[119,120] Only one of the oxygen atoms of *N,N′*-dioxide is participating in coordination in less electrophilic solvents (THF, PhCl etc.), and so the reaction proceeds *via* the reaction mechanism shown in Scheme 23. On the other hand, the *N,N′*-dioxide catalyst prefers formation of a bidentate complex in more electrophilic solvents (MeCN, DCM etc.). In that case, the reaction proceeds *via* cationic intermediates, as one of the chloride anions of $SiCl_3$ group needs to dissociate. This change of the mechanism is supposed to explain the high dependency of the level of enantioselectivity and moreover the configuration of the formed homoallylic alcohols on the used solvent.

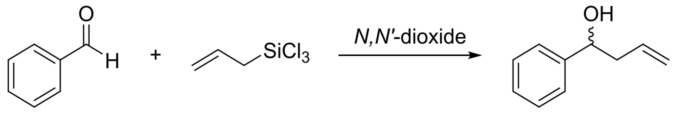
The first enantioselective allylation of aldehyde catalyzed by chiral *N,N′*-dioxide was conducted by Nakajima *et al.* in 1998.[121] For allylation of benzaldehyde **14**, they first used simple axially chiral *N,N′*-dioxide **127** based on the structure of BINOL, which provided the homoallylic alcohol **161** in 82% yield with promising 52% ee (Entry 1, Table 19). The enantioselectivity was then further improved to 71% ee by utilization of dioxide **128** (Entry 2). The reaction radically improved when it became clear that addition of diisopropylethylamine is rapidly accelerating the reaction, thus decreasing the reaction time from 2 h to 10 min without any sign of erosion of yield or ees (Entry 3). This opened the door for a possibility to decrease the reaction temperature and thereby enhance the enantioselectivity. The reaction at -78 °C catalyzed by **128** gave the product **161** in 88% ee

(Entry 4). After this first report, a number of different Lewis base-catalyzed allylation studies were released, however the most important problem was large amount of the *N,N′*-dioxide catalyst required for a successful course of the reaction. This problem was overcome in a report by Hayashi *et al.*, who showed that only 0.1 mol% of catalyst *ent*-**129** is sufficient to get the allylic product in high yield and ee in a short reaction time (2.5 h) (Entry 5).

Later on, the studies in Kotora's group showed that also unsymmetrically substituted *N,N′*-dioxides **130**–**132** (Entries 6–8) as well as symmetrically substituted *N,N′*-dioxide **133** (Entries 9 and 10) are suitable organocatalysts for this reaction. From the abovementioned results, it seemed that the absolute stereochemistry of the homoallylic alcohol is only dependent on the configuration of the chiral axis – the use (a*S*)-catalysts leads to the formation of (*R*)-alcohol and *vice versa*. The study in Kotora's group nonetheless revealed that also reaction media are influencing the absolute configuration of the product (Entries 9 and 10) by changing the coordination fashion of the catalyst (*vide supra*). The same explanation was used also by Zhu *et al.* in order to clarify the formation of opposite enantiomer of **161** when changing the *N,N′*-dioxide *ent*-**134** to *ent*-**135** (Entries 11 and 12). The proposed monodentate chelation of *ent*-**135** was then supported by experimental evidence when the bipyridine *N*-oxide (with only one of the bipyridine nitrogen atoms bearing oxygen) based on *ent*-**134** was used in the same reaction. This prevention of formation of bidentate coordination caused the formation of opposite enantiomer (*R*)-**161**.

The *N,N′*-dioxides with only elements of central chirality **124** and **122** were also used in the allylation reaction of benzaldehyde. While the former catalyzed the reaction in high yield and enantioselectivity (Entry 13), the latter provided the alcohol **161** in a low yield of 18% and 41% ee (Entry 14). These results were not improved by addition of methyl substituents in 3 and 3'-position to the structure *N,N′*-dioxide, which caused its additional axial chirality (Entry 15). The *N,N′*-dioxides possessing elements of both axial and central chirality were also studied in Kotora's group. The use of atropoisomers *ent*-**139** and **140** in allylation reaction showed that the stereochemistry of the product **161** is dependent on the configuration of the chiral axis, while the elements of central chirality have only minor effect (Entries 16 and 17). The best results up to now in terms of yield and enantioselectivity in allylation of benzaldehyde were obtained with unsymmetrically substituted *N,N′*-dioxides *ent*-**141** and **142** (Entries 18 and 19). These atropoisomeric bipyridine *N,N′*-dioxides developed in Kotora's group gave rise to alcohol **161** in the quantitative yield and excellent enantioselectivities of 93% and 96% ee, respectively.

Table 19. Allylation of benzaldehyde **14** catalyzed by *N,N'*-dioxides.



14

161

Entry	*N,N'*-dioxide	mol%	$(i\text{Pr})_2\text{NEt}$ (eq.)	Solvent	*T* (°C)	Yield (%)	ee (%)[a]
1[121]	**127**	10	-	DCM	23	82	52 (ND)
2[121]	**128**	10	-	DCM	23	90	71 (*R*)
3[121]	**128**	10	5	DCM	23	90	71 (*R*)
4[121]	**128**	10	5	DCM	-78	85	88 (*R*)
5[107]	*ent*-**129**	0.1	3	MeCN	-45	95	84 (*S*)
6[122]	**130**	5	1.2	DCM	-78	87[b]	74 (*R*)
7[122]	**131**	5	1.2	DCM	-78	53[b]	72 (*R*)
8[123]	**132**	5	1.2	DCM	-78	95[b]	80 (*R*)
9[124]	**133**	1	1.2	DCM	-78	>99[b]	55 (*R*)
10[124]	**133**	1	1.2	THF	-78	>99[b]	70 (*S*)
11[125]	*ent*-**134**	1	3	DCM	-80	88	95 (*S*)
12[109]	*ent*-**135**	1	3	DCM	-80	85	87 (*R*)
13[81]	**124**	10	5	DCM	-78	75	80 (*R*)
14[126]	**122**	10	5	DCM	-90	18[b]	41 (*R*)
15[127]	*ent*-**137**	10	-[c]	DCM	-60	52	14 (*R*)
16[124]	*ent*-**139**	1	1.2	DCM	-78	50[b]	59 (S)
17[124]	**140**	1	1.2	DCM	-78	44[b]	37 (*R*)
18[128]	*ent*-**141**	1	1.5	THF	-78	>99[b]	93 (*R*)
19[128]	**142**	1	1.5	THF	-78	98[b]	96 (*S*)

[a] ND – not determined. [b] Yield based on GC, HPLC or NMR analysis. [c] $n\text{Bu}_4\text{NI}$ (1 eq.) was used.

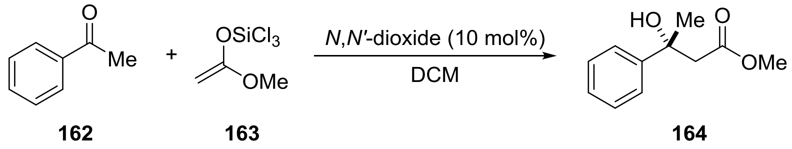
1.5.2.2 Aldol reactions

The aldol addition of trichlorosilyl ketene acetals to ketone acceptors represents another application of *N,N'*-dioxides as Lewis base catalysts. Although the addition of trichlorosilyl enol ethers is a well explored reaction with aldehyde substrates, its variants with ketones remain scarce.[114] The development of general and selective method of the aldol addition to ketones is, in comparison to aldehydes, facing two major challenges. The reactivity of ketones in this reaction is lower and the used catalyst needs to be able to discriminate between the two enantiotopic faces of the carbonyl groups of ketones, which have similar electronic and steric properties compared to aldehydes. The reactivity problem can be solved by application of reactive trichlorosilyl ketene acetals. Although they sluggishly react with ketones at 0 °C in noncoordinating solvents (DCM, $CHCl_3$), their reactivity can be rapidly increased by the use of Lewis base catalysts.[129,130]

Denmark *et al.* investigated a series of Lewis base promoters, among which the most promising results, in terms of yields, were obtained with phosphoramides and *N*-oxides.[129,130] While the former failed in the development of enantioselective variant of this reaction, the latter gave more promising results.

The preliminary results with simple axially chiral *N,N'*-dioxides *ent*-**127** and **128** in the reaction of trichlorosilyl ketene acetal of methyl acetate **163** with acetophenone **162** gave the tertiary alcohol **164** in only moderate yields and enantioselectivities (Entries 1 and 2, Table 20). With catalyst **123**, bearing elements of central chirality, it resulted in a completely racemic product (Entry 3). On the other hand, the application of *N,N'*-dioxides **125** and **126** based on the Bolm's ligand (*R*,*R*)-**8** gave the desired product **164** in almost quantitative yields and 55% and 64% ee, respectively (Entries 4 and 5).[129,130] The enantioselectivity was further improved by introduction of the element of axial chirality to the catalyst by additional methyl substituents in positions 3 and 3' (74% ee, Entry 6) and by lowering the reaction temperature (83% ee, Entry 7). The dominant role of axial chirality in the sense of asymmetric induction was observed when the opposite atropoisomer of **143**, the *N,N'*-dioxide *ent*-**145**, was used. It resulted in formation of the opposite enantiomer of the alcohol **164**, but in decreased level of ee (Entry 8). Even though the substituents in position 6 and 6' play obviously a secondary role, the change of the *n*-butyl group to bulkier 2,4,6-trimethylbenzyl (TMB) group (**144**) slightly increased the enantioselectivity to 87% ee (Entry 9). On the other hand, the change of *t*-butyl to more or less sterically hindered groups did not bring any improvement (Entries 10–12).

Table 20. Aldol reactions of acetophenone **162** with trichlorosilyl ketene acetal **163** catalyzed by *N,N'*-dioxides.



Entry	*N,N'*-dioxide	*T* (°C)	Yield (%)	ee (%)[a]
1	*ent*-**127**	0	45	45 (ND)
2	**128**	0	39	26 (ND)
3	**123**	0	15	*rac*
4	**125**	0	92	55 (ND)
5	**126**	0	94	64 (ND)
6	**143**	0	90	74 (*S*)
7	**143**	-20	94	83 (*S*)
8	*ent*-**145**	-20	89	42 (*R*)
9	**144**	-20	91	87 (*S*)
10	**146**	-20	93	64 (*S*)
11	**147**	-20	90	80 (*S*)
12	**148**	-20	87	47 (*S*)

[a] ND – not determined.

1.6 Catalytic [2+2+2] cocyclotrimerization of alkynes and nitriles

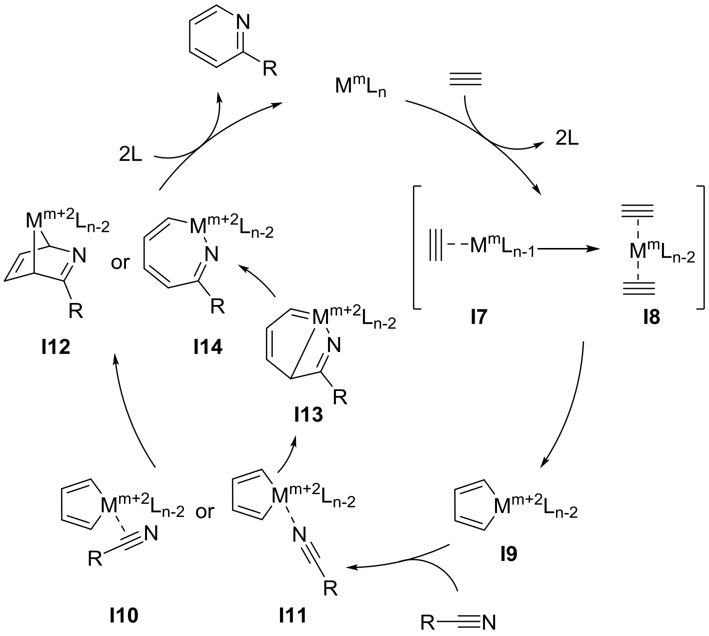
Catalytic [2+2+2] cocyclotrimerization of alkynes and nitriles represents one of the most powerful methods for construction of the pyridine ring. Its discovery can be dated to 1876 when Ramsay obtained a small amount of pyridine by passing acetylene and hydrocyanic acid through a bright-red-hot iron tube connected with Liebig's condenser.[131] This straightforward synthesis of pyridines by formation of two carbon–carbon and one carbon–nitrogen bonds in one synthetic step serves as an alternative for preparation of highly substituted aromatic products, which would be otherwise accessible by complicated series of electrophilic and nucleophilic aromatic substitutions.[132] In addition, further advantages of the reaction are: the use of mild reaction conditions, high atom-economy, tolerance of wide range of functional groups and availability of starting materials.[133]

1.6.1 Mechanism and selectivity

The [2+2+2] cyclotrimerization reaction is generally entropically disfavored, as it needs to bring three reactants together, which are combined to form one product. This problem can be overcome by using a metal catalyst.[134]

General mechanism of metal-catalyzed alkyne-nitrile [2+2+2] cocyclotrimerization, which is depicted in Scheme 24, starts by stepwise coordination of two molecules of alkyne on the metal catalyst (**I7** and **I8**) followed by their oxidative coupling resulting in a metallacylopentadiene **I9**.[132] In the next step, a nitrile coordinates to the metal center by side-on (**I10**) or end-on (**I11**) fashion depending on the electronical properties of the nitrile. The end-on complex **I11**, in which the nitrile acts as a σ-donor and coordinates to the metal center by its nitrogen lone pair, is favored for electron-poor nitriles, while the electron-rich nitriles prefer the side-on coordination by π-electrons of the C–N bond (**I10**).[135] The nitrile is then incorporated to the metallacycle *via* either formal [4+2] cycloaddition towards an azametallabicycle **I12** or by insertion to one of the C–M bond to form an azametallacycloheptatriene **I14** possibly *via* azametallabicycle **I13**. Albeit the insertion can proceed by formation of 2 regioisomers of **I14**, only the one with nitrogen situated just next to the metal atom plays a role in the mechanism. In the last step, the catalytic cycle is concluded by reductive elimination of the pyridine product, while the metal catalyst is regenerated to re-enter a new catalytic cycle.

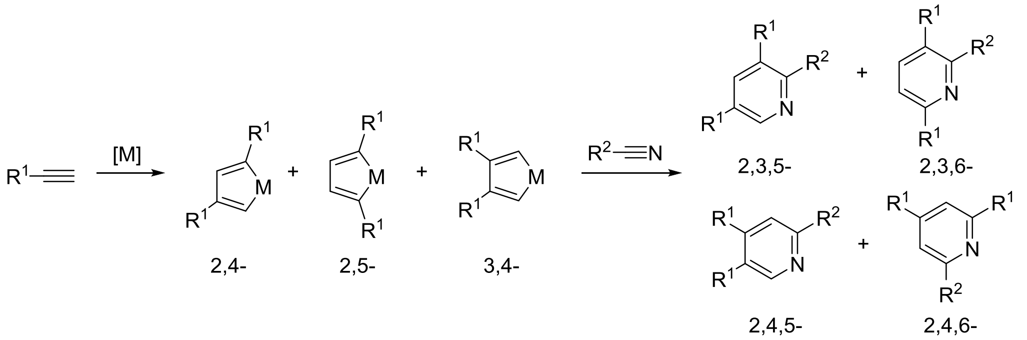
Although one can also imagine a formation of an azametallacyclopentadiene intermediate by the oxidative coupling of one molecule of alkyne and nitrile, this possibility was disproved by DFT calculations.[136] However, this intermediate cannot be excluded in some specific cases of partially or fully intramolecular type of this reaction.[135] It was also found by computational mechanistic study that the rate-determining step can be either oxidative coupling step[137] or addition of the nitrile to metallacycle depending on the used catalytic system.[136]



Scheme 24. General mechanism of metal-catalyzed [2+2+2] cocyclotrimerization of two alkynes and nitrile.

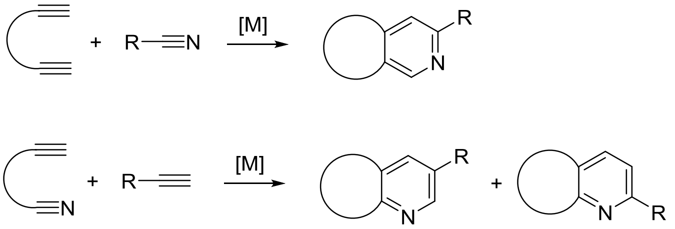
The metal complexes, which are able to catalyze [2+2+2] cocyclotrimerization of alkynes with nitriles, were found to be active also in other types of cycloaddition reactions.[138] This broad applicability could be, on the other hand, problematic in terms of chemoselectivity. From the chemoselectivity point of view, it is advantageous that the cyclotrimerization of nitriles is less favored than cyclotrimerization of alkynes.[139] Metal complexes in higher oxidation state (e.g. metallacyclopentadiene **I9)** coordinate the nitrogen lone pair of nitrile more easily than the third molecule of alkyne, thus the formation of pyridine instead of benzene products is preferred.[132] In addition, this selectivity can be supported by use of excess of nitrile and/or slow addition of the alkyne to the reaction mixture.[140]

Another selectivity problem can arise when one uses the unsymmetrically substituted alkynes as starting material. Theoretically three different regioisomers of metallacyclopentadiene can be formed in the case of monosubstituted acetylene, namely 2,4-, 2,5- and 3,4-, which results in the formation of four pyridine products with substitution in positions 2,3,5; 2,3,6; 2,4,5 or 2,4,6 (Scheme 25). Among those, the 2,3,6- and 2,4,6-trisubstituted pyridines are formed preferentially because of steric reasons.[141]



Scheme 25. Regioselectivity of cocyclotrimerization of unsymmetrically substituted alkynes with nitrile.

This regioselectivity can be influenced by the type of a metal catalyst or its ligands and steric or electronic properties of the substituents of alkynes. Such substituents could also have a function of regiodirecting group if they are able to coordinate to the metal center.[135,142,143] Another possibility how to decrease the number of possible products, is to tether the reacting triple bonds by a short temporary or permanent linker, which can be demonstrated on the reaction of diyne with nitrile or cyanoalkyne with asymmetric alkyne (Scheme 26).[144]



Scheme 26. Cocyclotrimerization of diyne with nitrile and ynenitrile with alkyne.

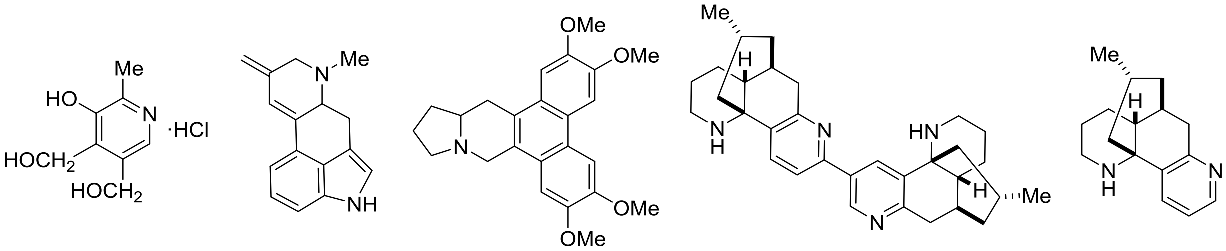
Another regioselectivity problem arises during cocyclotrimerization of two different alkynes with nitrile. Although this can be as well influenced by the abovementioned factors, it can be elegantly solved by stepwise addition of the alkynes to the metal center. This approach was developed for reactions mediated by zirconium and titanium complexes.[145,146] In this case, however, the use of stoichiometric amounts of the metal source is necessary to facilitate the reaction.

1.6.2 Catalysts

During the last decades, various types of transition metal catalysts suitable for cyclotrimerization reaction were developed. The complexes used in these reactions are based on cobalt,[147] ruthenium,[138] rhodium,[148] iridium,[149] nickel,[150] palladium,[151] iron,[152] gold,[153] zirconium,[145] niobium,[154] titanium[146] or tantalum[155]. Particularly CpCoL$_2$ (L = CO, PR$_3$, olefine), Cp*RuCl(cod) and [Rh(cod)$_2$]X/bisphosphine (X = BF$_4$, OTf, etc.) complexes are in the spotlight of chemists in the last decade. This can be documented by the fact that among 92 scientific studies published from 2009, 57 of them deals with these three catalytic systems.

1.6.2.1 CpCoL$_2$

Vollhardt's cobalt dicarbonyl cyclopentadiene complex (CpCo(CO)$_2$), which was first prepared by Wilkinson in the middle of 1950s, is definitely the most frequently used and studied catalyst not only for alkyne-nitrile cocyclotrimerization, but for cyclotrimerization generally.[156] It was used in a numerous reactions including key steps of the syntheses of natural products such as pyridoxine (vitamin B$_6$),[157] lysergene and LSD,[158] tylophorine and dehydrotylophorine,[159] complanadine A[160,161] or lycodine[161] (Figure 10).



Pyridoxine hydrochloride

Lysergene

Tylophorine

Complanadine A

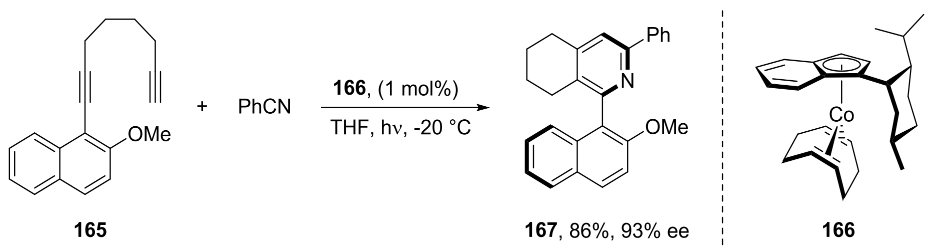
Lycodine

Figure 10. Natural products synthesized by cobalt-catalyzed alkyne-nitrile cocyclotrimerization.

Despite its indisputable value, it suffers from some imperfections.[162] It is air sensitive, which complicates its handling and storage, and it needs to be thermally or photochemically activated. In addition, substoichiometric or stoichiometric amounts of catalyst and harsh reaction conditions are required for the successful course of the reaction. Only electron-rich nitriles are providing the desired bipyridine product and the selectivity of the reaction is governed by both electronic and steric effects (the electronic ones are slightly more determinative).

Resulting from the general mechanism (Scheme 24), the release of two neutral ligands is necessary for generation of a coordinatively unsaturated complex, while the other ligands (often called spectator ligands) are coordinated to the cobalt metal center during the whole mechanism.[143] The cyclopentadienyl ligand is, in the case of $CpCo(CO)_2$ catalyst, the spectator ligand and therefore it governs the reactivity and stability of the complex and it has a prominent role in determination of selectivity of the cyclotrimerization reaction. On the other hand, neutral carbon monoxide ligands are responsible for smooth release of the active catalyst and its stability. This can be demonstrated on Jonas' analogue ($CpCo(H_2C{=}CH_2)_2$) of this ligand, which is bearing ethylene ligands instead of carbon monoxide. It is less stable, but more reactive and its ethylene ligands can be displaced by alkynes even at temperatures below 0 °C.[134] Some improvements in this area were recently achieved by Gandon *et al.* and Hapke *et al.*, who developed new cobalt catalysts with dimethyl fumarate (dmfu) ligand (CpCo(CO)(dmfu) and $CpCo(P(OEt)_3)$(dmfu)), which are air stable and, in the latter case, recyclable and reactive even with electron-poor nitriles.[163,164]

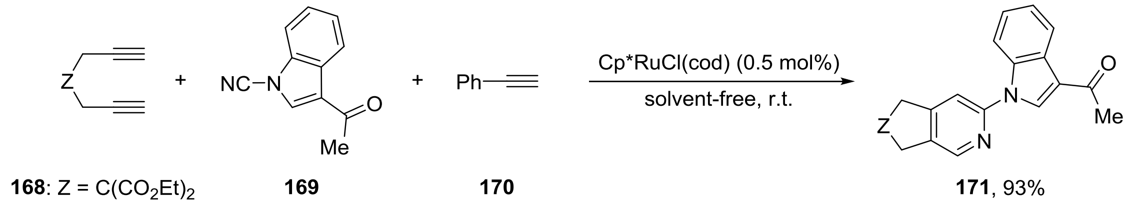
Regarding the cyclopentadienyl ligand, it was experimentally found that complexes with electron-donating substituents on Cp-ligand prefer alkyne cyclotrimerization, while catalysts with electron-withdrawing substituents promote alkyne-nitrile cocyclotrimerization but with lower regioselectivity.[165] The cyclopentadienyl ligands can be also derivatized by polar groups that increase solubility of the catalyst in water and so enable performing the reactions in aqueous media.[166] Moreover, the change of simple cyclopentadienyl ligand to chiral one opens the door toward enantioselective reactions. This was shown on the synthesis of axially chiral isoquinoline derivative **167** from diyne **165** and benzonitrile catalyzed by complex **166**. The product **167** was obtained in 86% isolated yield and 93% ee (Scheme 27).[167]



Scheme 27. Enantioselective cocyclotrimerization catalyzed by chiral cobalt catalyst.

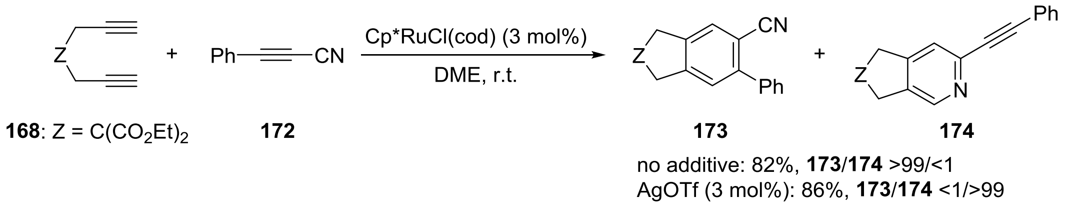
1.6.2.2 Cp*RuCl(cod)

Chloro(1,5-cyclooctadiene)(pentamethylcyclopentadienyl)ruthenium Cp*RuCl(cod) is a homogeneous catalyst, which is active in various types of cyclization reactions especially [2+2+2] homocyclotrimerization of alkynes, or cocyclotrimerization of alkynes with alkenes, nitriles, isocyanides, isothiocyanides etc.[168] First [2+2+2] cocyclotrimerization of alkynes with nitriles catalyzed by this complex was reported by Itoh *et al.* in 2001 when Cp*RuCl(cod) was found to be reactive in cocyclotrimerization of diynes with electron-poor nitriles, while the reactions with simple nitriles such as acetonitrile or benzonitrile failed.[169] Because of that, it has become a good alternative to the already known Vollhardt's catalyst, which produces pyridine products only with electron-rich or neutral nitriles. During the next years various scientific groups found a number of benefits of this catalyst. Teplý *et al.* proved its robustness by reaction on air and even in fetal bovine serum.[170] The reaction can be also performed in pure water when water-soluble phosphine is used as a ligand,[171] or under solvent-free conditions.[169] The chemoselectivity is in high preference toward pyridine product, nevertheless, if the benzene product is formed, it is possible to reduce its yield by slow addition of alkyne/diyne.[169] Moreover, Goswami *et al.* have recently demonstrated high chemoselectivity of this reaction in a three component reaction mixture, which consist of diyne **168**, nitrile **169** and alkyne **170** in equimolar ratios.[172] Even though several products could have been formed, the pyridine derivative **171** was obtained exclusively in 93% yield and phenylacetylene **170** remained untouched (Scheme 28).



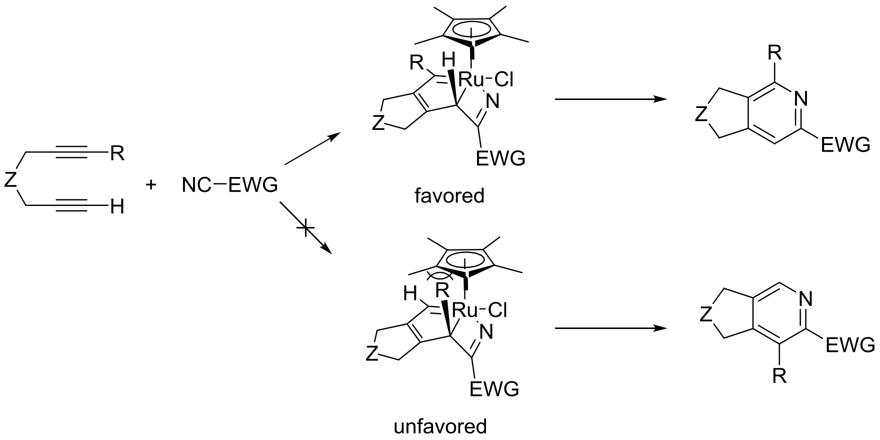
Scheme 28. Chemoselectivity of alkyne-nitrile cocyclotrimerization catalyzed by Cp*RuCl(cod).

Even more interesting finding has been recently reported by the same group in the reaction of diynes with alkynylnitrile.[173] Albeit the reaction of these reactants under the standard conditions furnished solely benzene product **173**, this selectivity could have been completely shifted towards pyridine product **174** by addition of catalytic amount of silver(I) triflate (Scheme 29).



Scheme 29. Additive-controlled switchable chemoselectivity of reaction of diyne **168** and alkynylnitrile **172**.

The regioselectivity of reactions catalyzed by Cp*RuCl(cod) are mostly governed by the efforts to avoid the steric repulsion between Cp* ligand and the alkyne/diyne substituents in intermediate **I13** (Scheme 24, Scheme 30). Its role in mechanism was confirmed by several computational studies.[136]



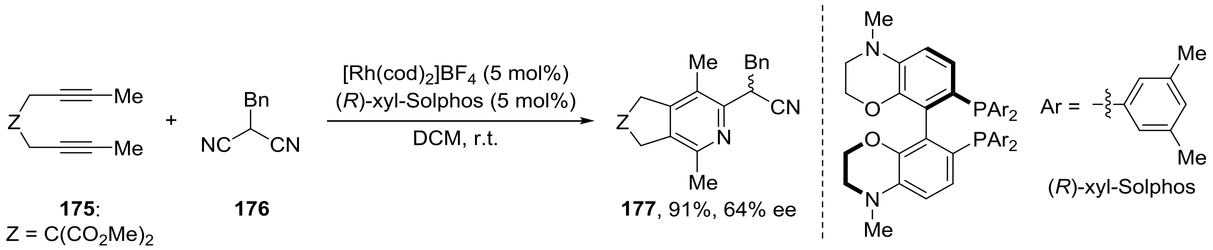
Scheme 30. Regioselectivity explanation on the basis of steric repulsions in intermediate **I13**.

1.6.2.3 [Rh(cod)$_2$]X/bisphosphine

Although the rhodium complexes were reported as useful catalysts for cocylotrimerization of alkynes with nitriles already in 1987, they were often ignored in the pioneering studies of this reaction as their efficiency was low due to the large amount of arene biproducts.[174] However, since Tanaka *et al.* in 2006 reported cationic [Rh(cod)$_2$]BF$_4$/ 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as a versatile catalytic system for cyclotrimerization of both electron-rich and electron-poor nitriles under mild reaction conditions, they started to engage interest of the chemical community.[175]

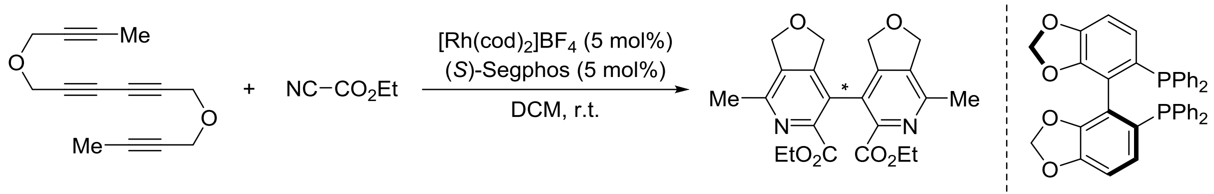
The high relevance of [Rh(cod)$_2$]X/bisphosphine catalyst is based on the fact that the simple change of either anion X or bisphospine ligand enables to modulate either its activity or selectivities of the reaction.[176] Regarding the selectivity, the most valuable is the enantioselectivity, which can be achieved by simple use of readily accessible chiral phosphine ligands. It was also found that the described catalysts could provide products with central, axial as well as planar chirality.[148]

Already in 2006 Tanaka *et al.* used [Rh(cod)$_2$]BF$_4$ in combination with chiral (*R*)-xyl-Solphos ligand in desymmetrization of malonitrile derivative **176**.[175] The pyridine product **177** was obtained in excellent yield and promising enantioselectivity of 64% ee (Scheme 31).



Scheme 31. Desymmetrization of nitrile **176** in enantioselective cyclotrimerization with alkyne **175**.

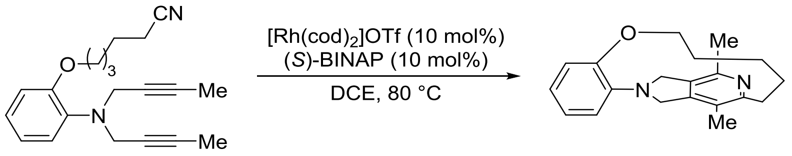
The same Rh(I) complex with (*S*)-Segphos ligand was used for the synthesis of axially chiral 3,3'-bipyridines.[177] The double cocyclotrimerization of tetrayne **178** with ethyl cyanoformate **179a** furnished chiral bipyridine **180** in excellent ee, but only moderate yield due to the low regioselectivity of the reaction (Scheme 32).



178 **179a** **180**, 38%, 98% ee (*S*)-Segphos

Scheme 32. Synthesis of axially chiral bipyridine **180** by enantioselective Rh-catalyzed cyclotrimerization.

In 2009 Shibata *et al.* also published a synthesis of tripodal cage pyridines with planar chirality.[178] The pyridine derivative **182** was obtained in 52% yield and 94% ee utilizing Rh(I)-triflate complex with (*S*)-BINAP as chiral ligand (Scheme 33). This type of compounds could be potentially used as chiral discriminators, polymers or ligands.[179]



181 **182**, 52%, 94% ee

Scheme 33. Synthesis of chiral tripodal cage pyridine **182** by Rh-catalyzed enantioselective cyclotrimerization.

1.6.3 Synthesis of 2,2'-bipyridines *via* [2+2+2] cocyclotrimerization

As it was mentioned in Chapter 0, one of the methods for synthesis of 2,2'-bipyridine is [2+2+2] cocyclotrimerization of alkynes with nitriles. The cyclotrimerization reactions can be divided into groups by the number of pyridine rings constructed in one [2+2+2] cocyclotrimerization step and by the type of cyclotrimerization. If the reaction proceeds with three reactants, from which each of them bears one of the reacting triple bonds (i.e. two alkynes and one nitrile), the reaction is intermolecular. On the other hand, if all the starting triple bonds are joined by a linker, then the reaction is intramolecular. The last class of these reactions is partially intramolecular (or partially intermolecular). Only two out of the three reacting triple bonds are tethered in that case.

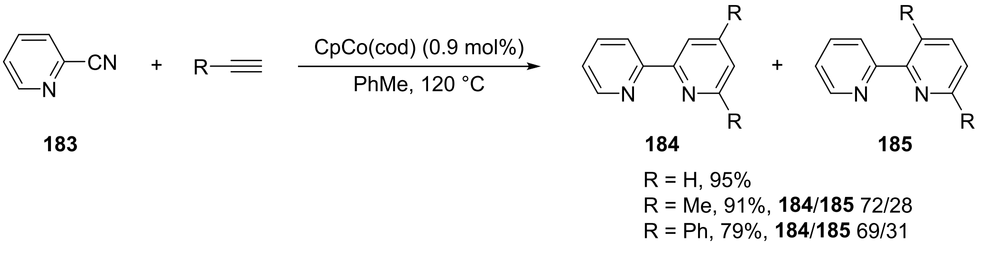
It should be noted that bipyridines are extremely good ligands able to chelate almost all metals including those, which catalyze cyclotrimerization reaction. Therefore the reduced yields or necessity to use higher catalyst load, which can be observed in some cases of cyclotrimerization reactions that lead to the formation of resulting in bipyridine products, can be explained by deactivation of the catalyst by trapping the metal species by molecules of the bipyridine.[180,181]

Some representative examples from each of the defined categories will be briefly reviewed in the following paragraphs.

1.6.3.1 Construction of one pyridine ring

Intermolecular reactions

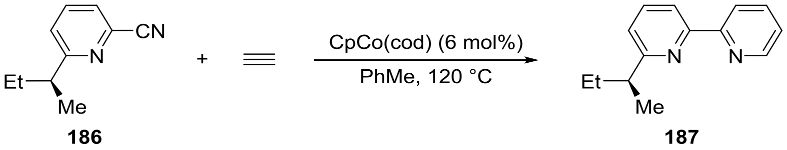
The fully intermolecular cocyclotrimerization of alkyne and 2-cyanopyridine **183**, which was published by Bönnemann *et al.* already in 1975, was the first example of synthesis of 2,2'-bipyridine by this methodology.[182] The reactions catalyzed by CpCo(cod) provided the bipyridines **184** and **185** in high to excellent yields, but in moderate regioselectivities (Scheme 34).



R = H, 95%
R = Me, 91%, **184**/**185** 72/28
R = Ph, 79%, **184**/**185** 69/31

Scheme 34. Synthesis of bipyridines by intermolecular cocyclotrimerization of alkynes with 2-cyanopyridine **183**.

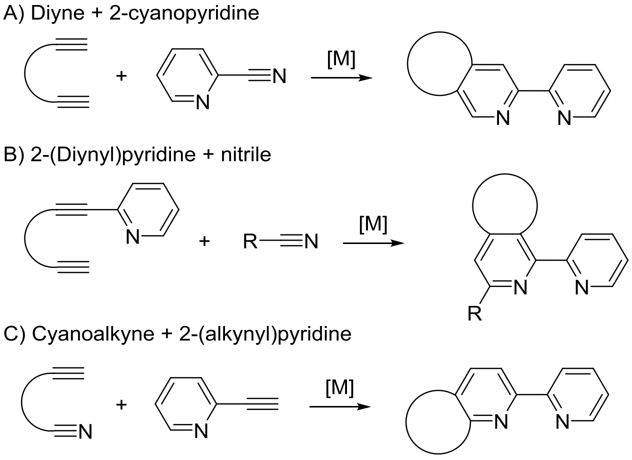
Several years later, Botteghi *et al.* showed that also chiral 2-cyanopyridines are applicable in this reaction by cocyclotrimerization of 2-cyanopyridine **186** with acetylene (Scheme 35).[183] The formed chiral 2,2'-bipyridine **187** was then used as a ligand in Rh-catalyzed enantioselective transfer hydrogenation[184] and hydrosilylation[185] of ketones but with low enantioselectivity.



Scheme 35. Synthesis of chiral bipyridine **187** by intermolecular cocyclotrimerization of chiral 2-cyanopyridine **186** with acetylene.

Partially intramolecular reactions

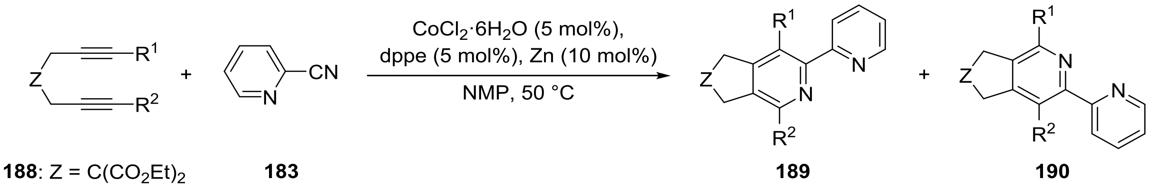
This class covers three types of reactions depending on which triple bonds are tethered by a linker and which of the reactants are substituted by the pyridyl substituent. The general reaction scheme of each type is depicted in Scheme 36.



Scheme 36. Partially intramolecular cocyclotrimerization furnishing 2,2'-bipyridines.

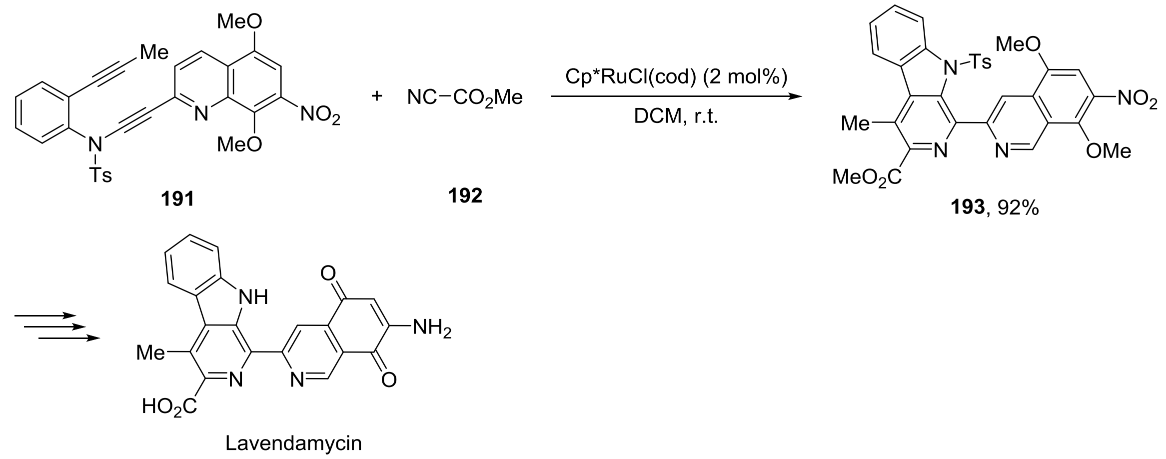
For cocyclotrimerization of diynes with 2-cyanopyridine (A, Scheme 36) Okamoto *et al.* used a Co(I)-catalyst generated *in situ* by reduction of cobalt(II) chloride with zinc powder in the presence of 1,2-bis(diphenylphosphino)ethane (dppe).[186] The reaction with all unsymmetrical diynes **188** furnished one of the possible 2,2'-bipyridines in excellent regioselectivity (Table 21). Interestingly, it was shown that alkylated diynes with one terminal triple bond are providing only regioisomer **189**, in which substituent is situated in position 3 of the pyridine ring (Entries 1 and 2). On the other hand, the opposite regioisomer **190** is preferred in reaction of diyne with phenyl substituent on the triple bond (Entry 3). The trimethylsilyl group also prefers position 3 forming isomer **189** as a sole product (Entry 4). In addition, the preferential location of the TMS group in position 3 and the phenyl group in position 2 was observed even with methyl or *n*-butyl substituted diynes (Entries 5 and 6).

Table 21. Regioselectivity of cocyclotrimerization of diyne **188** with 2-cyanopyridine **183**.



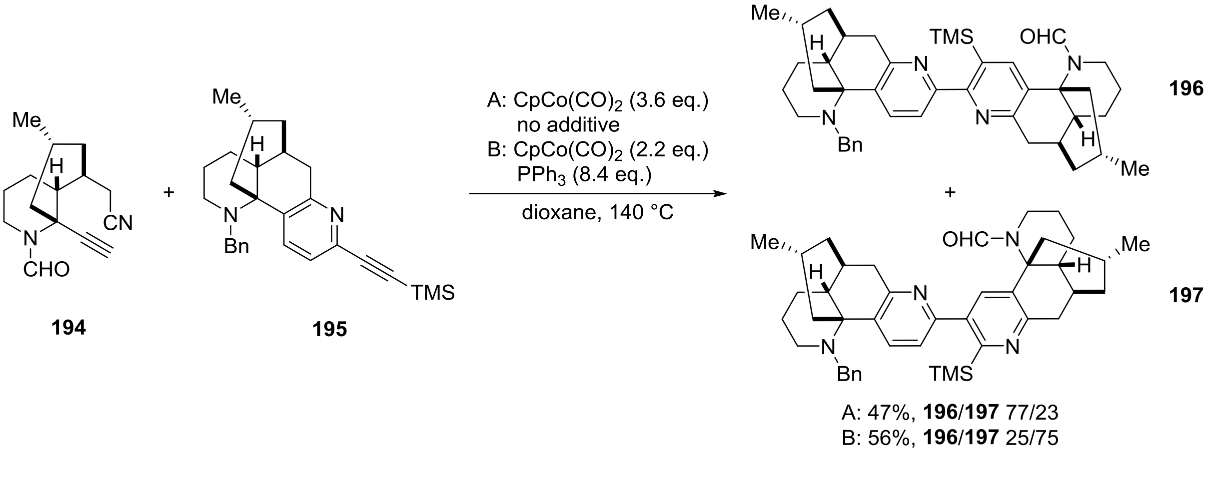
Entry	R^1	R^2	Yield (%)	**189**/**190**
1	Me	H	78	>99/<1
2	*n*Bu	H	67	>99/<1
3	Ph	H	78	<1/>99
4	TMS	H	76	>99/<1
5	Ph	Me	47	<1/>99
6	TMS	*n*Bu	91	>99/<1

A reaction of 2-(diynyl)pyridine with nitrile is the second type of partially intramolecular cocyclotrimerization for construction of one pyridine ring (B, Scheme 36). This type of cyclotrimerization reaction was applied in total synthesis of lavendamycin, which is an interesting natural compound derived from bacteria, with antitumor and antibiotic properties.[187] The cyclotrimerization of 2-(diynyl)pyridine **191** with methyl cyanoformate **192** provided the lavendamycin precursor **193** as the only regioisomer in excellent yield (Scheme 37). The authors are suggesting that the exclusive selectivity is caused by the difference of steric repulsions in the two possible cyclotrimerization intermediates as is shown in the Scheme 30. The reaction of the starting materials with [Rh(cod)$_2$]BF$_4$ and BINAP ligand gave the undesired opposite regioisomer of the product **193**.



Scheme 37. Cocyclotrimerization reaction in total synthesis of lavendamycin.

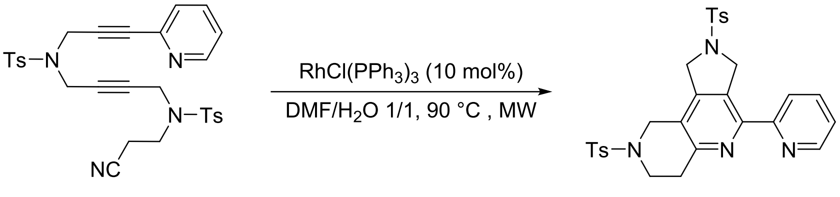
The partially intramolecular cocyclotrimerization during construction of one pyridine ring of a 2,2'-bipyridine can also proceed by a reaction of a cyanoalkyne with a 2-(alkynyl)pyridine (C, Scheme 36). The key step of the total synthesis of complanadine A (Figure 10) can serve as a representative example of this reaction.[160,161] The [2+2+2] cocyclotrimerization of cyanoalkyne **194** with 2-(alkynyl)pyridine **195** mediated by Vollhardt's complex furnished both possible regioisomers – 2,2'-bipyridine **196** and 2,3'-bipyridine **197** (Scheme 38). Interestingly, although the reaction without any additive provided preferentially 2,2'-bipyridine, the second regioisomer was formed when an excess of triphenylphosphine was added to the reaction mixture. It should be also mentioned that 2.2 or 3.6 equivalents of the Co-complex were needed for successful course of the reaction.



Scheme 38. Cyclotrimerization of cyanoakyne **194** with 2-alkynylpyridine **195** in total synthesis of complanadine A.

Intramolecular reaction

The only example of fully intramolecular construction of one pyridine ring in synthesis of 2,2'-bipyridine have been until now reported by Pla-Quintana, Roglans *et. al.*[188] The compound **198** bearing two C–C triple bonds, cyano- and 2-pyridyl substituent was smoothly cyclotrimerized by Wilkinson's catalyst under MW heating to bipyridine **199** in 89% isolated yield (Scheme 39).



198 **199**, 89%

Scheme 39. Intramolecular synthesis of bipyridine **199**.

1.6.3.2 Construction of two pyridine rings

During the course of these reactions, six triple bonds need to react in the correct combination, therefore the reactions suffer from low selectivity towards double cyclotrimerized product and of course also from low regioselectivity and chemoselectivity. Tethering the reacting triple bonds by several linkers is required in order to ensure the formation of as few products as possible.

Partially intramolecular reactions

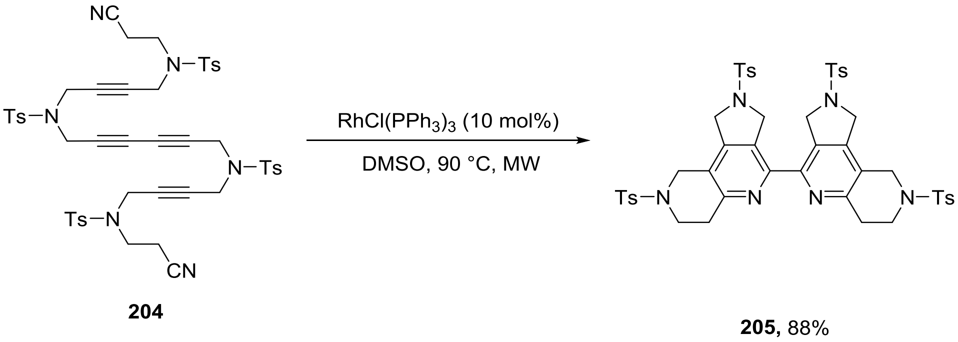
Examples of two types of partially intramolecular reaction, cocyclotrimerization of 1,3-diyne with cyanoalkyne and cyclotrimerization of tetrayne with nitriles, can be found in the literature.

Saá *et al.* studied the regioselectivity of the first type of this cyclotrimerization on reaction of cyanoalkyne **200** and 1,3-diyine **201**.[142,189] Although three possible regioisomers (2,2'-, 2,3'- and 3,3'-bipyridines) can be formed, only 2,2'- and 2,3'-bipyridines (**202** and **203**) were actually observed (Table 22). All reactions provided bipyridine products in low to moderate yields (Entries 1–5) except the trimethylsilylated diyne, which furnished only product of monocyclotrimerization (Entry 2). The regioselectivity can be influenced by the presence of directing groups, which are able to coordinate to cobalt during the course of the reaction (Entries 3–5). The best results, in terms of yield and selectivity, were obtained with diyne substituted with dimethylamino directing group (Entry 5).

The cocyclotrimerizations of tetraynes with nitriles were studied by three groups – group of Yamamoto (Entry 1, Table 23), Okamoto (Entry 2) and Kotora (Entry 3). They showed that the reaction can be catalyzed by either Ru- or Co-complexes. The formation of only 2,2'-bipyridine regioisomers was observed independently on reaction conditions and reacting substrates.

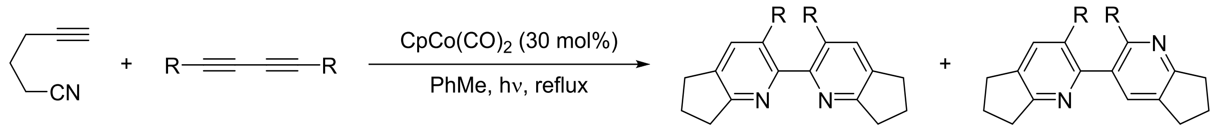
Intramolecular reaction

The only example of fully intramolecular reaction of symmetric compound **204** bearing four C–C triple bonds and two C–N triple bonds was reported by Pla-Quintana, Roglans *et al.*[188] The cyclotrimerization catalyzed by Wilkinson's catalyst under MW heating provided the bipyridine **205** in excellent yield of 88% (Scheme 40).



Scheme 40. Intramolecular cyclotrimerization of dicyanotetrayne **204**.

Table 22. Cyclotrimerization od cyanoalkyne **200** and 1,3-diyne **201**.

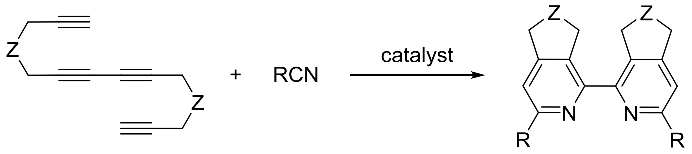


200 **201** **202** **203**

Entry	R	Yield (%)	**202/203**
1	Me	48	63/37
2	TMS	77[a]	-
3	CH_2OH	9	>99/<1
4	CH_2OMe	63	73/27
5	CH_2NMe_2	49	>99/<1

[a] Yield of the monocyclotrimerized product.

Table 23. Cyclotrimerization of tetraynes and nitriles.

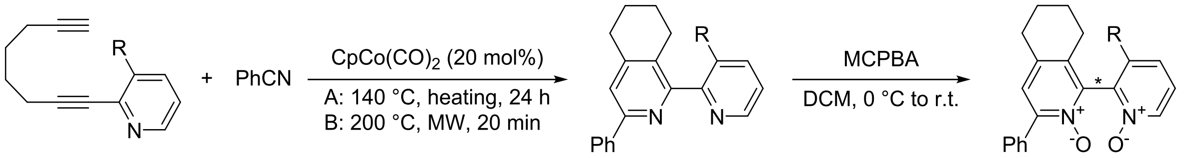


Entry	Z	R	Catalyst	mol%	Additive (mol%)	Solvent	*T* (°C)	Yield (%)
1[190]	$C(CO_2Me)_2$	$ClCH_2$	Cp*RuCl(cod)	10		DCE	80	71
2[186]	$C(CO_2Et)_2$	Me	$CoCl_2·6H_2O$	5	dppe (5), Zn (10)	NMP	50	87
3[124]	CH_2CH_2	Me	$CpCo(CO)_2$	19	-	-	200 (MW)	36

1.6.4 Synthesis of 2,2'-bipyridine *N,N'*-dioxides *via* [2+2+2] cocyclotrimerization

The possibility of synthesis of 2,2'-bipyridine *N,N'*-dioxides by using cocyclotrimerization as the key step was studied in Kotora's group. Although these syntheses in most cases lead to *N,N'*-dioxides through the stages of 2,2'-bipyridines, they are discussed separately in this chapter.

The [2+2+2] cocyclotrimerization reaction was, for example, used as the key step in the synthesis of axially chiral bipyridine *N,N'*-dioxides **130** and **131** (Scheme 41).[122] The starting 2-(diynyl)pyridines **206** and **207** were cocyclotrimerized with benzonitrile at first with conventional heating activation of Vollhardt's catalyst. As the yields were disappointingly low, which was caused by polymerization of the starting diyne, the reaction was carried out under MW irradiation. This change resulted in improvement of the reaction yield and reduction of the reaction time. The following oxidation furnished racemic mixture of the target *N,N'*-dioxides, which were separated by semipreparative HPLC with a chiral stationary phase.



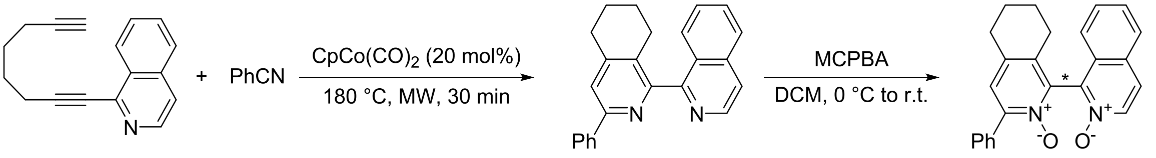
206: R = Me
207: R = CF_3

208: R = Me, A: 27%, B: 84%
209: R = CF_3, A: 24%, B: 35%

130 + *ent*-**130**: R = Me, 25%
131 + *ent*-**131**: R = CF_3, 23%

Scheme 41. Synthesis of *N,N'*-dioxides **130** and **131** *via* cocyclotrimerization method.

The same method was also used for preparation of *N,N'*-dioxide **132**, starting from isoquinoline diyne **210** (Scheme 42).[123] The separation of atropoisomers **132** and *ent*-**132** was conducted by BINOL cocrystallization technique. A single crystal X-ray analysis revealed that (*R*)-BINOL forms complex with *ent*-**132** with (a*R*)-configuration by forming hydrogen bonds between protons of BINOL hydroxyls and oxygen atoms of the N–O moieties of *ent*-**132** (Figure 11).



210

211: 48%

132 + *ent*-**132**, 47%

Scheme 42. Synthesis of *N,N'*-dioxide **132** *via* cocyclotrimerization method.

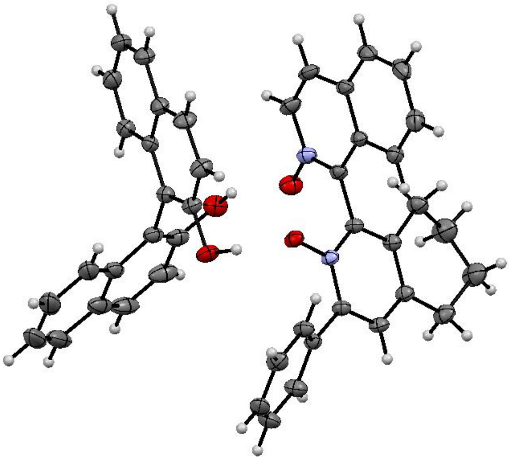
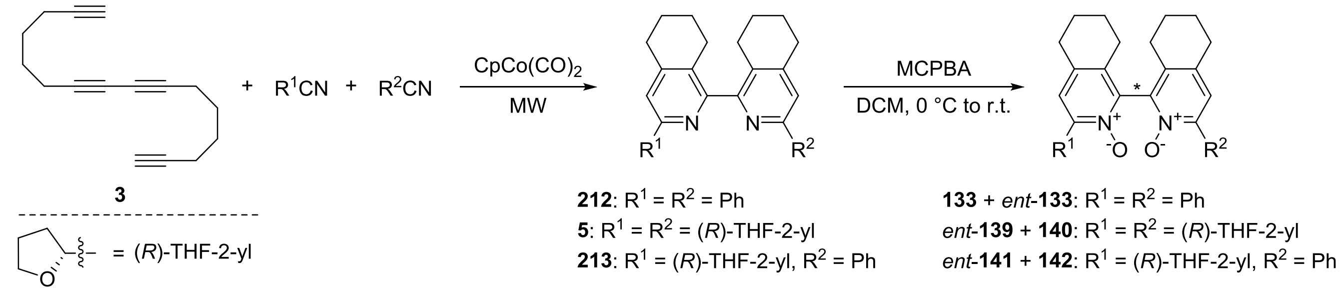


Figure 11. ORTEP drawing of complex of *ent*-**132** (right) and (*R*)-BINOL (left) (grey C, red O, blue N).

The C_2-symmetric bipyridines **212** and **5** were synthesized by cocyclotrimerization of tetrayne **3** with benzonitrile and commercially available (*R*)-tetrahydrofuran-2-carbonitrile in 51% and 48% yield, respectively (Entries 1 and 2, Table 24).[124] As the stepwise synthesis of bipyridine bearing both phenyl and (*R*)-tetrahydrofuran-2-yl failed, this "cross-product" was prepared by a double cyclotrimerization with these two nitriles in one step.[128] The subsequent oxidations of bipyridines **212**, **5** and **213** under classical MCPBA conditions resulted in mixtures of atropoisomeric *N,N'*-dioxides, which were separated by chromatography with normal (*ent*-**139** and **140**, *ent*-**141** and **142**) or chiral stationary (**133** and *ent*-**133**) phase.

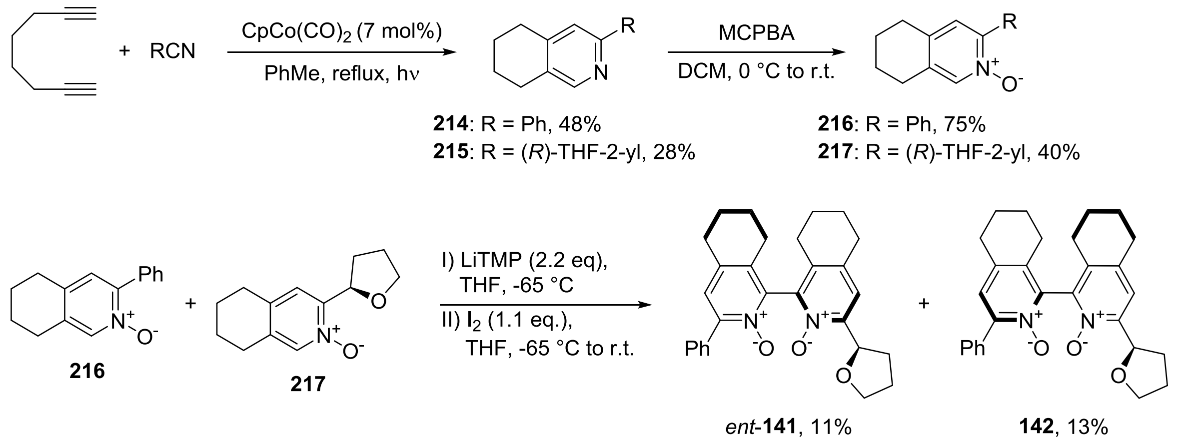
Although *N,N'*-dioxides *ent*-**141** and **142** gave the best results as catalysts in allylation reactions (Chapter 1.5.2.1), their wide application suffered from the low yields and selectivities during their synthesis (2% overall combined yield of *ent*-**141** and **142** starting from 1,7-octadiyne, which was in the first step dimerized to get tetrayne **3**). It was attempted to improve the overall yield by application of different reaction sequence (Scheme 43).[111] The cocyclotrimerization of 1,7-octadiyne with benzonitrile and (*R*)-tetrahydrofuran-2-carbonitrile gave pyridines **214** and **215** in 48% and 28% yield, respectively. Their following oxidation provided the *N*-oxides **216** and **217**, which were then cross-coupled by oxidative method invented by Denmark *et al.* for synthesis of symmetrically substituted *N,N'*-dioxides (Chapter 1.5.1, Scheme 20).[110] Although the conversion of the starting *N*-oxides was full and also the cross-coupled products *ent*-**141** and **142** were formed in fairly high combined yield (60–70%), their complicated separation caused a radical drop of the isolated yields to 11% and 13% respectively. The overall yield was then even lower (1%).

Table 24. Synthesis of *N,N′*-dioxides by cocyclotrimerization of tetrayne **3** and nitriles.



Entry	$CpCo(CO)_2$ (mol%)	*T* (°C)	*t* (min)	R^1	R^2	Yield, step 1 (%)	Yield, step 2 (%)
1	19	200	30	Ph	Ph	51	41
2	19	200	30	(*R*)-THF-2-yl	(*R*)-THF-2-yl	48	76[a]
3	20	180	25	Ph	(*R*)-THF-2-yl	28[b]	50[c]

[a] *ent*-**139**/**140** 63/37. [b] also 20% of **212** was formed. [c] *ent*-**141**/**142** 75/25.



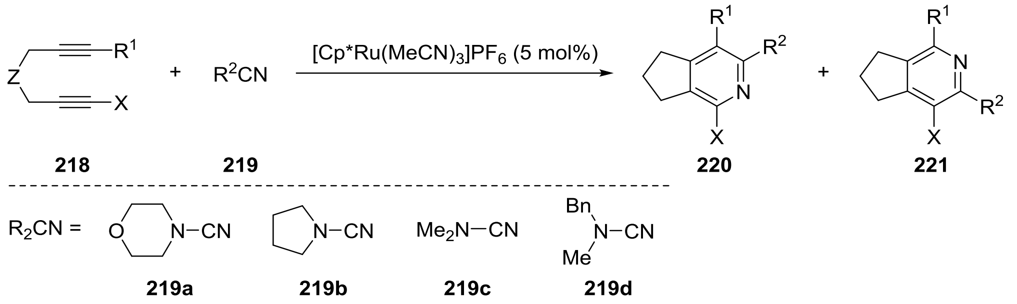
Scheme 43. Synthesis of *N,N′*-dioxides *ent*-**141** and **142** *via* cocyclotrimerization and oxidative dimerization.

1.6.5 Synthesis of 2-halopyridines *via* [2+2+2] cocyclotrimerization

During my work on preparation of 2-halopyridines *via* [2+2+2] cocyclotrimerization of halodiynes with nitriles, there was no report dealing with this reaction. Following this study, two reports have been published by Michelet *et al.*[191,192]

Both studies dealt with cocyclotrimerization of variously substituted diynes including halodiynes **218** with electron-rich cyanamide **219** catalyzed by a ruthenium complex. The scaffold of the target aminopyridines can be found in several biologically active compounds.[191] They studied the influence of different linkers, substituents on the triple bonds and type of halogen on the reactivity and regioselectivity (Table 25). It was clearly shown that this reaction is compatible with a wide range of substrates bearing chlorine, bromine or iodine substituent and the linker tethering two reacting triple bonds bearing carbon, nitrogen or oxygen atom. All reactions were providing selectively aminopyridines **220**. One of the limitations of the reaction turned out to be the use of dibromodiyne (Entry 3), which did not furnish any product probably because of the steric hindrance caused by two bulky bromide substituents. These substituents probably prevented the formation of the ruthenacycle intermediate. The second limitation was found by using diyne with the terminal triple bond, this substrate was probably because it undergoes homocyclotrimerization (Entry 5).

Table 25. Cyclotrimerization of halodiynes **218** with cyanamides **219**.



Entry	Z	X	R^1	**219**	Solvent	*T* (°C)	Yield (%)[a]	**220**/**221**
1	$(MeO_2C)_2C$	Br	Me	**219a**	solvent-free	r.t.	80	96/4
2	$(MeO_2C)_2C$	I	Me	**219a**	DCM	50	83	>99/<1
3	$(MeO_2C)_2C$	Br	Br	**219a**	DCM	50	NR	-
4[b]	O	Br	Me	**219a**	DCM	50	85	98/2
5	O	Br	H	**219a**	DCM	r.t.	65	98/2
6	TsN	Br	Me	**219a**	DCM	50	67	>99/<1
7	TsN	Br	Me	**219b**	DCM	50	92	>99/<1
8	TsN	Br	Me	**219c**	DCM	50	93	99/1
9	TsN	Br	Me	**219d**	DCM	50	75	98/2
10	TsN	Cl	Me	**219c**	DCM	50	99	>99/<1
11	O	Br	Me	**219b**	solvent-free	50	57	98/2
12	O	Br	Me	**219c**	solvent-free	50	40	96/4

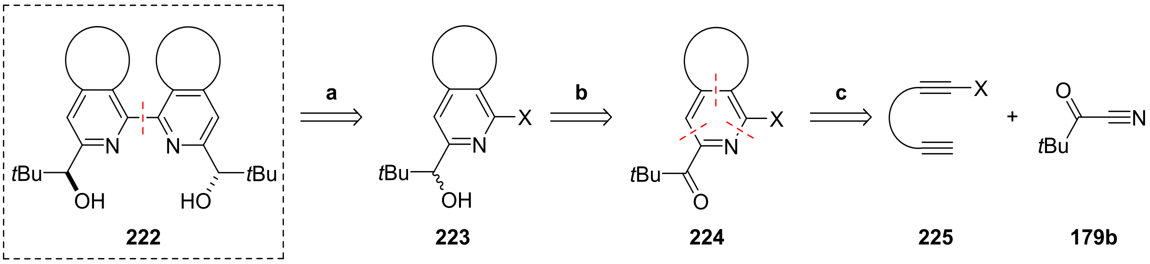
[a] NR – no reaction. [b] 2 mol% of Ru-catalyst were used.

2 AIMS OF THE WORK

1. To develop a new method of synthesis of 2,2'-bipyridines based on the structure of Bolm's ligand **8** and bis(oxazolinyl)bipyridine **7** and to apply these newly developed compounds as ligands in metal-catalyzed asymmetric reactions.

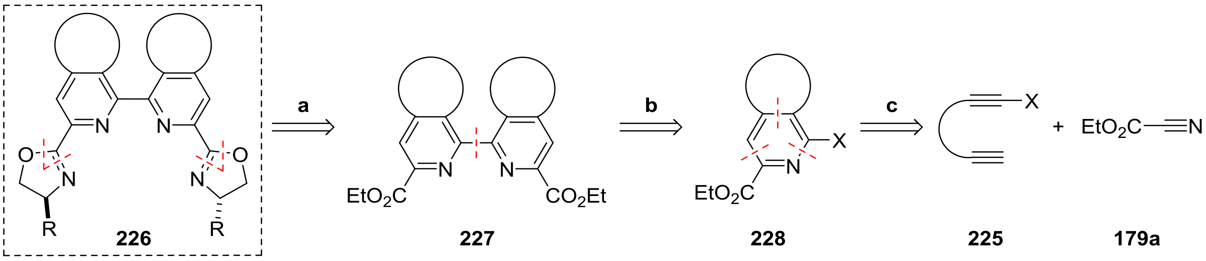
The structure of the new 2,2'-bipyridines was designed on the assumption that addition of substituents into positions 3 and 3' of the pyridine rings would cause a hindered rotation of the C2–C2' bond connecting two pyridine rings. The hindered rotation should cause increased rigidity of their complexes with metal salts. In addition, the electron-donating substituents in these positions could make the chelating abilities of the formed ligand stronger. Both of these factors were expected to have a positive influence on the asymmetric inductions of the metal-catalyzed reactions.

Retrosynthetically the target bipyridine diol **222** could be synthesized by a reductive dimerization of a 2-halopyridyl alcohol **223** (Step a, Scheme 44), the chiral alcohol moiety of which can be prepared by an enantioselective reduction of the keto group of a bicyclic 2-halopyridyl ketone **224** (Step b). The bicyclic 2-halopyridyl ketone **224** was envisioned to be prepared by cocyclotrimerization reaction of a halodiyne **225** with a pivaloyl nitrile **179b** (Step c).



Scheme 44. Retrosynthetic analysis of the designed analogues of Bolm's 2,2'-bipyridine.

The bis(oxazolinyl)bipyridine (BipyMOX) **226** could be prepared by the standard methods used for formation of oxazoline rings from a bipyridine diester **227** (Step a, Scheme 45), which was envisioned to be synthesized by reductive dimerization of a 2-halopyridine **228** (Step b). This compound could be prepared by cocyclotrimerization of a halodiyne **225** with ethyl cyanoformate **179a** (Step c).



226 **227** **228** **225** **179a**

Scheme 45. Retrosynthetic analysis of bis(oxazolinyl)bipyridines **226**.

2. To develop and study cocyclotrimerization of halodiynes with nitriles as a new type of cyclotrimerization reaction.
3. To synthesize new chiral *N,N′*-dioxides and to use them as Lewis base organocatalysts in asymmetric reactions, namely in allylation of aldehydes and aldol reactions.

3 RESULTS AND DISCUSSION

3.1 Catalytic [2+2+2] cocyclotrimerization of halodiynes and nitriles

As it was shown in Chapter 1.6, a number of synthetic protocols have been developed for preparation of pyridine compounds by catalytic cyclotrimerization of alkynes with nitriles. However, most of these protocols deal with alkynes, substituents of which are difficult to convert to other functionality (alkyl, aryl substituents etc.). Although the cyclotrimerization of alkynes possessing halogen substituent as a reactive functional group with alkynes to give halobenzenes is a known reaction and is catalyzed by Co-,[193] Ru-[194] or Rh-complexes[195], the reaction with nitriles has not been reported yet.

3.1.1 Preparation of halodiynes

Several different halodiynes were prepared in order to study dependence of structural and electronical properties of the reactants on yield and selectivity of the cyclotrimerization reaction.

The structural features of a tethered halodiyne can be divided into four parts, out which three were varied in the screening (the two triple bonds are the fourth part): (a) the type of halogen atom X as a substituent on one of the triple bond of diyne (green, Figure 12), (b) the R substituent on the second triple bond (red), and (c) the linker tethering two triple bonds (blue). The methyl and bromine substituents and the oxygen linker, which are in frames, were chosen as the standards for the sake of simple preparation and modification and because of good preliminary results regarding reactivity in the cyclotrimerization reaction. All the halodiynes were prepared according to the published procedures and as their synthesis was not pivotal for this work, these synthetic steps were not optimized. The decreased yield of some of the following reactions can be explained by the volatility of the products.

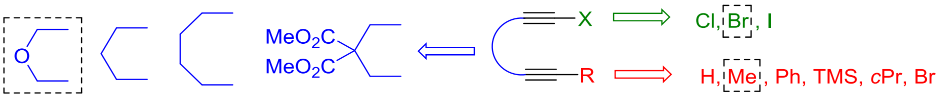
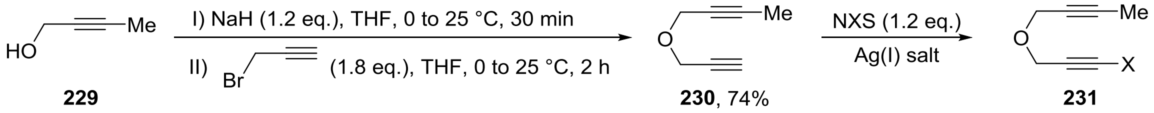


Figure 12. Variation of structure of halodiyne.

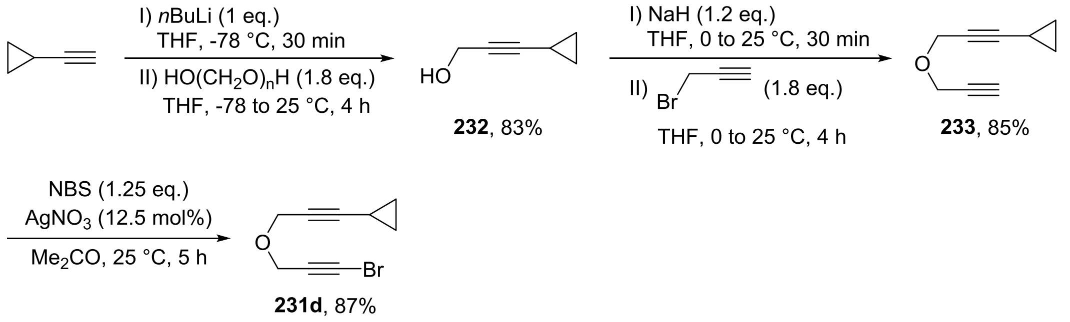
The diyne **230** was prepared by nucleophilic substitution of but-2-yn-1-ol **229** with propargyl bromide in 74% yield (Table 26). The subsequent halogenation by appropriate halosuccinimides catalyzed by silver salts furnished iodo-, bromo-, and chlorodiynes **231a**, **231b**, and **231c** in 72%, 78% and 80% yield, respectively.

Table 26. Synthesis of halodiynes **231a**, **231b** and **231c**.



Entry	X	231	Ag(I) salt (mol%)	Solvent	*T* (°C)	*t* (h)	Yield (%)
1	I	**231a**	$AgNO_3$ (12.5)	DMF	25	3	72
2	Br	**231b**	$AgNO_3$ (12.5)	Me_2CO	25	2	78
3	Cl	**231c**	AgOAc (10)	Me_2CO	80	2	80

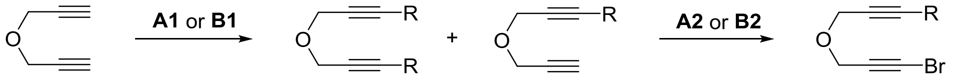
Next, I synthesized the halodiynes with different substituents R. The synthesis of the cyclopropylated diyne **231d** started from cyclopropyl ethyne, which was after deprotonation treated with paraformaldehyde (Scheme 46). The resulting alcohol **232** was then allowed to react with propargyl bromide to furnish diyne **233** in 85% yield. It was then brominated under the standard conditions (87% yield).



Scheme 46. Synthesis of bromodiyne **231d**.

A different approach was used for synthesis of bromodiynes **231e** and **231f** with the phenyl and trimethylsilyl substituents. The method started with monosubstitution of one of the protons of the two triple bonds of propargyl ether by the phenyl or trimethylsilyl group (Scheme 47). While Sonogashira cross-coupling reaction was used for the preparation of the former, lithiation followed by treatment with TMSCl was chosen for the latter. Both monosubstituted diynes **237** and **238** were formed along with disubstituted diynes **235** and **236**. The phenylated diynes **235** and **237**, which were formed in almost 1/1 ratio, were difficult to separate, thus the subsequent bromination was carried out with their mixture. The isolated yield of the bromodiyne **231e** was 33% after two steps.

On the other hand, the trimethylsilylation gave preferentially monotrimethylsilylated diyne **238**, which was obtained in 68% yield. Silver salts can serve as a deprotecting agent for silylacetylenes, therefore bromination was carried out by a careful deprotonation of the second triple bond using *n*BuLi followed by a reaction with NBS (96% yield). The two-step procedure without separation of compounds **236** and **238** was not applicable in this case, because **236** and **231f** were found to be inseparable.



234

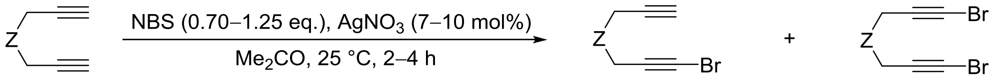
235: R = Ph **237**: R = Ph **231e**: R = Ph, **A1**+**A2**: 33%

236: R = TMS **238**: R = TMS, **B1**: 68% **231f**: R = TMS, **B2**: 96%

A1) PhI (1 eq.), $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), Et_2NH (9 eq.), THF, 25 °C, 4 h
B1) I) LiHMDS (1 eq.), THF, -78 °C, 1 h; II) TMSCl (1 eq.), THF, -78 to 25 °C, 1.5 h
A2) NBS (1.25 eq.), $AgNO_3$ (12.5 mol%), Me_2CO, 25 °C, 5 h
B2) I) *n*BuLi (0.9 eq.), THF, -78 °C, 30 min; II) NBS (0.9 eq), THF, -78 to 25 °C, 14 h

Scheme 47. Synthesis of bromodiynes **231e** and **231f**.

The monobrominated diynes **231g**, **231h**, **231i**, and **231j** with the terminal triple bond and symmetric dibromodiynes **231k**, **231l**, **231m**, and **231n** were synthesized by reactions of the corresponding diynes with NBS (Scheme 48). The diyne **241** with the malonyl linker was not, compared to propargyl ether **234**, hepta-1,6-diyne **239**, and octa-1,7-diyne **240**, commercially available, therefore it was prepared by propargylation of dimethyl malonate with excess of propargyl bromide in 73% yield. All mono- and dibrominated compounds were isolated in poor yields, which was mainly caused by their complicated separations.

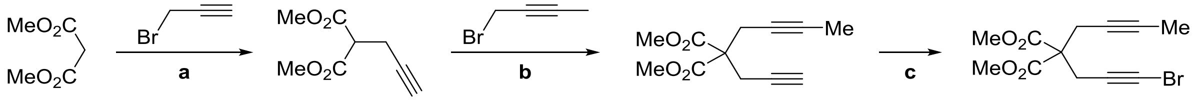


234: Z = O
239: Z = CH_2
240: Z = CH_2CH_2
241: Z = $(MeO_2C)_2C$

231g: Z = O, 26% **231k**: Z = O, 29%
231h: Z = CH_2, 32% **231l**: Z = CH_2, 16%
231i: Z = CH_2CH_2, 38% **231m**: Z = CH_2CH_2, 14%
231j: Z = $(MeO_2C)_2C$, 28% **231n**: Z = $(MeO_2C)_2C$, 10%

Scheme 48. Synthesis of bromodiynes **231g**–**231j** and dibromodiyne **231k**–**231n**.

Last but not least, bromodiyne **231o** was prepared by a three-step synthesis (Scheme 49). The reaction sequence started with monopropargylation of dimethyl malonate (33% yield) followed by alkylation with 1-bromobut-2-yne furnishing the diyne **243** in 81% yield. The bromination under the standard conditions (with NBS) gave bromodiyne **231o** in 76% yield.



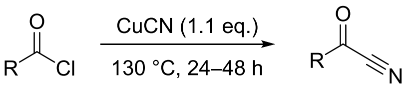
242, 33% **243**, 81% **231o**, 76%

a) I) NaH (1.2 eq.), THF, 0 to 25 °C, 1 h; II) propargyl bromide (1.2 eq.), THF, 25 °C to reflux, 2 h
b) I) NaH (1.2 eq.), THF, 0 to 25 °C, 1 h; II) 1-bromobut-2-yne (1.2 eq.), THF, 25 °C to reflux, 3 h
c) NBS (1.5 eq.), $AgNO_3$ (15 mol%), Me_2CO, 25 °C

Scheme 49. Synthesis of bromodiyne **231o**.

3.1.2 Preparation of nitriles

Most of the used nitriles were commercially available compounds, on the other hand, acyl cyanides **179b** and **179c** were prepared by a solvent-free reaction of appropriate acyl chlorides with copper(I) cyanide (Scheme 50). The products were separated from the copper salts by distillation. The distillates contained 6–11% of the starting chlorides, which were inseparable from the products. As the chlorides should be unreactive in the cyclotrimerization step, which was later on experimentally proved, the nitriles **179b** and **179c** were not further purified.



179b: R = *t*Bu, 84% (94% purity)
179c: R = Ph, 78% (89% purity)

Scheme 50. Synthesis of acyl cyanides **179b** and **179c**.

3.1.3 Optimization of reaction conditions

According to the proposed retrosyntheses of the target bipyridines, I was interested in cocyclotrimerization of halodiynes with nitriles bearing electron-withdrawing group. Cp*RuCl(cod) was the first-choice catalyst for the reaction of electron-poor nitriles, therefore it was used at the beginning in reaction of iododiyne **231a** with ethyl cyanoformate **179a** in dichloroethane at 25 °C. Two regioisomers, 2-iodopyridine **244aa** and 3-iodopyridine **245aa** were formed and their structures were unequivocally confirmed by single crystal X-ray analyses (Figure 13).

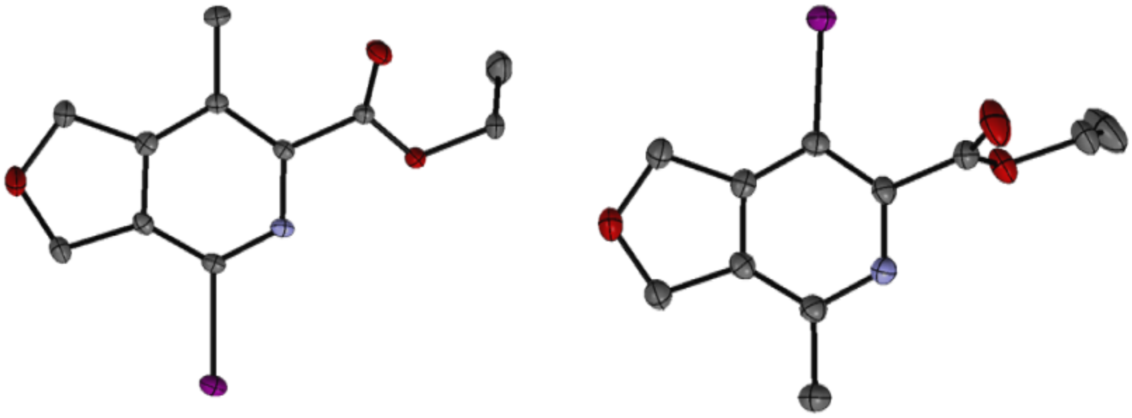


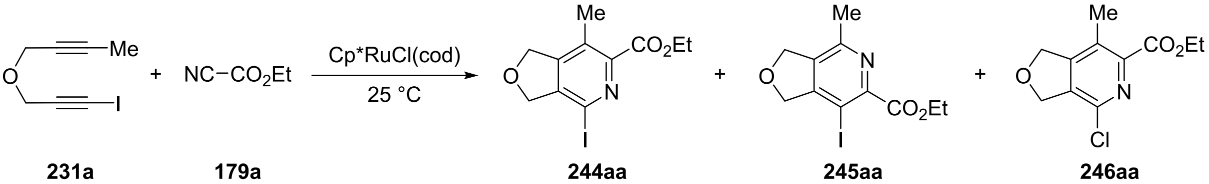
Figure 13. ORTEP drawing of **244aa** (left) and **245aa** (right) (grey C, red O, blue N, violet I). Hydrogen atoms were omitted for clarity.

Nevertheless, it was found out that 2-iodopyridine **244aa** was contaminated by some impurity even after the column chromatography. The identification of this side product was a bit puzzling, as its amount was very low. It was not possible to obtain it in the pure form and most of its signals in NMR spectra were overlapped with signals of **244aa**. Eventually, this compound was identified as 2-chloropyridine **246aa**, which had the same structure as **244aa**, but bore the chlorine atom instead of iodine. The formation of this compound was clarified by the later experiments (*vide infra*).

First, I screened the optimal diyne **231a** to nitrile **179a** ratio. All reactions, which were carried out with 5 mol% of Ru-catalyst in DCE at 25 °C, were stopped after 27 hours and analyzed by ^{1}H-NMR (Entries 1–4, Table 27). The combined yields increased when the amount of nitrile was raised from 1 to 2 equivalents (Entries 1 and 2). However, they started to decrease when 5 or more equivalents of nitrile were used (Entries 3 and 4). This phenomenon could be caused by multiple coordination of the nitrile to the Ru-catalyst before the coordination of the diyne, making the cocyclotrimerization reaction more difficult.

Optimization of the Ru-complex load (Entries 5–7) revealed that the best result in terms of the yield (79%) was obtained with 10 mol% of catalyst (Entry 7). Moreover, the yields were only marginally influenced by the used reaction media (Entries 8–11) and the reaction proceeded well even in etheric solvents (Entries 10 and 11). Although the best combined yield was obtained in chloroform, the results achieved in this solvent were not reproducible, therefore DCE was used for the later studies.

Table 27. Optimization of reaction conditions of cocyclotrimerization reaction.



Entry	**179a** (eq.)	[Ru] (mol%)	Solvent	*t* (h)	Yield (%) **244aa**	**245aa**	**246aa**	Combined
1	1	5	DCE	27	18[a]	19[a]	3[a]	40[a]
2	2	5	DCE	27	32[a]	39[a]	5[a]	76[a]
3	5	5	DCE	27	26[a]	28[a]	2[a]	56[a]
4	10	5	DCE	27	16[a]	21[a]	2[a]	39[a]
5	2	2	DCE	136	9	7	1	17
6	2	5	DCE	136	19	28	3	50
7	2	10	DCE	37	29	45	5	79
8	2	10	DCM	27	27	38	5	70
9	2	10	$CHCl_3$	35	35	47	7	89
10	2	10	THF	27	27	45	5	77
11	2	10	CPME	34	24	49	5	78

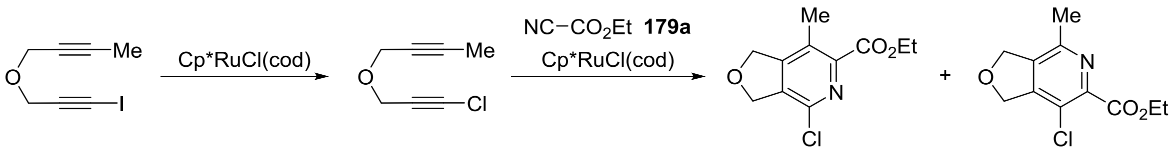
[a] ^{1}H-NMR yield.

Attempts to catalyze the reaction with $CpCo(P(OEt)_3)(dmfu)$, $[Rh(cod)_2]BF_4$, $[Ir(cod)Cl]_2$, or various Ru-catalysts (e.g. $RuCl_3$ or Grubbs' carbene complexes) were not successful and the reactions did not proceed.

3.1.4 Halogen exchange reaction

My efforts to stop the halogen exchange reaction by either increasing the amount of iodine anions ($n\mathrm{Bu}_4\mathrm{NI}$) or by addition of silver(I) triflate were not successful. Therefore I focused on elucidation of the origin of the chlorinated compound **246aa** in the reaction mixture. There were two potential sources of chlorine in the reaction – the chlorinated solvent and the ruthenium catalyst. The first one was excluded by performing the reaction in etheric solvent (the chlorinated compound was formed in the same yield, Entries 10 and 11, Table 27), hence the chlorine atom had to come from Cp*RuCl(cod) complex.

The halogen exchange reaction can potentially proceed in the stage of (a) starting material, or (b) products. If the iodine-chlorine exchange proceeded in the molecule of starting diyne **231a**, formation of compound **245ca** bearing chlorine atom in position 3 would be also observed (Scheme 51). As this was not the case, the most probable explanation of this phenomenon seemed to be the halogen exchange between the molecule of 2-iodopyridine **244aa** and the ruthenium complex.



231a **231c** **244ca** **(246aa)** **245ca**

Scheme 51. Result of potential halogen exchange in the stage of starting diyne **231a**.

This assumption was confirmed by formation of 2-chloropyridine **246aa** in the reaction of 2-iodopyridine **244aa** with the equimolar amount of Cp*RuCl(cod). The course of the exchange was studied by monitoring the reaction mixture in the deuterated dichloromethane by ^{1}H-NMR. While the ^{1}H-NMR spectrum the 2-iodopyridine **244aa** was represented by two triplets at 5.01 and 5.20 ppm belonging to the benzyl methylenes and by the singlet of the methyl group in position 5 at 2.32 ppm, both benzyl methylene signals of 2-chloropyridine **246aa** were found at 5.13 ppm and its 5-methyl group at 2.37 ppm. Some selected time points are shown in Figure 14. A slow disappearance of **244aa** and concominant increase of **246aa** can be clearly seen from the stacked spectra.

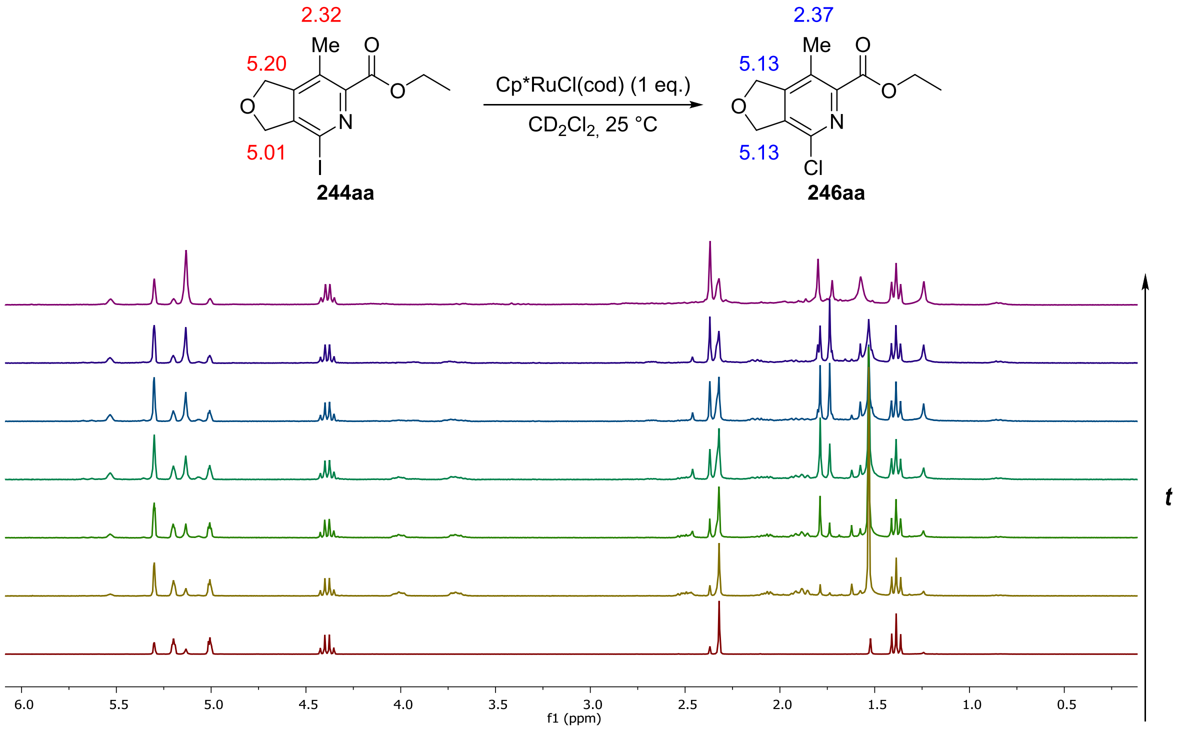


Figure 14. ^{1}H-NMR analysis of halogen exchange reaction of **244aa**.

The kinetic chart of the reaction represented by the amount of formed 2-chloropyridine **246aa**, which was calculated by integration of the methylene signals in ^{1}H-NMR spectra of both compounds **244aa** and **246aa**, in time is displayed in Figure 15. The conversion exceeded 50% after 10 hours and 70% after 1 day. Then the reaction rate slowed down (plateau phase) and the yield of **246aa** was stabilized at 78% after 1 week.

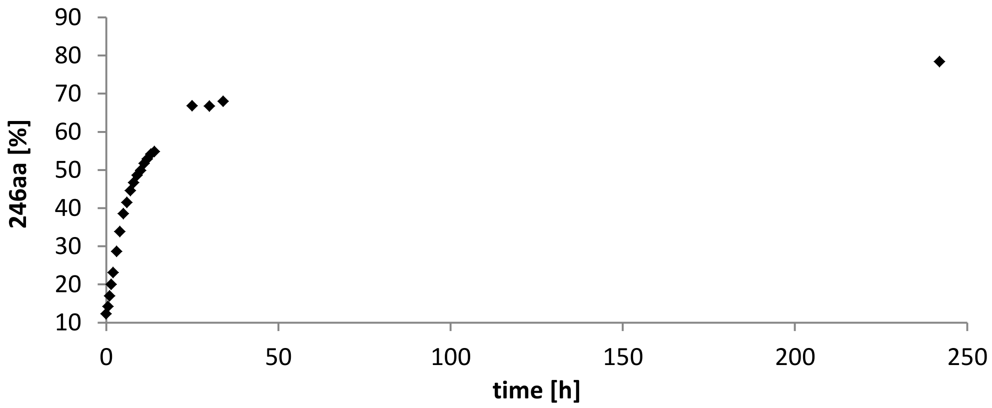


Figure 15. A kinetic chart of the halogen exchange reaction of **244aa**.

In order to explore, whether the halogen exchange reaction can proceed generally with 2-iodopyridines, the same experiment was performed on 2-iodopyridine **247**. While the signals of 2-iodopyridine **247** can be found at 8.32, 7.71, 7.32 and 7.27 ppm, the signals of its chlorinated analogue **248** appear at 8.35, 7.65, 7.32 and 7.22 (Figure 16). The reaction rate was in this case higher – 50% of **247** was converted to **248** within 5 h and the conversion was 91% already after 24 h (Figure 17).

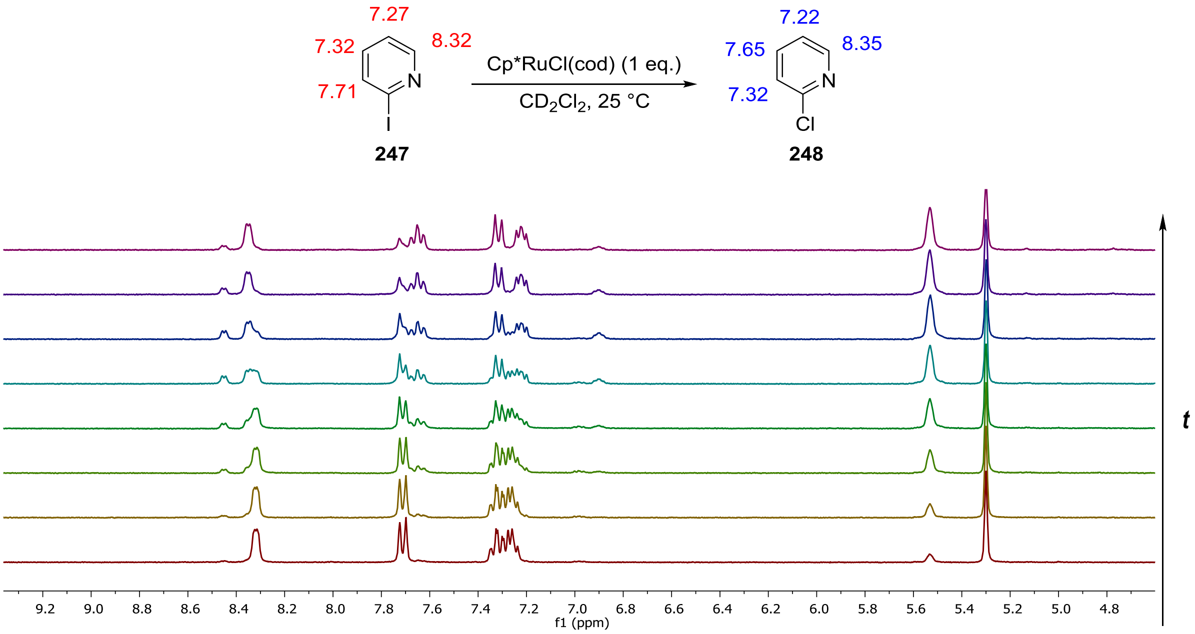


Figure 16. ^{1}H-NMR analysis of halogen exchange reaction of **247**.

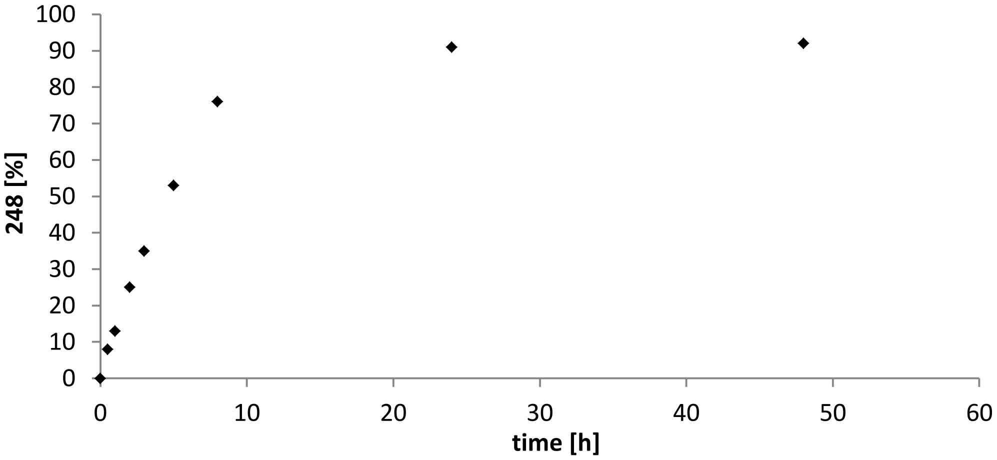
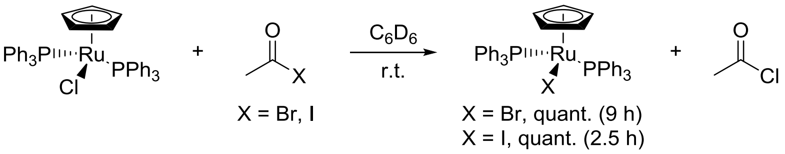


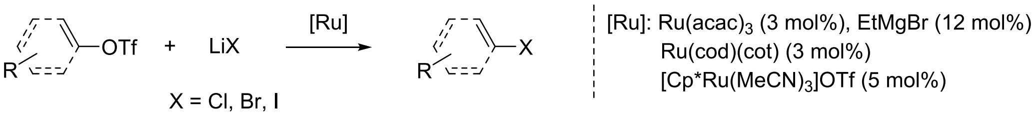
Figure 17. A kinetic chart of the halogen exchange reaction of **247**.

Halogen exchange reactions are interesting from the synthetic point of view and have been studied under various conditions with different transition metal compounds. Replacement of the chloride ligand in a structurally similar catalyst to bromide or iodide ligands by a reaction with acetyl bromide or iodide was described by Ehara *et al.* (Scheme 52).[196]



Scheme 52. Exchange of halogen ligands in a structure of Ru-catalyst.

Hayashi *et al.* developed the catalytic variant of a reaction of aryl or alkenyl triflates and lithium halides.[197,198] The reaction provided aryl or alkenyl chlorides, bromides or iodides in the presence of various Ru-catalysts (Scheme 53).



Scheme 53. Catalytic halogen exchange reaction reported by Hayashi *et al.*

As far as a tentative reaction mechanism is concerned, two hypotheses were proposed. The first one assumes that the reaction proceeds *via* an oxidative addition of an organohalide (or a pseudohalide) to the ruthenium complex followed by a halide ligand exchange and reductive elimination. The second one suggests a radical pathway *via* Ru(III)-species. This assumption has been supported by experimental as well as computational data.[196,197,198]

The driving force of the halogen exchange from 2-iodopyridine to 2-chloropyridine probably originates in the difference between the bond strength of C–Cl and C–I bond (BDE(C–Cl) = 95.8 kcal·mol^{-1}, BDE(C–I) = 63.1 kcal·mol^{-1} in **248** and **247**, respectively).[199] The chemoselectivity of this reaction can be explained by a difference of the dissociation energy of the C–halogen bonds in positions 2 and 3 of the pyridine ring, which are generally 3–5 kcal·mol^{-1} lower for the bonds in position 2 (e.g . BDE(C–Cl, 2-chloropyridine) = 95.8 kcal·mol^{-1}, BDE(C–Cl, 3-chloropyridine) = 99.7 kcal·mol^{-1}).[199,200] Suzuki cross-coupling reaction of 2,5-dibromopyridine that provided exclusively the product of coupling in position 2 can serve as an experimental proof supporting the abovementioned assumption.[201]

In view of the aforementioned, the feasibility of the catalytic halogen exchange was then tested. Unfortunately, the reaction of 2-iodopyridine **247** with excess of either lithium chloride or tetramethylammonium chloride in the presence of catalytic amount of Cp*RuCl(cod) in numerous solvents furnished only traces of the desired 2-chloropyridine **248**.

3.1.5 Scope of the reaction

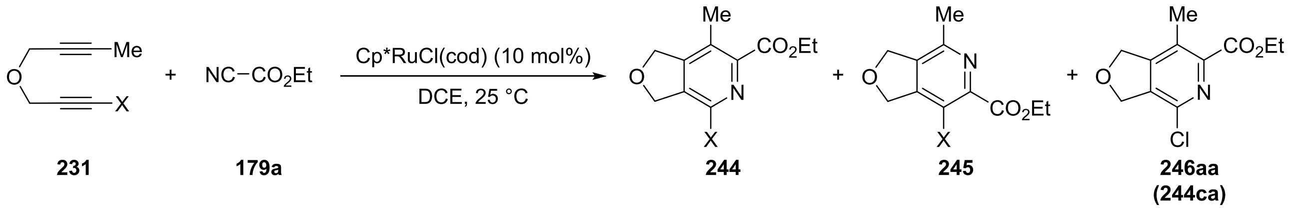
3.1.5.1 Modification of diyne structure

Next, I turned my attention to the reactivity of different diyne substrates. As it was depicted in Figure 12, three structural features could be varied in the molecule of diyne. First, I examined the reactivity of bromodiyne **231b** and chlorodiyne **231c** under the optimized reaction conditions (Table 28). The yields of the reaction with iododiyne **231a** (Entry 7, Table 27) are displayed only for comparison. The reaction with bromodiyne **231b** proceeded with full consumption of the starting material and provided the 2- and 3-bromopyridine (**244ba** and **245ba**) in 40% and 48% yield, respectively (Entry 2). Product **244ba** contained 7% of 2-chloropyridine **246aa**, which represents 3% yield of the cyclotrimerization reaction. The reaction with chlorodiyne **231c** gave two pyridine regioisomers **244ca** and **245ca** in equimolar ratio.

The regioselectivity of all reactions was rather low, but, surprisingly, a slight shift in favor of the 2-halopyridine was observed with decrease of the halogen atom diameter. This relationship was quite unexpected, as regioselectivity in majority of the reported Ru-catalyzed cyclotrimerizations has been assumed to be controlled by steric factors of diyne substituents. Hence, increased preference for formation of 2-halopyridine regioisomer bearing bulkier halogen atom was expected (0, Scheme 30).

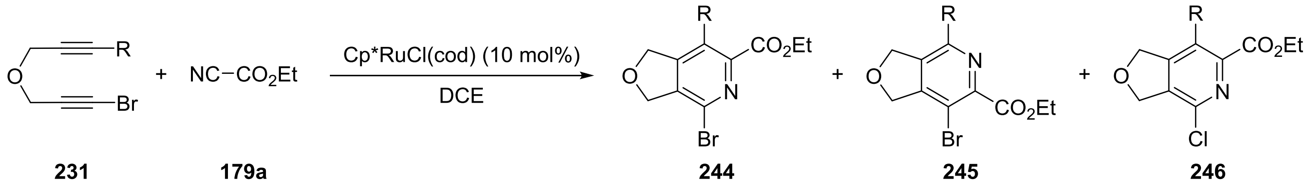
According to the previous screening, the use of the bromo substituent was advantageous with respect to yields of products; therefore variously substituted bromodiynes were used for further studies. First, I varied the substituents on the second triple bond of diyne. The reaction of the unsubstituted bromodiyne **231g** provided selectively only 2-bromopyridine **244ga**, while formation of the opposite regioisomer **245ga** was not observed (Entry 1, Table 29). The reaction of diyne **231e** with the phenyl substituent yielded 2- and 3-bromopyridine (**244ea** and **245ea**) in 2/1 ratio (Entry 2), while the reaction with trimethylsilyl-substituted diyne **231f** gave mixture of regioisomers **244fa** and **245fa** in 3/2 ratio (Entry 3). Only traces of the required products were isolated from the reaction of the cyclopropylated diyne **231d**, although the whole amount of the starting diyne was consumed (Entry 4). Moreover, the reaction furnished a complex and intractable mixture of cyclized products, in which the presence of the cyclopropyl ring was not detected.

Table 28. Diyne screening – halogen substituent.



Entry	X	231	*t* (h)	Yield (%)					
				244		**245**		**246aa**	Combined
1	I	**231a**	37	**244aa**	29	**245aa**	45	5	79
2	Br	**231b**	21	**244ba**	40	**245ba**	48	3	91
3	Cl	**231c**	21	**244ca**	36	**245ca**	36	-	72

Table 29. Diyne screening – substituent on the triple bond.



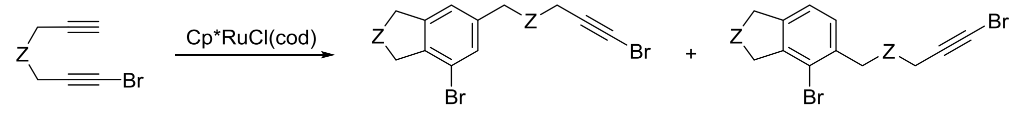
Entry	R	231	*T* (°C)	*t* (h)	Yield (%)						
					244		**245**		**246**		Combined
1	H	**231g**	25 then 50	66 then 24	**244ga**	32	**245ga**	ND	**246ga**	4	36
2	Ph	**231e**	25	22	**244ea**	32	**245ea**	17	**246ea**	6	55
3	TMS	**231f**	25	13	**244fa**	44	**245fa**	36	**246fa**	7	87
4	*c*Pr	**231d**	25 then 50	22 then 47	**244da**	Traces	**245da**	Traces	**246da**	ND	-

[a] ND – not detected.

Then I studied applicability of bromodiynes with a modified linker between two reacting triple bonds. For the initial screening, I chose symmetric dibromodiynes **231k**, **231l**, **231m**, and **231n**. The reaction furnished only one cyclotrimerization product, because of the presence of the element of symmetry in the molecule. In addition, I again observed formation of the halogen exchange product. The reaction with diyne **231k** gave products **249ka** and **250ka** in the combined 89% isolated yield (Entry 1, Table 30). A slightly lower yield of 83% gave the reaction of the structurally similar diyne **231l** possessing CH_2 group instead of the oxygen atom (Entry 2). A high yield was also obtained in the reaction of diyne **231n** possessing the dimethylmalonyl linker (80%, Entry 4). Unfortunately, diyne **231m** with the four atom linker provided only traces of dibromopyridine **249ma** even after a prolonged reaction time (Entry 3) or at increased reaction temperature (50 °C). Difficulty of closing of the six-membered ring during cyclotrimerization has been already reported.[193]

I also utilized monobromodiynes **231h**, **231i** and **231j** in order to examine influence of the tether on the regioselectivity of the reaction (Table 31). As it was already presented in Table 29, the reaction with diyne **231g** provided exclusively 2-bromopyridine regioisomer **244ga**, albeit in low yield of 32% (36% together with 2-chloropyridine **246ga**) The same level of regioselectivity was also observed when diyne **231j** was used, but the yield of product **244ja** was even lower (12%, Entry 4). Moreover, the reactions with diyne **231h** and **231i** gave only traces of the desired pyridine products (Entries 2 and 3).

The decreased yields of reactions in Entries 2 and 4 were caused by the formation of different products. The ^{1}H-NMR analyses of crude reaction mixtures revealed the presence of benzene aromatic proton signals, which appeared around 7 ppm. These products were later isolated and identified as compounds **251h** and **251j**, which were formed by homocyclotrimerization of diynes **231h** and **231j** (Scheme 54). The observed lower chemoselectivity can be explained by a decreased steric hindrance in unsubstituted bromodiynes compared to all previously used diynes with the fully substituted triple bonds. The products of homocyclotrimerization **251h** and **251j** were also formed regioselectively as the opposite regioisomers **252h** and **252j** were not detected in the reaction mixtures.



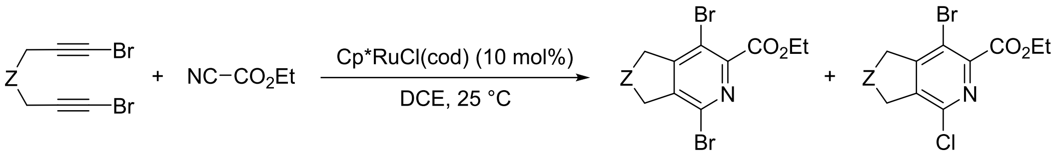
231h: Z = CH_2
231j: Z= $C(CO_2Me)_2$

251h: Z = CH_2
251j: Z= $C(CO_2Me)_2$

252h: Z = CH_2
252j: Z= $C(CO_2Me)_2$

Scheme 54. Homocyclotrimerization of diynes **231h** and **231j**.

Table 30. Diyne screening – linker tethering triple bonds, dibromodiynes.

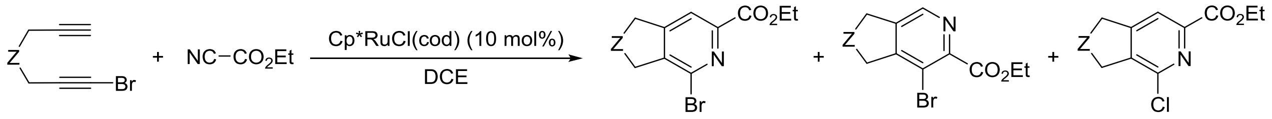


231 **179a** **249** **250**

Entry	Z	**231**	*t* (h)	Yield (%)[a]				
				249		**250**		Combined
1	O	**231k**	16	**249ka**	83	**250ka**	6	89
2	CH_2	**231l**	18	**249la**	81	**250la**	2	83
3	CH_2CH_2	**231m**	50	**249ma**	Traces	**250ma**	ND	-
4	$C(CO_2Me)_2$	**231n**	12	**249na**	77	**250na**	3	80

[a] ND – not detected.

Table 31. Diyne screening – linker tethering triple bonds, monobromodiynes.

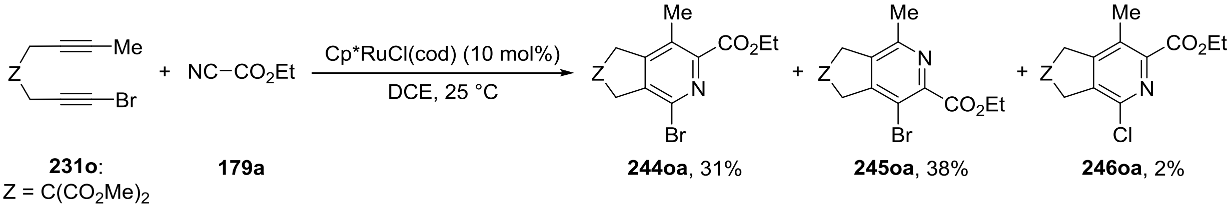


231 **179a** **244** **245** **246**

Entry	Z	**231**	*T* (°C)	*t* (h)	Yield (%)[a]						
					244		**245**		**246**		Combined
1	O	**231g**	25 then 50	66 then 24	**244ga**	32	**245ga**	ND	**246ga**	4	36
2	CH_2	**231h**	25	66	**244ha**	Traces	**245ha**	ND	**246ha**	ND	-
3	CH_2CH_2	**231i**	25 then 50	52 then 24	**244ia**	Traces	**245ia**	ND	**246ia**	ND	-
4	$C(CO_2Me)_2$	**231j**	25	82	**244ja**	12	**245ja**	ND	**246ja**	2	14

[a] ND – not detected.

The reaction with the unsymmetrically substituted bromodiyne **231o** bearing the dimethyl malonyl linker and the methyl group gave an almost equimolar mixture of both regioisomers **244oa** and **245oa** in a high combined isolated yield of 69% (Scheme 55).



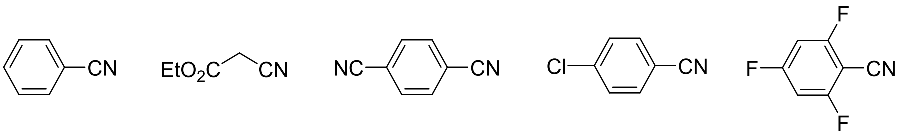
Scheme 55. Cyclotrimerization of diyne **231o** with ethyl cyanoformate **179a**.

3.1.5.2 Screening of nitriles

Then I turned my attention to applicability of different nitriles in the cocyclotrimerization reaction with halodiynes. I selected compound **231b** as the representative diyne, because it showed the best reactivity in the previous screenings. Although the reaction with ethyl cyanoformate **179a** proceeded in an almost quantitative yield (Entry 2, Table 28), the yields in reactions with other nitriles varied (Figure 18, Table 32). In general, it has been reported that cyclotrimerizations of diynes catalyzed by Cp*RuCl(cod) has been limited to only electron-poor nitriles.[169] This phenomenon was confirmed also in my case by the reaction with benzonitrile **179d** that did not give any cyclotrimerization product. The same result was obtained in the reaction with ethyl cyanoacetate **179e**, which structurally differs from ethyl cyanoformate **179a** by the presence of one extra methylene group. However, the longer distance of the electron-withdrawing substituent from the nitrile group caused its total unreactivity. On the other hand, malonitrile **179i** was easiliy cocyclotrimerized with diyne **231b** to a mixture of all products **244bi**, **245bi** and **246bi** in combined 74% isolated yield (Entry 1, Table 32). The reaction highly preferred formation of 2-bromopyridine **244bi** (5/1 ratio). It should be also noted that formation of the product of double cyclotrimerization was not observed. An exceptional reactivity of malonitrile was already reported previously.[202] The fact that one of the cyano groups of malonitrile **179i** remained intact, can be explained by its coordination to the ruthenium metal center, which should facilitate incorporation of the other cyano group into the pyridine product.[138] On the other hand, the reaction with 1,4-dicyanobenzene **179f** provided only traces of the expected products. The same result was also observed when *p*-chlorobenzonitrile **179g** was used. In view of the aforementioned, it can be concluded that only highly electron-deficient nitriles were suitable substrates for cyclotrimerization with halodiynes. Therefore I focused on this type of reactants in the further study. *p*-Nitrobenzonitrile **179j** was cocyclotrimerized at 25 °C in 38% yield with the preferential formation of regioisomer **244bj** (Entry 2). The yield was only marginally higher when the reaction was carried out at 50 °C, but the required reaction time for full consumption of the starting diyne rapidly decreased (Entry 3). As all three formed products were inseparable by any separation technique, their yields were determined in the isolated mixture by using ^{1}H-NMR analysis.

Next I studied suitability of fluorinated benzonitriles as substrates. A possible incorporation of fluorinated moieties into various compounds has been frequently studied because of their important role in the field of medicinal chemistry.[203] The cyclotrimerization with 3,5-difluorobenzonitrile **179k** and perfluobenzonitrile **179l** proceeded to give only 2-bromopyridine regioisomers, albeit in low yields (Entries 4 and 5). Reaction temperature did not have any effect on the reaction outcome (Entry 6). The reaction with 3,5-bis(trifluoromethyl)benzonitrile **179m** gave regioisomers **244bm** and **245bm** in 3/1 ratio with preference for 2-bromopyridine **244bm** (Entry 7). Surprisingly, the reaction with 2,4,6-trifluorobenzonitrile **179h** provided only traces of the pyridine products (Figure 18).

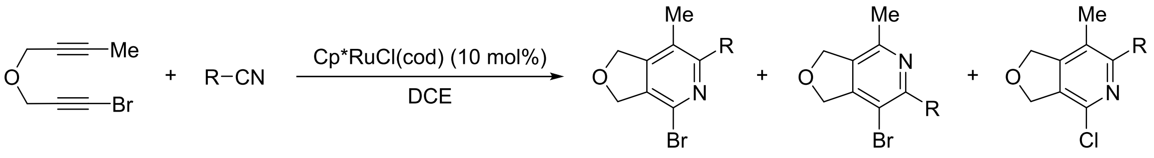
Then I focused my attention to acyl cyanides as they were proposed to be suitable substrates for a synthesis of Bolm's 2,2'-bipyridine analogues (Scheme 44). Fortunately, all reactions furnished the desired products in moderate to high yields (45–82%) with regioselectivity ranging between 4/1 to 3/2 ratio and with the preference for formation of 2-bromopyridine **244** (Entries 8–10). As usual, the 2-chloropyridines **246** were observed as inseparable impurity of 2-bromopyridine compounds **244**.



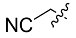
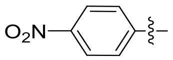
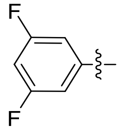
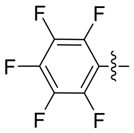
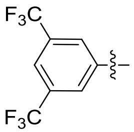
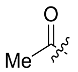
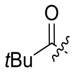
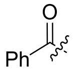
179d, NR **179e**, NR **179f**, traces **179g**, traces **179h**, traces

Figure 18. Structures of unreactive nitriles.

Table 32. Nitrile screening.



231b **179** **244** **245** **246**

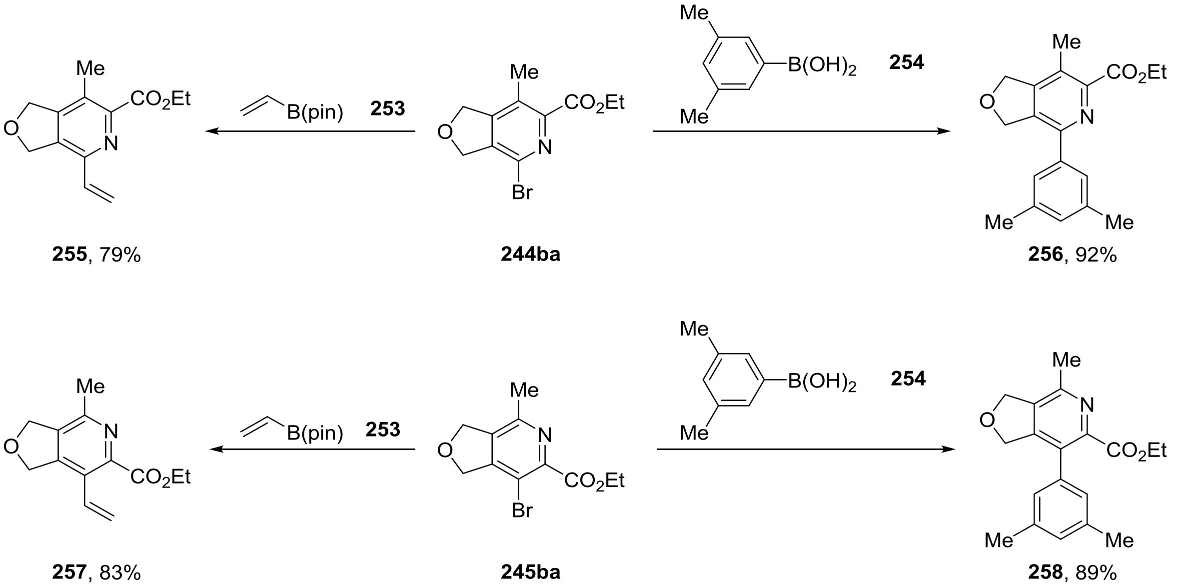
Entry	R	**179**	*T* (°C)	*t* (h)	Yield (%)						
					244		**245**		**246**		Combined
1		**179i**	25	13	**244bi**	59	**245bi**	13	**246bi**	2	74
2		**179j**	25	131	**244bj**	27	**245bj**	5	**246bj**	6	38[b]
3			50	10		31		8		5	44[b]
4		**179k**	25	143	**244bk**	16	**245bk**	Traces	**246bk**	3	19
5		**179l**	25	40	**244bl**	30	**245bl**	ND	**246bl**	5	35
6			50	20		30		ND		5	35
7		**179m**	25	69	**244bm**	31	**245bm**	12	**246bm**	5	48
8		**179n**	25	11	**244bn**	48	**245bn**	33	**246bn**	1	82
9		**179b**	25	15	**244bb**	32	**245bb**	11	**246bb**	2	45
10		**179c**	25	12	**244bc**	51	**245bc**	13	**246bc**	3	67

[a] ND – not detected. [b] Regioisomers were inseparable, their proportional representation was determined by ^{1}H-NMR.

3.1.6 Reactivity of 2- and 3-halopyridines

After finding the scope of this new type of cyclotrimerization reaction, I wanted to demonstrate applicability of newly prepared 2- and 3-halopyridines in further transformations. I selected Suzuki–Miyaura cross-coupling as a representative reaction for several reasons. First, the coupling has been frequently applied in industry as it uses organoboronic acids or their esters, which are, compared to organostannanes or organozinc compounds used in other coupling methods, less toxic and easily accessible.[204] Second, the reaction takes place in aqueous reaction media. Third it proceeds under mild reaction conditions. And finally, inorganic by-products are easily removable from the reaction mixture. All these factors are making Suzuki–Miyaura reaction the most environmentally friendly cross-coupling reaction known today.

Reactions were carried out under the previously developed conditions and were used without any optimization. In general, reactions with vinylboronic acid pinacol ester **253** as well as the reactions with 3,5-dimethylphenylboronic acid **254** proceeded smoothly furnishing the coupling products in high yields with only marginal difference in reactivity of 2- and 3-bromopyridines (Scheme 56). The reaction of boronic ester **253** with 2-bromopyridine **244ba** provided **255** in 79% yield, while the 3-bromopyridine **245ba** gave **257** in 83% yield. The reaction of boronic acid **254** under the same conditions with **244ba** gave **246** in 92% yield and with **245ba** gave **258** in 89% yield.



$Pd(PPh_3)_2Cl_2$ (10 mol%), CsF (3 eq.), dioxane/H_2O 2/1, 95 °C

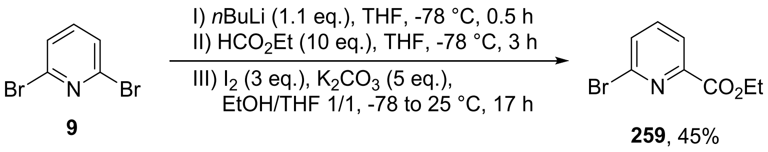
Scheme 56. Reactivity of formed 2- and 3-bromopyridines **244ba** and **245ba** in Suzuki reaction.

3.2 Synthesis of 2,2'-bipyridines bearing oxazoline rings

3.2.1 Synthesis of a model compound

With the new cocyclotrimerization method in hands, I turned my attention to the syntheses of new 2,2'-bipyridines. I assumed that the crucial step of syntheses will be the reductive dimerization of 2-halopyridines (Step a, Scheme 44 and Step b, Scheme 45), therefore I started with a study of this reaction. Starting 2-halopyridines **244ba** and **244bb,** which were proposed as intermediates in syntheses of the target bipyridines (Scheme 44 and Scheme 45), were accessible by several-step syntheses, thus I decided to use easily accessible ethyl 6-bromopicolinate **259** as a model compound for the preliminary screening of dimerization reaction.

Ethyl 6-bromopicolinate **259** was prepared by monolithiation of 2,6-dibromopyridine **9** followed by a reaction with ethyl formate and subsequently by a reaction with iodine in ethanol (Scheme 57). This three-step procedure furnished the required ethyl 6-bromopicolinate **259** in 45% yield.



Scheme 57. Synthesis of 6-bromopicolinate **259**.

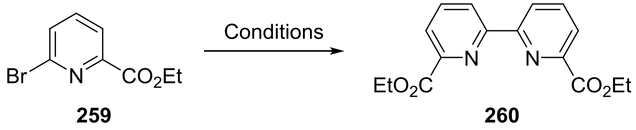
3.2.2 Reductive dimerization of the model compound

Out of a number of various dimerization methods of 2-halopyridines tolerant to the presence of alcohol and/or ester functional group, I selected several reaction conditions, which were examined in dimerization of 6-bromopicolinate **259** (Table 33). All reactions were analyzed by NMR or HPLC analysis. First of all, I tested three Ni(0)-mediated methods (Entries 1–3). The most common procedure using nickel(II) chloride, zinc, and triphenylphosphine, which was also used for synthesis of bipyridine (*R*,*R*)-**8** by Bolm *et al.*,[19] gave the bipyridine **260** in the quantitative yield (Entry 1). Also a high conversion of 80% was observed by using $NiBr_2(PPh_3)_2$ together with an excess of zinc and $n$$Bu_4NI$ (Entry 2).[205] In order to hamper the termination of the reaction by complexation of the formed bipyridine to the nickel catalyst, at least one equivalent of the nickel complex was essential for the satisfactory course of the reaction. On the other hand, Duan *et al.* reported a method, which is taking the complexation as an advantage, as the formed Ni-bipyridine complex catalyzes the bipyridine formation.[206] Thus only a catalytic amount of Ni(II) chloride is required in this case. This method furnished the desired bipyridine **260** in the quantitative yield (Entry 3).

Then I also tried to dimerize 6-bromopicolinate **259** using Pd-catalyzed processes. The first one, reported by Yoon *et al.*, used Pd(II) acetate, potassium carbonate and isopropyl alcohol,[207] while the second one was based on a two-step one-pot procedure *via* generation of an organotin intermediate followed by Stille-type cross-coupling reaction.[208] Nevertheless, both gave bipyridine **260** in excellent HPLC yields (Entries 4–5). As Lamaty's group is dealing with the development of environmentally friendly methods, I tested a possibility to use the MW irradiation for initiation of Pd-catalyzed reactions. All the protocols used Pd(0)-catalysts, which were generated *in situ* from Pd(II) acetate, and gave the product **260** in yields higher than 60% (Entries 6–8). The use of polyethylene glycol (PEG 3350) was simplifying both set-up and work-up of the reaction, as it is solid powder with the melting point around 56 °C with low solubility in diethyl ether. Hence it could be separated from the rest of the reaction mixture and potentially reused by a simple precipitation in pre-cooled Et_2O.

Then I also examined the ultrasound (US) irradiation in the dimerization reaction of 6-bromopicolinate **259** using Ni- and Pd-complexes. Albeit in both cases one hour irradiation caused decomposition of the starting material as well as that of the product (Entries 9 and 11), the careful optimization of the reaction conditions indicated that application of short ultrasound pulses (5 s), resulted in the formation of bipyridine **260** as the major product (Entries 10 and 12).

Table 33. Reductive dimerization of 6-bromopyridine **259** to bipyridine **260**.

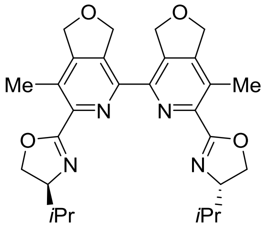


Entry	Ref.	M-source (eq.)	Salt/Ligand (eq.)	Additive (eq.)	Solvent	*T* (°C)	*t* (h)	Yield (%)[a]
1	19	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	60	20	>95
2	205	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	50	5	80
3	206	$NiCl_2$ (0.15), Zn (1.2)	LiCl (1)	I_2 (0.1), AcOH (0.1)	DMF	60	22	>95
4	207	$Pd(OAc)_2$ (0.15)	K_2CO_3 (1.5)	*i*PrOH (2)	DMF	100	17	>95 (>96)[b]
5	208	$Pd(PPh_3)_4$ (0.2), *n*Bu_6Sn_2 (0.5)	-	-	PhMe	120	18	90
6	208	$Pd(OAc)_2$ (0.15)	Cs_2CO_3 (1.2), dppp (0.1)	-	PhMe	200 (MW)	1.5	60
7	-	$Pd(OAc)_2$ (0.15)	K_2CO_3 (1.5)	*i*PrOH (2)	DMF	100 (MW)	1.5	80
8	-	$Pd(OAc)_2$ (0.15)	K_2CO_3 (3)	-	PEG 3400	100 (MW)	0.5	70
9	-	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	45 (US)	1	<10
10	-	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	45 (US)[c]	0.33	90
11	-	$Pd(OAc)_2$ (0.15)	K_2CO_3 (1.5)	*i*PrOH (2)	DMF	50 (US)	1	<10
12	-	$Pd(OAc)_2$ (0.15)	K_2CO_3 (1.5)	*i*PrOH (2)	DMF	30 (US)[c]	0.08	60

[a] Determined by ^{1}H-NMR and/or HPLC analysis. [b] Isolated yield of the scale-up reaction. [c] 5 s US pulses.

3.2.3 Synthesis of BipyMOX 261

With the promising results of the dimerization with compound **259** in hand, I explored dimerization of 2-bromopyridine **244ba**. Unfortunately, change to a more complex starting material resulted in a radical drop of yields in most of the cases (Table 34).

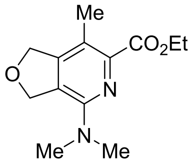


261

Figure 19. Structure of the target BipyMOX **261**.

While the nickel-mediated reactions dimerized 2-bromopyridine **244ba** to bipyridine **262** in moderate yields (40–50%, Entries 1 and 2, Table 34), the nickel-catalyzed dimerization gave product **262** in only 20% yield (Entry 3). Palladium catalyzed one-step as well as two-step procedure furnished bipyridine **262** in 50% yield (Entries 4 and 5). Surprisingly, using $PdCl_2(PhCN)_2$, which is *in situ* reduced by tetrakis(dimethylamino)ethylene (TDAE) to a Pd(0)-complex, gave only a negligible amount of **262** (Entry 6). Although this method was not tested for dimerization of model compound **259**, as TDAE was not accessible at the time of the study, this procedure was used by Kobayashi *et al.* for synthesis of Bolm's ligand (*S*,*S*)-**8**, which was obtained in an almost quantitative yield (Scheme 6).[11]

The classical procedure of Ullmann coupling reaction using copper powder did not give any product at 130 °C (Entry 7). On the other hand, when the reaction temperature was increased to 200 °C, compound **244ba** was converted to a new product, which was identified as amine **263** (Figure 20). I assume that it was formed by a reaction of 2-bromopyridine **244ba** with dimethyl amine formed by decomposition of *N*,*N*-dimethylformamide at a high temperature.



263

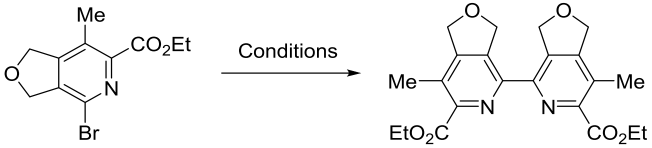
Figure 20. Structure of 2-aminopyridine **263**.

The use of microwave irradiation resulted in a further drop of yields (Entries 9–13 and 15) with one exception. It was the two-step procedure catalyzed by $Pd(PPh_3)_4$ proceeding *via* an organotin compound. It provided bipyridine **262** in excellent yield of 90% (Entry 14). However, modification of this method was required. First, a part of 2-bromopyridine **244ba** (two thirds of the total amount) was treated with $n\mathrm{Bu}_6\mathrm{Sn}_2$ together with a portion of the Pd-complex (also two thirds). After two hours of MW irradiation, the rest of **244ba** and the Pd-complex were added and irradiation was maintained for another two hours. Reactions run in a US reactor also did not bring any improvement and the target bipyridine **262** was obtained in only low to moderate yields together with mixtures of decomposition products (Entries 16–20).

I also tried to activate the starting compounds mechanically using a ball-mill (BM) reactor. Although most of the reactions did not give any products (Entries 21, 22 and 24), the procedure using $PdCl_2(PhCN)_2$ with TDAE gave under solvent-free conditions the desired product in 40% yield (Entry 23), which is a higher yield in comparison with MW or conventional heating conditions using this catalytic system. In addition, to the best of my knowledge, this is the first example of using mechanochemistry for synthesis of 2,2'-bipyridines by reductive dimerization of 2-halopyridines. MW irradiation procedure (Entry 14) was also used for preparation of this compound on larger scale (2 mmol). In this case was bipyridine **262** isolated in 94% yield.

Unfortunately, low solubility of the bipyridine **262** complicated its handling in the next step. Although the presence of dicarboxylic acid **264** was confirmed by HRMS analysis as an only product of the hydrolysis, it was not possible to purify it due to its amphoteric properties (Scheme 58). The reaction mixture containing **264** was therefore in the next step treated with an excess of thionyl chloride. The unreacted $SOCl_2$ was removed under reduced pressure and the crude residue was allowed to react with L-valinol. However, no trace of the product **266** was detected, even though the whole sequence was repeated several times.

Table 34. Reductive dimerization of 2-bromopyridine **244ba** to bipyridine **262**.

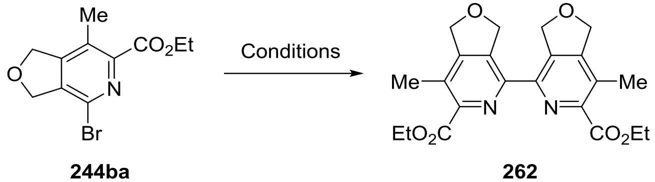


244ba **262**

Entry	M-source (eq.)	Salt/Ligand (eq.)	Additive (eq.)	Solvent	*T* (°C)	*t* (h)	Yield (%)[a]
1	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	60	20	50
2	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	60	15	40
3	$NiCl_2$ (0.15), Zn (1.2)	LiCl (1)	I_2 (0.1), AcOH (0.1)	DMF	60	27	20
4	$Pd(OAc)_2$ (0.15)	K_2CO_3 (1.5)	*i*PrOH (2)	DMF	100	24	50
5	$Pd(PPh_3)_4$ (0.2), *n*Bu_6Sn_2 (0.5)	-	-	PhMe	120	44	50
6	$PdCl_2(PhCN)_2$ (0.2)	-	TDAE (2)	DMF	80	10	10
7	Cu-powder (5)	-	-	DMF	130	60	ND
8	Cu-powder (5)	-	-	DMF	200	60	ND[b]
9	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	DMF	120 (MW)	4	<10
10	$Pd(OAc)_2$ (0.15)	Cs_2CO_3 (1.2), dppp (0.1)	-	PhMe	200 (MW)	2	20
11	$Pd(OAc)_2$ (0.15)	K_2CO_3 (1.5)	*i*PrOH (2)	DMF	100 (MW)	2	20
12	$Pd(OAc)_2$ (0.15)	K_2CO_3 (3)	-	PEG 3400	100 (MW)	2	20
13	$PdCl_2(PhCN)_2$ (0.2)	-	TDAE (2)	DMF	120 (MW)	4	10
14	$Pd(PPh_3)_4$ (0.2), *n*Bu_6Sn_2 (0.75)	-	-	PhMe	180 (MW)	4	90 (94)[c]
15	Cu-powder (5)	-	-	DMF	200 (MW)	4	10
16	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	45 (US)[d]	0.5	20
17	$Pd(OAc)_2$ (0.15)	K_2CO_3 (1.5)	*i*PrOH (2)	DMF	50 (US)[d]	1	40
18	$PdCl_2(PhCN)_2$ (0.2)	-	TDAE (2)	DMF	50 (US)[d]	2	10
19	Cu-powder (5)	-	-	DMF	50 (US)[d]	1	ND

[a] Determined by ^{1}H-NMR or HPLC analysis; ND – not detected. [b] Product **263** was isolated instead in the quantitative yield. [c] Isolated yield of large-scale reaction is in parenthesis. [d] 5 s US pulses.

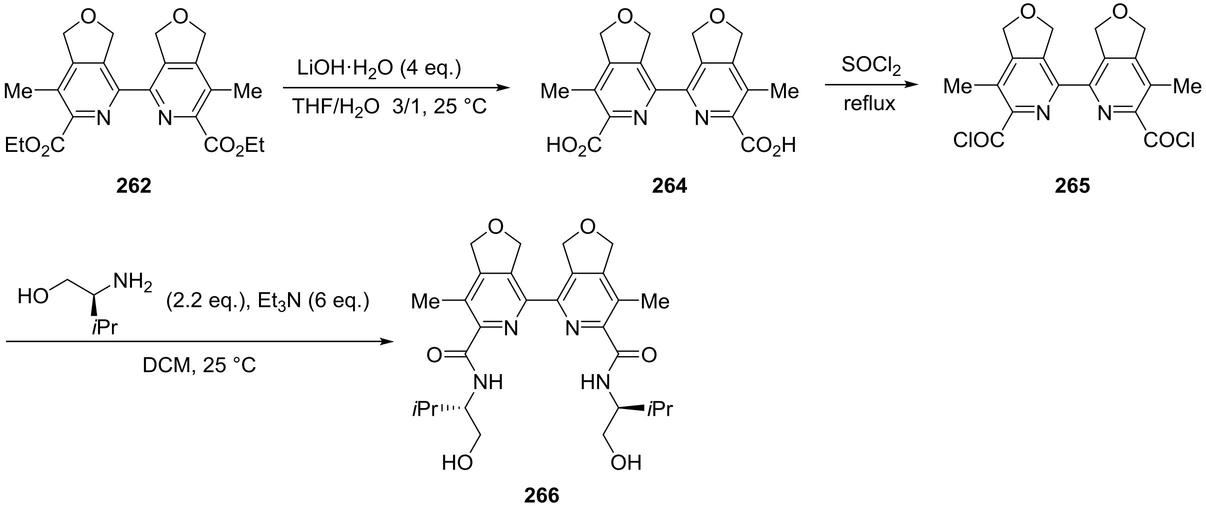
Table 34. **(continued)** Reductive dimerization of 2-bromopyridine **244ba** to bipyridine **262**.



244ba **262**

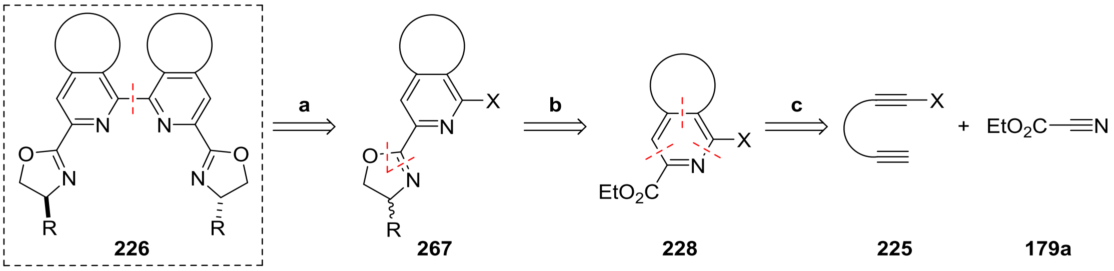
Entry	M-source (eq.)	Salt/Ligand (eq.)	Additive (eq.)	Solvent	*T* (°C)	*t* (h)	Yield (%)[a]
20	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	-	- (BM)	1	ND
21	$Pd(OAc)_2$ (0.15)	K_2CO_3 (1.5)	*i*PrOH (2)	-	- (BM)	1	ND
22	$PdCl_2(PhCN)_2$ (0.2)	-	TDAE (2)	-	- (BM)	1	40
23	Cu-powder (5)	-	-	-	- (BM)	1	ND

[a] Determined by ^{1}H-NMR or HPLC analysis; ND – not detected. [b] Product **263** was isolated instead in the quantitative yield.



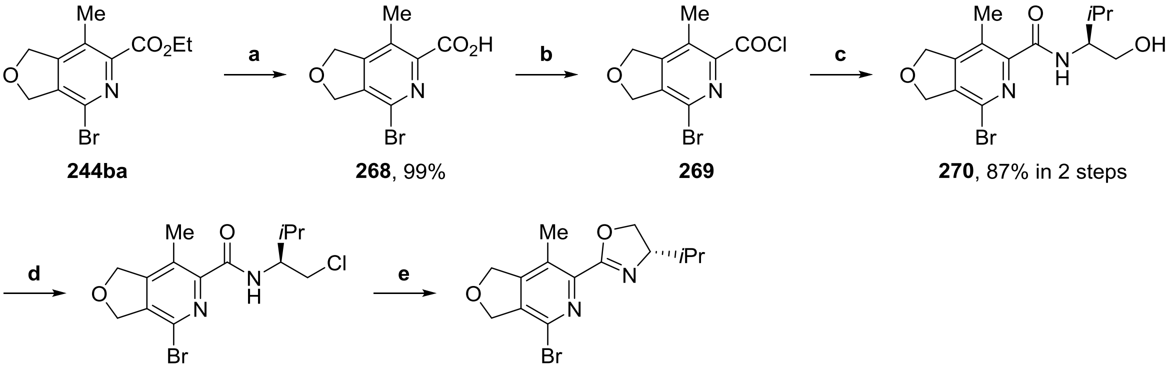
Scheme 58. An unsuccessful synthesis of bipyridine **261**.

The proposed reaction sequence for preparation of BipyMOX **261** was then changed in order to postpone the bipyridine formation to the last step. The target bipyridine was then proposed to be synthesized by the following retrosynthetic approach (Scheme 59): (a) the C2–C2' bond of BipyMOX **226** was envisioned to be formed by reductive dimerization of 2-halopyridine **267** (Step a) and (b) the oxazoline ring of 2-halopyridine will be formed by the standard procedure from ester **228** (Step b), (c) which should be accessible by cocyclotrimerization of halodiynes **225** with ethyl cyanoformate **179a** (Step c).



Scheme 59. New proposed synthesis of BipyMOXes.

The first step of the sequence was hydrolysis of the ester group of 2-bromopyridine **244ba** to carboxylic acid **268** (99%, Scheme 60). Next, treatment of acid **268** with thionyl chloride gave carbonyl chloride **269**, which was used for a reaction with L-valinol to give amide **270** in 87% yield after two steps. Replacement of thionyl chloride by oxalyl chloride resulted in a drop of yield to 50%. Then alcohol **270** was transformed to chloride **271** using thionyl chloride in quantitative yield. Chloride **271** was subsequently converted to 2-bromopyridine **272** bearing the oxazoline ring in 93% yield using sodium hydride and tetrabutylammonium iodide.



244ba **268**, 99% **269** **270**, 87% in 2 steps

271, >96% **272**, 93%

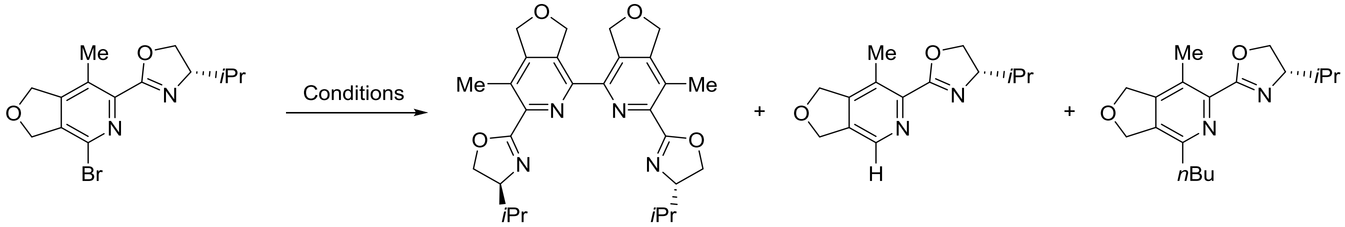
a) LiOH·H_2O (2 eq.), THF/H_2O 3/1, 25 °C, 3 h
b) $SOCl_2$, reflux, 12 h
c) L-valinol (1.1 eq.), Et_3N (2 eq.), DCM, 0 to 25 °C, 23 h
d) $SOCl_2$ (2 eq.), DCM, reflux, 27 h
e) NaH (5 eq.), *n*Bu_4NI (10 mol%), THF, 25 to 50 °C, 18 h

Scheme 60. Formation of oxazoline ring – synthesis of 2-bromopyridine **272**.

The last step of the proposed synthesis of bipyridine **261** was dimerization of **272**. Due to time demanding screening of all possible dimerization methods along with a high value of the starting material (synthesized by an eight-step synthesis), only four methods, which in the previous studies gave the bipyridines in highest yields, were tested. In this study, I also focused on determination of formed side products. The side products were identified using HPLC-HRMS analysis and after their partial isolation and purification also using NMR.

Bipyridine **261** was formed in 60% yield by using nickel(II) chloride, zinc and triphenylphosphine mixture (Entry 1, Table 35). The only side product of the reaction was the product of reductive dehalogenation **273**, which is generally a typical undesired product in this type of reaction. Even careful degassing of the solvent, which is recommended in order to reduce the amount of this product, did not improve the yields of bipyridine **261**. On the other hand, the reaction using $NiBr_2(PPh_3)_2$ gave bipyridine **261** in the quantitative yield without any traces of the side products (Entry 2). The Pd(0)-catalyzed reaction using $PdCl_2(PhCN)_2$ and TDAE furnished bipyridine **261** in 60% yield (Entry 3). In spite of the prolonged reaction time, conversion of the starting material was not completed and 20% of 2-bromopyridine **272** remained unreacted. The Pd(0)-catalyzed two-step procedure gave bipyridine **261** in a low yield of 30% (Entry 4). Besides the dehalogenated compound **273** (30% yield), I observed also formation of compound **274** (40% yield) bearing the *n*-butyl substituent, which probably originated from undesired transmetalation reaction between tris(*n*-butyl)organotin **275** compound and organopalladium species **276** followed by reductive elimination (second line, Scheme 61).

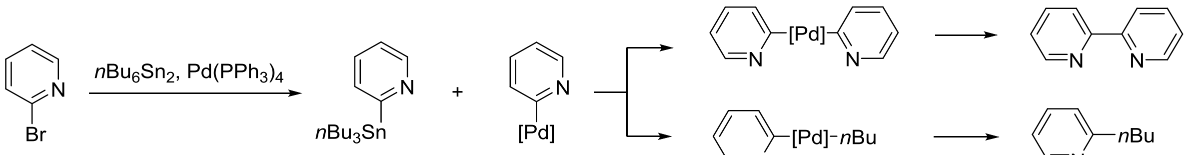
Table 35. Reductive dimerization of 2-bromopyridine **272** to bipyridine **261**.



272 **261** **273** **274**

Entry	M-source (eq.)	Salt/Ligand (eq.)	Additive (eq.)	Solvent	T (°C)	t (h)	Yield (%)[a]		
							261	**273**	**274**
1	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	70	21	60	40	ND
2	$NiBr_2(PPh_3)_2$ (1), Zn (5)	nBu$_4$NI (5)	-	THF	60	18	>95 (51)	ND	ND
3	$PdCl_2(PhCN)_2$ (0.2)	-	TDAE (2)	DMF	80	10	60	20	ND
4	$Pd(PPh_3)_4$ (0.2), nBu$_6$Sn$_2$ (0.75)	-	-	PhMe	180 (MW)	4	30	30	40

[a] Determined by HPLC analysis (isolated yield); ND – not detected.



275 **276**

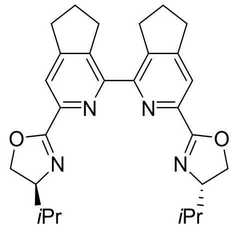
Scheme 61. Proposed origin of *n*-butyl substituent of **265** during reductive dimerization reaction.

Although the Ni(0)-mediated method (Entry 2) provided bipyridine **261** as the sole compound in the quantitative yield (as judged from HPLC analysis), a problem arose during the purification of this compound, namely, its separation from triphenylphosphine oxide (TPPO) formed by spontaneous oxidation of triphenylphosphine. Unfortunately, both compounds had almost the same R_f during column chromatography using either a normal or a reverse stationary phase. They had very similar solubility properties in all solvents including low solubility in Et_2O. Also attempts to convert bipyridine to its bipyridinium salt followed by its extraction to water phase were unsuccessful as TPPO has very similar protonation properties. In addition, bipyridine **261** turned out to be unstable under acidic conditions and the products of decomposition complicated further purification. A possibility of taking advantage of complexation properties of TPPO, which was reported by Weix *et al.*,[209] was not feasible when taking the account the complexation properties of bipyridines. Bipyridine **261** was then isolated by using repetitively column chromatography, which, of course, resulted in a drop of the isolated yield to 51%.

In order to check possible racemization, racemic bipyridine (*rac*)-**261** was synthesized by the same reaction sequence using racemic valinol. The enantiopurity of bipyridine **261** was determined to be higher than 99% ee.

3.2.4 Synthesis of BipyMOX 277

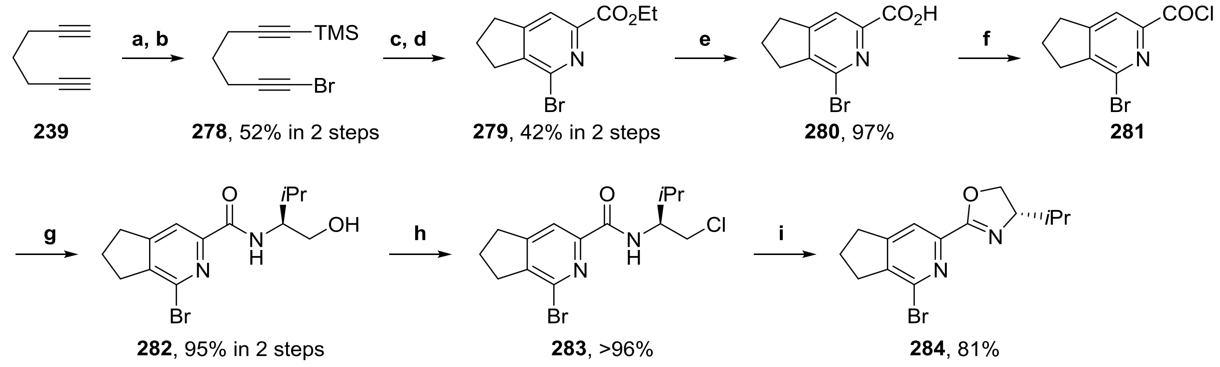
Generality of the developed reaction sequence was demonstrated in a synthesis of bipyridine **277**, which bears the five-membered all-carbon ring and no substituent in position 5, compared to bipyridine **261**.



277

Figure 21. Structure of the target BipyMOX **277**.

I started its synthesis from hepta-1,6-diyne **239**, which was in the first step trimethylsilylated and, without any separation of the monosilylated from the bissilylated products, brominated (Scheme 62). Diyne **278** was isolated in 52% yield after two steps. Its cyclotrimerization with ethyl cyanoformate **179a** gave 3/2 ratio mixture of regioisomeric cycloadducts (2-bromopyridine was the major product) in 80% combined isolated yield. The cyclotrimerization reaction proceeded even with a lower load of Ru-catalyst (7 mol%). The crude mixture was quickly filtered through a silica gel pad to remove the unreacted nitrile and Ru-salts, because of low stability of regioisomers on silica gel during the separation process. The mixture of 2- and 3-bromopyridines was then desilylated using tetrabutylammonium fluoride (TBAF) providing the desired 2-bromopyridine **279** in 42% isolated yield. Albeit the presence of the halogen exchange product was observed, its amount could not be determined as all its signals in ^{1}H-NMR spectra were overlapping with the signals of **279**. The ensuing hydrolysis furnished carboxylic acid **280** in 97% yield. The subsequent formation of acyl chloride **281** and its reaction with L-valinol proceeded without any problem giving amide **282** in 95% yield. Transformation of the hydroxy group of **282** to chloride with $SOCl_2$ gave pyridine **283** in the quantitative yield. Formation of the oxazoline ring was completed by a reaction with sodium hydride, which gave 2-bromopyridine **284** in 81% yield.



239

278, 52% in 2 steps

279, 42% in 2 steps

280, 97%

281

282, 95% in 2 steps

283, >96%

284, 81%

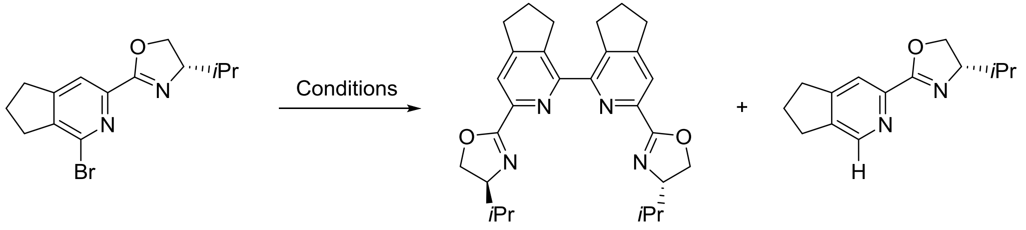
a) I) LiHMDS (1 eq.), THF, -78 °C, 1 h; II) TMSCl (1 eq.), -78 °C, 1 h
b) I) *n*BuLi (1 eq.), THF, -78 °C, 30 min; II) NBS (1.2 eq.), -78 °C to 25 °C, 12 h
c) I) ethyl cyanoformate **179a** (2 eq.), Cp*RuCl(cod) (7 mol%), DCE, 25 °C, 15 h
d) TBAF (1.2 eq.), THF, 25 °C, 1 h
e) LiOH·H_2O (2 eq.), THF/H_2O 4/1, 25 °C, 3 h
f) $SOCl_2$, reflux, 12 h
g) L-valinol (1.1 eq.), Et_3N (2 eq.), DCM, 0 to 25 °C, 18 h
h) $SOCl_2$ (2 eq.), DCM, reflux, 15 h
i) NaH (5 eq.), *n*Bu_4NI (10 mol%), THF, 25 °C, 17 h

Scheme 62. Synthesis of 2-bromopyridine **284**.

Sursprisingly, reductive dimerization of 2-bromopyridine **284** turned out to be even more complicated (Table 36). The procedure, which was optimal for dimerization of structurally similar 2-bromopyridine **284**, gave bipyridine **277** in a rather poor yield of 30% together with a high amount of the dehalogenated product **285** (Entry 2). In addition, the dehalogenated pyridine **285** was the only product of the Pd-catalyzed reaction, which proceeded with a low conversion of the starting material (Entry 3). Fortunately, the Ni-mediated procedure ($NiCl_2$, Zn, PPh_3) furnished bipyridine **277** in 70% HPLC yield (Entry 1). Column chromatography using either normal or reverse stationary phase could not completely separate bipyridine **277** from TPPO, therefore different phosphine ligands were tested in the reaction. The use of triphenylphosphine on a solid support did not result in the formation of the desired product (Entry 4). Obviously, the active catalyst was not formed, because the density of triphenylphospine molecules on surface of the polystyrene resins wass, probably, too low to serve as ligands for the Ni-species. Also the reaction with trimethylphosphine did not give any product, although the Ni(0)-complex was probably formed (a change of the reaction mixture color from blue to dark violet was observed) (Entry 5). Slightly better results were obtained by using 1,4-bis(diphenylphosphino)butane (dppb) as formation of bipyridine **277** was observed in 30% yield (Entry 6). On the other hand, the full conversion of the starting material to the dehalogenated product **285** was observed when 1,1'-bis(diphenylphosphino)ferrocene (dppf) was used (Entry 7).

Since the change of the phosphine ligands while keeping the high yields of the bipyridine seemed not to be possible, I tried to optimize the work-up procedure of the reaction using triphenylphosphine (Entry 1). The best separation of bipyridine **277** and TPPO was achieved after lengthy optimization. Bipyridine **277** was initially converted to bipyridinium chloride using 0.5% aqueous solution of hydrochloric acid and extracted with DCM. The aqueous phase was promptly alkalized by adding a solution of sodium hydroxide re-forming bipyridine **277**, which was subsequently transferred to the organic phase by extraction with DCM. Three-time repeated process of acidification, extraction, alkalization, and extraction furnished a solution of bipyridine **277** free of TPPO. However, the use of a complicated separation process resulted in decrease of bipyridine **277** isolated yield to 49%.

Table 36. Reductive dimerization of 2-bromopyridine **284** to bipyridine **277**.



284 **277** **285**

Entry	M-source (eq.)	Salt/Ligand (eq.)	Additive (eq.)	Solvent	*T* (°C)	*t* (h)	Yield (%)[a] **277**	Yield (%)[a] **285**
1	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	70	21	70 (49)	30
2	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	60	18	30	70
3	$PdCl_2(PhCN)_2$ (0.2)	-	TDAE (2)	DMF	80	10	ND	20
4	$NiCl_2$ (1.2), Zn (1.3)	PL-TPP Resin(4.8)	-	DMF	70	13	NR	NR
5	$NiCl_2$ (1.2), Zn (1.3)	PMe_3 (4.8)	-	DMF	70	13	NR	NR
6	$NiCl_2$ (1.2), Zn (1.3)	dppb (2.4)	-	DMF	70	13	30	70
7	$NiCl_2$ (1.2), Zn (1.3)	dppf (2.4)	-	DMF	70	13	ND	>95

[a] Determined by HPLC analysis (isolated yield); ND – not detected; NR – no reaction.

3.3 Synthesis of analogues of Bolm's 2,2'-bipyridines

3.3.1 Synthesis of 2-bromopyridyl alcohols

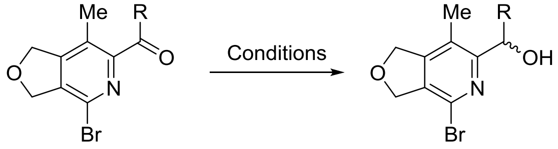
According to the proposed synthesis of Bolm's ligand analogues, the next step after the cyclotrimerization reaction should be asymmetric reduction of a 2-bromopyridyl ketone (Scheme 44).

Although the reduction of 2-bromopyridyl ketone **244bb** using sodium borohydride gave racemic alcohol **286** in the quantitative yield (Entry 1, Table 37), attempts to carry out enantioselective reduction failed. A reaction catalyzed by RuCl[(*S*,*S*)-Tsdpen](*p*-cymene), which was used by Kobayashi *et al.* during the synthesis of (*R*,*R*)-**8**,[11] did not proceed at all at either at 25 or at 50 °C (Entries 2 and 3). The second procedure using a chiral borane (used for synthesis of (*S*,*S*)-**8** by Bolm *et al.*) ended up with the same result (Entries 4 and 5).[19] Disappointingly, reduction with the Corey–Bakshi–Shibata catalyst furnished the desired alcohol **286** in low yield and poor enantiopurity (Entry 6). Reductions of 2-bromopyridyl ketone **244bc** proceeded with the same results – reduction with sodium borohydride gave racemic alcohol **287** (Entry 7), while enantioselective reductions did not proceed and only the starting material was recovered from the reaction mixture (Entries 8 and 9).

I assumed that the steric hindrance caused by the methyl group in position 5 of the pyridine ring prevented the access of a sterically more hindered Ru-catalyst or a chiral organoborane to the carbonyl group, while a sterically less demanding sodium borohydride is small enough to enable the successful reduction.

Bromopyridyl ketones **292** and **293** (without any substituent in position 5) were prepared from diynes **278** and **231f** by cyclotrimerization with pivaloyl cyanide **179b** followed by desilylation (Scheme 63). The cyclotrimerization of diynes **278** and **231f** with pivaloyl cyanide **179b** catalyzed by Cp*RuCl(cod) gave cyclotrimerization products **288** and **290**, **289** and **291** in the combined 71% and 72% isolated yields with a high preference for 2-bromopyridines **288** and **289** (56% and 60% yield, respectively). Again, the products of the halogen exchange reaction were detected in the reaction mixtures, but their yields were not determined due to the overlapped signals in ^{1}H-NMR spectra. A fast isolation and desilylation of the products was essential, because of their instability. The low stability could also explain low reproducibility of desilylation of **289** using TBAF. Therefore I used an alternative method for the carbon–silicon bond cleavage using potassium carbonate, which furnished bromopyridine ketone **293** in 93% yield. On the other hand, 2-bromopyridine **288** was desilylated without any problem using the classical TBAF procedure in 94% yield.

Table 37. Reduction of 2-bromopyridyl ketones **244bb** and **244bc** to 2-bromopyridyl alcohols **286** and **287**.



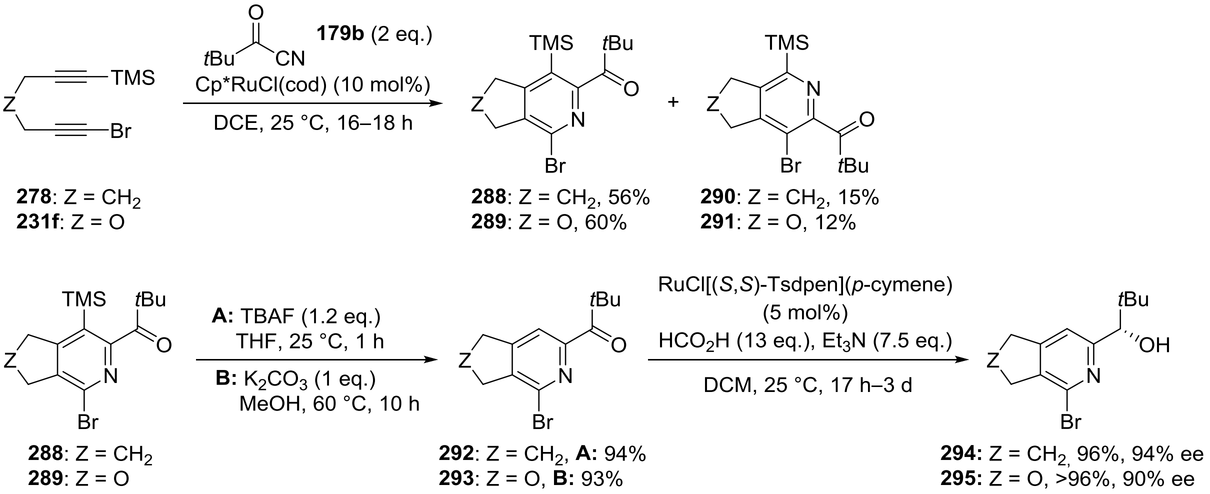
244bb: R = *t*Bu
244bc: R = Ph

286: R = *t*Bu
287: R = Ph

Entry	R	Catalyst (mol%)[a]	Reductant (eq.)	Solvent	*T* (°C)	*t* (h)	Yield (%)[b]	ee (%)[c]
1	*t*Bu	-	$NaBH_4$ (1.5)	MeOH	25	2	99	*rac*
2	*t*Bu	[Ru] (10)	HCO_2H (13), Et_3N (7.5)	-	25	240	NR	-
3	*t*Bu	[Ru] (10)	HCO_2H (13), Et_3N (7.5)	-	50	40	NR	-
4	*t*Bu	-	(–)-Ipc_2BCl (1.2)	DCM	25	240	NR	-
5	*t*Bu	-	(–)-Ipc_2BCl (1.2)	DCM	50	40	NR	-
6	*t*Bu	CBS (12)	$BH_3 \cdot THF$ (1)	THF	0	18	32	13 (ND)
7	Ph	-	$NaBH_4$ (1.5)	MeOH	25	3	96	*rac*
8	Ph	[Ru] (10)	HCO_2H (13), Et_3N (7.5)	-	50	40	NR	-
9	Ph	-	(–)-Ipc_2BCl (1.2)	DCM	50	40	NR	-

[a] [Ru] – RuCl[(*S*,*S*)-Tsdpen](*p*-cymene); CBS – (*R*)-2-methyl-CBS-oxazaborolidine. [b] NR – no reaction. [c] Determined by HPLC with chiral stationary phase; ND – not determined.

The subsequent enantioselective transfer hydrogenation using a ruthenium catalyst provided chiral alcohols **294** and **295** in excellent yields and enantiopurities (96% yield, 94% ee; 99% yield, 90% ee). If needed, enantiopurity of both alcohols could be increased to >99% ee by recrystallization from chloroform. The (*S*)-configurations of both alcohols were unequivocally confirmed by single crystal X-ray analyses (Figure 22).



Scheme 63. Synthesis of 2-bromopyridines **294** and **295**.

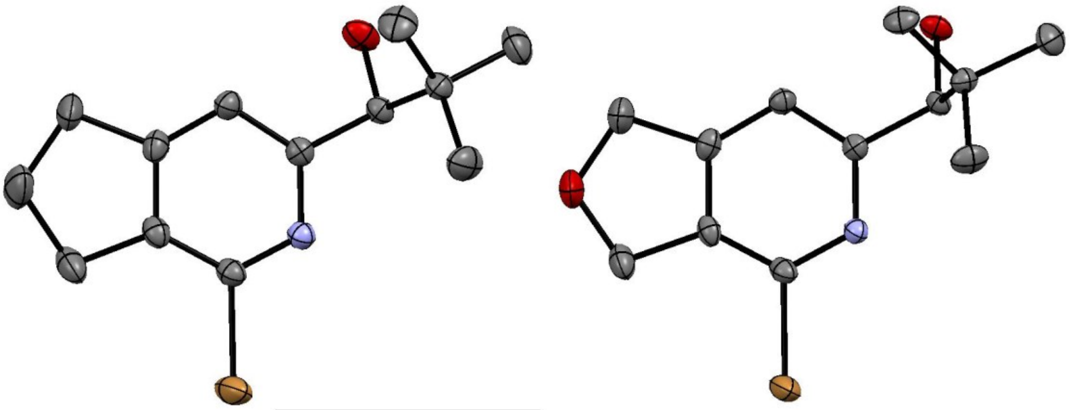
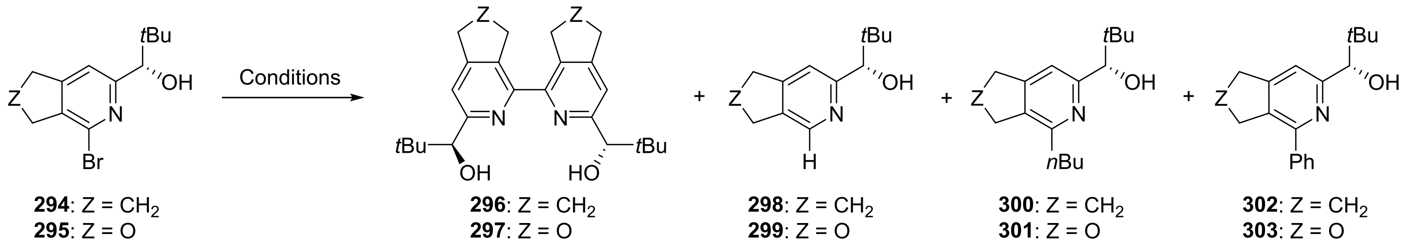


Figure 22. ORTEP drawing of **294** (left) and **295** (right) (grey C, red O, blue N, orange Br). Hydrogen atoms were omitted for clarity.

3.3.2 Reductive dimerization of 2-bromopyridyl alcohols

The crucial step of Bolm’s ligand analogues synthesis turned out to be the reductive dimerization of alcohols **294** and **295**. While the Ni-mediated reaction of alcohol **294** using Ni(II) chloride gave bipyridine **296** in an acceptable HPLC yield of 50%, its complicated isolation resulted again in a partial loss of the product, which was then obtained in low 35% yield (Entry 1, Table 38). In addition, the yield could not be improved by either the second method using Ni-complex or any of the Pd-catalyzed procedures (Entries 2–4). Although alcohol **295** was dimerized using $NiBr_2(PPh_3)_2$ in a good HPLC yield (Entry 7), isolation of diol **297** was not successful. Formation of new types of side products such as **302** and **303**, bearing phenyl groups, was observed in the reactions when triphenylphosphine ligand was present. Although the origin of this compound was not clarified, its formation could be explained by aryl-aryl exchange between the metal center and the phosphine ligand. This phenomenon was reported to take place in various types of metal complexes including palladium and nickel catalysts.[210]

Table 38. Reductive dimerization of 2-bromopyridyl alcohols **294** and **295**.

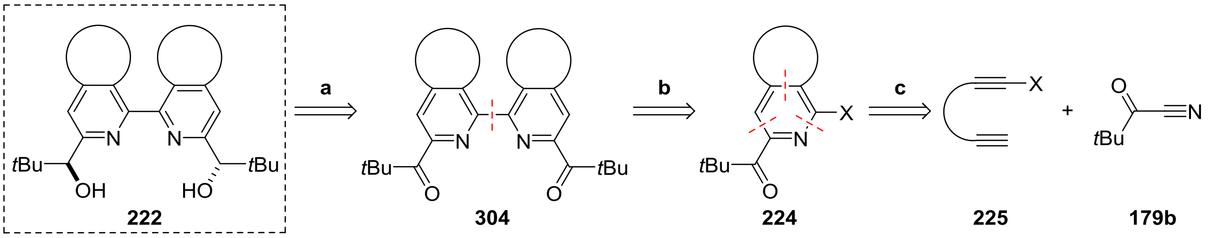


Entry	Z	M-source (eq.)	Salt/Ligand (eq.)	Additive (eq.)	Solvent	*T* (°C)	*t* (h)	Yield (%)[a]			
								296/297	**298/299**	**300/301**	**302/303**
1	CH_2	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	70	15	50 (35)	50	ND	ND
2	CH_2	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	60	48	20	60	ND	20
3	CH_2	$Pd(OAc)_2$ (0.2)	K_2CO_3 (1.5)	*i*PrOH (2)	DMF	100	66	20	20	ND	ND
4	CH_2	$PdCl_2(PhCN)_2$ (0.2)	-	TDAE (2)	DMF	80	120	30	60	ND	ND
5	CH_2	$Pd(PPh_3)_4$ (0.2), *n*Bu_6Sn_2 (0.75)	-	-	PhMe	180 (MW)	4	10	35	35	ND
6	O	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	70	20	20	50	ND	30
7	O	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	60	13	50 (0)	25	ND	25

[a] Determined by HPLC analysis (isolated yield); ND – not detected.

3.3.3 Reductive dimerization of 2-bromopyridyl ketones and reduction of bipyridine diketones

Since dimerization of alcohol **294** gave bipyridine **296** in a low yield and bipyridine **297** was not obtained at all by dimerization of alcohol **295**, I decided to change the approach to analogues of Bolm's ligand and to try to dimerize the 2-bromopyridyl ketone **224** to diketone **304** (Step b, Scheme 64) and to reduce then to diol **222** afterwards (Step a).

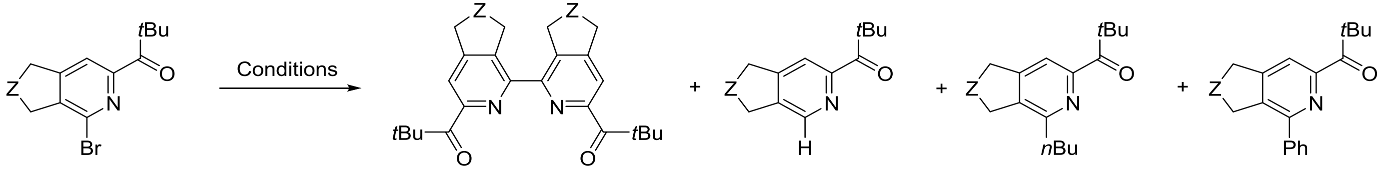


Scheme 64. New proposed synthesis of analogues of Bolm's ligand.

Treatment of ketone **292** with a mixture of $NiCl_2$, Zn and PPh_3 gave bipyridine **305** in 70% HPLC yield (Entry 1, Table 39) and the same reaction starting from ketone **293** proceeded in a slightly lower HPLC yield of 50% (Entry 6). Work-up procedures of the reactions proceeded without any problem and bipyridines **305** and **306** were isolated in 66% and 46% yield, respectively. Other homocoupling methods of **292** gave bipyridine **305** in lower yields (Entries 2–5).

Reduction of diketone **305** gave 45% of racemic diol **296** ((*S*,*S*)-**296** and (*R*,*R*)-**296**) and the same amount of the *meso*-diastereoisomer ((*meso*)-**296**) (Entry 1, Table 40). Enantioselective transfer hydrogenation using a chiral Ru-catalyst gave rise to ketoalcohol **313**, in which only one carbonyl group was reduced (Entry 2). Both a higher load of the catalyst and heating of the reaction mixture to 40 °C increased the yield of **313**, but only traces of the target diol **296** were obtained (Entries 3 and 4). Finally, further increase of the reaction temperature to 60 °C furnished diol **296** with excellent enantioselectivity (97% ee), but in moderate yield of 48% (Entry 5). Reduction of diketone **305** by a chiral organoborane did not give any product and only the starting bipyridine was isolated from the reaction mixture (Entry 6). Surprisingly, even reduction of diketone **306** with sodium borohydride failed (Entry 7). The starting diketone **306** was fully consumed, however, the reduced product **297** could not be isolated from the reaction mixture, even though it was detected as the only product by HPLC-HRMS analysis.

Table 39. Reductive dimerization of 2-bromopyridyl ketones **292** and **293**.



292: Z = CH_2
293: Z = O

305: Z = CH_2
306: Z = O

307: Z = CH_2
308: Z = O

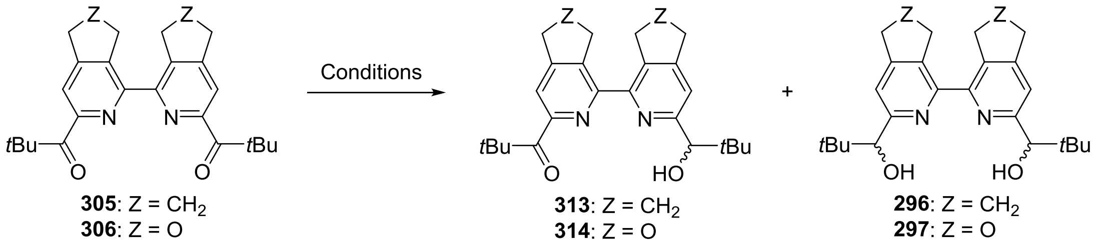
309: Z = CH_2
310: Z = O

311: Z = CH_2
312: Z = O

Entry	Z	M-source (eq.)	Salt/Ligand (eq.)	Additive (eq.)	Solvent	*T* (°C)	*t* (h)	Yield (%)[a]			
								305/306	**307/308**	**309/310**	**311/312**
1	CH_2	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	70	15	70 (66)	30	ND	ND
2	CH_2	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	60	86	30	60	ND	10
3	CH_2	$Pd(OAc)_2$ (0.2)	K_2CO_3 (1.5)	*i*PrOH (2)	DMF	100	120	35	45	ND	ND
4	CH_2	$PdCl_2(PhCN)_2$ (0.2)	-	TDAE (2)	DMF	80	120	50	50	ND	ND
5	CH_2	$Pd(PPh_3)_4$ (0.2), *n*Bu_6Sn_2 (0.75)	-	-	PhMe	180 (MW)	6	20	30	20	20
6	O	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	70	13	50 (46)	20	ND	30

[a] Determined by HPLC analysis (isolated yield); ND – not detected.

Table 40. Reduction of diketone **305** and **306**.



Entry	Z	Catalyst (mol%)[a]	Reductant (eq.)	Solvent	T (°C)	t (h)	Yield (%)[b] **313/314**	Yield (%)[b] **296/297**	ee **296** (%)[c]
1	CH$_2$	-	NaBH$_4$ (4)	MeOH	25	3	ND	90[d]	*rac*
2	CH$_2$	[Ru] (5)	HCO$_2$H (13), Et$_3$N (7.5)	-	25	48	18	ND	-
3	CH$_2$	[Ru] (10)	HCO$_2$H (13), Et$_3$N (7.5)	DCM	25	216	35[e]	Traces	-
4	CH$_2$	[Ru] (10)	HCO$_2$H (13), Et$_3$N (7.5)	DCM	40	216	50[e]	Traces	-
5	CH$_2$	[Ru] (10)	HCO$_2$H (13), Et$_3$N (7.5)	DCM	60	96	37	48	97 (*S*,*S*)
6	CH$_2$	-	(–)-Ipc$_2$BCl (2)	THF	25	120	NR	NR	-
7	O	-	NaBH$_4$ (8)	MeOH	25	3	-	-	-

[a] [Ru] – RuCl[(*S*,*S*)-Tsdpen](*p*-cymene). [b] Isolated yield unless otherwise noted; ND – not detected; NR – no reaction. [c] Determined by HPLC with chiral stationary phase. [d] Combined yield of (*rac*)-**296** (45%) and (*meso*)-**296** (45%). [e] ^{1}H-NMR yield.

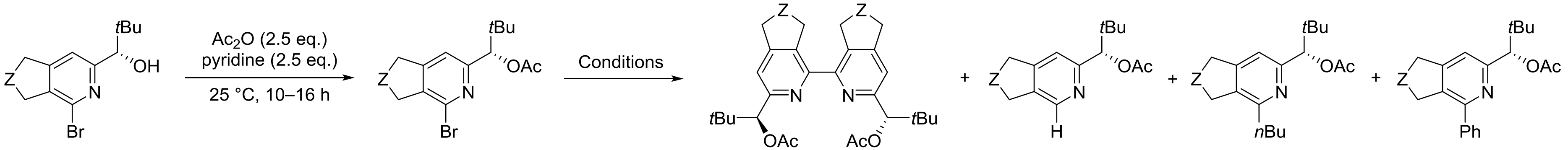
3.3.4 Synthesis *via* protected alcohols

The results of the syntheses of diols **296** and **297** were not satisfying, thus I decided to change the strategy again. Even though authors of the reports dealing with the used dimerization procedures claimed tolerance to free hydroxy groups, the difference between the isolated yields of the dimerization reaction of 2-bromopyridyl alcohols **294** and **295** and the appropriate ketones **292** and **293** hinted the opposite. Therefore I decided to try to prepare analogues of Bolm's ligand **296** and **297** by using reductive dimerization of 2-bromopyridyl alcohols with protected hydroxy groups.

The hydroxyl groups of alcohols **294** and **295** were protected by the acetyl groups using the standard synthetic procedure with acetic anhydride and pyridine providing esters **315** and **316** in quantitative yields (Scheme of Table 41). Although the Pd-catalyzed dimerization methods failed again even with **315** (Entries 3 and 4, Table 41), the Ni-mediated methods gave with acetates **315** and **316** better results (Entries 1, 2, 5, and 6). The one using $NiCl_2$, Zn and PPh_3 gave rise to diacetates **317** and **318** in 70% HPLC yields. They were subsequently isolated in 68% and 62% yield, respectively (Entries 1 and 5). It should be noted that besides the depicted side products (Table 41), I also isolated traces of (*meso*)-**317** and (*meso*)-**318**, which were separated during column chromatography. Removal of *meso*-compounds resulted in the increase of enantiopurity of the desired bipyridine to >99% ee.

Surprisingly, deprotection of diacetates **317** and **318** resulted in different outcomes. Deprotection of **317** under basic conditions proceeded without problems and diol **296** was obtained as an optically pure compound in 96% yield (Scheme 65). The optical purity of the formed bipyridine diol **296** was determined by HPLC analysis with a chiral startionary phase. The (*S*,*S*)-configuration of the diol **296** was confirmed by a single crystal X-ray analysis (Figure 23). Racemic diol **296** was synthesized by reduction of diketone **305** with sodium borohydride (Entry 1, Table 40).

Table 41. Acetylation of 2-bromopyridyl alcohols **294** and **295** and reductive dimerization of 2-bromopyridines **315** and **316**.



294: Z = CH_2
295: Z = O

315: Z = CH_2, >96%
316: Z = O, >96%

317: Z = CH_2
318: Z = O

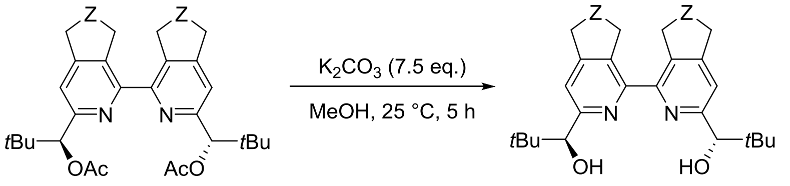
319: Z = CH_2
320: Z = O

321: Z = CH_2
322: Z = O

323: Z = CH_2
324: Z = O

Entry	Z	M-source (eq.)	Salt/Ligand (eq.)	Additive (eq.)	Solvent	*T* (°C)	*t* (h)	Yield (%)[a]			
								317/318	**319/320**	**321/322**	**323/324**
1	CH_2	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	70	14	70 (68)	30	ND	ND
2	CH_2	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	60	48	50	30	ND	20
3	CH_2	$PdCl_2(PhCN)_2$ (0.2)	-	TDAE (2)	DMF	80	48	10	60	ND	ND
4	CH_2	$Pd(PPh_3)_4$ (0.2), *n*Bu_6Sn_2 (0.75)	-	-	PhMe	180 (MW)	4	10	40	20	30
5	O	$NiCl_2$ (1.2), Zn (1.3)	PPh_3 (4.8)	-	DMF	70	13	70 (62)	30	ND	ND
6	O	$NiBr_2(PPh_3)_2$ (1), Zn (5)	*n*Bu_4NI (5)	-	THF	60	15	50	20	ND	30

[a] Determined by HPLC analysis (isolated yield); ND – not detected.



317: Z = CH_2
318: Z = O

296: Z = CH_2, >96%, >99% ee
297: Y = O

Scheme 65. Deacetylation of **317** and **318**.

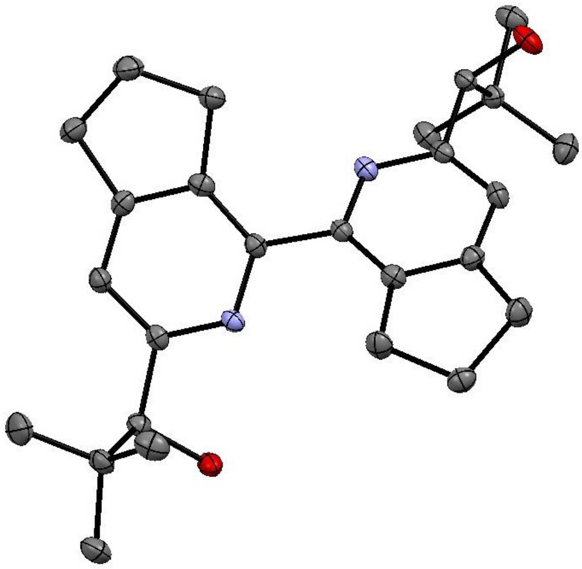


Figure 23. ORTEP drawing of **296** (grey C, red O, blue N). Hydrogen atoms were omitted for clarity.

On the other hand, deprotection of diacetate **318** provided only an insoluble material. The HPLC-HRMS analysis of a highly diluted solution of the product showed only one peak. Its mass value perfectly fitted the calculated mass of the target diol **297**. Therefore I then tried to carefully monitor the course of the deacetylation reaction. The starting diacetate was initially converted to the monodeacetyled product, which was then fully consumed to form the insoluble material. Other deprotection methods using 4Å molecular sieves or NH_4OH provided the same kind of material. A suspension of this material in THF was finally dissolved after addition of the equimolar amount of bismuth(III) triflate, which after slow evaporation of THF provided crystals suitable for a single crystal X-ray analysis. Surprisingly it did not show the expected Bi-complex of diol **297**, but triflate **325** (Figure 24). I assumed that this compound was formed from diol **297** by Lewis acid activation of the five-membered ether ring, which was then opened by the attack of the lone pair of the pyridine nitrogen atom (Scheme 66).

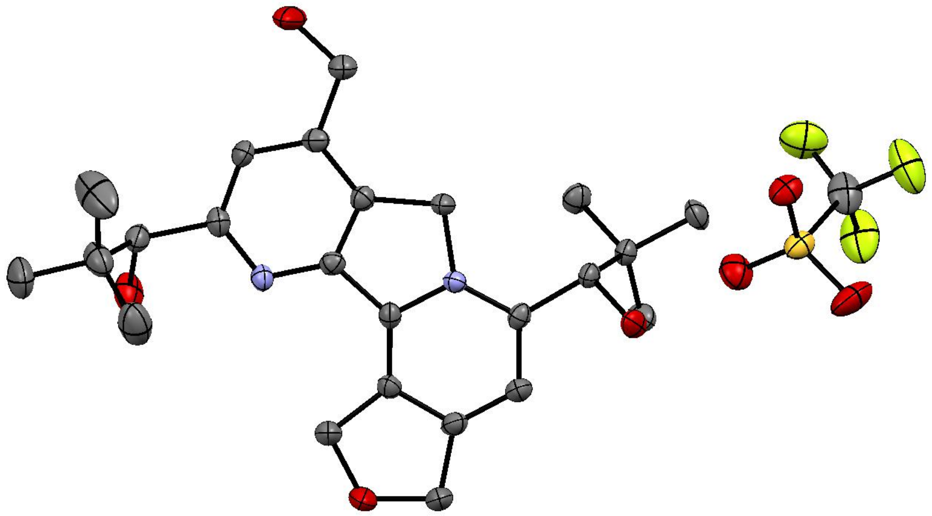
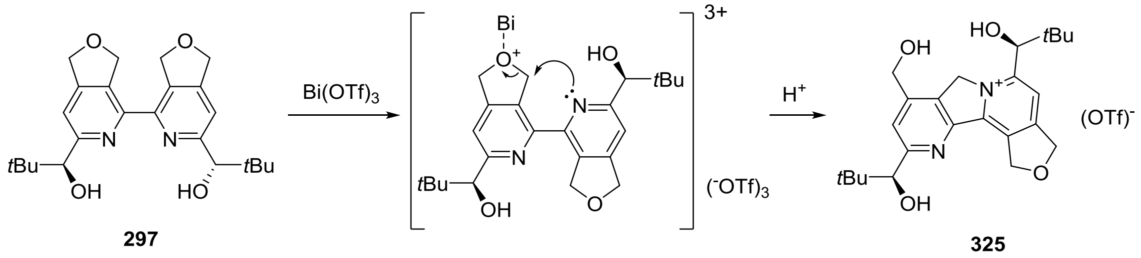
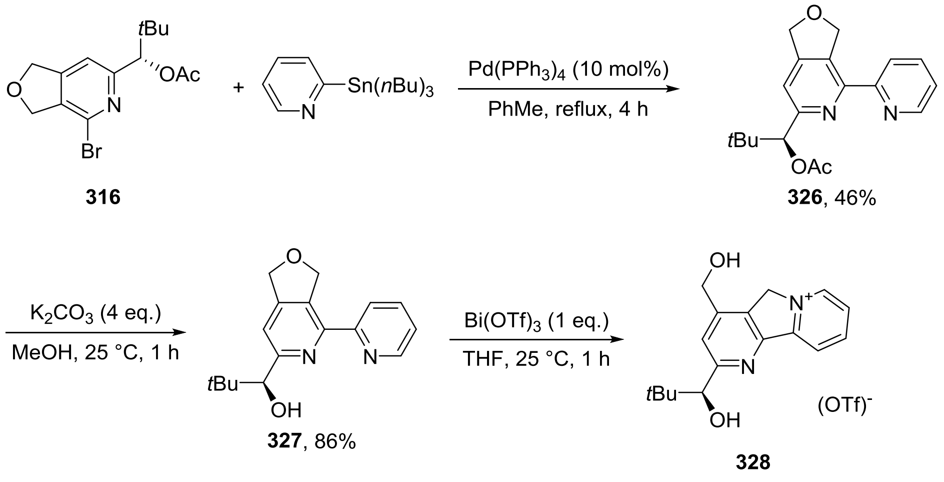


Figure 24. ORTEP drawing of triflate **325** (grey C, red O, blue N, orange S, yellow-green F). Hydrogen and disordered atoms were omitted for clarity.



Scheme 66. Proposed mechanism of the formation of triflate **325**.

In order to figure out, whether the ring-opening reaction was strictly limited to diol **297**, I prepared a structurally similar bipyridine **327** by Pd-catalyzed cross-coupling of 2-bromopyridine **316** with the commercially available 2-(tributylstannyl)pyridine (46% yield, Scheme 67) followed by deprotection of the hydroxy group (86% yield). Treatment of bipyridine **327**, which was well soluble in common organic solvents (DCM, THF, MeCN), with bismuth(III) triflate resulted in a partial formation of triflate **328** (NMR and HPLC-HRMS analyses). Unfortunately, attempts to isolate **328** from the reaction mixture were not successful.



Scheme 67. Synthesis of bipyridine **327** and its LA-mediated decomposition.

Even though I was not able to fully characterize bipyridine **297**, the fact that the same type of a decomposition product was also formed from bipyridine **327**, I assumed that bipyridine **297** was indeed formed by deacetylation of **318**. In view of the aforementioned, bipyridine **297** was also formed by reduction of diketone **306** (Table 40) as well as by reductive dimerization of bromopyridyl alcohols **295** (Table 38). Unfortunately, its properties did not allow its isolation and full characterization. I decided not to pursue further studies in this direction, because of observation that **297** undergoes decomposition to **325** in the presence of Lewis acids.

3.3.5 Rotation barrier experiments and calculations

Then, I carried out NMR studies at different temperatures in collaboration with Martin Dračínský from IOCB in order to determine rotation barrier around C2–C2' bond of bipyridine **296**. Albeit the diastereotopicity of the hydrogen atoms of CH_2 groups resulted in their non-equivalency, no split of these signals due to the restricted rotation was observed in the recorded spectra in the range of -80–100 °C. This observation might have two explanations: (a) the rotation barrier is very low or (b) the resonance frequencies of the signals of two atropoisomers are very similar.

As the NMR method did not give us a simple answer, Martin Dračínský also performed DFT calculations of the energy barrier of the rotation (Figure 25). He also calculated the rotation barrier of 2,2'-dimethylbiphenyl **329**, value of which is known from literature, to verify the computation method ($\Delta G^{\#}$ = 18.1 kcal/mol at 25 °C by Böhm *et al.*[211] and $\Delta G^{\#}$ = 16.7 kcal/mol by our measurement). In addition, we speculated that the energy barriers of rotations around C1–C1' axis in **329** and C2–C2' in **296** could be comparable. The dependence of the relative energy of compounds **329** and **296** on C2–C1–C1'–C2' (**329**) and N–C2–C2'–N' (**296**) torsion angle revealed noticeable difference. While 2,2'-dimethylbiphenyl **329** has two energy peaks (0° and 180°), only one energy maximum can be find in the energy curve of 2,2'-bipyridine **296**, which lies at the point of the periplanar arrangement of the compound (0°). On the other hand, the 2,2'-bipyridine **296** in the antiperiplanar conformation (180°) is reaching the shallow energy minimum. The non-existence of the second maximum in **296** means that the energy needed for the conversion of one potential atropoisomer to another is too low. Hence, this transformation is proceeding spontaneously.

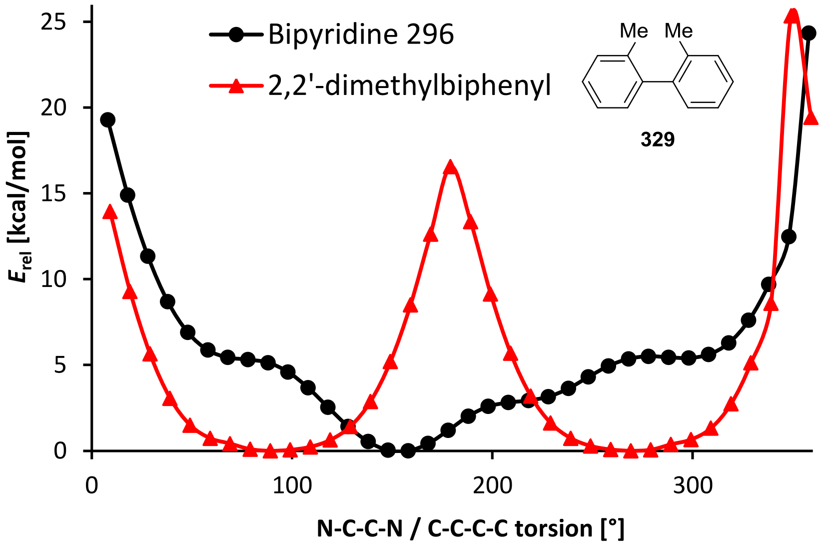


Figure 25. Dependence of relative energy of **329** and **296** on the dihedral angle during the rotation around biphenyl or bipyridine axis.

3.3.6 Metal complexes of bipyridine 296

As the conformation of metal complexes of bipyridine **296** could help me to gain information about the structure of chiral metal pre-catalyst bearing chiral bipyridines, I tried to crystallize compound **296** with various metal salts such as $Bi(OTf)_3$, $FeBr_2$, $Fe(ClO_4)_2$, $[RuCl_2(p\text{-cymene})]_2$, $CoCl_2$, $[CuCl(cod)]_2$, $CuCl_2$, and $Cu(MeCN)_4PF_6$. Although the color changes of the bipyridine solutions with the metal salts indicated formation of the corresponding complexes, their crystals suitable for X-ray analysis were obtained only in handful of cases, namely with copper salts.

As it was discussed in Chapter 0, Bolm's ligand **8** forms with copper(II) salts monomeric tridentate complexes with the square-pyramidal arrangement having both nitrogen and one oxygen atoms chelating one copper metal center. In addition, both protons of free hydroxy groups of **8** were retained. Surprisingly, single crystal X-ray analyses of copper complexes with **296** revealed completely different types of arrangement. It should be pointed out that the copper atoms were in all the complexes in the oxidation state 2^+ despite the fact that two complexes were prepared from copper(I) salts.

The complexation of **296** with $[CuCl(cod)]_2$ resulted in the formation of $[Cu_4\mathbf{296}_2(OH)_2Cl_4]$ complex (Figure 26), which was a symmetrical dimer consisting of four atoms of copper and two molecules of bipyridine **296**. One hydroxy group per molecule was deprotonated. Each copper metal center, which adopted the square pyramidal arrangement, was chelated by one oxygen and one nitrogen atom of one molecule of bipyridine **296** and also by one oxygen atom coming from the second molecule of **296**. In addition, two monomeric parts of the whole complex were connected through two hydroxy anions. The complexation environment of each copper center was completed by one chloride anion.

A similar type of complex was formed with $CuCl_2$. $[Cu_4\mathbf{296}_2Cl_5(MeOH)_4]Cl$ was also composed of four copper atoms and two molecules of bipyridine **296**, which again beared negative charge because one hydroxy group in each bipyridine was deprotonated (Figure 27). This complex was also a symmetric dimer bound together by one Cl^- apex shared by all four copper squared pyramids. The pyridine rings of bipyridine scaffold in both of the complexes – $[Cu_4\mathbf{296}_2(OH)_2Cl_4]$ and $[Cu_4\mathbf{296}_2(OH)_2Cl_4]$ – adopted perpendicular conformation with dihedral angles (N–C2–C2'–N) close to 90°.

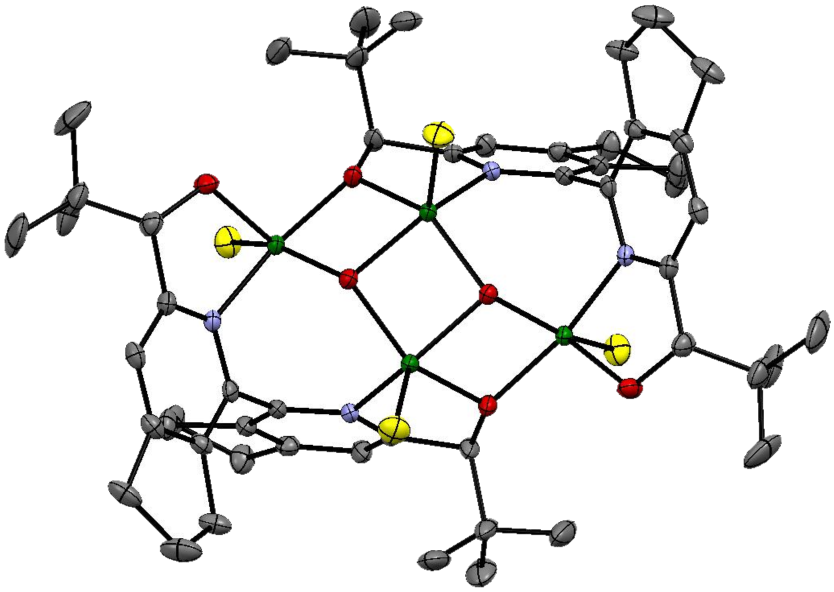


Figure 26. ORTEP drawing of [$Cu_4\mathbf{296}_2(OH)_2Cl_4$] (grey C, red O, blue N, green Cu, yellow Cl). Hydrogen atoms were omitted for clarity.

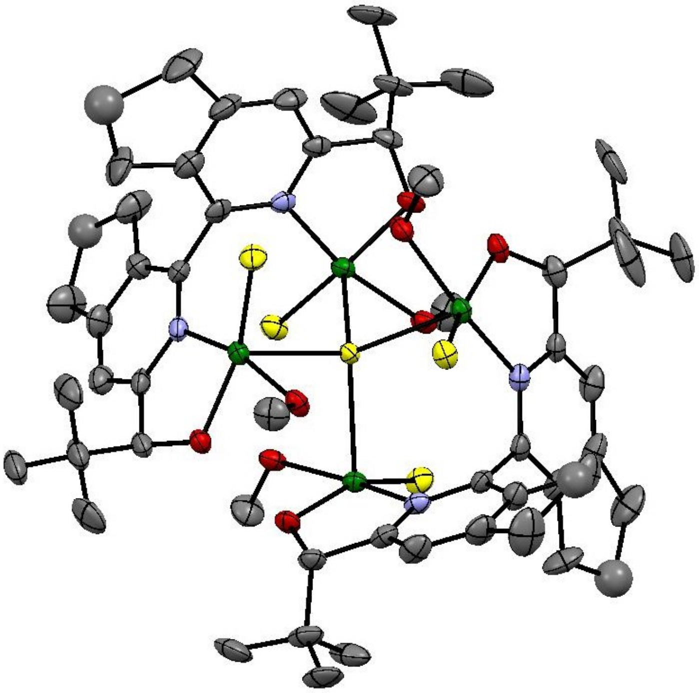


Figure 27. ORTEP drawing of [$Cu_4\mathbf{296}_2Cl_5(MeOH)_4$]Cl (grey C, red O, blue N, green Cu, yellow Cl). Hydrogen atoms and chloride anion were omitted for clarity.

A different type of a complex was formed by complexation of bipyridine **296** with $Cu(MeCN)_4PF_6$. Each of the bipyridine molecules in $[Cu_2$**296**$_2](PF_6)_2$ acted as a pure chelate ligand with all four electron donor atoms (two nitrogens and two oxygens) coordinated to one copper center (Figure 28). One of the hydroxy groups of bipyridine **296** was missing a proton, while the proton of the second OH group served for binding two monomeric structures to each other. As the results of the DFT calculation determined the maximal relative energy of the bipyridine **296** in the periplanar conformation (Figure 25), the tetradentate chelation of one metal center was rather unexpected. However due to the flexibility of bipyridine **296**, the pyridine rings were in $[Cu_2$**296**$_2](PF_6)_2$ twisted by 20° from the planar arrangement in order to lower the steric repulsion of the CH_2 groups. Such a high value of the twist has been found for only 0.4% of bipyridine metal complexes in CSD database.

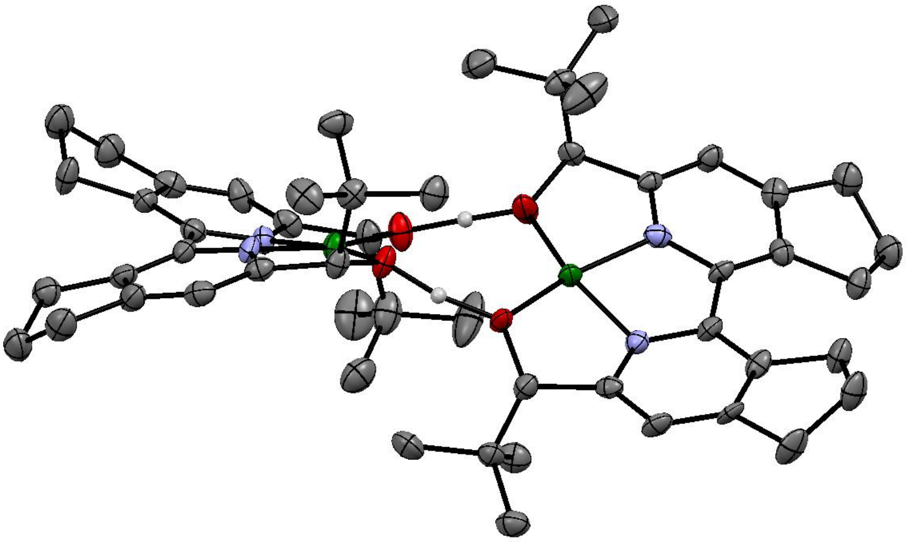


Figure 28. ORTEP drawing of $[Cu_2$**296**$_2](PF_6)_2$ (grey C, red O, blue N, green Cu, yellow Cl). Hydrogen atoms (except two making hydrogen bonding) and PF_6 anions were omitted for clarity.

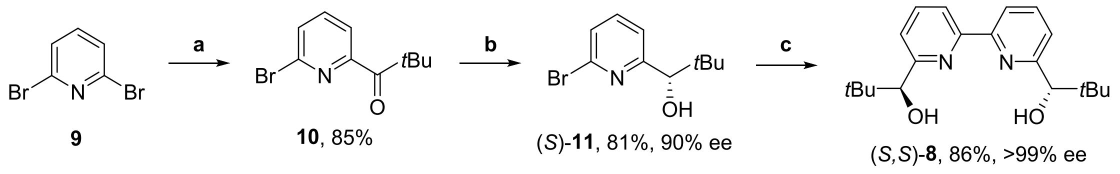
It should be noted that $[Cu_4$**296**$_2Cl_5(MeOH)_4]Cl$ and $[Cu_2$**296**$_2](PF_6)_2$ complexes provided crystals with highly disordered arrangement of chloride and PF_6 anions and solvating methanol molecules in their unit cells, which did not allow to determine exactly the structures of these complexes. On the other hand, the binding fashion of bipyridine **296** to copper center was resolved unambiguously, which was the pivotal goal of this study.

3.4 Application of bipyridines

With new bipyridines in hand, the next step of my study was to examine their reactivity as chiral ligands in various metal-catalyzed reactions. As the structures of my new bipyridine compounds are based on Bolm's ligand **8**, I used them in reactions, in which metal complexes with Bolm's ligand **8** showed interesting catalytic activity, furnishing products with high enantioselectivity (diastereoselectivity). These reactions were Mukaiyama aldol reaction, hydroxymethylation, conjugate addition, C–H activation of indoles, and epoxide ring opening. The goal of this study was to assess the activity of the complexes with the newly prepared bipyridines, to compare it with Bolm's ligand complexes, and to see, how the structural changes influence properties of the respective complexes. Because of that, the procedures for metal-catalyzed enantioselective reactions were used as reported without any optimization. In order to ensure comparability of the results obtained using the new bipyridines with the results using Bolm's ligand, all reactions were carried out in parallel set-ups.

3.4.1 Synthesis of Bolm's ligand

Initially, I synthesized Bolm's ligand according to the protocol reported by Kobayashi *et al.* discussed in Chapter 1.2.1.[11] Monolithiation of 2,3-dibromopyridine **9**, a reaction with pivalonitrile, and the subsequent hydrolysis provided ketone **10** in 85% yield (Scheme 68). Ketone **10** was then reduced by Ru-catalyzed transfer hydrogenation to alcohol (*S*)-**11**, which was obtained in 81% yield and 90% ee. Its enantiopurity was increased to 98% ee by recrystallization of the product from hexane. Reductive dimerization catalyzed by an *in situ* generated Pd(0)-complex furnished Bolm's ligand (*S*,*S*)-**8** in 86% yield as an optically pure compound.

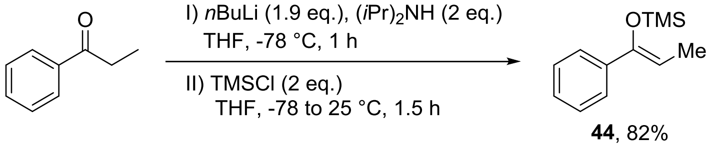


a) I) *n*BuLi (1.1 eq.), Et_2O, -78 °C, 30 min; II) *t*BuCN (1.2 eq.), Et_2O, -78 to 25 °C, 1 h; III) H_2SO_4, H_2O, 60 °C, 2 h
b) RuCl[(*S,S*)-Tsdpen](*p*-cymene) (1 mol%), HCO_2H (4.3 eq.), Et_3N (2.5 eq.), 25 °C, 20 h
c) $PdCl_2(PhCN)_2$ (5 mol%), TDAE (2 eq.), DMF, 50 °C, 28 h

Scheme 68. Synthesis of Bolm's ligand (*S*,*S*)-**8**.

3.4.2 Mukaiyama aldol reaction

Activity of bipyridine complexes with iron(II) salts were first tested in Mukaiyama aldol reaction of benzaldehyde with propiophenone-derived silicon enolate **44** (the reaction reported by Kobayashi *et al.*[51] and Ollevier *et al.*[64]). The (*Z*)-silyl enol ether **44** was prepared selectively by a reaction of propiophenone with freshly prepared LDA (lithium diisopropylamine) followed by the treatment with trimethylsilyl chloride in 82% yield (Scheme 69).



Scheme 69. Preparation of silyl enol ether **44**.

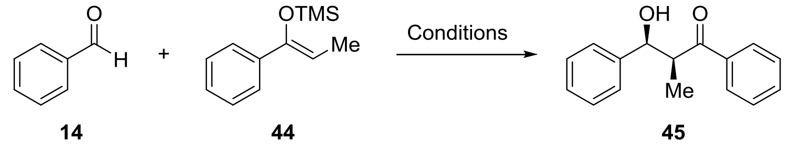
The newly prepared bipyridines **296**, **297**, and **261** and commercially available bipyridine **7** together with iron(II) triflate and pyridine were tested in dimethoxyethane-water mixture at 0 °C (conditions A). A reaction using Fe(II)-**296** complex gave aldol product **45** in the quantitative yield with excellent diastereoselectivity (99/1) and enantioselectivity (92% ee, Entry 3, Table 42), which were comparable results with those obtained using Bolm's ligand (*S*,*S*)-**8** (Entry 2) as well as with the result reported by Kobayashi *et al.* (Entry 1).[51] I also tried to utilize the insoluble material **297** obtained from deacetylation of **318** (Scheme 65) in Mukaiyama aldol reaction. Nevertheless, only racemic aldol **45** was isolated (Entry 4). The racemic aldol **45** was also obtained from reactions catalyzed by iron(II) triflate and BipyMOXes **7** and **261** (Entries 5 and 6), although the formation of the Fe(II)-BipyMOX complexes was observed due to the intensive dark red color of the reaction mixture.

The reaction performed with Fe(ClO$_4$)$_2$, benzoic acid, and bipyridine **296** (conditions B) provided aldol **45** in the quantitative yield with 98/2 dr and 90% ee (Entry 9). Very similar results were also obtained by using Bolm's ligand (*S*,*S*)-**8** by us (Entry 8) as well as by Kobayashi *et al.* (Entry 7).[51] A reaction performed in a micellar system formed by iron(II) dodecyl sulfate and bipyridine (*S*,*S*)-**8** in water (conditions C) proceeded with a slightly lower diastereoselectivity and enantioselectivity (Entry 11) in comparison with the result obtained by Ollevier *et. al.* (Entry 10). I attributed this lower enantioselectivity to difficulties accompanying preparation of Fe(DS)$_2$. Nevertheless, a reaction utilizing bipyridine **296** provided aldol **45** with a higher diastereoselectivity and enantiontioselectivity (Entry 12).

From the beginning of the study, I had troubles to reproduce Mukaiyama aldol reaction with the same level of yield, diastereoselectivity, and enantioselectivity as reported by Kobayashi *et al.* and Ollevier *et al.*[51,64] After a lengthy and time-consuming screening of various reaction conditions, I found that the reaction was very sensitive to quality of all involved reagents. In order to obtain the results displayed in Entries 2–6, 8–9, and 11–12, the reactants and reagents had to be meticulously purified. Namely, benzaldehyde **14** had to be purified by distillation and silyl enol ether **44** by filtration through a silica gel pad prior to use. Interestingly, Kugelrohr distillation of **44** was not sufficient to provide it in the required purity, even though NMR spectra showed the opposite. A newly purchased bottle of iron(II) perchlorate was immediately after opening transferred and kept in a desiccator or a dry box. Purity of commercially available iron(II) triflate was not high enough (>85%), thus it was prepared by a reaction of iron and trifluoromethanesulfonic acid and stored in a desiccator or a dry box as well. Pyridine as well as DME were freshly distilled from CaH_2 and stored under argon in the presence of molecular sieves. Benzoic acid was recrystallized and stored in a desiccator. And finally both solvents (DME and water) were degassed by freeze-pump-thaw method or by bubbling argon through and irradiating by US.

The importance of such careful purification can be demonstrated in reactions with iron(II) salts, which were stored in closed bottles in non-oxygen-free environment for a few days. Using conditions A and Bolm’s ligand (*S*,*S*)-**8**, aldol **45** was obtained in the quantitative ^{1}H-NMR yield, 95/5 dr, and 86% ee. These values were lower by 2% for dr and 7% for ee in comparison with the optimized reaction conditions (Entry 2 *vs*. Entry 13). On the other hand, the drop in selectivities under the same reaction conditions using bipyridine **296** was not so dramatic and aldol **45** was obtained with the same enantioselectivity and only 2% lower dr (Entry 3 *vs*. Entry 14). The difference in enantioselectivity under the optimized and the non-optimized conditions B using Bolm’s ligand (*S*,*S*)-**8** was even higher – 15% ee (Entry 8 *vs*. Entry 15). Gratifyingly, when bipyridine **296** was used, enantioselectivity under the non-optimized conditions B was lower only by 7% ee than enatioselectivity under the optimized conditions (Entry 9 *vs*. Entry 16).

Table 42. Mukaiyama aldol reaction catalyzed by iron(II)-bipyridine complexes.



Conditions:

A: $Fe(OTf)_2$ (3 mol%), pyridine (7.2 mol%), bipyridine (3.6 mol%), DME/H_2O 9/1, 0 °C
B: $Fe(ClO_4)_2$ (3 mol%), $PhCO_2H$ (3.6 mol%), bipyridine (3.6 mol%), DME/H_2O 7/3, 0 °C
C: $Fe(DS)_2$ (5 mol%), $PhCO_2H$ (5 mol%), bipyridine (15 mol%), H_2O, 25 °C

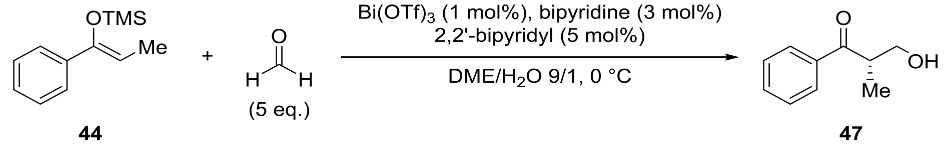
Entry	Conditions	Bipyridine	*t* (h)	Yield[a]	dr (*syn*/*anti*)[b]	ee (*syn*) (%)[c]
1[51]	A	(*S*,*S*)-**8**	24	90	97/3	91
2	A	(*S*,*S*)-**8**	40	>96[d]	97/3	93
3	A	**296**	40	>96	99/1	92
4	A	**297**	40	80	91/9	*rac*
5	A	**7**	40	90	90/10	*rac*
6	A	**261**	40	87	91/9	*rac*
7[51]	B	(*S*,*S*)-**8**	24	85	97/3	88
8	B	(*S*,*S*)-**8**	40	95[d]	97/3	91
9	B	**296**	40	>96	98/2	90
10[51]	C	(*S*,*S*)-**8**	24	80	91/9	92
11	C	(*S*,*S*)-**8**	40	88[d]	88/12	84
12	C	**296**	40	87	93/7	88
13	A[e]	(*S*,*S*)-**8**	37	>96[d]	95/5	86
14	A[e]	**296**	37	96	97/3	92
15	B[e]	(*S*,*S*)-**8**	37	>96[d]	96/4	76
16	B[e]	**296**	37	90	97/3	83

[a] Isolated yield unless otherwise noted. [b] Determined by ^{1}H-NMR. [c] Determined by HPLC with chiral stationary phase. [d] ^{1}H-NMR yield. [e] Non-optimized conditions.

3.4.3 Hydroxymethylation

Applicability of a bipyridine **296** was also examined in Bi(III)-catalyzed hydroxymethylation (Table 43). Reproducibility of the conditions published by Kobayashi *et al.* (Entry 1) was again tested first by using Bolm's ligand (*S*,*S*)-**8**.[26] Starting from same propiophenone-derived silicon enolate **44**, the aldol product **47** was obtained in the quantitative yield and 89% ee when the Bolm's ligand (*S*,*S*)-**8** was used (Entry 2). Application of bipyridine **296** resulted in the formation of aldol **47** in the quantitative yield and 86% ee (Entry 3).

Table 43. Hydroxymethylation catalyzed by Bi(III)-bipyridine complexes.

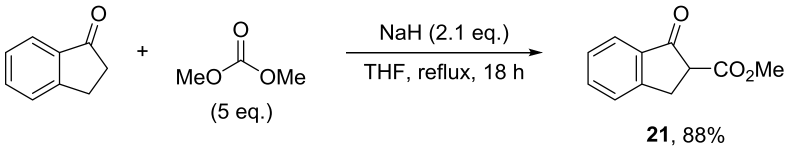


Entry	Bipyridine	*t* (h)	Yield (%)[a]	ee (%)[b]
1[26]	(*S*,*S*)-**8**	21	93	91
2	(*S*,*S*)-**8**	22	>96	89
3	**296**	22	>96	86

[a] Isolated yield. [b] Determined by HPLC with chiral stationary phase.

3.4.4 Conjugated addition

As the third application of bipyridines was selected Michael addition of β-keto ester **21** to methyl vinyl ketone (MVK) **22** catalyzed by Sc(III)-bipyridine complexes.[40] The starting β-keto ester **21** was prepared by a reaction of indanone with dimethyl carbonate in 88% yield (Scheme 70). The resulting compound **21** was obtained as 95/5 mixture of its keto/enol form.

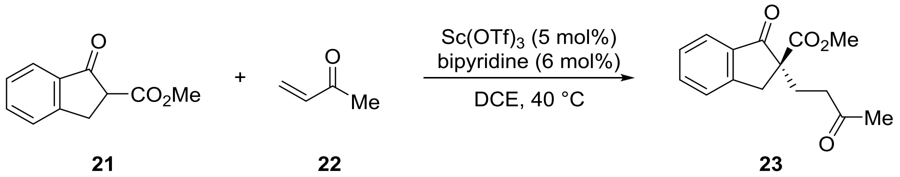


Scheme 70. Preparation of starting β-keto ester **21**.

Michael addition of β-keto ester **21** to MVK **22** catalyzed by Sc(III)-bipyridine **296** complex under conditions reported by Kobayashi *et al.* with Bolm's ligand (Entry 1, Table 44) furnished adduct **23** in the quantitative yield and 81% ee (Entry 3). A reaction catalyzed by Sc(III)-(*S*,*S*)-**8** provided adduct **23** in 94% ^{1}H-NMR yield and 90% ee (Entry 2). On the other hand, a complex with BipyMOX **7** provided ester **23** in a moderate yield and poor ee (Entry 4), and a complex with BipyMOX **261** brought about formation of ester **23** in the quantitative yield, but as racemate (Entry 5).

Enantioselectivity of the reaction catalyzed by Sc(III)-**8** complex also depended on quality of the reagents. Without pre-drying of Sc(OTf)$_3$ and distillation of MVK prior to use, enantioselectivity of the reaction decreased to 67% ee (24% ee drop, Entry 2 *vs.* Entry 6). Delightfully, enantioselectivity of the reaction catalyzed by Sc-**296** complex was retained (Entry 3 *vs.* Entry 7), which illustrated the ligand's robustness. It could be explained by formation of stronger coordination bonds between metal center and bipyridine **296**, which could be caused by presence of electron-donating substituents on the pyridine rings of bipyridine **296**.

Table 44. Michael addition catalyzed by Sc(III)- bipyridine complexes.



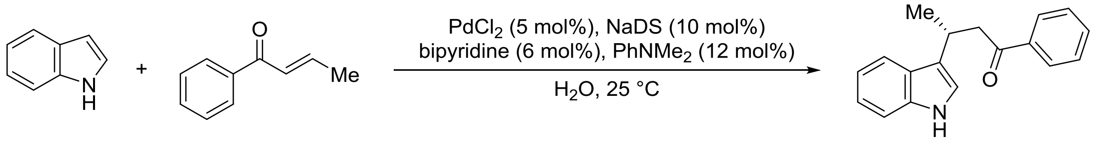
Entry	Bipyridine	*t* (h)	Yield (%)[a]	ee (%)[b]
1[40]	(*S*,*S*)-**8**	50	94	92
2	(*S*,*S*)-**8**	14	94[c]	90
3	**296**	14	>96	81
4	**7**	138	48	14
5	**261**	15	>96	*rac*
6[d]	(*S*,*S*)-**8**	15	>96	67
7[d]	**296**	15	>96	81

[a] Isolated yield unless otherwise noted. [b] Determined by HPLC with chiral stationary phase. [c] ^{1}H-NMR yield. [d] Non-optimal conditions.

3.4.5 C–H activation of indole

Bipyridines **296** and **261** were also tested in a Pd-complex catalyzed C–H activation of indole (Table 45). Although the results obtained by Kobayashi *et al.* with Bolm's ligand (*S*,*S*)-**8** were reproduced without any problem (Entries 1 and 2), a significant loss of enantioselectivity was observed in the reaction catalyzed by Pd-**296** complex (Entry 3). In addition, even after a prolonged reaction time, the starting material was not fully consumed and the substituted indole **51** was formed only in 69% yield. Reaction using BipyMOX **261** gave racemic indole derivative **51** in poor yield (Entry 4).

Table 45. C–H activation of indole catalyzed by Pd-bipyridine complexes.

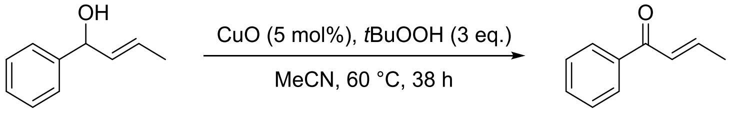


42 **50** **51**

Entry	Bipyridine	*t* (h)	Yield (%)[a]	ee (%)[b]
1[69]	(*S*,*S*)-**8**	24	79	91
2	(*S*,*S*)-**8**	43	94[c]	89
3	**296**	91	69	72
4	**261**	91	8	*rac*

[a] Isolated yield unless otherwise noted. [b] Determined by HPLC with chiral stationary phase. [c] ^{1}H-NMR yield.

It should be also noted that the starting enone **50** was prepared using a newly developed environmentally friendly oxidation method with *tert*-butyl hydroperoxide (*t*BuOOH) and a catalytic amount of copper(II) oxide (Scheme 71). I also tested its applicability on wide range of secondary alcohols.[†]



330 **50**, 80%

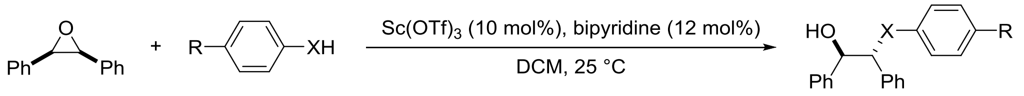
Scheme 71. Preparation of the starting enone **50**.

[†] Preparation of the manuscript dealing with this new environmentally friendly method for oxidation of alcohols to ketones is currently in progress.

3.4.6 Opening ring of *meso*-epoxides

Last but not least, activity of bipyridine **296** was also tested in Sc-catalyzed ring opening of *meso*-epoxides by benzyl alcohol and aniline (Table 46)‡. A Sc-complex with bipyridine **296** showed extraordinary activity in this reaction, which resulted in formation of products **331** and **99** with excellent enantioselectivity of 98% ee in both cases (Entries 3 and 6).

Table 46. Opening of *meso*-epoxides catalyzed by Sc(III)- bipyridine complexes.



38

331: X = OCH_2, R = OMe
99: X = NH, R = H

Entry	X	R	Bipyridine	Yield (%)^{a}	ee (%)^{b}
1	CH_2O	OMe	(*R*,*R*)-**8**	82	97 (*R*,*R*)
2	CH_2O	OMe	(*S*,*S*)-**8**	90^{c}	95 (*S*,*S*)
3	CH_2O	OMe	**296**	82	98 (*S*,*S*)
4	NH	H	(*S*,*S*)-**8**	95	93 (*S*,*S*)
5	NH	H	(*S*,*S*)-**8**	86^{c}	94 (*S*,*S*)
6	NH	H	**296**	82	98 (*S*,*S*)

^{a} Isolated yield unless otherwise noted. ^{b} Determined by HPLC with chiral stationary phase. ^{c} ^{1}H-NMR yield

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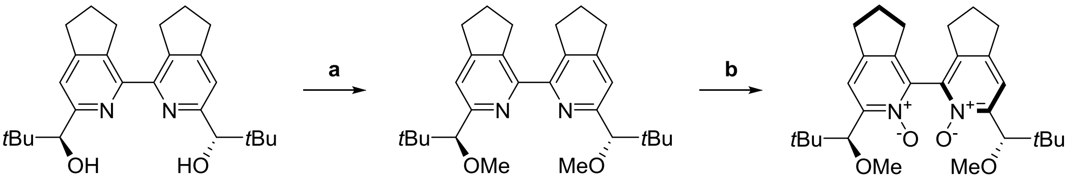
‡ This part was carried out under my supervision by Štefan Malatinec, bachelor student of Kotora's group. As this work was a part of his bachelor project, and as he will continue on the study of this reaction during his master studies, I will not discuss it in detail.

3.5 Synthesis of bipyridine *N*,*N'*-dioxides

DFT calculation of dependence of relative energy of bypyridine **296** on torsion angle of N–C2–C2'–N' clearly showed that periplanar conformation of the two pyridine rings in bipyridine **296** is energetically disnfavored, whereas bipyridine **296** in antiperiplanar conformation is in its energy minimum (Figure 25). Nevertheless, oxidation of bipyridine **296** to bipyridine *N*,*N'*-dioxide should result in an increase of energy of the antiperiplanar conformation, and so in formation of an element of axial chirality. Such axially chiral *N*,*N'*-dioxides were found to be active Lewis base-organocatalysts (Chapter 1.5).

3.5.1 Synthesis *via* reductive dimerization

The simplest way to synthesize bipyridine *N*,*N'*-dioxides is oxidation of the appropriate bipyridines using MCPBA. In order to achieve that, protection of the free hydroxy groups of diol **296** was necessary to avoid their oxidation to ketones. Thus, diol **296** was converted into dimethyl diether **332** by a reaction with methyl iodide in 83% isolated yield (Scheme 72). The subsequent oxidation with MCPBA provided surprisingly a single atropoisomer, which was isolated in 93% yield. The (a*R*) configuration of the formed *N*,*N'*-dioxide **333** was unambiguously determined by a single crystal X-ray analysis (Figure 29). During the attempts to crystallize *N*,*N'*-dioxide (*S*,*S*,a*R*)-**333**, its slow conversion to the opposite atropoisomer was observed. For example, one hour reflux in toluene converted 20% of (*S*,*S*,a*R*)-**333** to (*S*,*S*,a*S*)-**333**. Both atropoisomers were readily separated by a simple column chromatography.



296 **332**, 83% (*S*,*S*,a*R*)-**333**, 93%

a) I) NaH (3 eq.), THF, 25 °C, 30 min; II) MeI (12 eq.), THF, 50 °C, 24 h
b) MCPBA (3 eq.), DCM, 0 to 25 °C, 7 h

Scheme 72. Synthesis of bipyridine *N*,*N'*-dioxide (*S*,*S*,a*R*)-**333**.

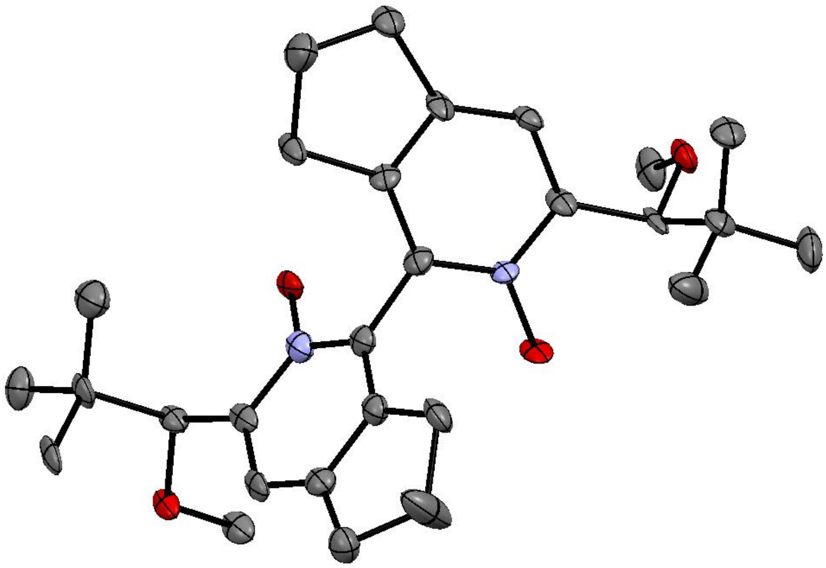
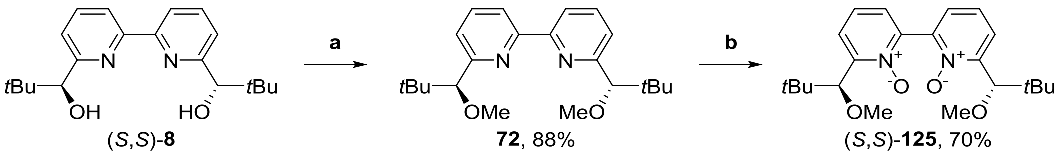


Figure 29. ORTEP drawing of *N*,*N*′-dioxide (*S*,*S*,a*R*)-**333** (grey C, red O, blue N). Hydrogen atoms were omitted for clarity.

N,*N*-dioxide **125** was synthesized by the same reaction sequence. The hydroxy groups of Bolm's ligand (*S*,*S*)-**8** were protected by methylation in 88% yield (Scheme 73). Oxidation using 3 eq. of MCPBA proceeded sluggishly, hence the amount of oxidating agent was increased to 6 eq. to get the *N*,*N*′-dioxide (*S*,*S*)-**125** in a sufficient yield (70%). Because of the lack of substituents in positions 3 and 3' in (*S*,*S*)-**125**, the rotation around the C2–C2' bond is not hindered. As the result, an additional element of axial chirality was not formed.

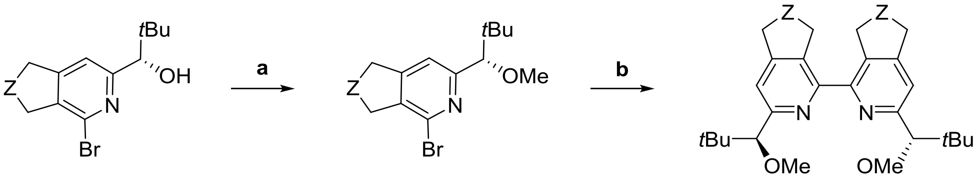


a) I) NaH (3 eq.), THF, 25 °C, 1 h; II) MeI (4 eq.), THF, 25 °C, 16 h
b) MCPBA (6 eq.), DCM, 0 to 25 °C, 21 h

Scheme 73. Synthesis of *N*,*N*′-dioxide (*S*,*S*)-**125**.

As the current reaction sequence for synthesis of bipyridine *N*,*N*′-dioxides **333** consists of two redundant steps (acetylation of 2-bromopyridyl alcohol **294** and deacetylation of bipyridine **317**), which could be potentially omitted, I studied a possibility to protect alcohol **294** as methyl ether prior to the reductive dimerization. In addition, this pathway could have also facilitated synthesis of *N*,*N*′-dioxides **334**, because the appropriate bipyridine diol **297** was difficult to handle owing its insolubility (Chapter 3.3.4).

The hydroxy groups of 2-bromopyridyl alcohols **294** and **295** were methylated under the standard conditions using methyl iodide and the corresponding methyl ethers **335** and **336** were obtained in 87% and the quantitative yield, respectively (Scheme 74). The methyl ethers were afterwards successfully dimerized using Ni-mediated method to bipyridines **332** (68%) and **337** (78%). Because of satisfactory yield, I did not test other dimerization methods.



294: Z = CH_2
295: Z = O

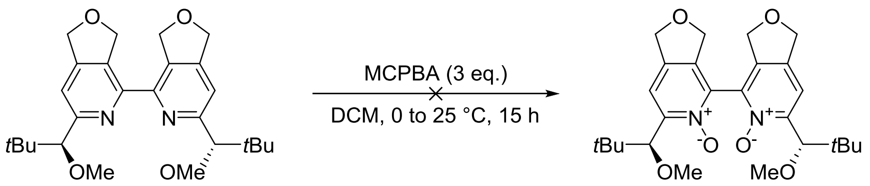
335: Z = CH_2, 87%
336: Z = O, >96%

332: Z = CH_2, 68%
337: Z = O, 78%

a) I) NaH (1.5 eq.), THF, 0 to 25 °C, 30 min; II) MeI (2 eq.), THF, 25 °C, 2 h
b) $NiCl_2$ (1.2 eq.), Zn (1.3 eq.), PPh_3 (4.8 eq.), DMF, 70 °C, 12 h

Scheme 74. Synthesis of bipyridines **332** and **337**.

Although oxidation of bipyridine **332** to *N*,*N'*-dioxide **333** proceeded without any problem (Scheme 72), a reaction starting from bipyridine **337** under the same conditions brought about the formation of a complex mixture of products that could not be separated (Scheme 75). Nevertheless, the HPLC-HRMS analysis showed the presence of several peaks, the mass values corresponded to the mass values of either starting bipyridine **337**, the corresponding bipyridine mono-*N*-oxide, or *N*,*N'*-dioxide **334** increased by 14 or 28 Da. Taking into account these results together with ^{1}H-NMR analysis, I assumed that the formation of a lactone moiety in the five-membered ether ring by oxidation of the benzylic methylene groups took place during the reaction. Disappointingly, other procedures using various hydroperoxides, sodium hypochlorite, percarbonate, Oxone®, methyltrioxorhenium, tetrapropylammonium perruthenate, TEMPO, *tert*-butyl nitrite, or organic aziridines did not improve the selectivity of the reaction towards the formation of bipyridine *N*,*N'*-dioxide **334**.



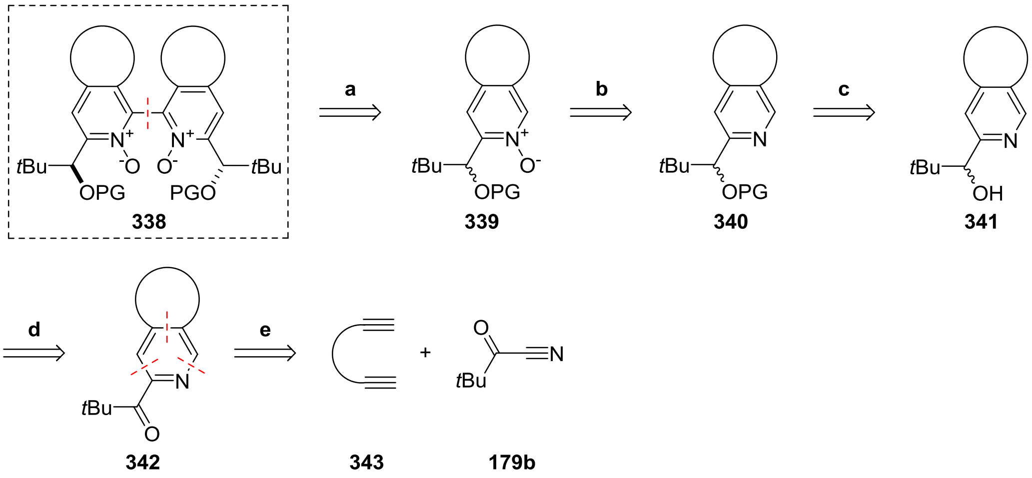
337

334

Scheme 75. An unsuccessful oxidation of **337** to dioxide **334**.

3.5.2 Synthesis *via* oxidative dimerization

As it was discussed in Chapter 1.5.1, there is an alternative approach for the synthesis of bipyridine *N*,*N′*-dioxides *via* oxidative dimerization of pyridine *N*-oxides. Therefore it was envisioned that pyridine *N*-oxide rings of *N*,*N′*-dioxide **338** could be connected by oxidative dimerization reaction (Step a, Scheme 76). The pyridine *N*-oxide could be accessed by oxidation (Step b) and protection (Step c) of chiral pyridyl alcohol **341**. The chiral pyridyl alcohol **341** was envisioned to be formed by enantioselective reduction of pyridyl ketone **342** (Step d), which should be accessible by alkyne-nitrile cocyclotrimerization (Step e).

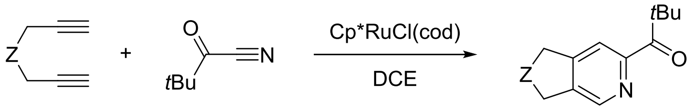


Scheme 76. Retrosynthetic synthesis of bipyridine *N*,*N′*-dioxides **338** *via* oxidative dimerization of pyridine *N*-oxide.

My motivation to explore this approach was based on the following ideas: (a) a shorter reaction pathway together with cocyclotrimerization of a symmetric diyne could increase the overall yield of *N*,*N′*-dioxide, (b) oxidation of one nitrogen atom belonging to the pyridine ring in comparison to two-fold oxidation of the sterically more encumbered bipyridine nitrogen atoms should decrease the amount of side products (namely oxidation of the benzylic methylene groups), and (c) the dimerization step could result in the formation of both atropoisomers of axially chiral *N*,*N′*-dioxides.

Catalytic cocyclotrimerization of unsubstituted diynes (hepta-1,6-diyne **239** and propargyl ether **234**) with pivaloyl cyanide **179b** was the first step of the proposed bipyridine *N*,*N'*-dioxide synthesis. The general cocyclotrimerization of unsubstituted diynes with electron-deficient nitriles was described by e.g. Yamamoto *et al.*,[140] however, the cocyclotrimerization of such diynes with pivaloyl cyanide **179b** have not been reported yet. The Yamamoto's procedure using 5 mol% of Cp*RuCl(cod) catalyst and 1.5 equivalent of nitrile in DCE was thus applied to my substrates, but furnished the desired pyridines **307** and **308** only in moderate ^{1}H-NMR yield of 48% and 58%, respectively (Entries 1 and 2, Table 47). Besides the pyridine products **307** and **308**, I observed also formation of homocyclotrimerized products. The procedure was then briefly optimized using hepta-1,6-diyne **239** as the starting material. The change of heating process together with slow addition of diyne by a syringe-pump resulted in only marginal increase of yield of pyridine **307** (51% ^{1}H-NMR yield, Entry 3). Gratifyingly, the chemoselectivity of the reaction was improved and no product of homocyclotrimerization was observed. Increasing the catalyst load to 10 mol% resulted in a further increase of pyridine **307** yield (77% ^{1}H-NMR yield, 75% isolated yield, Entry 4). The yield was slightly decreased when the reaction temperature was increased to 60 °C (Entry 5). An attempt to improve the yield by increasing the nitrile/diyne ratio was not successful and pyridine **307** was obtained in only 36% ^{1}H-NMR yield (Entry 6). Propargyl ether **234** was then cocyclotrimerized with pivaloyl cyanide **179b** under the optimized reaction conditions. The pyridine **308** was obtained in excellent isolated yield of 89% (Entry 7).

Table 47. Cocyclotrimerization of unsubstituted diyned with pivaloyl cyanide.



239: Z = CH_2
234: Z = O

179b

307: Z = CH_2
308: Z = O

Entry	Z	**179b** (eq.)	[Ru] (mol%)	*T* (°C)	t_1 (h)[a]	t_2 (h)[b]	Yield (%)[c]
1	CH_2	1.5	5	25 to 60	0.25	2.5	48 (44)
2	O	1.5	5	25 to 60	0.25	2.5	58 (58)
3	CH_2	1.5	5	25	10	7	51
4	CH_2	1.5	10	25	10	3	77 (75)
5	CH_2	1.5	10	60	2	12	70
6	CH_2	5	10	25	10	4	36
7	O	1.5	10	25	10	5	91 (89)

[a] Time of the addition of diyne by syringe-pump. [b] Time from the end of addition of diyne until the work-up. [c] ^{1}H-NMR yield (isolated yield).

It was then planned to reduce pyridyl ketones **307** and **308** to pyridyl alcohols **298** and **299** (Table 48). Initially, reduction with sodium borohydride provided racemic mixtures of alcohols **298** and **299** in quantitative yields (Entries 1 and 2). Surprisingly, enantioselective transfer hydrogenation catalyzed by a chiral Ru-catalyst, which was successfully applied in the previous cases, turned out to be unsuitable. A reaction at 25 °C proceeded sluggishly and even after 12 days ketones **307** and **308** were not fully consumed. In addition, analyses of products **298** and **299** by HPLC with a chiral stationary phase showed only moderate enantioselectivity, 55% ee for **298** and 78% ee for **299** (Entries 3 and 4). Neither the use of chiral boranes nor reduction with the Corey–Bakshi–Shibata catalyst provided alcohol **298** (Entries 5–8). I attempted to carry out the transfer hydrogenation of ketone **298** at 40 °C. Gratifyingly, not only the rate and the yield of the reaction (88%), but also its enantioselectivity (74% ee) were improved (Entry 9). The reaction rate and the yield were further improved by refluxing the reaction mixture; however a drop in enantioselectivity to 67% ee was observed (Entry 10). Ketone **308** was thus reduced under the optimized reaction conditions furnishing the alcohol **299** in the quantitative yield and high enantioselectivity of 89% ee (Entry 11). Furthermore, the product recrystallization from hexane yielded enantiomerically pure alcohols **298** and **299** (Entries 9 and 11). It should be noted that special attention needed to be payed to the recrystallization procedure. While racemic alcohols **298** and **299** crystallized from over-concentrated boiling solutions, enantiomerically pure crystals are formed by a slow evaporation of their hexane solutions at 25 °C. The expected (*S*)-configuration of the alcohol **298** was confirmed by a single crystal X-ray analysis (Figure 30).

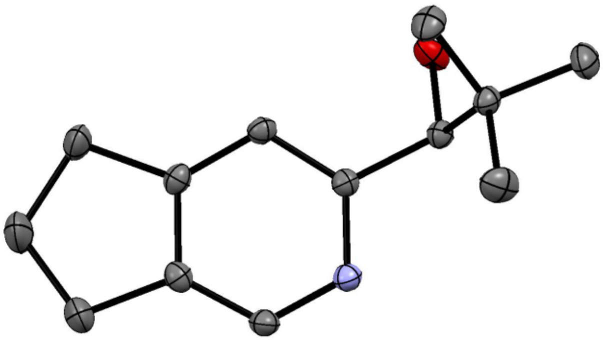
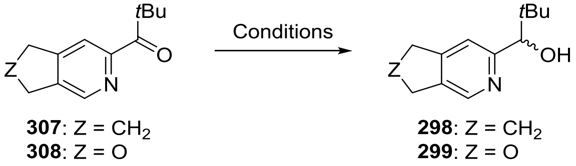


Figure 30. ORTEP drawing of pyridyl alcohol **298** (grey C, red O, blue N). Hydrogen atoms were omitted for clarity.

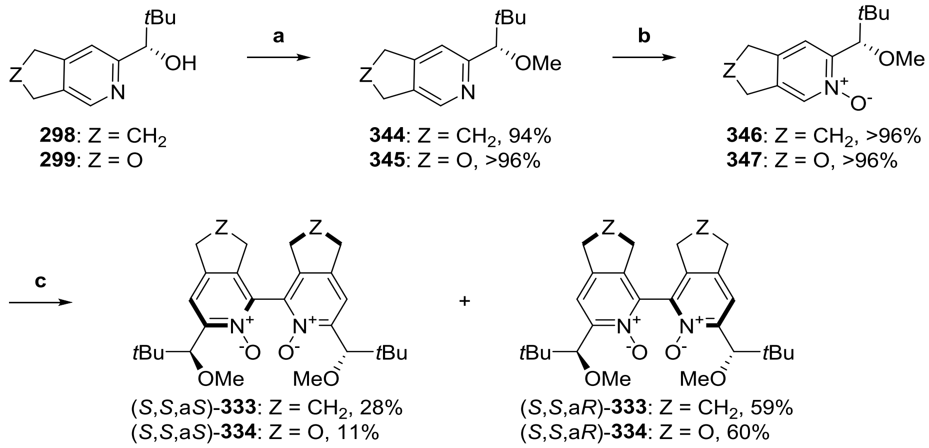
Table 48. Reduction of pyridyl ketone **307** and **308** to pyridyl alcohols **298** and **299**.



Entry	Z	Catalyst (mol%)[a]	Reductant (eq.)	Solvent	*T* (°C)	*t*	Yield (%)[b]	ee (%)[c]
1	CH_2	-	$NaBH_4$ (1.5)	MeOH	25	1 h	>96	*rac*
2	O	-	$NaBH_4$ (1.5)	MeOH	25	2 h	96	*rac*
3	CH_2	[Ru] (5)	HCO_2H (13), Et_3N (7.5)	DCM	25	12 d	47	55 (*S*)
4	O	[Ru] (5)	HCO_2H (13), Et_3N (7.5)	DCM	25	12 d	79	78 (*S*)
5	CH_2	-	(–)-Ipc_2BCl (1.5)	THF	25	3 d	NR	-
6	CH_2	-	(–)-Ipc_2BCl (1.5)	THF	50	3 d	NR	-
7	CH_2	CBS (14)	$BH_3\cdot THF$ (1)	THF	0	5 d	NR	-
8	CH_2	CBS (14)	$BH_3\cdot THF$ (1)	THF	25	5 d	NR	-
9	CH_2	[Ru] (5)	HCO_2H (13), Et_3N (7.5)	DCM	40	6 d	88 (48)	74 (>99) (*S*)
10	CH_2	[Ru] (5)	HCO_2H (13), Et_3N (7.5)	DCM	reflux	14 h	>96	67 (*S*)
11	O	[Ru] (5)	HCO_2H (13), Et_3N (7.5)	DCM	40	44 h	>96 (68)	89 (>99) (*S*)

[a] [Ru] – RuCl[(*S*,*S*)-Tsdpen](*p*-cymene), CBS – (*R*)-2-methyl-CBS-oxazaborolidine. [b] Isolated yield (yield after recrystallization from hexane); NR – no reaction. [c] Determined by HPLC with chiral stationary phase (ee after recrystallization from hexane).

The chiral alcohols **298** and **299** were then protected by methylation using the standard procedure furnishing methyl ethers **344** and **345** in 94% and the quantitative yield, respectively (Scheme 77). Their oxidation using MCPBA proceeded smoothly to give *N*-oxides **346** and **347** in quantitative yields. No oxidation of benzylic methylene groups of **347** was observed. Ensuing oxidative dimerization using freshly prepared LiTMP for lithiation of the carbon atom in position 2 followed by treatment with iodine provided a mixture of both *N*,*N′*-dioxide atropoisomers. (*S*,*S*,a*S*)-**333** and (*S*,*S*,a*R*)-**333** were obtained in a 1/2 ratio and 87% combined isolated yield, while *N*,*N′*-dioxides (*S*,*S*,a*S*)-**334** and (*S*,*S*,a*R*)-**334** were obtained in a 1/6 ratio and 71% combined isolated yield. Enantiomeric purities of all four *N*,*N′*-dioxides were determined to be higher than 99% (HPLC equipped with chiral stationary phases). Racemic *N*,*N′*-dioxides were synthesized by the oxidative dimerization pathway using racemic alcohols **298** and **299** that were obtained by reduction of ketones **307** and **308** with sodium borohydride (Entries 1 and 2, Table 48).



a) I) NaH (1.6 eq.), THF, 0 to 25 °C, 20–30 min; II) MeI (2 eq.), THF, 0 to 25 °C, 1–2 h

b) MCPBA (1.5 q.), DCM, 0 to 25 °C, 1 h

c) I) LiTMP (1.1 eq.), Et_2O, THF, -73 °C, 16 h; II) I_2 (1.1 (**346**) or 2 (**347**) eq.), Et_2O, THF, -73 to 25 °C, 4–5 h

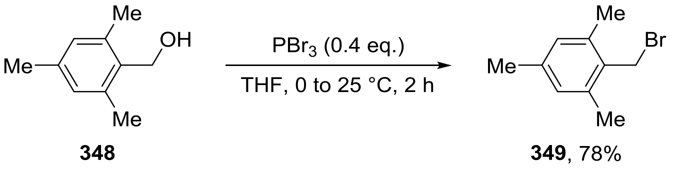
Scheme 77. Synthesis of bipyridine *N*,*N′*-dioxides **333** and **334**.

Interestingly, diastereoselectivity of the last steps of both pathways were contradictory to observation reported by Denmark *et al.*[110] While oxidation of bipyridine **332** to *N*,*N′*-dioxide **333** was in my hands highly diastereoselective and furnished only bipyridine (*S*,*S*,a*R*)-**333** (Scheme 72), Denmark *et al.* described formation of both diastereoisomers in 5/2 ratio starting from a structurally similar bipyridine (see Chapter 1.5.1). In a similar manner, oxidative dimerization of Denmark's pyridine *N*-oxides furnished only one atropoisomer of bipyridine *N*,*N′*-dioxides (Scheme 20, Chapter 1.5.1), while in my case, the same type of reaction starting from *N*-oxides **346** and **347** gave mixtures of both atropoisomers of **333** and **334** in 1/2 and 1/6 ratio, respectively (Scheme 77).

3.5.3 Synthesis of bipyridine *N*,*N′*-dioxide with trimethylbenzyl substituent

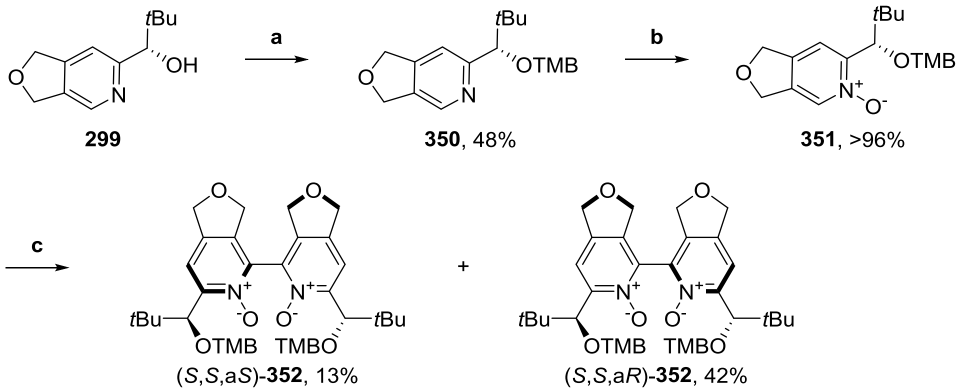
In order to gain excess to structurally modified *N*,*N′*-dioxides, I decided to synthesize a *N*,*N′*-dioxide possessing the 2,4,6-trimethylbenzyl (TMB) substituent instead of the methyl one in the ether part of the dioxide. Rationale for choosing this substituent was based on Denmark's study of aldol reaction catalyzed by bipyridine *N*,*N′*-dioxides, which showed that the presence of sterically hindered TMB group in **144** was enhancing the enantioselectivity of the reaction (Chapter 0).[130]

The benzylation agent, 2,4,6-trimethylbenzyl bromide **349**, was prepared according to the standard procedure starting from the commercially available 2,4,6-trimethylbenzyl alcohol **348** (Scheme 78). The nucleophilic substitution using phosphorus tribromide furnished bromide **349** in 78% isolated yield.



Scheme 78. Synthesis of benzylbromide **349**.

The target *N*,*N′*-dioxides (*S*,*S*,a*S*)-**352** and (*S*,*S*,a*R*)-**352** were synthesized by an oxidative dimerization pathway (Scheme 79). Although the starting enantiomerically pure alcohol **299** was fully consumed and no other products were observed, the benzylated product **350** was isolated in moderate yield of 48%. The subsequent oxidation of pyridine **350** with MCPBA furnished pyridine *N*-oxide **351** in the quantitative yield. Oxidative dimerization provided the target *N*,*N′*-dioxides (*S*,*S*,a*S*)-**352** and (*S*,*S*,a*R*)-**352** in 55% combined isolated yield and 1/3 ratio of (a*S*)/(a*R*)-atropoisomers. It should be noted that none of the reaction steps was optimized.



a) I) NaH (1.5 eq.), NaI (1 eq.), THF, 25 °C, 30 min; II) **349** (2 eq.), THF, 25 °C, 20 h

b) MCPBA (1.5 eq.), DCM, 0 to 25 °C, 2 h

c) I) LiTMP (1.1 eq.), Et_2O, THF, -73 °C, 16 h; II) I_2 (1.1 eq.), Et_2O, THF, -73 to 25 °C, 5 h

Scheme 79. Synthesis of bipyridine *N*,*N'*-dioxides **352**.

3.6 Application of bipyridine *N*,*N′*-dioxides

The last aim of my PhD thesis was to examine the activity of the newly prepared *N*,*N′*-dioxides in Lewis base-catalyzed asymmetric reactions, namely allylation of aldehydes and aldol reaction of ketones.

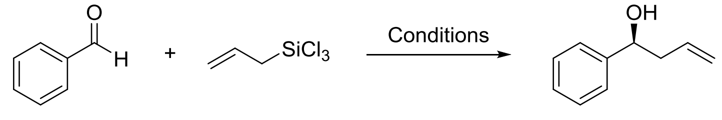
3.6.1 Allylation of benzaldehyde

First, I examined the activity of my new *N*,*N′*-dioxide catalysts in this reaction, as the allylation reactions have become a testing ground for many Lewis base catalysts including bipyridine *N*,*N′*-dioxides. Moreover, to the best of my knowledge, no bipyridine *N*,*N′*-dioxide based on Bolm's bipyridine scaffold (i.e. **125**, **126**, and **143**–**148**) has been tested in this reaction yet.

According to my experience with the study of metal-bipyridine complex-catalyzed reactions, I initially tested the reproducibility of the allylation reaction with dioxide **142** developed in Kotora's group.[128] The allylation of benzaldehyde **14** by allyltrichlorosilane under reaction conditions optimized previously in Kotora's group (0.5 mol% of *N*,*N′*-dioxide, 1.5 eq. of $(i\text{Pr})_2\text{NEt}$, THF, -78 °C) gave allyl alcohol **161** in 93% ^{1}H-NMR yield and 95% ee (Entry 2, Table 49). The results were comparable with those obtained previously in Kotora's group with the same catalyst (Entry 1).[111] Unfortunately, only two *N*,*N′*-dioxides, (*S*,*S*)-**125** and (*S*,*S*,a*R*)-**333**, turned out to be catalytically active under these conditions providing allyl alcohol **161** in low yields and moderate to high enantiopurity (Entries 3 and 5), while reactions catalyzed by *N*,*N′*-dioxides (*S*,*S*,a*S*)-**333**, (*S*,*S*,a*S*)-**334** and (*S*,*S*,a*R*)-**334** did not furnish any product (Entries 4, 6, and 7). Increase of the reaction temperature to -40 °C improved the yields of the reaction, while the enantioselectivity noticeably dropped (Entries 8 and 10). The dioxides (*S*,*S*,a*S*)-**333**, (*S*,*S*,a*S*)-**334** and (*S*,*S*,a*R*)-**334** were catalytically inactive even under these condition (Entries 9, 11, and 12). Increasing the amount of the base did not have a positive influence on the yield (Entries 13–17), and furthermore, if the allyl alcohol **161** was formed, it was obtained with decreased enantiopurity (Entries 13 and 15). Three times higher load of the catalyst turned out to have slightly beneficial effect on yields of the reactions using dioxides (*S*,*S*)-**125** and (*S*,*S*,a*R*)-**333**, while the effect on enantioselectivity was only marginal if any (Entries 18 and 20). The reaction catalyzed by 1.5 mol% of *N*,*N′*-dioxide (*S*,*S*,a*S*)-**333** provided product **161** in 68% ee but only in a trace amount (Entry 19). Even increased catalytic amounts of *N*,*N′*-dioxides (*S*,*S*,a*S*)-**334** and (*S*,*S*,a*R*)-**334** did not result in the formation of any product (Entries 21 and 22). The change of solvent from tetrahydrofurane to acetonitrile markedly increased the yields of the reaction to up to 96% furnishing the product in all cases (Entries 23–27). Nevertheless, the enantioselectivities reached only moderate levels (33–54% ee). The change of solvent to dichloromethane resulted in the formation of the product in the best ee (82%) so far, using (*S*,*S*)-**125** (Entry 28). A reasonable enantioselectivity (72% ee) was also observed when *N*,*N'*-dioxide (*S*,*S*,a*R*)-**334** was used, but the yield of the reaction was low (27%, Entry 32). On the other hand, *N*,*N'*-dioxides (*S*,*S*,a*S*)-**333** and (*S*,*S*,a*S*)-**334** were again inactive (Entries 29 and 31) and *N*,*N'*-dioxide (*S*,*S*,a*R*)-**333** furnished the product in high yield but only in moderate ee (77%, 46% ee, Entry 30). An increased amount of amine in the reaction in DCM resulted in a drop of the yield, while a higher load of catalyst did not affect the reaction almost at all (Entries 33 and 34).

It can be generally stated that the absolute stereochemistry of the prepared alcohol was independent on the configuration of the axis of chirality and the (*S*)-alcohol **161** was obtained in all cases. Although the yield as well as enantioselectivity of the reaction was highly influenced by the used solvents, their electrophilicity did not have any effect on configuration of the obtained allylic alcohols (as was observed in Kotora's group in the previous studies). The best results of the allylation reaction under all reaction conditions were observed using *N*,*N'*-dioxide (*S*,*S*)-**125** that did not possess the element of axial chirality. Regarding the axially chiral *N*,*N'*-dioxides (*S*,*S*,a*S*)-**333**, (*S*,*S*,a*R*)-**333**, (*S*,*S*,a*S*)-**334** and (*S*,*S*,a*R*)-**334**, compounds bearing all carbon five-membered rings ((*S*,*S*,a*S*)-**333** and (*S*,*S*,a*R*)-**333**) were mostly providing allylic alcohol **161** in higher yield but lower enantioselectivity in comparison with dioxides (*S*,*S*,a*S*)-**334** and (*S*,*S*,a*R*)-**334**, possessing the oxygen atom in the five-membered rings. In general, (a*R*)-atropoisomers such as (*S*,*S*,a*R*)-**333** and (*S*,*S*,a*R*)-**334** were more catalytically active and provided allylation products in higher yields, whereas the use of (a*S*)-atropoisomers resulted in higher enantiopurity of the products.

Table 49. Allylation of benzaldehyde catalyzed by bipyridine *N*,*N'*-dioxides.



14 **161**

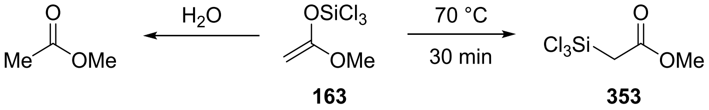
Entry	*N*,*N'*-dioxide	mol%	(*i*Pr)$_2$NEt (eq.)	Solvent	*T* (°C)	*t* (h)	Yield (%)[a]	ee (%)[b]
1[111]	**142**	0.5	1.5	THF	-78	2	97	94
2	**142**	0.5	1.5	THF	-78	4	93	95
3	(*S*,*S*)-**125**	0.5	1.5	THF	-78	13	17	69
4	(*S*,*S*,a*S*)-**333**	0.5	1.5	THF	-78	13	NR	-
5	(*S*,*S*,a*R*)-**333**	0.5	1.5	THF	-78	13	14	48
6	(*S*,*S*,a*S*)-**334**	0.5	1.5	THF	-78	13	NR	-
7	(*S*,*S*,a*R*)-**334**	0.5	1.5	THF	-78	13	NR	-
8	(*S*,*S*)-**125**	0.5	1.5	THF	-40	13	40	21
9	(*S*,*S*,a*S*)-**333**	0.5	1.5	THF	-40	13	NR	-
10	(*S*,*S*,a*R*)-**333**	0.5	1.5	THF	-40	13	57	10
11	(*S*,*S*,a*S*)-**334**	0.5	1.5	THF	-40	13	NR	-
12	(*S*,*S*,a*R*)-**334**	0.5	1.5	THF	-40	13	NR	-
13	(*S*,*S*)-**125**	0.5	5	THF	-78	15.5	18	47
14	(*S*,*S*,a*S*)-**333**	0.5	5	THF	-78	15.5	NR	-
15	(*S*,*S*,a*R*)-**333**	0.5	5	THF	-78	15.5	10	43
16	(*S*,*S*,a*S*)-**334**	0.5	5	THF	-78	15.5	NR	-
17	(*S*,*S*,a*R*)-**334**	0.5	5	THF	-78	15.5	NR	-
18	(*S*,*S*)-**125**	1.5	1.5	THF	-78	12	27	70
19	(*S*,*S*,a*S*)-**333**	1.5	1.5	THF	-78	12	6	68
20	(*S*,*S*,a*R*)-**333**	1.5	1.5	THF	-78	12	42	49
21	(*S*,*S*,a*S*)-**334**	1.5	1.5	THF	-78	12	NR	-
22	(*S*,*S*,a*R*)-**334**	1.5	1.5	THF	-78	12	NR	-
23	(*S*,*S*)-**125**	0.5	1.5	MeCN	-40	13.5	93	54
24	(*S*,*S*,a*S*)-**333**	0.5	1.5	MeCN	-40	13.5	11	40
25	(*S*,*S*,a*R*)-**333**	0.5	1.5	MeCN	-40	13.5	96	33
26	(*S*,*S*,a*S*)-**334**	0.5	1.5	MeCN	-40	13.5	39	51
27	(*S*,*S*,a*R*)-**334**	0.5	1.5	MeCN	-40	13.5	93	45
28	(*S*,*S*)-**125**	0.5	1.5	DCM	-78	15.5	76	82
29	(*S*,*S*,a*S*)-**333**	0.5	1.5	DCM	-78	15.5	NR	-
30	(*S*,*S*,a*R*)-**333**	0.5	1.5	DCM	-78	15.5	77	46
31	(*S*,*S*,a*S*)-**334**	0.5	1.5	DCM	-78	15.5	NR	-
32	(*S*,*S*,a*R*)-**334**	0.5	1.5	DCM	-78	15.5	27	72
33	(*S*,*S*)-**125**	0.5	5	DCM	-78	17	40	83
34	(*S*,*S*)-**125**	1.5	1.5	DCM	-78	17	73	81

[a] ^{1}H-NMR yield; NR – no reaction. [b] Determined by HPLC with chiral stationary phase.

3.6.2 Aldol reaction

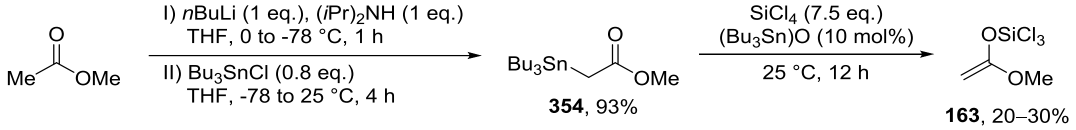
The catalytic activity of new *N*,*N'*-dioxides was also examined in aldol reaction of ketone with trichlorosilyl ketene acetal. This reaction was chosen because of two reasons: (a) the best results so far have been obtained by Denmark *et al.*, who used structurally similar *N*,*N'*-dioxides to our catalysts and (b) the best achieved enantioselectivity reached 87% ee. Hence, there is still enough room for improvement.[130]

Trichlorosilyl ketene acetals are highly reactive compounds that instantaneously undergo hydrolytic decomposition in the presence of water. In addition, they easily thermally isomerize to their *C*-silyl isomers, e.g. *O*-silyl acetal **163** derived from methyl acetate fully isomerize to *C*-trichlorosilyl acetate **353** at 70 °C within 30 minutes (Scheme 80).[130,212,213]



Scheme 80. Instability of trichlorosilyl ketene acetal **163**.

The preparation of acetal **163** was based on a two-step procedure starting from methyl acetate.[130] Methyl acetate was in the first step treated with freshly prepared LDA followed by a reaction with tributyltin chloride providing *C*-tributyltin acetate **354** in 93% yield (Scheme 81). In the second step, the *C*-tributyltin acetate **354** reacted with an excess of tetrachlorosilane in the presence of a catalytic amount of tributyltin oxide providing the desired trichlorosilyl acetate **163**. Because it was found that acetal **163** is labile at higher temperature and upon the exposure to tin compounds, the volatile compounds ($SiCl_4$ and product **163**) were rapidly distilled off from the reaction mixture at the lowest possible temperature under reduced pressure to the receiving flask pre-cooled to -78 °C and connected to a dry-ice condenser. Then an excess of $SiCl_4$ was removed by the second distillation under reduced pressure. Although I observed a full conversion of tributyltin acetate **354** to product **163**, its handling and purification turned out to be very problematic and acetate **163** was lost during the first attempts of its isolation. In addition, the reported boiling point (25 °C, 6.7 mbar) seemed to be in my hands higher and the mixture needed to be heated up to at least 50 °C to initiate the distillation of **163**, even though the pressure in the apparatus was as low as 2–5 mbar. The purity of the formed trichlorosilyl ketene acetal **163** was determined by the amount of the created aldol product by the reaction of **163** with the excess of benzaldehyde (30–48%). Despite several attempts, it was not possible to obtain the trichlorosilyl ketene acetal **163** in higher than 30% yield.



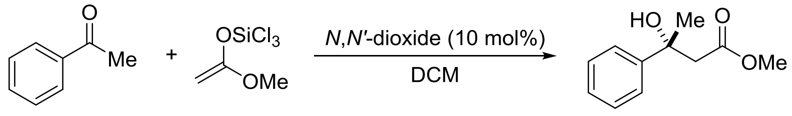
Scheme 81. Preparation of trichlorosilyl ketene acetal **163**.

The trichlorosilyl ketene acetal **163** was then subjected to reactions with acetophenone catalyzed by bipyridine *N*,*N'*-dioxides under different conditions. First, the reproducibility of the reported results of the reaction was demonstrated by the reaction with *N*,*N'*-dioxide **125**. The chiral alcohol **164** was obtained in the same yield and with a slightly higher enantioselectivity than reported in the literature (Entries 1 and 2, Table 50). The reported reaction conditions (10 mol% of *N*,*N'*-dioxide, DCM, -20 °C) were then applied to reactions using newly prepared *N*,*N'*-dioxides without any further optimization.

The use of (*S*,*S*,a*S*)-**333** gave the alcohol **164** in almost the same yield and enantioselectivity (93%, 60% ee, Entry 3) as (*S*,*S*)-**125** (92%, 61% ee, Entry 2) but with the opposite configuration on the center of chirality ((*S*)-alcohol with (*S*,*S*,a*S*)-**333** *vs.* (*R*)-alcohol with (*S*,*S*)-**125**). On the other hand, the reaction catalyzed by the opposite atropoisomer (*S*,*S*,a*R*)-**333** furnished the opposite enantiomer ((*R*)-alcohol) of ester **164**, but with only poor enantioselectivity (87%, 15% ee, Entry 4). Both *N*,*N'*-dioxides (*S*,*S*,a*R*)-**334** and (*S*,*S*,a*S*)-**334**, possessing oxygen atom in the five-membered ring provided (*R*)-alcohol **164** in quantitative yields and 57% and 78% ee, respectively (Entries 5 and 6). The use of *N*,*N'*-dioxides (*S*,*S*,a*S*)-**352** and (*S*,*S*,a*R*)-**352** bearing TMB substituents provided alcohol **164** in moderate yields and 24% and 70% ee (Entries 7 and 8). Then I decided to examine the catalytic activity of *N*,*N'*-dioxides **142** and *ent*-**141**, which were developed in Kotora's group and provided the best results in allylation reaction,[128] however, they have never been tested as catalysts for aldol reaction. Catalysis by *N*,*N'*-dioxide **142** provided (*S*)-alcohol **164** in 86% yield and 40% ee, while the use of *ent*-**141** gave rise to (*R*)-alcohol **164** in 93% yield and 65% ee (Entries 9 and 10). Further lowering of the reaction temperature did not result in any improvement of enantioselectivity (Entries 11 and 12). Finally, the change of the solvent from DCM to THF resulted in considerable decrease of enantioselectivity of the reaction (Entry 13).

It should be noted that reactions presented in Entries 7, 8, and 13 were performed with different batch of trichlorosilyl ketene acetal **163**. Although the purity of the starting material was determined as in the previous cases and its amount was accordingly recalculated, the decreased yields of all reactions are indicating probable loss of compound **163** by its careless handling, which could have resulted in its decomposition. Nevertheless, I truly believe that the purity of the starting acetal **163** is not influencing the enantioselectivity of the asymmetric reaction.

Table 50. Aldol reaction catalyzed by bipyridine *N,N′*-dioxides.



162 **163** **164**

Entry	*N,N′*-dioxide	*T* (°C)	*t* (h)	Yield (%)[a]	ee (%)[b]
1[130]	(*R*,*R*)-**125**	0	2.5	92	55 (ND)
2	(*S*,*S*)-**125**	0	3	92	61 (*R*)
3	(*S*,*S*,a*S*)-**333**	-20	18	93	60 (S)
4	(*S*,*S*,a*R*)-**333**	-20	18	87	15 (*R*)
5	(*S*,*S*,a*S*)-**334**	-20	18	>95	57 (*R*)
6	(*S*,*S*,a*R*)-**334**	-20	18	>95	78 (*R*)
7	(*S*,*S*,a*S*)-**352**	-20	18	67[c]	24 (*S*)
8	(*S*,*S*,a*R*)-**352**	-20	18	56[c]	70 (*R*)
9	**142**	-20	18	86	40 (*S*)
10	*ent*-**141**	-20	18	93	65 (*R*)
11	(*S*,*S*,a*R*)-**334**	-50	36	81	75 (*R*)
12	*ent*-**141**	-50	36	81	68 (*R*)
13[d]	**142**	-50	36	42[c]	9 (*S*)

[a] ^{1}H-NMR yield. [b] Determined by HPLC with chiral stationary phase; ND – not determined. [c] Different batch of trichlorosilyl ketene acetal **163**. [d] THF was used as solvent.

4 CONCLUSION

1. A new variant of cyclotrimerization reaction was developed and studied in detail. The reaction is applicable to a wide variety of halodiynes and nitriles bearing electron-withdrawing group and providing mixtures of 2- and 3-halopyridines in good isolated yields (up to 91%). A synthetically interesting halogen exchange reaction between 2-iodo-or 2-bromopyridine and the ruthenium catalyst, which was observed as side reaction to cyclotrimerization, was studied by NMR.

2. A new 2,2'-bipyridine analogue of Bolm's ligand and two new BipyMOXes were synthesized *via* an innovative reaction pathway based on two key steps – the newly developed cocyclotrimerization of halodiynes with nitriles and reductive dimerization of 2-halopyridines.

These bipyridines were then tested as suitable ligands in metal-complex catalyzed asymmetric reactions. High level of asymmetric induction was observed mainly in the cases of iron(II)-catalyzed Mukaiyama aldol reaction (92% ee) and Sc(III)-catalyzed opening of epoxides (98% ee) with analogue of Bolm's ligand **296**. In addition, metal-**296** complexes evinced higher robustness than previously reported structurally similar complexes, which resulted in its lower sensitivity to impurities in reagents used in metal-**296** complex-catalyzed reactions. The conformation and chelation properties of **296** were then examined by NMR analysis, DFT calculations of bipyridine **296**, and X-ray analysis of its copper complexes. These analyses revealed that although the periplanar conformation of bipyridine **296** is energetically disfavored, complexation of the metal salt together with a slight twist of the two pyridine rings is making this arrangement stable.

3. A new series of axially chiral bipyridine *N*,*N'*-dioxides was synthesized by two different approaches. The first one, which is based on reductive dimerization of 2-halopyridines followed by oxidation of bipyridines, resulted in diastereoselective formation of a single atropoisomer. Both atropoisomers were, on the other hand, formed *via* an oxidative dimerization pathway. Both approaches led to large improvement regarding the overall yield of the synthesis of axially chiral C_2-symmetric *N*,*N'*-dioxides (up to 33% yield). These new *N*,*N'*-dioxides were then tested as organocatalysts in asymmetric reactions The best results in allylation reaction were obtained by *N*,*N'*-dioxide (*S*,*S*)-**125** (76% yield, 82% ee), while *N*,*N'*-dioxide (*S*,*S*,a*R*)-**334** provided the highest yield and ee (>95% yield, 78% ee) in aldol reaction.

5 EXPERIMENTAL PART

5.1 General

All chemicals were purchased from common commercial sources – Sigma Aldrich (Merck), Acros Organics, Strem chemicals and PENTA. Dry solvents for reactions were purified and dried by distillation from sodium/benzophenone (THF, Et_2O, PhMe), CaH_2 (DCM, DCE) or by standing over molecular sieves (DMF, MeCN). Freeze-pump-thaw technique or sonication while bubbling argon through the solvent was used for their degassing. Solvents for column chromatography were distilled prior to use. Benzaldehyde, acetophenone, methyl vinyl ketone, tetrachlorosilane, diisopropylamine, *N,N*-diisopropylethylamine, tributyltin chloride, oxalyl chloride, and thionyl chloride were purified by distillation prior to use. Benzoic acid was purified by recrystallization from water. Other solvents and chemicals were used without any further purification. Argon or nitrogen was used as an inert gas. Experiments with MW initiation were done by Biotage Initiator reactor, US irradiation by Vibra-Cell probe, and mechanical grinding by Vibratory Ball-mill Retsch MM200.

Silica gel 60 (0.040–0.063 mm) was used for column chromatography, TLC was performed on aluminum sheets with layer of Silica gel 60 F_{254}, both purchased from MERCK. Spots on TLC plates were detected by using UV lamp (λ = 254 nm), basic permanganate solution or acidic *p*-anisaldehyde solution.

NMR spectra were recorded on Varian VNMRS 300 ($\nu(^1H)$ = 299.94 MHz, $\nu(^{13}C)$ = 75.43 MHz), on Bruker Avance III (400 MHz) ($\nu(^1H)$ = 400.13 MHz, $\nu(^{13}C)$ = 100.61 MHz, $\nu(^{19}F)$ = 376.50 MHz), or on Bruker Avance III (600 MHz) ($\nu(^1H)$ = 600.17 MHz, $\nu(^{13}C)$ = 150.04 MHz) in deuterated solvents and referenced to residual solvent peak ($CDCl_3$ ^1H: 7.26 ppm, ^{13}C: 77.16 ppm, CD_2Cl_2 ^1H: 5.30 ppm, d_3-MeCN ^1H: 1.94 ppm, ^{13}C: 1.32, 118.26 ppm, d_6-Me_2CO ^1H: 2.05 ppm, ^{13}C: 29.84, 206.26 ppm). ^1H-NMR yields were determined by using 1,3,5-trimethylbenzene or 1,2,4,5-tetramethylbenzene. Chemical shifts are given in δ-scale, coupling constants J are given in Hz. The following abbreviations were used to define the signal multiplicity: s – singlet, brs – broad singlet, d – doublet, t – triplet, q – quartet, p – pentet, dd – doublet of doublet, dt – doublet of triplet, dq – doublet of quartet, dm – doublet of multiplet, ddd – doublet of doublet of doublet, td – triplet of doublet, qd – quartet of doublet, m – multiplet.

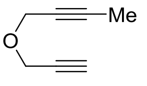
Mass spectra were recorded on VG-Analytical ZAB-SEQ and Synapt G2-S. HPLC-HRMS analyses were performed on Agilent 6530 Accurate-Mass Q-TOF LC/MS.

Infrared spectra were recorded in KBr and measured on spectrometer Hermo Nicolet AVATAR 370 FT-IR. All melting points are uncorrected and were determined on Kofler apparatus. Optical rotations were measured on automatic polarimeter Autopol III and are given in deg·mL·g^{-1}·dm^{-1} with accuracy ±2 and the mass concentrations in g/100 mL. HPLC analyses of chiral products were done on Shimadzu chromatograph with Daicel Chiralpak® columns and Lux Columns, and on Beckman chromatograph with Daicel Chiralpak® columns.

Bipymox **7** was purchased from Sigma Adrich. Compound **232** was prepared by Eliška Matoušová, former post-doc of Kotora's group.[214] The study of application of bipyridine **296** in Sc(III)-catalyzed opening of *meso*-epoxide rings was done by Štefan Malatinec, bachelor student in Kotora's group (the experimental details can be found in his Bachelor thesis or in ref. 215)

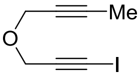
5.2 Catalytic [2+2+2] cocyclotrimerization of halodiynes and nitriles

5.2.1 Preparation of halodiynes



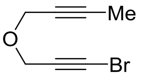
1-(Prop-2-yn-1-yloxy)but-2-yne (230).[216] 2-Butyn-1-ol (2.041 g, 28.5 mmol) was added into a cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 1.360 g, 34.0 mmol) in dry THF (100 mL) under Ar atmosphere. After stirring at 25 °C for 30 min, propargyl bromide (80% solution in toluene, 7.595 g, 51.0 mmol) was added slowly to the cooled (0 °C) reaction mixture and stirring continued at 25 °C for 2 h. The reaction was quenched by pouring into $NaHCO_3$ (sat. aq. sol., 100 mL) and extracted with Et_2O (3×150 mL). The combined organic fractions were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 cyclohexanes/Et_2O) furnished 2.290 g (74%) of the title compound as a colorless volatile oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.24 (d, J = 2.4 Hz, 2H, CH_2), 4.22 (q, J = 2.3 Hz, 2H, CH_2), 2.43 (t, J = 2.4 Hz, 1H, CH), 1.86 (t, J = 2.3 Hz, 3H, CH_3). The recorded values were in agreement with the published data.[217]



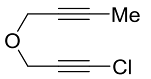
1-((3-Iodoprop-2-yn-1-yl)oxy)but-2-yne (231a).[218] Diyne **230** (493 mg, 4.6 mmol), NIS (1.353 g, 5.7 mmol), $AgNO_3$ (97 mg, 0.57 mmol), and DMF (27 mL) were stirred in a flask covered by aluminum foil at 25 °C for 3 h. The reaction was quenched by addition of $Na_2S_2O_3$ (sat. aq. sol., 100 mL) and extracted with Et_2O (100 mL). The organic phase was washed with water (2×50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (50/1 hexanes/EtOAc) furnished 768 mg (72%) of the title compound as a yellowish solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.38 (s, 2H, CH_2), 4.20 (q, J = 2.3 Hz, 2H, CH_2), 1.86 (t, J = 2.3 Hz, 3H, CH_3). The recorded values were in agreement with the published data.[218]



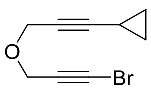
1-((3-Bromoprop-2-yn-1-yl)oxy)but-2-yne (231b).[219] Diyne **230** (1.81 g, 16.7 mmol), NBS (3.905 g, 20.9 mmol), $AgNO_3$ (355 mg, 2.1 mmol), and Me_2CO (60 mL) were stirred at 25 °C for 2 h. The reaction was quenched by addition of water (50 mL) and extracted with pentane (3×100 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 100/1→50/1 hexanes/Et_2O) furnished 2.422 g (78%) of the title compound as a yellowish liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.26 (s, 2H, CH_2), 4.20 (q, J = 2.3 Hz, 2H, CH_2), 1.86 (t, J = 2.3 Hz, 3H, CH_3).



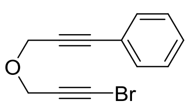
1-((3-Chloroprop-2-yn-1-yl)oxy)but-2-yne (231c).[220] Diyne **230** (150 mg, 1.4 mmol), NCS (227 mg, 1.7 mmol), AgOAc (23 mg, 0.14 mmol), and Me_2CO (5 mL) were stirred at 80 °C for 2 h. After spontaneous cooling down to 25 °C, the reaction was quenched by addition of water (5 mL) and extracted with pentane (3×20 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient pure hexanes→100/1 hexanes/Et_2O) furnished 158 mg (80%) of the title compound as a yellowish volatile liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.24 (s, 2H, CH_2), 4.19 (q, J = 2.3 Hz, 2H, CH_2), 1.86 (t, J = 2.3 Hz, 3H, CH_3).



(3-((3-Bromoprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)cyclopropane (231d).[219] Diyne **233** (105 mg, 0.78 mmol), NBS (183 mg, 0.98 mmol), $AgNO_3$ (17 mg, 0.1 mmol), and Me_2CO (3 mL) were stirred at 25 °C for 5 h. The reaction was quenched by addition of water (10 mL) and extracted with pentane (3×20 mL). The combined organic fractions were washed with with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 100/1→50/1 hexanes/EtOAc) furnished 145 mg (87%) of the title compound as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.25 (s, 2H, CH_2), 4.19 (d, J = 2.0 Hz, 2H, CH_2), 1.33–1.20 (m, 1H, CH), 0.83–0.65 (m, 4H, 2×CH_2).

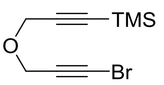


(3-((3-Bromoprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)benzene (231e). Step 1:[216] Propargyl ether **234** (735 mg, 7.7 mmol) followed by iodobenzene (1.591 g, 7.7 mmol) and Et_2NH (7.5 mL) were added into a solution of $Pd(PPh_3)_4$ (447 mg, 0.4 mmol) and CuI (149 mg, 0.77 mmol) in dry THF (50 mL) under Ar atmosphere. After stirring at 25 °C for 4 h, the reaction was quenched by pouring into NH_4Cl (sat. aq. sol., 30 mL) and extracted with Et_2O (3×50 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient pure hexanes→50/1 hexane/Et_2O)

furnished an inseparable mixture of **235** and **237** in 53/47 ratio. The mixture was used directly in the next reaction step without any further purification.

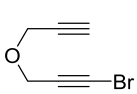
Step 2:[219] The mixture of diynes **235** and **237**, NBS (207 mg, 1.1 mmol), $AgNO_3$ (19 mg, 0.11 mmol), and Me_2CO (3 mL) were stirred at 25 °C for 5 h. The reaction was quenched by addition of water and extracted with pentane (4×10 mL). The combined organic fractions were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 5/1→3/2 hexanes/DCM) furnished 620 mg (33% in two steps) of the title compound as a yellowish liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48–7.41 (m, 2H, 2×Ar-H), 7.35–7.29 (m, 3H, 3×Ar-H), 4.48 (s, 2H, CH_2), 4.35 (s, 2H, CH_2).

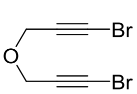


(3-((3-Bromoprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)trimethylsilane (231f). *n*BuLi (1.6 M solution in hexane, 11.8 mL, 16.3 mmol) was added dropwise to a cooled (-78 °C) solution of diyne **238** (3.000 g, 18.1 mmol) in dry THF (120 mL) under Ar atmosphere. After stirring at -78 °C for 30 min, NBS (3.046 g, 16.3 mmol) was added. The reaction mixture was allowed to warm up to 25 °C and stirred for 14 h. The reaction was quenched by pouring into NH_4Cl (sat. aq. sol., 50 mL) and extracted with Et_2O (3×150 mL). The combined organic fractions were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 100/1→8/1 hexanes/DCM) furnished 4.234 g (96%) of the title compound as a slightly yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.27 (s, 2H, CH_2), 4.24 (s, 2H, CH_2), 0.18 (s, 9H, 3×CH_3).



231g

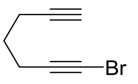


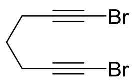
231k

1-Bromo-3-(prop-2-yn-1-yloxy)prop-1-yne (231g) and 1-bromo-3-((3-bromoprop-2-yn-1-yl)oxy)prop-1-yne (231k).[219] Propargyl ether **234** (735 mg, 7.7 mmol), NBS (1792 mg, 9.6 mmol), $AgNO_3$ (130 mg, 0.77 mmol), and Me_2CO (40 mL) were stirred at 25 °C for 2 h. The reaction mixture was quenched by addition of water (50 mL) and extracted with pentane (3×100 mL). The combined fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient pure hexanes→20/1 hexanes/Et_2O) furnished 350 mg (26%) of **231g** and 556 mg (29%) of **231k** as colorless volatile liquids.

231g: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.29 (s, 2H, CH_2), 4.25 (d, J = 2.4 Hz, 2H, CH_2), 2.46 (t, J = 2.4 Hz, 1H, CH).

231k: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.28 (s, 4H, 2×CH_2). The recorded values were in agreement with the published data.[193]

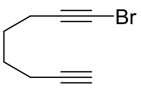

231h

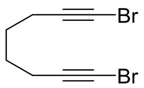

231l

1-Bromohepta-1,6-diyne (231h) and 1,7-dibromohepta-1,6-diyne (231l).[219] Hepta-1,6-diyne **239** (650 mg, 6.8 mmol), NBS (897 mg, 4.8 mmol), $AgNO_3$ (81 mg, 0.48 mmol), and Me_2CO (25 mL) were stirred at 25 °C for 4 h. The reaction was quenched by addition of water (40 mL) and extracted with pentane (3×80 mL). The combined organic fractions were washed with with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (pure hexanes) furnished 378 mg (32%) of **231h** and 276 mg (16%) of **231l** as colorless volatile liquids.

231h: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.40–2.26 (m, 4H, 2×CH_2), 1.97 (t, J = 2.6 Hz, 1H, CH), 1.80–1.67 (m, 2H, CH_2).

231l: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.33 (t, J = 7.0 Hz, 4H, 2×CH_2), 1.73 (p, J = 7.0 Hz, 2H, CH_2). The recorded values were in agreement with the published data.[193]


231i

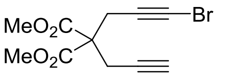

231m

1-Bromoocta-1,7-diyne (231i) and 1,8-dibromoocta-1,7-diyne (231m).[219] Octa-1,7-diyne **240** (643 mg, 5.9 mmol), NBS (889 mg, 4.7 mmol), $AgNO_3$ (81 mg, 0.48 mmol), and Me_2CO (22 mL) were stirred at 25 °C for 3 h. The reaction was quenched by addition of water (40 mL) and extracted with pentane (3×60 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (pure hexanes) furnished 421 mg (38%) of **231i** and 214 mg (14%) of **231m** as colorless volatile liquids.

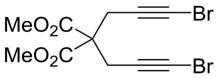
231i: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.30–2.18 (m, 4H, 2×CH_2), 1.95 (t, J = 2.6 Hz, 1H, CH), 1.69–1.60 (m, 4H, 2×CH_2).

231m: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.24 (t, J = 6.0 Hz, 4H, 2×CH_2), 1.66–1.58 (m, 4H, 2×CH_2). The recorded values were in agreement with the published data.[193]

Dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(prop-2-yn-1n-yl)malonate (231j) and dimethyl 2,2-bis(3-bromoprop-2-yn-1-yl)malonate (231n).[219] Diyne **241** (646 mg, 3.1 mmol), NBS (407 mg, 2.2 mmol), $AgNO_3$ (37 mg, 0.22 mmol), and Me_2CO (10 mL) were stirred at 25 °C for 3 h. The reaction was quenched by addition of water (20 mL) and extracted with Et_2O (3×50 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1→1/1 hexanes/DCM) furnished 250 mg (28%) of **231j** and 118 mg (10%) of **231n** as colorless viscous liquids.



231j

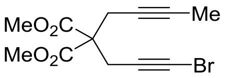


231n

231j: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 6H, 2×CH_3), 3.02 (s, 2H, CH_2), 2.97 (d, J = 2.6 Hz, 2H, CH_2), 2.04 (t, J = 2.7 Hz, 1H, CH).

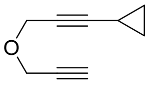
231n: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H, 2×CH_3), 2.99 (s, 4H, 2×CH_2). The recorded values were in agreement with the published data.[193]

Dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(but-2-yn-1-yl)malonate (231o).[219] Diyne **243** (226 mg, 1.0 mmol), NBS (286 mg, 1.5 mmol), $AgNO_3$ (26 mg, 0.15 mmol), and Me_2CO (4 mL) were stirred at 25 °C for 3 h. The reaction was quenched by addition of water (15 mL) and extracted with Et_2O (3×40 mL). The combined organic fractions were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1→25/1 hexanes/EtOAc) furnished 232 mg (76%) of the title compound as a colorless solid.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 6H, 2×CH_3), 2.99 (s, 2H, CH_2), 2.90 (q, J = 2.5 Hz, 2H, CH_2), 1.75 (t, J = 2.6 Hz, 3H, CH_3).

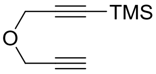
(3-(Prop-2-yn-1-yloxy)prop-1-yn-1-yl)cyclopropane (233).[216] 3-Cyclopropylprop-2-yn-1-ol **232** (243 mg, 2.5 mmol) was added to a cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 202 mg, 5.1 mmol) in dry THF (17 mL) under Ar atmosphere. After stirring at 25 °C for 30 min, propargyl bromide (80% solution in toluene, 677 mg, 4.6 mmol) was slowly added and stirring continued for next 4 h. The reaction was quenched by pouring into $NaHCO_3$ (sat. aq. sol., 50 mL) and extracted with Et_2O (3×100 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the



residue on silica gel (50/1 hexanes/EtOAc) furnished 287 mg (85%) of the title compound as a colorless volatile liquid.

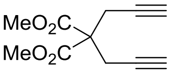
^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.24–4.19 (m, 4H, 2×CH_2), 2.42 (t, J = 2.4 Hz, 1H, CH), 1.31–1.21 (m, 1H, CH), 0.82–0.66 (m, 4H, 2×CH_2). The recorded values were in agreement with the published data.[214]

Trimethyl(3-(prop-2-yn-1-yloxy)prop-1-yn-1-yl)silane (238).[216] LiHMDS (1 M solution in THF, 26.3 mL, 26.6 mmol) was added dropwise to a cooled (-78 °C) solution of propargyl ether **234** (2.550 g, 26.6 mmol) in dry THF (135 mL) under Ar atmosphere. After stirring for 1 h at -78 °C, TMSCl (3.5 mL, 27.0 mmol) was added. After the complete consumption of the starting diyne (1.5 h), the reaction mixture was allowed to warm up to 25 °C. The reaction was quenched by pouring into NH_4Cl (sat. aq. sol., 50 mL) and extracted with Et_2O (3×100 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient pure hexanes→5/1 hexanes/DCM) furnished 3.005 g (68%) of the title compound as a colorless volatile liquid.

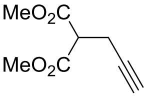


^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.25 (s, 2H, CH_2), 4.25 (d, J = 2.4 Hz, 2H, CH_2), 2.44 (t, J = 2.4 Hz, 1H, CH), 0.18 (s, 9H, 3×CH_3). The recorded values were in agreement with the published data.[221]

Dimethyl 2,2-di(prop-2-yn-1-yl)malonate (241).[222] A solution of dimethyl malonate (600 mg, 4.5 mmol) in dry THF (7 mL) was added into a cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 534 mg, 13.4 mmol) in dry THF (7.2 mL) under Ar atmosphere. After stirring at 25 °C for 1 h, propargyl bromide (80% solution in toluene, 1.588 g, 10.7 mmol) was added slowly and the mixture was refluxed for 2 h. The reaction was quenched by pouring into NH_4Cl (sat. aq. sol., 100 mL) and extracted with Et_2O (3×150 mL). The combined organic fractions were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 40/1→20/1 hexanes/EtOAc) furnished 680 mg (73%) of the title compound as a colorless solid.

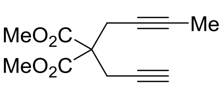


^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H, 2×CH_3), 2.99 (d, J = 2.7 Hz, 4H, 2×CH_2), 2.03 (t, J = 2.7 Hz, 2H, 2×CH). The recorded values were in agreement with the published data.[222]



Dimethyl 2-(prop-2-yn-1-yl)malonate (242).[222] A solution of dimethyl malonate (600 mg, 4.5 mmol) in dry THF (6 mL) was slowly added to a cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 214 mg, 5.3 mmol) in dry THF (8 mL) under Ar atmosphere. After stirring at 25 °C for 1 h, propargyl bromide (80% solution in toluene, 0.58 mL, 5.3 mmol) was added slowly and and the mixture was refluxed for 2 h. The reaction was quenched by pouring into NH_4Cl (sat. aq. sol., 100 mL) and extracted with Et_2O (3×150 mL). The combined organic fractions were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 40/1→20/1 hexanes/EtOAc) furnished 252 mg (33%) of the title compound as a colorless volatile liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 6H, 2×CH_3), 3.61 (t, J = 7.7 Hz, 1H, CH), 2.79 (dd, J = 7.7, 2.6 Hz, 2H, CH_2), 2.02 (t, J = 2.6 Hz, 1H, CH). The recorded values were in agreement with the published data.[222]

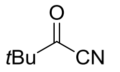


Dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (243).[222] A solution of alkyne **242** (240 mg, 1.4 mmol) in dry THF (2 mL) was added to a cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 68 mg, 1.7 mmol) in dry THF (2.3 mL) under Ar atmosphere. After stirring at 25 °C for 1 h, 1-bromo-2-butyne (227 mg, 1.7 mmol) was slowly added and and the mixture was refluxed for 3 h. The reaction was quenched by pouring into NH_4Cl (sat. aq. sol., 40 mL) and extracted with Et_2O (3×60 mL). The combined organic fractions were washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1→25/1 hexanes/EtOAc) furnished 253 mg (81%) of the title compound as a colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 6H, 2×CH_3), 2.97 (d, J = 2.6 Hz, 2H, CH_2), 2.95–2.90 (m, 2H, CH_2), 2.01 (t, J = 2.6 Hz, 1H, CH), 1.75 (t, J = 2.4 Hz, 3H, CH_3). The recorded values were in agreement with the published data.[223]

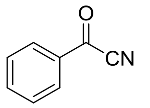
5.2.2 Preparation of nitriles

Pivaloyl cyanide (179b).[224] Pivaloyl chloride (5.869 g, 48.6 mmol) and copper(I) cyanide (4681 mg, 53.5 mmol) were stirred at 130 °C for 24 h. Distillation of the crude mixture furnished 4.865 g of colorless distillate, which contained 6% of the starting pivaloyl chloride and 94% of the title compound (84% yield).



^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.28 (s, 9H, 3×CH_3). ^{13}C-NMR (600 MHz, $CDCl_3$) δ 183.29, 112.26, 45.15, 24.66. The recorded values were in agreement with the published data.[225]

Benzoyl cyanide (179c).[224] Benzoyl chloride (6.638 g, 47.2 mmol) and copper(I) cyanide (4.540 g, 52.0 mmol) were stirred at 130 °C for 48 h. Distillation of the crude product furnished 5.458 g of colorless distillate, which contained 11% of the starting benzyl chloride and 89% of the title compound (78% yield).



^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.18–8.12 (m, 2H, 2×Ar-H), 7.82–7.77 (m, 1H, Ar-H), 7.64–7.59 (m, 2H, 2×Ar-H). ^{13}C-NMR (600 MHz, $CDCl_3$) δ 168.04, 137.00, 133.51, 130.63, 129.67, 112.87. The recorded values were in agreement with the published data.[226]

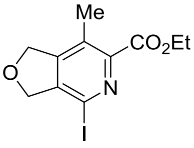
5.2.3 Scope of Ru-catalyzed cocyclotrimerization of halodiynes with nitriles

General procedure of cocyclotrimerization of halodiynes with nitriles

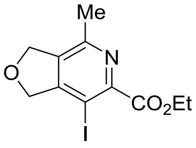
A solution of diyne **231** (0.2 mmol) in DCE (1.2 mL) was added to a solution of Cp*RuCl(cod) (7.6 mg, 0.02 mmol) and nitrile **179** (0.4 mmol) in DCE (1 mL) under Ar atmosphere during the course of 15 min. The reaction mixture was stirred at 25 or 50 °C until the starting diyne was fully consumed (disappearance of the respective spot on TLC), then volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc or hexanes/DCM) provided the corresponding products.

The determination of regioisomers was done by analysis of a typical peak of carbon bearing a halogen atom. This peak can be found in ^{13}C-NMR of the regioisomer **245** in the area around 110 ppm for C–Br (80 ppm for C–I and 122 ppm for C–Cl). In the case of the regioisomer **244**, this peak is downfielded to the area around 130 ppm for C–Br (106 ppm for C–I and 128 ppm for C–Cl).

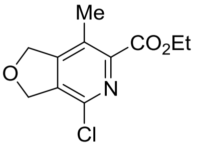
Ethyl 4-iodo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (244aa), ethyl 7-iodo-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (245aa), and ethyl 4-chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (246aa also 244ca).



244aa



245aa



246aa (**244ca**)

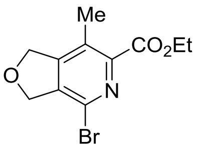
Reactants: diyne **231a** (47 mg, 0.2 mmol) and nitrile **179a** (40 mg, 0.4 mmol). Column chromatography on silica gel (gradient 10/1→5/1 hexanes/EtOAc) furnished 22 mg of an inseparable mixture of **244aa** and **246aa** (29% and 5% determined by ^{1}H-NMR) and 30 mg (45%) of **245aa** as colorless solids. The combined yield 79%.

244aa: Mp = 168 °C (for a mixture containing **246aa**). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.24 (t, J = 2.4 Hz, 2H, CH_2), 5.05 (t, J = 2.4 Hz, 2H, CH_2), 4.44 (q, J = 7.1 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.42 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 165.23, 150.24, 148.83, 143.74, 128.30, 106.17, 76.44, 74.52, 62.18, 15.76, 14.37. IR (**244aa**+**246aa**) (drift KBr) υ_{max} 2977, 1709, 1467, 1413, 1380, 1281, 1183, 1063, 1099, 905 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{11}H_{12}NO_3I$ (M) 332.9862, found 332.9861. R_f (5/1 hexanes/EtOAc) = 0.31 (the same value for **244aa** and **246aa**).

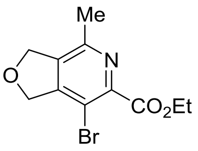
245aa: Mp = 113 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.26 (t, J = 2.1 Hz, 2H, CH_2), 5.06 (t, J = 2.1 Hz, 2H, CH_2), 4.47 (q, J = 7.1 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.44 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.17, 155.36, 151.49, 151.02, 135.65, 80.69, 78.74, 73.78, 62.53, 21.70, 14.31. IR (drift KBr) υ_{max} 1730, 1419, 1377, 1335, 1308, 1204, 1159, 1060, 905, 854 cm^{-1}. HRMS (EI-TOF) *m/z* calculated for $C_{11}H_{12}NO_3I$ (M) 332.9862, found 332.9864. R_f (5/1 hexanes/EtOAc) = 0.16.

246aa: For characterization see **244ca**.

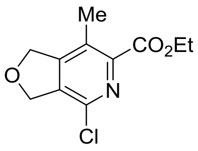
Ethyl 4-bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (244ba), ethyl 7-bromo-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (245ba), and ethyl 4-chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (246aa also 244ca).



244ba



245ba



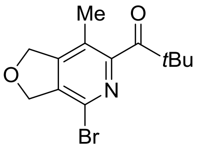
246aa (**244ca**)

Reactants: diyne **231b** (37 mg, 0.2 mmol) and nitrile **179a** (40 mg, 0.4 mmol). Column chromatography on silica gel (gradient 10/1→5/1 hexanes/EtOAc) furnished 24 mg of an inseparable mixture of **244ba** and **246aa** (40% and 3% determined by ^{1}H-NMR) as a colorless solid and 27 mg (48%) of **245ba** as a yellowish oil. The combined yield 91%.

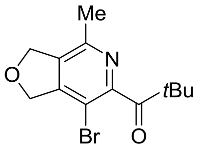
244ba: Mp = 116.5 °C (for a mixture containing **246aa**). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.21–5.19 (m, 2H, CH_2), 5.14–5.11 (m, 2H, CH_2), 4.44 (q, J = 7.1 Hz, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.42 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 165.14, 152.29, 148.08, 139.20, 131.38, 128.8, 74.24 (2×C), 62.20, 15.85, 14.37. IR (**244ba**+**246aa**) (drift KBr) υ_{max} 2971, 1718, 1470, 1413, 1317, 1290, 1183, 1063, 1039, 905 cm^{-1}. HRMS (EI-TOF) *m/z* calculated for $C_{11}H_{12}NO_3Br$ (M) 285.001, found 285.003. R_f (5/1 hexanes/EtOAc) = 0.30 (the same value for **244ba** and **246aa**).

245ba: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.21 (t, J = 2.2 Hz, 2H, CH_2), 5.13 (t, J = 2.3 Hz, 2H, CH_2), 4.47 (q, J = 7.1 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.43 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 165.41, 151.13, 150.35, 148.39, 136.76, 109.74, 75.36, 73.49, 62.49, 21.84, 14.30. IR (drift KBr) υ_{max} 2926, 2736, 1416, 1386, 1329, 1302, 1201, 1165, 1060, 1018 cm^{-1}. HRMS (EI-TOF) *m/z* calculated for $C_{11}H_{12}NO_3Br$ (M) 285.0001, found 285.0001. R_f (5/1 hexanes/EtOAc) = 0.16.

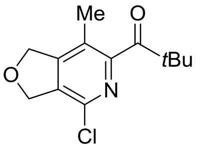
246aa: For characterization see **244ca**.



244bb



245bb



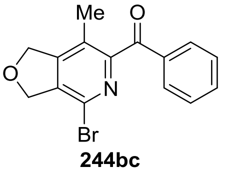
246bb

1-(4-Bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-one (244bb), 1-(7-bromo-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-one (245bb), and 1-(4-chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-one (246bb). Reactants: diyne **231b** (700 mg, 3.7 mmol) and nitrile **179b** (885 mg, 7.5 mmol). Column chromatography on silica gel (20/1 hexanes/EtOAc) furnished 370 mg of an inseparable mixture of **244bb** and **246bb** (32% and 2% determined by ^{1}H-NMR) and 120 mg (11%) of **245bb** as colorless oils. The combined yield 45%.

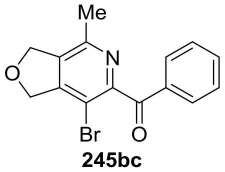
244bb: ^{1}H-NMR (600 MHz, CDCl$_3$) δ 5.18–5.16 (m, 2H, CH$_2$), 5.12–5.10 (m, 2H, CH$_2$), 2.14 (s, 3H, CH$_3$), 1.33 (s, 9H, 3×CH$_3$). ^{13}C-NMR (150 MHz, CDCl$_3$) δ 209.09, 155.78, 151.64, 137.21, 129.95, 125.08, 74.18, 74.14, 44.89, 27.42, 15.21. IR (**244bb**+**246bb**) (drift KBr) υ_{max} 2968, 1697, 1565, 1476, 1386, 1281, 1096, 1063, 949, 911 cm^{-1}. HRMS (ESI) *m*/*z* calculated for C$_{13}$H$_{17}$NO$_2$Br (M+H) 298.0437, found 298.0439. R$_f$ (5/1 hexanes/EtOAc) = 0.56 (the same value for **244bb** and **246bb**).

245bb: ^{1}H-NMR (600 MHz, CDCl$_3$) δ 5.19 (t, J = 2.0 Hz, 2H, CH$_2$), 5.10 (t, J = 2.3 Hz, 2H, CH$_2$), 2.40 (s, 3H, CH$_3$), 1.32 (s, 9H, 3×CH$_3$). ^{13}C-NMR (150 MHz, CDCl$_3$) δ 209.60, 156.06, 150.13, 149.26, 134.98, 107.17, 75.13, 73.45, 44.60, 27.22, 21.78. IR (drift KBr) υ_{max} 2964, 1784, 1700, 1479, 1458, 1383, 1329, 1072, 1015, 899 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for C$_{13}$H$_{16}$NO$_2$Br (M) 297.0364, found 297.0354. R$_f$ (5/1 hexanes/EtOAc) = 0.44.

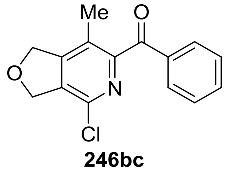
246bb: ^{1}H-NMR (600 MHz, CDCl$_3$) δ 5.20–5.18 (m, 2H, CH$_2$), 5.08–5.06 (m, 2H, CH$_2$), 2.16 (s, 3H, CH$_3$), 1.33 (s, 9H, 3×CH$_3$). ^{13}C-NMR intensity of signals was too low to be assigned.



244bc



245bc



246bc

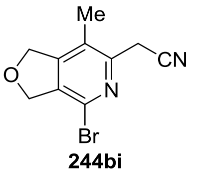
(4-Bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)(phenyl)methanone (244bc), (7-bromo-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)(phenyl)methanone (245bc), and (4-chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)(phenyl)methanone (246bc). Reactants: diyne **231b** (300 mg, 1.6 mmol) and nitrile **179c** (473 mg, 3.2 mmol). Column chromatography on silica gel (gradient 20/1→8/1 hexanes/EtOAc) furnished 274 mg of an inseparable mixture of **244bc** and **246bc** (51% and 3% determined by ^{1}H-NMR) and 67 mg (13%) of **245bc** as colorless solids. The combined yield 67%.

244bc: Mp = 134.5 °C (for a mixture containing **246bc**). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.90–7.86 (m, 2H, 2×Ar-H), 7.62–7.58 (m, 1H, Ar-H), 7.49–7.45 (m, 2H, 2×Ar-H), 5.24–5.23 (m, 2H, CH_2), 5.18–5.16 (m, 2H, CH_2), 2.23 (s, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 193.52, 155.08, 151.97, 137.97, 135.98, 133.94, 130.81, 130.74, 128.65, 126.42, 74.19, 74.15, 14.99. IR (**244bc**+**246bc**) (drift KBr) υ_{max} 1661, 1598, 1320, 1290, 1180, 1060, 946, 902, 698, 677 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{15}H_{13}NO_2Br$ (M+H) 318.0124, found 318.0126. R_f (5/1 hexanes/EtOAc) = 0.61 (the same value for **244bc** and **246bc**).

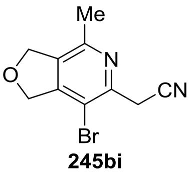
245bc: Mp = 142.0 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.87–7.84 (m, 2H, 2×Ar-H), 7.64–7.59 (m, 1H, Ar-H), 7.50–7.45 (m, 2H, 2×Ar-H), 5.26 (t, *J* = 2.1 Hz, 2H, CH_2), 5.16 (t, *J* = 2.3 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 193.58, 154.55, 150.55, 150.18, 135.92, 135.26, 134.15, 130.54, 128.76, 108.62, 75.12, 73.50, 21.83. IR (drift KBr) υ_{max} 1676, 1592, 1449, 1338, 1222, 1063, 890, 734, 716, 671 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{15}H_{12}NO_2Br$ (M) 317.0051, found 317.0049. R_f (5/1 hexanes/EtOAc) = 0.50.

246bc: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.90–7.86 (m, 2H, 2×Ar-H), 7.62–7.58 (m, 1H, Ar-H), 7.49–7.45 (m, 2H, 2×Ar-H), 5.21 (s, 2H, CH_2), 2.23 (s, 3H, CH_3). ^{13}C-NMR intensity of signals was too low to be assigned.

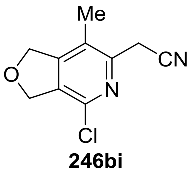
2-(4-Bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)acetonitrile (244bi), 2-(7-bromo-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)acetonitrile (245bi), and 2-(4-chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)acetonitrile (246bi). Reactants: diyne **231b** (37 mg, 0.2 mmol) and nitrile **179i** (40 mg, 0.4 mmol). Column chromatography on silica gel (gradient 3/1→2/1 hexanes/EtOAc) furnished 30 mg of an inseparable mixture of **244bi** and **246bi** (59% and 2% determined by ^{1}H-NMR) and 7 mg (13%) of **245bi** as yellowish oils. The combined yield 74%.



244bi



245bi



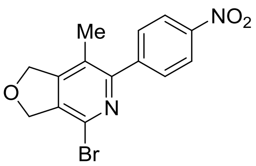
246bi

244bi: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.18 (t, *J* = 2.1 Hz, 2H, CH_2), 5.10 (t, *J* = 2.1 Hz, 2H, CH_2), 3.89 (s, 2H, CH_2), 2.26 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.93, 148.81, 137.21, 131.55, 125.37, 115.92, 73.98, 73.95, 24.32, 14.93. IR (**244bi**+**246bi**) (drift KBr) υ_{max} 1580, 1395, 1359, 1302, 1269, 1042, 919, 893, 827, 779 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{10}H_9N_2OBr$ (M) 251.9898, found 255.9897. R_f (5/1 hexanes/EtOAc) = 0.33 (the same value for **244bi** and **246bi**).

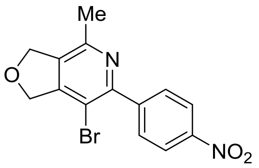
245bi: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.20–5.18 (m, 2H, CH_2), 5.09 (t, *J* = 2.2 Hz, 2H, CH_2), 4.03 (s, 2H, CH_2), 2.42 (s, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 150.79, 150.66, 147.32, 135.32, 116.15, 111.18, 75.06, 73.37, 26.33, 21.77. IR (drift KBr) υ_{max} 2911, 2863, 1425, 1401, 1356, 1063, 1036, 919, 902, 887 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{10}H_9N_2OBr$ (M) 251.9898, found 251.9895. R_f (5/1 hexanes/EtOAc) = 0.25.

246bi: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 4H, 2×CH_2), 3.88 (s, 2H, CH_2), 2.28 (s, 3H, CH_3). ^{13}C-NMR intensity of signals was too low to be assigned.

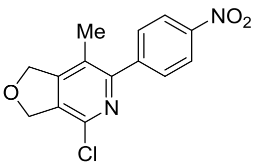
4-Bromo-7-methyl-6-(4-nitrophenyl)-1,3-dihydrofuro[3,4-*c*]pyridine (244bj), 7-bromo-4-methyl-6-(4-nitrophenyl)-1,3-dihydrofuro[3,4-*c*]pyridine (245bj), and 4-chloro-7-methyl-6-(4-nitrophenyl)-1,3-dihydrofuro[3,4-*c*]pyridine (246bj). Reactants: diyne **231b** (37 mg, 0.2 mmol) and nitrile **179j** (60 mg, 0.4 mmol). Column chromatography on silica gel (gradient 10/1→5/1 hexanes/EtOAc) furnished 29 mg of an inseparable mixture of **244bj**, **245bj** and **246bj** (31%, 8% and 5% determined by ^{1}H-NMR) as a colorless solid. The combined yield 44%.



244bj



245bj



246bj

244bj: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.34–8.29 (m, 2H, 2×Ar-H), 7.72–7.68 (m, 2H, 2×Ar-H), 5.24–5.22 (m, 2H, CH_2), 5.18–5.15 (m, 2H, CH_2), 2.21 (s, 3H, CH_3).

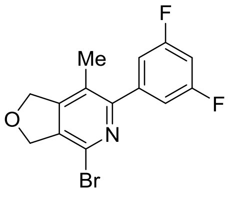
245bj: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.34–8.29 (m, 2H, 2×Ar-H), 7.85 (d, *J* = 8.8 Hz, 2H, 2×Ar-H), 5.28–5.26 (m, 2H, CH_2), 5.18–5.15 (m, 2H, CH_2), 2.48 (s, 3H, CH_3).

246bj: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.34–8.29 (m, 2H, 2×Ar-H), 7.72–7.68 (m, 2H, 2×Ar-H), 3.22–3.21 (m, 2H, CH_2), 5.21–5.19 (m, 2H, CH_2), 2.24 (s, 3H, CH_3).

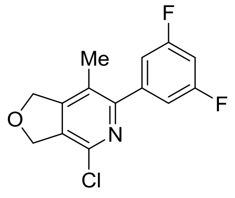
244bj+245bj+246bj: Mp = 238.4 °C. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 156.43, 156.02, 154.30, 152.90, 152.11 (2×C), 151.30, 150.53, 147.94, 147.90, 145.35, 144.94, 144.86, 141.78, 136.55, 134.97, 133.61, 131.89, 130.75, 130.48, 130.46, 124.60, 124.23, 123.69 (2×C), 123.44, 110.39, 75.56, 74.26, 74.13, 74.08, 73.53, 73.07, 21.95, 16.23 (2×C). IR (drift KBr) υ_{max} 1601, 1559, 1527, 1413, 1395, 1347, 1296, 1063, 863, 854 cm^{-1}. R_f (5/1 hexanes/EtOAc) = 0.28.

244bj+245bj: HRMS (EI-TOF) *m*/*z* calculated for $C_{14}H_{11}N_2O_3Br$ (M) 333.9953, found 333.9956.

4-Bromo-6-(3,5-difluorophenyl)-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine (244bk) and 4-chloro-6-(3,5-difluorophenyl)-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine (246bk).



244bk



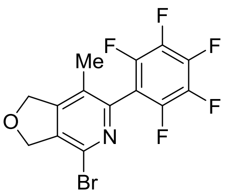
246bk

Reactants: diyne **231b** (37 mg, 0.2 mmol) and nitrile **179k** (56 mg, 0.2 mmol). Column chromatography on silica gel (gradient 40/1→30/1 hexanes/EtOAc) furnished 12 mg of an inseparable mixture of **244bk** and **246bk** (16% and 3% determined by ^{1}H-NMR) as a colorless solid. The combined yield 19%.

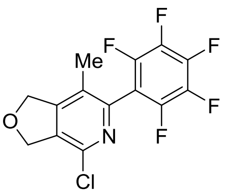
244bk: Mp = 165.9 °C (for a mixture containing **246bk**). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.06–7.01 (m, 2H, 2×Ar-H), 6.87 (tt, J = 8.9, 2.3 Hz, 1H, Ar-H), 5.22–5.20 (m, 2H, CH_2), 5.16–5.14 (m, 2H, CH_2), 2.20 (s, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 162.90 (dd, J = 249.3, 12.8 Hz), 156.45–156.27 (m), 152.01, 141.64 (t, J = 9.4 Hz), 136.22, 131.58, 124.39, 112.56 (dd, J = 20.5, 5.5 Hz), 104.13 (t, J = 25.2 Hz), 74.26, 74.10, 16.17. ^{19}F-NMR (400 MHz, $CDCl_3$) δ -109.26—109.35 (m, 2F). IR (**244bk**+**246bk**) (drift KBr) υ_{max} 1595, 1446, 1395, 1305, 1239, 1117, 1066, 985, 899, 839 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{14}H_{10}NOF_2Br$ (M) 324.9914, found 324.9915. R_f (5/1 hexanes/EtOAc) = 0.73 (the same value for **244bk** and **246bk**).

246bk: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.06–7.01 (m, 2H, 2×Ar-H), 6.90–6.84 (m, 1H, Ar-H), 5.20–5.19 (m, 2H, CH_2), 5.19–5.17 (m, 2H, CH_2), 2.23 (s, 3H, CH_3). ^{13}C-NMR intensity of signals was too low to be assigned. ^{19}F-NMR (400 MHz, $CDCl_3$) δ -109.26—109.35 (m, 2F).

4-Bromo-7-methyl-6-(perfluorophenyl)-1,3-dihydrofuro[3,4-*c*]pyridine (244bl) and 4-chloro-7-methyl-6-(perfluorophenyl)-1,3-dihydrofuro[3,4-*c*]pyridine (246bl).



244bl



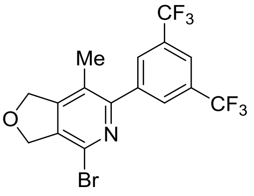
246bl

Reactants: diyne **231b** (37 mg, 0.2 mmol) and nitrile **179l** (77 mg, 0.4 mmol). Column chromatography on silica gel (gradient 3/1→2/1 hexanes/DCM) furnished 12 mg of an inseparable mixture of **244bl** and **246bl** (30% and 5% determined by ^{1}H-NMR) as a colorless solid. The combined yield 35%.

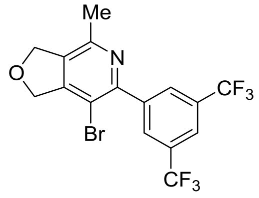
244bl: Mp = 119.5 °C (for a mixture containing **246bl**). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.25–5.23 (m, 2H, CH_2), 5.19–5.16 (m, 2H, CH_2), 2.08 (s, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 151.67, 145.42–145.40 (m), 144.54 (dm, J = 249.6 Hz), 141.81 (dm, J = 255.9 Hz), 137.90, 137.88 (dm, J = 249.6 Hz), 132.02, 127.54, 113.35–112.91 (m), 74.18, 74.14, 15.16. ^{19}F-NMR (400MHz, $CDCl_3$) δ-140.51 (dd, J = 22.7, 8.0 Hz, 2F), -152.82 (tt, J = 20.8, 1.9 Hz, 1F), -161.10–-161.28 (m, 2F). IR (**244bl**+**246bl**) (drift KBr) υ_{max} 1524, 1500, 1455, 1398, 1301, 1117, 1063, 985, 917, 860 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{14}H_7NOBrF_5$ (M) 378.9631, found 378.9632. R_f (5/1 hexanes/EtOAc) = 0.50 (the same value for **244bl** and **246bl**).

246bl: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.23–5.20 (m, 4H, 2×CH_2), 2.10 (s, 3H, CH_3). ^{13}C-NMR intensity of signals was too low to be assigned. ^{19}F-NMR (400MHz, $CDCl_3$) δ -140.51–-140.64 (m, 2F), -152.74–-152.90 (m, 1F), -161.10–-161.28 (m, 2F).

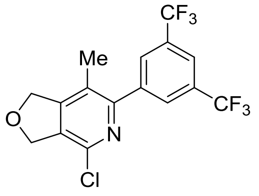
6-(3,5-Bis(trifluoromethyl)phenyl)-4-bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine (244bm), 6-(3,5-bis(trifluoromethyl)phenyl)-7-bromo-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridine (245bm), and 6-(3,5-bis(trifluoromethyl)phenyl)-4-chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine (246bm). Reactants: diyne **231b** (37 mg, 0.2 mmol) and nitrile **179m** (98 mg, 0.4 mmol). Column chromatography on silica gel (1/1 hexanes/DCM) furnished 30 mg of an inseparable mixture of **244bm** and **246bm** (31% and 5% determined by ^{1}H-NMR) and 10 mg (12%) of **245bm** as colorless solids. The combined yield 48%.



244bm



245bm



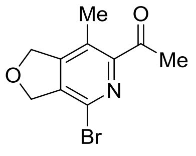
246bm

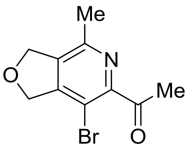
244bm: Mp = 154.0 °C (for a mixture containing **246bm**). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.98 (s, 2H, 2×Ar-H), 7.94 (s, 1H, Ar-H), 5.24–5.22 (m, 2H, CH_2), 5.18–5.15 (m, 2H, CH_2), 2.21 (s, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 155.62, 152.25, 140.54, 136.80, 132.00, 131.93 (q, *J* = 33.5 Hz), 129.63, 124.59, 123.34 (q, *J* = 272.8 Hz), 122.47, 74.25, 74.11, 16.11. ^{19}F-NMR (400 MHz, $CDCl_3$) δ -62.83 (s, 6F). IR (**244bm**+**246bm**) (drift KBr) υ_{max} 1365, 1347, 1308, 1278, 1174, 1132, 1114, 1069, 899, 680 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{16}H_{10}NOBrF_6$ (M) 424.9850, found 424.9851. R_f (5/1 hexanes/EtOAc) = 0.78 (the same value for **244bm** and **246bm**).

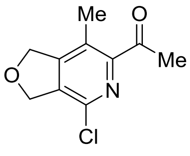
245bm: Mp = 76.4 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 2H, 2×Ar-H), 7.93 (s, 1H, Ar-H), 5.27 (t, *J* = 2.1 Hz, 2H, CH_2), 5.17 (t, *J* = 2.3 Hz, 2H, CH_2), 2.48 (s, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 153.42, 151.45, 150.74, 140.94, 135.14, 131.57 (q, *J* = 33.5 Hz), 130.06, 123.40 (q, *J* = 272.9 Hz), 122.63–122.46 (m), 110.34, 75.56, 73.52, 21.93. ^{19}F-NMR (400 MHz, $CDCl_3$) δ -62.84. IR (drift KBr) υ_{max} 1365, 1317, 1299, 1284, 1198, 1177, 1126, 899, 704, 677 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{16}H_{10}NOBrF_6$ (M) 424.9850, found 424.9851. R_f (5/1 hexanes/EtOAc) = 0.75.

246bm: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.98 (s, 2H, 2×Ar-H), 7.94 (s, 1H, Ar-H), 5.22–5.21 (m, 2H, CH_2), 5.21–5.19 (m, 2H, CH_2), 2.24 (s, 3H, CH_3). ^{13}C-NMR intensity of signals was too low to be assigned. ^{19}F-NMR (400 MHz, $CDCl_3$) δ -62.83 (s, 6F).

1-(4-Bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)ethan-1-one (244bn), 1-(7-bromo-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)ethan-1-one (245bn), and 1-(4-chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)ethan-1-one (246bn). Reactants: diyne **231b** (303 mg, 1.6 mmol) and nitrile **179n** (250 mg, 3.2 mmol). Column chromatography on silica gel (gradient 20/1→10/1 hexanes/EtOAc) furnished 203 mg of an inseparable mixture of **244bn** and **246bn** (48% by 1% determined by ^{1}H-NMR) and 137 mg (33%) of **245bn** as colorless solids. The combined yield 82%.


244bn


245bn

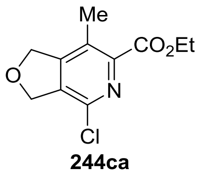

246bn

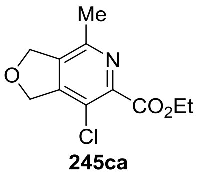
244bn: Mp = 99.0 °C (for a mixture containing **246bn**). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.22–5.19 (m, 2H, CH_2), 5.15–5.11 (m, 2H, CH_2), 2.69 (s, 3H, CH_3), 2.41 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.83, 152.72, 151.86, 139.61, 130.46, 128.07, 74.24, 74.23, 28.59, 16.17. IR (**244bn**+**246bn**) (drift KBr) υ_{max} 1697, 1398, 1353, 1287, 1242, 1159, 1060, 952, 965, 785, 567 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{10}H_{10}NO_2Br$ (M) 254.9895, found 254.9896. R_f (5/1 hexanes/EtOAc) = 0.68 (the same value for **244bn** and **246bn**).

245bn: Mp = 125.8 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.22 (t, *J* = 2.4 Hz, 2H, CH_2), 5.14–5.12 (m, 2H, CH_2), 2.69 (s, 3H, CH_3), 2.44 (s, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 199.71, 151.71, 151.09, 149.47, 137.16, 108.63, 75.49, 73.49, 28.41, 21.78. IR (drift KBr) υ_{max} 1703, 1410, 1377, 1353, 1320, 1305, 1168, 1153, 1057, 899 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{10}H_{10}NO_2Br$ (M) 254.9895, found 254.9896. R_f (5/1 hexanes/EtOAc) = 0.58.

246bn: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.18 (s, 4H, 2×CH_2), 2.69 (s, 3H, CH_3), 2.43 (s, 3H, CH_3). ^{13}C-NMR intensity of signals was too low to be assigned.

Ethyl 4-chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (244ca also 246aa) and ethyl 7-chloro-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (245ca). Reactants: diyne **231c** (28 mg, 0.2 mmol) and nitrile **179a** (40 mg, 0.4 mmol). Column chromatography on silica gel (gradient 10/1→5/1 hexanes/EtOAc) furnished 17 mg of **244ca** (36%) and 17 mg (36%) of **245ca** as colorless solids. The combined yield 72%.

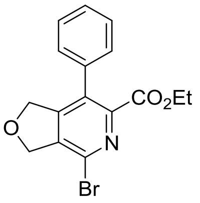

244ca


245ca

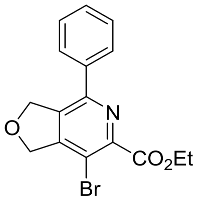
244ca: Mp = 112.4 °C. ^{1}H-NMR (600 MHz, CDCl$_3$) δ 5.18 (s, 4H, 2×CH$_2$), 4.44 (q, J = 7.1 Hz, 2H, CH$_2$), 2.41 (s, 3H, CH$_3$), 1.42 (t, J = 7.1 Hz, 3H, CH$_3$). ^{13}C-NMR (150 MHz, CDCl$_3$) δ 165.21, 153.15, 147.58, 141.41, 136.33, 128.08, 74.08, 73.18, 62.20, 15.88, 14.38. IR (drift KBr) υ_{max} 1715, 1470, 1416, 1311, 1290, 1260, 1186, 1066, 1039, 905 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{11}H_{12}NO_3Cl$ (M) 241.0506, found 241.0503. R$_f$ (5/1 hexanes/EtOAc) = 0.30.

245ca: Mp = 56.8 °C. ^{1}H-NMR (600 MHz, CDCl$_3$) δ 5.19–5.15 (m, 4H, 2×CH$_2$), 4.47 (q, J = 7.1 Hz, 2H, CH$_2$), 2.46 (s, 3H, CH$_3$), 1.42 (t, J = 7.1 Hz, 3H, CH$_3$). ^{13}C-NMR (150 MHz, CDCl$_3$) δ 164.82, 149.77, 148.90, 146.53, 137.17, 122.39, 73.71, 73.31, 62.43, 21.86, 14.29. IR (drift KBr) υ_{max} 1720, 1419, 1380, 1332, 1305, 1198, 1066, 1027, 902, 716 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{11}H_{12}NO_3Cl$ (M) 241.0506, found 241.0506. R$_f$ (5/1 hexanes/EtOAc) = 0.15.

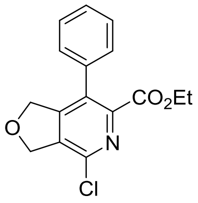
Ethyl 4-bromo-7-phenyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (244ea), ethyl 7-bromo-4-phenyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (245ea), and ethyl 4-chloro-7-phenyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (246ea). Reactants: diyne **231e** (50 mg, 0.2 mmol) and nitrile **179a** (40 mg, 0.4 mmol). Column chromatography on silica gel (20/1 hexanes/EtOAc) furnished 26 mg of an inseparable mixture of **244ea** and **246ea** (32% and 6% determined by ^{1}H-NMR) as an amorphous colorless solid and 12 mg (17%) of **245ea** as a colorless solid. The combined yield 45%.



244ea



245ea



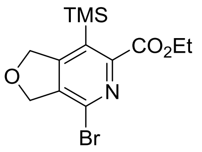
246ea

244ea: ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.46–7.38 (m, 3H, 3×Ar-H), 7.25–7.20 (m, 2H, 2×Ar-H), 5.17 (t, J = 2.2 Hz, 2H, CH$_2$), 5.07 (t, J = 2.3 Hz, 2H, CH$_2$), 4.13 (q, J = 7.1 Hz, 2H, CH$_2$), 1.02 (t, J = 7.1 Hz, 3H, CH$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$) δ 164.30, 150.51, 148.18, 138.06, 134.05, 132.24, 130.07, 127.90, 127.79, 126.89, 73.32, 73.06, 61.03, 12.79. IR (**244ea**+**246ea**) (drift KBr) υ_{max} 1730, 1293, 1189, 1159, 1117, 1063, 1009, 800, 740, 707 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{16}H_{14}NO_3Br$ (M) 347.0157, found 347.0162. R$_f$ (5/1 hexanes/EtOAc) = 0.43 (the same value for **244ea** and **246ea**).

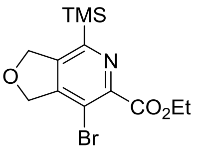
245ea: Mp = 123.4 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.76–7.71 (m, 2H, 2×Ar-H), 7.52–7.42 (m, 3H, 3×Ar-H), 5.46 (t, J = 2.1 Hz, 2H, CH$_2$), 5.17 (t, J = 2.1 Hz, 2H, CH$_2$), 4.50 (q, J = 7.1 Hz, 2H, CH$_2$), 1.45 (t, J = 7.1 Hz, 3H, CH$_3$). ^{13}C-NMR (150 MHz, CDCl$_3$) δ 165.44, 152.64, 150.35, 149.00, 137.32, 135.36, 129.84, 129.05, 127.97, 110.60, 74.93, 74.49, 62.44, 14.34. IR (drift KBr) υ_{max} 2989, 2953, 2926, 2854, 1733, 1452, 1254, 1210, 1150, 692 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{16}H_{14}NO_3Br$ (M) 347.0157, found 347.0161. R_f (5/1 hexanes/EtOAc) = 0.35.

246ea: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46–7.38 (m, 3H, 3×Ar-H), 7.25–7.20 (m, 2H, 2×Ar-H), 5.22 (t, J = 2.2 Hz, 2H, CH_2), 5.04 (t, J = 2.2 Hz, 2H, CH_2), 4.14 (q, J = 7.1 Hz, 2H, CH_2), 1.03 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C-NMR intensity of signals was too low to be assigned.

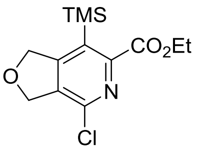
Ethyl 4-bromo-7-(trimethylsilyl)-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (244fa), ethyl 7-bromo-4-(trimethylsilyl)-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (245fa), and ethyl 4-chloro-7-(trimethylsilyl)-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (246fa). Reactants: diyne **231f** (49 mg, 0.2 mmol) and nitrile **179a** (40 mg, 0.4 mmol). Column chromatography on silica gel (gradient 50/1→30/1 hexanes/EtOAc) furnished 35 mg of an inseparable mixture of **244fa** and **246fa** (44% and 7% determined by ^{1}H-NMR) as a colorless solid and 25 mg of **245fa** (36%) as a colorless oil. The combined yield 87%.



244fa



245fa

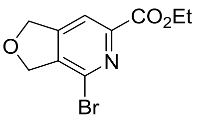


246fa

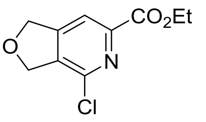
244fa: Mp = 68.1 °C (for a mixture containing **246fa**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.22–5.21 (m, 2H, CH_2), 5.07–5.04 (m, 2H, CH_2), 4.41 (q, J = 7.2 Hz, 2H, CH_2), 1.41 (t, J = 7.2 Hz, 3H, CH_3), 0.31 (s, 9H, 3×CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.14, 157.84, 155.55, 137.97, 135.62, 127.65, 75.86, 72.96, 62.51, 14.26, 0.62. IR (**244fa**+**246fa**) (drift KBr) υ_{max} 2988, 1733m 1544, 1312, 1284, 1175, 1053, 1020, 933, 909, 846 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{13}H_{19}NO_3BrSi$ (M+H) 344.0318, found 344.0321. R_f (10/1 hexane/EtOAc) = 0.19 (the same value for **244fa** and **246fa**).

245fa: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.28 (t, J = 1.8 Hz, 2H, CH_2), 5.08 (t, J = 1.8 Hz, 2H, CH_2), 4.47 (q, J = 7.1 Hz, 2H, CH_2), 1.43 (t, J = 7.1 Hz, 3H, CH_3), 0.31 (s, 9H, 3×CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.17, 159.46, 149.13, 148.53, 143.36, 112.04, 74.37, 73.88, 62.16, 14.28, -1.71. IR (drift KBr) υ_{max} 2966, 1704, 1479, 1249, 1150, 1057, 1013, 942, 895, 845 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{13}H_{19}NO_3BrSi$ (M+H) 344.0318, found 344.0319. R_f (10/1 hexane/EtOAc) = 0.23.

246fa: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.22–5.20 (m, 2H, CH_2), 5.12–5.10 (m, 2H, CH_2), 4.43 (q, J = 7.2 Hz, 2H, CH_2), 1.42 (t, J = 7.2 Hz, 3H, CH_3), 0.32 (s, 9H, 3×CH_3). ^{13}C-NMR intensity of signals was too low to be assigned.



244ga

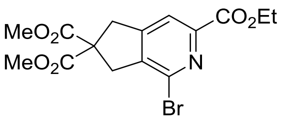


246ga

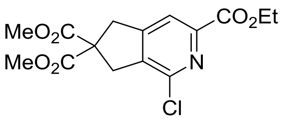
Ethyl 4-bromo-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (244ga) and ethyl 4-chloro-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (246ga). Reactants: diyne **231g** (35 mg, 0.2 mmol) and nitrile **179a** (40 mg, 0.4 mmol). Column chromatography on silica gel (gradient 10/1→2/1 hexanes/EtOAc) furnished 20 mg of an inseparable mixture of **244ga** and **246ga** (32% and 4% determined by ^{1}H-NMR) as a colorless solid. The combined yield 36%.

244ga: Mp = 96.7 °C (for a mixture containing **246ga**). ^{1}H-NMR (300 MHz, $\mathrm{CDCl_3}$) δ 7.98 (s, 1H, Ar-H), 5.26–5.22 (m, 2H, $\mathrm{CH_2}$), 5.13–5.10 (m, 2H, $\mathrm{CH_2}$), 4.47 (q, J = 7.1 Hz, 2H, $\mathrm{CH_2}$), 1.42 (t, J = 7.1 Hz, 3H, $\mathrm{CH_3}$). ^{13}C-NMR (100 MHz, $\mathrm{CDCl_3}$) δ 163.92, 152.11, 148.80, 141.17, 135.19, 117.63, 74.25, 73.48, 62.53, 14.40. IR (**244ga**+**246ga**) (drift KBr) υ_{max} 1712, 1556, 1383, 1317, 1286, 1230, 1177, 1021, 896, 782 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $\mathrm{C_{10}H_{10}NO_3Br}$ (M) 270.9844, found 270.9846. R_f (5/1 hexanes/EtOAc) = 0.23 (the same value for **244ga** and **246ga**).

246ga: ^{1}H-NMR (300 MHz, $\mathrm{CDCl_3}$) δ 7.96 (s, 1H, Ar-H), 5.22–5.20 (m, 2H, $\mathrm{CH_2}$), 5.18–5.15 (m, 2H, $\mathrm{CH_2}$), 4.51–4.42 (m, 2H, $\mathrm{CH_2}$), 1.47–1.39 (m, 3H, $\mathrm{CH_3}$). ^{13}C-NMR intensity of signals was too low to be assigned.



244ja



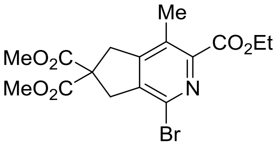
246ja

3-Ethyl 6,6-dimethyl 1-bromo-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-3,6,6-tricarboxylate (244ja) and 3-ethyl 6,6-dimethyl 1-chloro-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-3,6,6-tricarboxylate (246ja). Reactants: diyne **231j** (43 mg, 0.15 mmol) and nitrile **179a** (30 mg, 0.3 mmol). Column chromatography on silica gel (gradient 5/1→1/1 hexanes/EtOAc) furnished 8 mg of an inseparable mixture of **244ja** and **246ja** (12% and 2% determined by ^{1}H-NMR) as a yellowish oil. The combined yield 14%. As a side product was isolated **251j**.

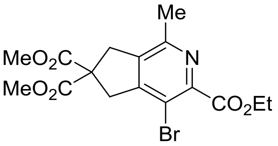
244ja: ^{1}H-NMR (300 MHz, $\mathrm{CDCl_3}$) δ 7.93 (s, 1H, Ar-H), 4.45 (q, J = 7.1 Hz, 2H, $\mathrm{CH_2}$), 3.79 (s, 6H, 2×$\mathrm{CH_3}$), 3.74 (s, 2H, $\mathrm{CH_2}$), 3.67 (s, 2H, $\mathrm{CH_2}$), 1.41 (t, J = 7.1 Hz, 3H, $\mathrm{CH_3}$). ^{13}C-NMR (150 MHz, $\mathrm{CDCl_3}$) δ 171.02, 164.13, 152.63, 148.23, 142.17, 138.75, 120.75, 62.36, 58.66, 53.59, 41.32, 41.08, 14.42. IR (**244ja**+**246ja**) (drift KBr) υ_{max} 1736, 1553, 1437, 1383, 1290, 1245, 1216, 1180, 1099, 1075 cm^{-1}.HRMS (EI-TOF) *m*/*z* calculated for $\mathrm{C_{15}H_{17}NO_6Br}$ (M+H) 386.0234, found 386.0235. R_f (2/1 hexanes/EtOAc) = 0.60 (the same value for **244ja** and **246ja**).

246ja: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.93 (s, 1H, Ar-H), 4.48–4.42 (m, 2H, CH$_2$), 3.79 (s, 6H, 2×CH$_3$), 3.72 (s, 2H, CH$_2$), 3.70 (s, 2H, CH$_2$), 1.41 (t, J = 7.1 Hz, 3H, CH$_3$). ^{13}C-NMR intensity of signals was too low to be assigned.

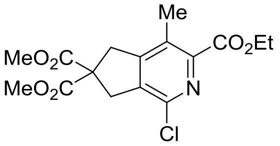
3-Ethyl 6,6-dimethyl 1-bromo-4-methyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-3,6,6-tricarboxylate (244oa), 3-ethyl 6,6-dimethyl 4-bromo-1-methyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-3,6,6-tricarboxylate (245oa), and 3-ethyl 6,6-dimethyl 1-chloro-4-methyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-3,6,6-tricarboxylate (246oa). Reactants: diyne **231o** (60 mg, 0.2 mmol) and nitrile **179a** (40 mg, 0.4 mmol). Column chromatography on silica gel (gradient 5/1→4/1 hexanes/EtOAc) furnished 26 mg of an inseparable mixture of **244oa** and **246oa** (31% and 2% determined by ^{1}H-NMR) and 30 mg (38%) of **245oa** as colorless solids. The combined yield 71%.



244oa



245oa



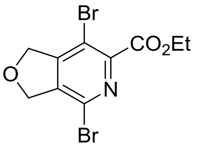
246oa

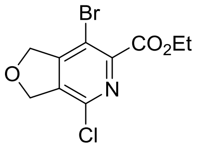
244oa: Mp = 98.0 °C (for a mixture containing **246oa**). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 4.41 (q, J = 7.1 Hz, 2H, CH$_2$), 3.78 (s, 6H, 2×CH$_3$), 3.66 (s, 4H, 2×CH$_2$), 2.39 (s, 3H, CH$_3$), 1.39 (t, J = 7.1 Hz, 3H, CH$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$) δ 171.15, 165.42, 152.64, 147.75, 140.08, 134.95, 130.33, 62.04, 58.30, 53.56, 41.34, 40.85, 15.53, 14.35. IR (**244oa**+**246oa**) (drift KBr) υ_{max} 1763, 1730, 1721, 1437, 1293, 1278, 1254, 1204, 1177, 1162 cm^{-1}.HRMS (ESI) *m*/*z* calculated for $C_{16}H_{19}BrNO_6$ (M+H) 400.1390, found 400.1394. R$_f$ (5/1 hexanes/EtOAc) = 0.48 (the same value for **244oa** and **246oa**).

245oa: Mp = 137.1 °C. ^{1}H-NMR (600 MHz, CDCl$_3$) δ 4.45 (q, J = 7.1 Hz, 2H, CH$_2$), 3.78 (s, 6H, 2×CH$_3$), 3.67 (s, 4H, 2×CH$_2$), 2.46 (s, 3H, CH$_3$), 1.41 (t, J = 7.1 Hz, 3H, CH$_3$). ^{13}C-NMR (150 MHz, CDCl$_3$) δ 171.17, 165.75, 152.68, 151.51, 148.38, 137.45, 112.91, 62.35, 58.45, 53.56, 42.61, 39.90, 21.69, 14.28. IR (drift KBr) υ_{max} 1748, 1724, 1425, 1377, 1329, 1323, 1293, 1269, 1201, 1165 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{19}NO_6Br$ (M+H) 400.0390, found 400.0393. R$_f$ (5/1 hexanes/EtOAc) = 0.33.

246oa: ^{1}H-NMR (400 MHz, CDCl$_3$) δ 4.44–4.37 (m, 2H, CH$_2$), 3.79 (s, 6H, 2×CH$_3$), 3.69 (s, 4H, 2×CH$_2$), 3.64 (s, H, 2×CH$_2$), 2.42 (s, 3H, CH$_3$), 1.42–1.38 (m, 3H, CH$_3$). ^{13}C-NMR intensity of signals was too low to be assigned.

Ethyl 4,7-dibromo-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (249ka) and ethyl 7-bromo-4-chloro-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (250ka). Reactants: diyne **231k** (51 mg, 0.2 mmol) and nitrile **179a** (40 mg, 0.4 mmol). Column chromatography on silica gel (20/1 hexanes/EtOAc) furnished 63 mg of an inseparable mixture of **249ka** and **250ka** (83% and 6% determined by ^{1}H-NMR) as a colorless solid. The combined yield 89%.

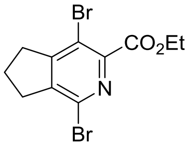

249ka

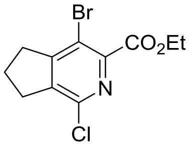

250ka

249ka: Mp = 64.7 °C (for a mixture containing **250ka**). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.19 (s, 4H, 2×CH_2), 4.46 (q, J = 7.1 Hz, 2H, CH_2), 1.42 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.77, 153.53, 149.26, 140.25, 132.75, 112.07, 76.08, 74.64, 62.82, 14.23. IR (**249ka**+**250ka**) (drift KBr) υ_{max} 1733, 1410, 1380, 1284, 1266, 1183, 1156, 1051, 1018, 931 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{10}H_9NO_3Br_2$ (M+H) 349.9022, found 349.9023. R_f (5/1 hexanes/EtOAc) = 0.73 (the same value for **249ka** and **250ka**).

250ka: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.26–5.23 (m, 2H, CH_2), 5.18–5.16 (m, 2H, CH_2), 4.50–4.42 (m, 2H, CH_2), 1.46–1.39 (m, 3H, CH_3). ^{13}C-NMR intensity of signals was too low to be assigned.

Ethyl 1,4-dibromo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-3-carboxylate (249la) and ethyl 4-bromo-1-chloro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-3-carboxylate (250la). Reactants: diyne **231l** (50 mg, 0.2 mmol) and nitrile **179a** (40 mg, 0.4 mmol). Column chromatography on silica gel (gradient 40/1→30/1 hexanes/EtOAc) furnished 58 mg of an inseparable mixture of **249la** and **250la** (81% and 2% determined by ^{1}H-NMR) as a colorless solid. The combined yield: 83%.

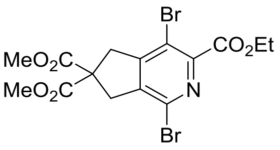

249la


250la

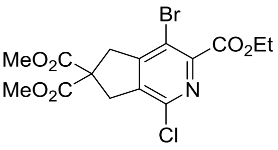
249la: Mp = 68.3 °C (for a mixture containing **250la**). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.45 (q, J = 7.1 Hz, 2H, CH_2), 3.11 (t, J = 7.7 Hz, 2H, CH_2), 3.10 (t, J = 7.7 Hz, 2H, CH_2), 2.23–2.16 (m, 2H, CH_2), 1.42 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 164.56, 157.98, 148.38, 145.03, 136.90, 115.85, 62.56, 36.19, 34.63, 22.44, 14.26. IR (**249la**+**250la**) (drift KBr) υ_{max} 1730, 1425, 1368, 1296, 1281, 1260, 1186, 1129, 1114, 1018 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{11}H_{11}NO_2Br_2$ (M) 346.9157, found 346.9153. R_f (5/1 hexanes/EtOAc) = 0.79 (the same value for **249la** and **250la**).

250la: ^{1}H-NMR overlapped with **249la**. ^{13}C-NMR intensity of signals was too low to be assigned.

3-Ethyl 6,6-dimethyl 1,4-dibromo-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-3,6,6-tricarboxylate (249na) and 3-ethyl 6,6-dimethyl 4-bromo-1-chloro-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-3,6,6-tricarboxylate (250na). Reactants: diyne **231n** (50 mg, 0.13 mmol) and nitrile **179a** (27 mg, 0.27 mmol). Column chromatography on silica gel (gradient 6/1→5/1 hexanes/EtOAc) furnished 51 mg of an inseparable mixture of **249na** and **250na** (77% and 3% determined by ^{1}H-NMR) as a colorless solid. The combined yield: 80%.



249na

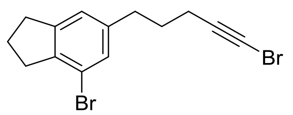


250na

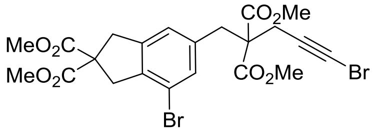
249na: Mp = 143.8 °C (for a mixture containing **250na**). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 4.44 (q, J = 7.1 Hz, 2H, CH$_2$), 3.80 (s, 6H, 2×CH$_3$), 3.74 (s, 2H, CH$_2$), 3.74 (s, 2H, CH$_2$), 1.40 (t, J = 7.1 Hz, 3H, CH$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$) δ 170.72, 164.11, 153.82, 149.12, 140.96, 136.31, 115.21, 62.69, 57.49, 53.70, 43.39, 41.87, 14.22. IR (**249na**+**250na**) (drift KBr) υ_{max} 1745, 1730, 1437, 1425, 1305, 1269, 1207, 1186, 1162, 1090 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{15}H_{16}NO_6Br_2$ (M+H) 463.9339, found 463.9340. R$_f$ (2/1 hexanes/EtOAc) = 0.38 (the same value for **249na** and **250na**).

250na: ^{1}H-NMR overlapped with **249na**. ^{13}C-NMR intensity of signals was too low to be assigned.

5.2.4 Homocyclotrimerized side products



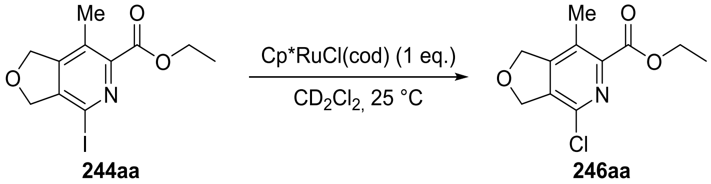
4-Bromo-6-(5-bromopent-4-yn-1-yl)-2,3-dihydro-1*H*-indene (251h). Undesired product of reaction of diyne **231h** and nitrile **179a**. Silica gel column chromatography (gradient 10/1→3/1 hexanes/EtOAc). A colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.12 (s, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 2.98 (t, J = 7.6 Hz, 2H, CH_2), 2.90 (t, J = 7.5 Hz, 2H, CH_2), 2.64 (t, J = 7.6 Hz, 2H, CH_2), 2.21 (t, J = 7.0 Hz, 2H, CH_2), 2.10–2.04 (m, 2H, CH_2), 1.83–1.77 (m, 2H, CH_2). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 146.32, 142.29, 141.75, 129.34, 123.66, 119.87, 79.94, 38.43, 34.28, 34.12, 34.11, 30.07, 24.46, 19.21. IR (drift KBr) υ_{max} 2950, 2929, 2863, 2839, 1556, 1464, 1458, 1428, 1437, 866 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{14}H_{14}Br_2$ (M) 339.9462, found 339.9469. R_f (hexanes) = 0.60.



Dimethyl 4-bromo-6-(5-bromo-2,2-bis(methoxycarbonyl)pent-4-yn-1-yl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (251j). Undesired product of reaction of diyne **231j** and nitrile **179a**. Silica gel column chromatography (gradient 50/1→1/1 hexanes/EtOAc). A colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.07 (s, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 3.76 (s, 6H, 2×CH_3), 3.75 (s, 6H, 2×CH_3), 3.65 (s, 2H, CH_2), 3.58 (s, 2H, CH_2), 3.29 (s, 2H, CH_2), 2.70 (s, 2H, CH_2). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 171.79, 169.84, 141.98, 139.66, 136.72, 131.58, 124.73, 119.38, 75.08, 59.18, 58.31, 53.30, 53.06, 42.67, 41.81, 41.54, 37.26, 23.67. IR (drift KBr) υ_{max} 1730, 1565, 1434, 1281, 1251, 1207, 1177, 1075, 1054, 878 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{23}O_8Br_2$ (M+H) 572.9754, found 572.9757. R_f (2/1 hexanes/EtOAc) = 0.65.

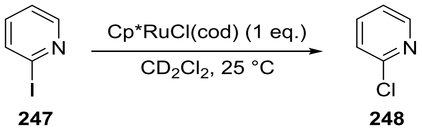
5.2.5 Halogen exchange reaction

Halogen exchange study of 244aa



2-Iodopyridine **244aa** (5.6 mg, 0.017 mmol) in CD_2Cl_2 (0.5 mL) and Cp*RuCl(cod) (6.5 mg, 0.017 mmol) in CD_2Cl_2 (0.3 mL) were added to a NMR tube. The course of the reaction was monitored by ^{1}H-NMR. The proportional representations of **246aa** in the measured reaction mixture were derived from the integration of peaks of its CH_2 group at 5.13 ppm in ^{1}H-NMR spectra.

Halogen exchange study of 247



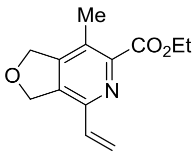
2-Iodopyridine **247** (5 mg, 0.02 mmol) in CD_2Cl_2 (0.4 mL) and Cp*RuCl(cod) (9.5 mg, 0.02 mmol) in CD_2Cl_2 (0.4 mL) were added to a NMR tube. The course of the reaction was monitored by ^{1}H-NMR. The proportional representations of 2-chloropyridine **248** in the measured reaction mixture was derived from the integration of peaks of its CH group at 7.65 ppm in ^{1}H-NMR spectra.

5.2.6 Reactivity of 2- and 3-halopyridines

General method for Suzuki–Miyaura cross coupling reaction[227]

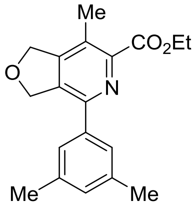
$Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol), CsF (46 mg, 0.3 mmol) and vinylboronic acid pinacol ester **253** (0.2 mmol) or (3,5-dimethylphenyl)boronic acid **254** (0.15 mmol) were added to a solution of starting pyridine derivative **244ba** or **245ba** (0.1 mmol) in dioxane (0.3 mL) and water (0.15 mL) under Ar atmosphere. The reaction mixture was stirred at 95 °C for 15 h. Then the mixture was diluted with EtOAc (10 mL), the organic phase was washed with water (3×5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc or DCM/EtOAc) furnished the corresponding products.

Ethyl 7-methyl-4-vinyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (255). Reactants: the pyridine derivative **244ba** (28 mg, 0.1 mmol) and vinylboronic acid pinacol ester **253** (32 mg, 0.2 mmol). Column chromatography on silica gel (10/1 hexanes/EtOAc) furnished 18 mg (79%) of the title compound as a colorless solid.



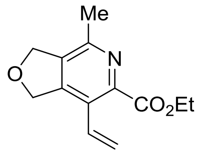
Mp = 45.1 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 17.7, 11.2 Hz, 1H, CH), 5.94 (d, *J* = 17.7 Hz, 1H, CH_2), 5.58 (d, *J* = 11.2 Hz, 1H, CH_2), 5.26 (t, *J* = 2.1 Hz, 2H, CH_2), 5.12–5.09 (m, 2H, CH_2), 4.44 (q, *J* = 7.1 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 1.42 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.62, 150.58, 147.53, 146.84, 135.02, 134.17, 126.59, 120.49, 73.34, 72.95, 61.80, 15.99, 14.39. IR (drift KBr) υ_{max} 1712, 1437, 1320, 1227, 1195, 1060, 1042, 931, 896, 776 cm^{-1}. HRMS (EI-TOF) *m/z* calculated for $C_{13}H_{15}NO_3$ (M) 233.1052, found 233.1053. R_f (5/1 hexanes/EtOAc) = 0.13.

Ethyl 4-(3,5-dimethylphenyl)-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (256). Reactants: pyridine derivative **244ba** (28 mg, 0.1 mmol) and (3,5-dimethylphenyl)boronic acid **254** (23 mg, 0.15 mmol). Column chromatography on silica gel (10/1 hexanes/EtOAc) furnished 28 mg (92%) of the title compound as a colorless solid.



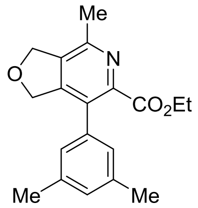
Mp = 114.5 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 (brs, 2H, 2×Ar-H), 7.05 (brs, 1H, Ar-H), 5.37 (t, *J* = 2.1 Hz, 2H, CH_2), 5.15 (t, *J* = 2.0 Hz, 2H, CH_2), 4.47 (q, *J* = 7.1 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 2.39–2.36 (m, 6H, 2×CH_3), 1.45 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.82, 151.04, 149.55, 147.76, 138.37, 134.26, 130.86, 126.01, 125.65, 74.07, 72.94, 61.74, 21.56, 15.81, 14.41, one peak is overlapped. IR (drift KBr) υ_{max} 1712, 1703, 1428, 1317, 1278, 1210, 1195, 1078, 1045, 746 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{19}H_{21}NO_3$ (M) 311.1521, found 311.1518. R_f (5/1 hexanes/EtOAc) = 0.30.

Ethyl 4-methyl-7-vinyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (257). Reactants: the pyridine derivative **245ba** (28 mg, 0.1 mmol) and vinylboronic acid pinacol ester **253** (32 mg, 0.2 mmol). Column chromatography on silica gel (gradient pure DCM→20/1 DCM/EtOAc) furnished 19 mg (83%) of the title compound as a yellowish oil.



^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 17.8, 11.5 Hz, 1H, CH), 5.53 (d, *J* = 11.6 Hz, 1H, CH_2), 5.31 (d, *J* = 17.9 Hz, 1H, CH_2), 5.23 (t, *J* = 2.2 Hz, 2H, CH_2), 5.13 (t, *J* = 2.1 Hz, 2H, CH_2), 4.45 (q, *J* = 7.1 Hz, 2H, CH_2), 2.50 (s, 3H, CH_3), 1.42 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.81, 150.15, 147.72, 147.17, 136.26, 131.92, 126.17, 119.85, 74.21, 72.42, 62.16, 22.25, 14.37. IR (drift KBr) υ_{max} 1727, 1709, 1446, 1329, 1308, 1192, 1168, 1069, 1027, 914 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{13}H_{15}NO_3$ (M) 233.1052, found 233.1052. R_f (5/1 hexanes/EtOAc) = 0.10.

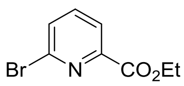
Ethyl 7-(3,5-dimethylphenyl)-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (258). Reactants: the pyridine derivative **245ba** (28 mg, 0.1 mmol) and (3,5-dimethylphenyl)boronic acid **254** (23 mg, 0.15 mmol). Column chromatography on silica gel (4/1 hexanes/EtOAc) furnished 27 mg (89%) of the title compound as a colorless solid.



Mp = 89.9 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.99 (brs, 1H, Ar-H), 6.84 (brs, 2H, 2×Ar-H), 5.17 (t, *J* = 2.1 Hz, 2H, CH_2), 5.01 (t, *J* = 2.2 Hz, 2H, CH_2), 4.15 (q, *J* = 7.1 Hz, 2H, CH_2), 2.53 (s, 3H, CH_3), 2.33–2.29 (m, 6H, 2×CH_3), 1.02 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.21, 150.16, 148.84, 148.31, 138.17, 136.13, 135.21, 129.82, 129.21, 125.82, 73.59, 72.82, 61.54, 22.15, 21.38, 13.79. IR (drift KBr) υ_{max} 2854, 1783, 1601, 1443, 1407, 1374, 1332, 1201, 1048, 716 cm^{-1}. HRMS (EI-TOF) *m*/*z* calculated for $C_{19}H_{21}NO_3$ (M) 311.1521, found 311.1522. R_f (5/1 hexanes/EtOAc) = 0.25.

5.3 Synthesis of 2,2'-bipyridines

5.3.1 Synthesis of a model compound



Ethyl 6-bromopicolinate (259).[228], *n*BuLi (1.35 M solution in hexane, 4.5 mL, 6.0 mmol) was dropwise added to a cooled (-78 °C) solution of 2,6-dibromopyridine **9** (1.295 g, 5.5 mmol) in dry THF (9 mL) under Ar atmosphere. After stirring at -78 °C for 30 min, ethyl formate (4.5 mL, 54.7 mmol) was added. The reaction mixture was stirred at -78 °C for 3 h, then iodine (4.16 g, 16.4 mmol), K_2CO_3 (3.78 g, 27.3 mmol), and dry EtOH (8 mL) were added. The reaction mixture was allowed to warm up to 25 °C and stirring continued for another 17 h. The reaction was quenched by addition of $Na_2S_2O_3$ (sat. aq. sol, 20 mL) and extracted with DCM (3×50 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (10/1 cyclohexane/EtOAc) furnished 567 mg (45%) of the title compound as a colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J = 6.9, 1.7 Hz, 1H, Ar-H), 7.72–7.63 (m, 2H, 2×Ar-H), 4.47 (q, J = 7.1 Hz, 2H, CH_2), 1.43 (t, J = 7.1 Hz, 3H, CH_3). HRMS (ESI) *m/z* calculated for $C_8H_8NO_2BrNa$ (M+H) 251.9636, found 251.9641. R_f (5/1 hexanes/EtOAc) = 0.40. The recorded values were in agreement with the published data.[228]

5.3.2 Reductive dimerization of 2-bromopyridines

Selected general methods of dimerization of 2-bromopyridines:

Method A:[19] PPh_3 (0.94 mmol) and Zn (0.25 mmol) were added to a warmed (70 °C) solution of $NiCl_2$ (0.24 mmol) in dry DMF (0.8 mL). The solution was sonicated while being bubbled through by Ar for 10 min and then stirred at 70 °C for 1 h. Then 2-bromopyridine (0.2 mmol) in DMF (0.7 mL) was added and reaction was stirred at 70 °C for the corresponding time. The course of the reaction was monitored by TLC. After DMF was distilled off from the reaction mixture under reduced pressure, water (3 mL) was added and the reaction mixture was extracted with Et_2O (3×10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$ or Na_2SO_4, filtered, and concentrated under reduced pressure. The yield of the reaction was determined by ^{1}H-NMR and/or HPLC-HRMS analysis.

Method B:[205] A suspension of 2-bromopyridine (0.2 mmol), $NiBr_2(PPh_3)_2$ (0.2 mmol), Zn (1.0 mmol), and *n*Bu_4NI (1.0 mmol) in dry THF (1.5 mL) under Ar atmosphere was stirred at 50–60 °C or irradiated in MW reactor (120 °C) for the corresponding time. The course of the reaction was monitored by TLC (heating method). The reaction was quenched by addition of water (3 mL) and extracted with Et_2O (3×10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$ or Na_2SO_4, filtered, and concentrated under reduced pressure. The yield of the reaction was determined by ^{1}H-NMR and/or HPLC-HRMS analysis.

Method C:[206] 2-Bromopyridine (0.2 mmol), Zn (0.24 mmol), and LiCl (0.2 mmol) were added to a warmed (40 °C) solution of $NiCl_2$ (0.03 mmol) in dry DMF (0.4 mL). After stirring at 50 °C for 10 min, iodine (0.02 mmol) and AcOH (0.02 mmol) were added and reaction was stirred at 70 °C for the corresponding time. The course of the reaction was monitored by TLC. The reaction was quenched by addition of water (3 mL) and extracted with Et_2O (3×10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield of the reaction was determined by ^{1}H-NMR and/or HPLC-HRMS analysis.

Method D:[207] A suspension of 2-bromopyridine (0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), K_2CO_3 (0.3 mmol), and *i*PrOH (0.4 mmol) in dry DMF (0.6 mL) was stirred at 100 °C or irradiated in MW reactor (100 °C) for the corresponding time. The course of the reaction was monitored by TLC (heating method). The reaction was quenched by addition of water (3 mL) and extracted with Et_2O (3×10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield of the reaction was determined by ^{1}H-NMR and/or HPLC-HRMS analysis.

Method E:[11] TDAE (0.4 mmol) was added to a solution of 2-bromopyridine (0.2 mmol) and $PdCl_2(PhCN)2$ (0.04 mmol) in dry DMF (1 mL). The reaction mixture was stirred at 80 °C for or irradiated in MW reactor (120 °C, 100 W) for the corresponding time. The course of the reaction was monitored by TLC (heating method). The reaction was quenched by addition of water (3 mL) and extracted with Et_2O (3×10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$ or Na_2SO_4, filtered, and concentrated under reduced pressure. The yield of the reaction was determined by ^{1}H-NMR and/or HPLC-HRMS analysis.

Method F:[208] A suspension of 2-bromopyridine (0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), dppp (0.02 mmol), and Cs_2CO_3 (0.25 mmol) in dry toluene (2.5 mL) was irradiated in MW reactor (200 °C) for the corresponding time. After addition of water (3 mL), the reaction was extracted with EtOAc (3×10 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield of the reaction was determined by ^{1}H-NMR and/or HPLC-HRMS analysis.

Method G:[229] A suspension of 2-bromopyridine (0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), K_2CO_3 (0.6 mmol), and PEG 3350 (1 g) was irradiated in MW reactor (100 °C, initiation power 400 W) for the corresponding time. Then the reaction mixture was dissolved in minimal amount of DCM and poured into Et_2O (50 mL) and cooled down to 4 °C. The formed suspension was filtered and the filtrate was concentrated under reduced pressure. The yield of the reaction was determined by ^{1}H-NMR and/or HPLC-HRMS analysis.

Method H:[208] A solution of 2-bromopyridine (0.2 mmol), $Pd(PPh_3)_4$ (0.04 mmol) and $n\mathrm{Bu}_6\mathrm{Sn}_2$ (0.23 mmol) in dry toluene (1.0 mL) was irradiated in MW reactor (150 °C) for 2 h. Then 2-bromopyridine (0.1 mmol) and $Pd(PPh_3)_4$ (0.02 mmol) were added and the reaction was irradiated in MW reactor (180 °C) for another 2 h. After the evaporation of toluene under reduced pressure, the reaction mixture was diluted by MeOH (10 mL). Then solution Na_2EDTA (1 mmol) in water (2 mL) was added and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was then extracted with DCM (3×15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield of the reaction was determined by ^{1}H-NMR and/or HPLC-HRMS analysis.

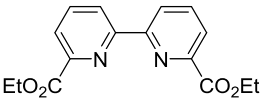
Method I:[230] The suspension of 2-bromopyridine (0.2 mmol) and Cu-powder (1.0 mmol) in DMF (1 mL) were stirred at 120 or 200 °C, or irradiated in MW reactor (200 °C) for the corresponding time. The course of the reaction was monitored by TLC (heating method). The reaction was quenched by addition of water (3 mL) and extracted with Et_2O (3×10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield of the reaction was determined by ^{1}H-NMR.

Reactions in ultrasound reactor: All the components of the reaction mixture were mixed in 2 mL MW vial with cone-shaped bottom. The reaction was irradiated by ultrasound (5 s pulses – 5 s ON, 2 s OFF, 45 or 50 °C temperature of ultrasound tip, 35% amplitude) for the corresponding time. The work-up of the reaction followed the procedure used for conventional heating or MW irradiation procedures (*vide supra*).

Reactions in ball-mill: All the components of the reaction mixture were mixed in 0.5 mL stainless steel ball-mill jar. The reaction mixture was grinded in vibratory ball-mill (2 stainless steel balls, 30 Hz frequency) for the corresponding time. The work-up of the reaction followed the procedure used for conventional heating or MW irradiation procedures (*vide supra*).

5.3.3 Dimerization of model compound

Diethyl [2,2'-bipyridine]-6,6'-dicarboxylate (260). Following general method D for

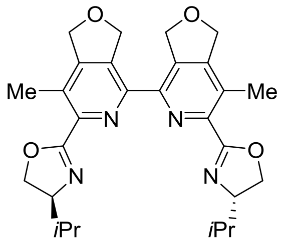


dimerization of 2-bromopyridines, a suspension of 2-bromopyridine **259** (230 mg, 0.57 mmol), $Pd(OAc)_2$ (19 mg, 0.085 mmol), K_2CO_3 (117 mg, 0.85 mmol), and *i*PrOH (90 µL, 1.1 mmol) in dry DMF (1.6 mL) was stirred at 100 °C for 17 h. The reaction was quenched by addition of water (10 mL) and extracted with Et_2O (3×30 mL). The combined organic fractions were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography on silica gel (3/1 cyclohexane/EtOAc) furnished 83 mg (98%) of the title compound as a colorless solid.

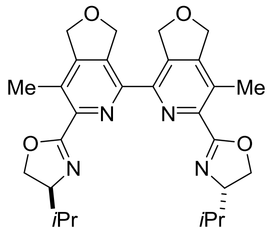
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.74 (dd, J = 7.9, 1.1 Hz, 1H, Ar-H), 8.12 (dd, J = 7.7, 1.1 Hz, 1H, Ar-H), 7.96 (t, J = 7.8 Hz, 1H, Ar-H), 4.47 (q, J = 7.1 Hz, 2H, CH_2), 1.44 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.25, 155.53, 147.87, 138.06, 125.46, 124.76, 61.97, 14.40. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{17}N_2O_4$ (M+H) 301.1188, found 301.1189. R_f (3/1 hexanes/EtOAc) = 0.30. The recorded values were in agreement with the published data.[231]

5.3.4 Synthesis of bipyridine 261

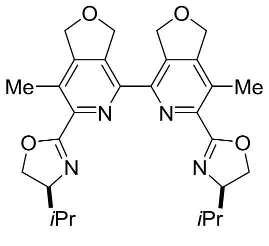
6,6'-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-7,7'-dimethyl-1,1',3,3'-tetrahydro-4,4'-bifuro[3,4-*c*]pyridine (261). Following the general method B for dimerization of 2-bromopyridines, a suspension of 2-bromopyridine **272** (288 mg, 0.89 mmol), $NiBr_2(PPh_3)_2$ (665 mg, 0.89 mmol), Zn (289 mg, 4.43 mmol), and *n*Bu_4NI (1.636 g, 4.43 mmol) in dry THF (7 mL) under Ar atmosphere was stirred at 60 °C for 14 h. The reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol, 15 mL) and extracted with DCM (3×50 mL). The combined organic fractions dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then diluted by MeOH (30 mL) and Na_2EDTA (1 M aq. sol., 10 mL) was added. After stirring at 25 °C for 1 h, the mixture was extracted with DCM (3×50 mL). The combined organic fractions dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Repeated column chromatographies of the residue on silica gel (20/1 PhMe/MeOH; gradient 2/1→1/2 hexanes/EtOAc) furnished 111 mg (51%, >99% ee) of the title compound as a colorless solid.



Mp = 166.5 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.76–5.65 (m, 4H, 2×CH_2), 5.19–5.07 (m, 4H, 2×CH_2), 4.48–4.42 (m, 2H, 2×CH), 4.25–4.19 (m, 2H, CH_2), 4.19–4.14 (m, 2H, CH_2), 2.53 (s, 6H, 2×CH_3), 1.94–1.85 (m, 2H, 2×CH), 1.07 (d, J = 6.7 Hz, 6H, 2×CH_3), 1.00 (d, J = 6.7 Hz, 6H, 2×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.57, 151.27, 147.20, 144.06, 135.74, 128.11, 76.03, 73.58, 72.36, 69.98, 33.08, 18.97, 18.52, 16.52. IR (drift KBr) υ_{max} 2956, 2934, 2870, 1637, 1426, 1160, 1060, 1028, 1012, 903 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{28}H_{35}N_4O_2$ (M+H) 491.2653, found 491.2652. R_f (1/1 hexane/EtOAc) = 0.32. $[\alpha]_D^{20}$ = -93.8° ($CHCl_3$, c = 0.30). HPLC: Daicel Chiralpak IA *n*-heptane/IPA 98/2, 1 mL/min, 245 nm, $t_{S,S}$ = 48.0 min, $t_{R,R}$ = ND.



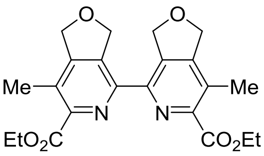
(*rac*)-**261**



(*meso*)-**261**

6,6'-Bis((*RS*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-7,7'-dimethyl-1,1',3,3'-tetrahydro-4,4'-bifuro[3,4-*c*]pyridine ((*rac*)-261) and (*RS,SR*)-6,6'-bis(4-isopropyl-4,5-dihydrooxazol-2-yl)-7,7'-dimethyl-1,1',3,3'-tetrahydro-4,4'-bifuro[3,4-*c*]pyridine ((*meso*)-261). The unseparable mixture of a racemic mixture of **261** ((*S*,*S*)-**261**/(*R*,*R*)-**261** 1/1) and (*meso*)-**261** was prepared using the same reaction sequence as for synthesis of the chiral bipyridine **261** using racemic mixture of valinol.

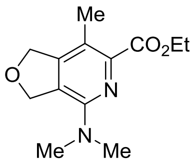
HPLC: Daicel Chiralpak IA *n*-heptane/IPA 98/2, 1 mL/min, 245 nm, $t_{R,R}$ = 23.9 min, t_{meso} = 30.8 min, $t_{S,S}$ = 48.0 min.



Diethyl 7,7'-dimethyl-1,1',3,3'-tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine]-6,6'-dicarboxylate (262). Following general method H for dimerization of 2-bromopyridines, a solution of 2-bromopyridine **244ba** (387 mg, 1.4 mmol), Pd(PPh$_3$)$_4$ (313 mg, 0.27 mmol) and *n*Bu$_6$Sn$_2$ (800 µL, 1.5 mmol) in dry toluene (9.0 mL) was irradiated in MW reactor (150 °C, 140 W) for 2 h. Then 2-bromopyridine (193 mg, 0.68 mmol) and Pd(PPh$_3$)$_4$ (156 mg, 0.14 mmol) were added and reaction was irradiated in MW reactor (180 °C, 290 W) for another 2 h. After the evaporation of toluene under reduced pressure, the reaction mixture was diluted by MeOH (60 mL). Then solution Na$_2$EDTA (6 mmol) in water (12 mL) was added and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was then extracted with DCM (3×100 mL). The combined organic fractions were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The solid residue was then suspended in Et$_2$O (50 mL) and centrifuged. The mother liquor was removed and the suspension was washed with Et$_2$O (2×50 mL). The suspension was then dried under reduced pressure. This method provided 393 mg (94%) of the titled compound as a colorless solid.

Mp = 282.3 °C. ^{1}H-NMR (600 MHz, CDCl$_3$) δ 5.75 (t, J = 2.0 Hz, 4H, 2×CH$_2$), 5.17–5.15 (m, 2H, 2×CH$_2$), 4.46 (q, J = 7.1 Hz, 4H, 2×CH$_2$), 1.49 (t, J = 7.1 Hz, 6H, 2×CH$_3$). ^{13}C-NMR (125 MHz, CDCl$_3$) δ 166.33, 151.97, 147.03, 145.74, 137.01, 128.82, 76.09, 72.34, 61.52, 16.10, 14.54. IR (drift KBr) υ_{max} 1713, 1456, 1418, 1302, 1261, 1186, 1118, 1066, 1049, 1030, 908 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{13}H_{19}NO_3BrSi$ (M+H) 344.0318, found 344.0321. R$_f$ (3/1 hexane/EtOAc) = 0.24.

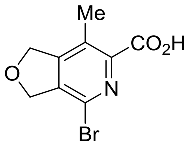
Ethyl 4-(dimethylamino)-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (263).



Following general method I for dimerization of 2-bromopyridines, the suspension of 2-bromopyridine **244ba** (58 mg, 0.2 mmol) and Cu-powder (64 mg, 1.0 mmol) in DMF (1 mL) were stirred at 200 °C for 60 h. The reaction was quenched by addition of water (3 mL) and extracted with Et_2O (3×10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (1/1 cyclohexane/EtOAc) provided 46 mg (91%) of the title compound as a colorless oil.

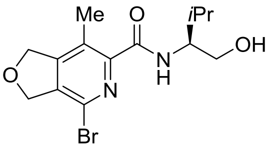
^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.30 (t, J = 2.6 Hz, 2H, CH_2), 5.02 (t, J = 2.6 Hz, 2H, CH_2), 4.40 (q, J = 7.1 Hz, 2H, CH_2), 3.04 (s, 6H, 2×CH_3), 2.25 (s, 3H, CH_3), 1.41 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.14, 153.14, 151.62, 144.93, 120.92, 117.03, 74.46, 73.20, 61.32, 39.14, 14.82, 14.42. HRMS (ESI) *m*/*z* calculated for $C_{13}H_{19}NO_3BrSi$ (M+H) 344.0318, found 344.0321. R_f (3/1 hexane/EtOAc) = 0.30.

4-Bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylic acid (268).[232] LiOH·H_2O



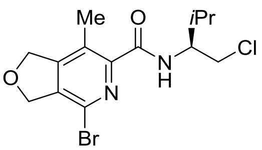
(420 mg, 9.8 mmol) was added to a solution of 2-bromopyridine **244ba** (1.403 g, 4.9 mmol) in THF (15 mL) and water (5 mL). The reaction was stirred at 25 °C for 3 h and then the reaction mixture was acidified by HCl (1 M aq. sol.) to pH 7. The formed suspension was filtered, the solids were washed with water and dried under reduced pressure. This method provided 1.254 g (99%) of the title compound as a colorless solid.

Mp = 185.5 °C. ^{1}H-NMR (400 MHz, d_6-Me_2CO) δ 5.30–5.28 (m, 2H, CH_2), 5.13–5.11 (m, 2H, CH_2), 2.50 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, d_6-Me_2CO) δ 166.25, 155.75, 148.03, 141.86, 131.47, 131.37, 75.38, 75.08, 16.63. IR (drift KBr) υ_{max} 1716, 1396, 1279, 1244, 1186, 1060, 918, 891, 806, 669 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_9H_7BrNO_3$ (M-H) 255.9615, found 255.9615. R_f (EtOAc) = 0.08.



(*S*)-4-Bromo-*N*-(1-hydroxy-3-methylbutan-2-yl)-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxamide (270). Step 1:[17] A solution of acid **268** (1.254 g, 4.86 mmol) in $SOCl_2$ (15 mL) was refluxed under condenser for 12 h. Then the excess of $SOCl_2$ was distilled off from the reaction mixture and the residue was subjected to the next step without any further purification. Step 2:[233] A solution of the residue from step 1 in DCM (16 mL) was slowly added to a cooled (0 °C) solution of L-valinol (563 mg, 5.2 mmol) and Et_3N (1.3 mL, 9.4 mmol) in DCM (12 mL). After stirring for 13 h at 25 °C, the reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 30 mL) and extracted with DCM (3×100 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1→1/2 cyclohexane/EtOAc) provided 1.456 g (87%) of the title compound as a colorless solid.

Mp = 132.5 °C. ^1H-NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.3 Hz, 1H, NH), 5.21–5.17 (m, 2H, CH_2), 5.12–5.08 (m, 2H, CH_2), 3.91–3.72 (m, 3H, CH, CH_2), 2.70 (brs, 1H, OH), 2.54 (s, 3H, CH_3), 2.10–1.95 (m, 1H, CH), 1.02 (d, J = 6.7 Hz, 3H, CH_3), 1.00 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.41, 153.49, 147.41, 139.02, 129.75, 129.26, 74.31, 74.13, 64.23, 57.67, 29.34, 19.81, 18.93, 16.28. IR (drift KBr) υ_{max} 3368, 1656, 1531, 1395, 1307, 1196, 1047, 902, 623 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{20}BrN_2O_3$ (M+H) 343.0652, found 343.0653. R_f (1/1 hexane/EtOAc) = 0.24.

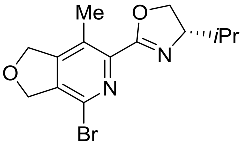


(*S*)-4-Bromo-*N*-(1-chloro-3-methylbutan-2-yl)-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxamide (271).[233] $SOCl_2$ (0.6 mL, 8.2 mmol) was added to a solution of alcohol **270** (1.408 mg, 4.1 mmol) in dry DCM (20 mL). After refluxing for 27 h, the reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 30 mL) and extracted with DCM (3×100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 3/1→2/1 cyclohexane/EtOAc) provided 1.453 g (98%) of the title compound as a colorless solid.

Mp = 155.6 °C. ^1H-NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 9.1 Hz, 1H, NH), 5.23–5.20 (m, 2H, CH_2), 5.14–5.12 (m, 2H, CH_2), 4.13–4.04 (m, 1H, CH), 3.78 (dd, J = 11.4, 4.5 Hz, 1H, CH), 3.73 (dd, J = 11.4, 4.3 Hz, 1H, CH), 2.59 (s, 3H, CH_3), 2.17–2.07 (m, 1H, CH), 1.04 (d, J = 6.7 Hz, 3H, CH_3), 1.01 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.40, 153.53, 147.10, 139.18, 129.87, 129.43, 74.37, 74.20, 55.34, 46.46, 29.52, 19.61, 18.79, 16.29. IR (drift KBr) υ_{max} 3373, 2968, 1671, 1510, 1391, 1311, 1184, 1062, 904, 639 cm^{-1}.

HRMS (ESI) *m/z* calculated for $C_{14}H_{19}BrClN_2O_2$ (M+H) 361.0313, found 361.0315. R_f (2/1 hexane/EtOAc) = 0.59.

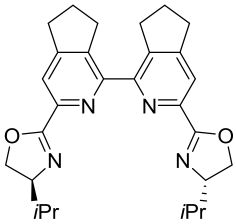
(*S*)-4-Bromo-6-(4-isopropyl-4,5-dihydrooxazol-2-yl)-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine (272).[233] A solution of chloride **271** (550 mg, 1.5 mmol) in dry THF (12 mL) was slowly added to a suspension of NaH (60% w/w in mineral oil, 304 mg, 7.6 mmol) and *n*Bu_4NI (56 mg, 0.15 mmol) in dry THF (12 mL). After stirring for 17 h at 25 °C, the reaction was warmed up to 50 °C for 1 h. Then the reaction was quenched by addition of water (10 mL) and extracted with EtOAc (3×40 mL). The combined organic fractions were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (3/1 cyclohexane/EtOAc) provided 487 mg (93%) of the title compound as a colorless solid.



Mp = 86.3 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.20–5.16 (m, 2H, CH_2), 5.12–5.08 (m, 2H, CH_2), 4.44 (td, *J* = 7.3, 1.4 Hz, 1H, CH), 4.20–4.08 (m, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.90–1.77 (m, 1H, CH), 1.02 (d, *J* = 6.7 Hz, 3H, CH_3), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.95, 151.93, 154.66, 138.09, 131.11, 128.61, 74.27, 74.17, 73.69, 70.14, 33.04, 19.04, 18.59, 16.53. IR (drift KBr) υ_{max} 2961, 2873, 1649, 1421, 1300, 1159, 1065, 1014, 904 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{14}H_{18}BrN_2O_2$ (M+H) 325.0546, found 325.0548. R_f (2/1 hexane/EtOAc) = 0.39. $[\alpha]_D^{20}$ = -55.2° ($CHCl_3$, *c* = 0.36)

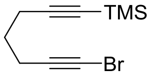
5.3.5 Synthesis of bipyridine 277

3,3'-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-1,1'-bi(cyclopenta[*c*]pyridine) (277). Following the general method A for dimerization of 2-halopyridines, PPh_3 (814 mg, 3.1 mmol) and Zn (56 mg, 0.84 mmol) were added to a warmed (70 °C) solution of $NiCl_2$ (103 mg, 0.78 mmol) in dry DMF (2 mL). The solution was sonicated while being bubbled through by Ar for 10 min and then stirred at 70 °C for 1 h. Then 2-bromopyridine **284** (200 mg, 0.65 mmol) in DMF (3 mL) was added and reaction was stirred at 70 °C for 21 h. After DMF was distilled off from the reaction mixture under reduced pressure, the residue was diluted by DCM (30 mL) and filtered through Celite®. The filtrate was extracted with $NaHCO_3$ (sat. aq. sol., 1 mL) and the aqueous phase was washed with DCM (2×30 mL). The combined organic fractions were concentrated (20 mL) under reduced pressure and extracted with HCl (0.5% aq. sol., 3×10 mL). The aqueous phase was rapidly alkalized by NaOH (1 M aq. sol.) to pH 12 and extracted with DCM (3×50 mL). The extraction with HCl, alkalization with NaOH, and extraction with DCM was repeated until the product **277** was free of TPPO (at least 3×). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The column chromatography on silica gel (40/1 PhMe/MeOH) provided 72 mg (49%) of the title compound as amorphous solid.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 2H, Ar-H), 4.52–4.44 (m, 2H, 2×CH), 4.22–4.08 (m, 4H, 2×CH_2), 3.37–3.16 (m, 2H, CH_2), 3.25–3.15 (m, 2H, CH_2), 2.98 (t, J = 7.6 Hz, 4H, 2×CH_2), 2.20–2.04 (m, 4H, 2×CH_2), 1.93–1.81 (m, 2H, 2×CH), 1.05 (d, J = 6.7 Hz, 6H, 2×CH_3), 0.94 (d, J = 6.7 Hz, 6H, 2×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.50, 156.26, 152.93, 143.90, 142.69, 119.96, 72.87, 70.82, 33.03, 32.86, 32.27, 24.94, 19.23, 18.39. IR (drift KBr) υ_{max} 2956, 2866, 1637, 1559, 1440, 1377, 1305, 1266, 1251, 1210, 1171, 1138, 1072, 976, 936 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{28}H_{35}N_4O_2$ (M+H) 459.2755, found 459.2749. R_f (2/1 hexanes/EtOAc) = 0.23. $[\alpha]_D^{20}$ = -122.2° ($CHCl_3$, c = 0.32).

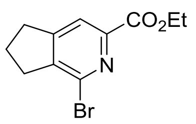
(7-Bromohepta-1,6-diyn-1-yl)trimethylsilane (278). Step 1:[216] LiHMDS (1 M solution in THF, 20.5 mL, 20.5 mmol) was added dropwise to a cooled (-78 °C) solution of hepta-1,6-diyne **239** (2.4 mL, 20.5 mmol) in dry THF (100 mL). After stirring at -78 °C for 1 h, TMSCl (2.6 mL, 20.5 mmol) was added dropwise. After 1 more hour at -78 °C, the reaction was quenched by pouring into NH_4Cl (sat. aq. sol., 50 mL) and extracted with Et_2O (3×200 mL). The combined organic phases were washed with brine (100 mL),



dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The mixture was filtered through short silica gel pad (20/1 hexane/Et_2O) and subjected to the next step without any further purification.

Step 2: *n*-BuLi (1.6 M solution in hexane, 11.1 mL, 17.6 mmol) was added dropwise to a cooled (-78 °C) solution of the crude reaction mixture from step 1 (which according to ^{1}H-NMR consists of 17.6 mmol of monosilylated product) in dry THF (23 mL). After vigorous stirring at -78 °C for 30 min, NBS (3950 mg, 21.1 mmol) was added in one portion and the mixture was allowed to warm up to 25 °C and stirred for 12 h. The reaction mixture was quenched by pouring into the NH_4Cl (sat. aq. sol., 50 mL) and extracted with Et_2O (3×150 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient pure hexanes→100/1 hexanes/DCM) furnished 2.62 g (52% in 2 steps) of the title compound as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.26–2.29 (m, 4H, 2×CH_2), 1.73 (p, J = 7.0 Hz, 2H, CH_2), 0.15 (s, 9H, 3×CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 106.12, 85.49, 79.52, 38.54, 27.52, 19.15, 18.94, 0.27. R_f (50/1 hexanes/Et_2O) = 0.43. The recorded values were in agreement with the published data.[234]

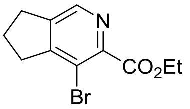


Ethyl 1-bromo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-3-carboxylate (279) Step 1: Following the general procedure for cyclotrimerization of halodiynes with nitriles, a solution of diyne **278** (1.000 g, 4.11 mmol) in DCE (20 mL) was added to a solution of Cp*RuCl(cod) (111 mg, 0.29 mmol) and nitrile **179a** (0.8 mL, 8.2 mmol) in DCE (20 mL) under Ar atmosphere during the course of 1 h. The reaction mixture was stirred at 25 °C for 14 h and then volatiles were evaporated under reduced pressure. Filtration of the residue through a silica gel pad (20/1 cyclohexane/EtOAc) furnished a mixture of 2- and 3-bromopyridines, which were subjected to the step without any further purification.

Step 2:[235] TBAF (1 M solution in THF, 3.6 mL, 3.6 mmol) was added dropwise to a solution of the residue from the step 1 in THF (15 mL). After 1 h of stirring at 25 °C, the reaction was quenched by addition of water (20 mL) and extracted with DCM (3×70 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 15/1→8/1 cyclohexane/EtOAc) provided the 471 mg (42% in 2 steps) of the title compound and 349 mg (31%) of the second regioisomer **355** as colorless solids.

279: Mp = 52.1 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* 7.92 (s, 1H, Ar-H), 4.44 (q, *J* = 7.1 Hz, 2H, CH_2), 3.11–3.03 (m, 2H, CH_2), 2.99 (t, *J* = 7.5 Hz, 2H, CH_2), 2.17 (p, *J* = 7.7 Hz, 2H, CH_2), 1.41 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) *δ* 164.52, 156.84, 147.30, 146.25, 139.30, 121.06, 62.15, 33.89, 33.48, 23.50, 14.41. IR (drift KBr) υ_{max} 2956, 1716, 1434, 1396, 1376, 1300, 1287, 1224, 1184, 1150, 1098 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{14}H_{21}NO_2BrSi$ (M+H) 342.0525, found 342.0524. R_f (5/1 hexane/EtOAc) = 0.31.

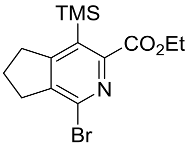
355: Mp = 38.4 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* 8.37 (s, 1H, Ar-H), 4.45 (q, *J* = 7.1 Hz, 2H, CH_2), 3.08 t, *J* = 7.6 Hz, 2H, CH_2), 3.00 (t, *J* = 7.6 Hz, 2H, CH_2), 2.15 (p, *J* = 7.7 Hz, 2H, CH_2), 1.41 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) *δ* 165.63, 156.56 (2×), 147.23, 143.43, 116.71, 62.21, 34.91, 31.64, 23.76, 14.29. IR (drift KBr) υ_{max} 1977, 1721, 1430, 1395, 1377, 1307, 1284, 1270, 1180, 1152, 1120, 930 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{14}H_{21}NO_2BrSi$ (M+H) 342.0525, found 342.0524. R_f (3/1 hexane/EtOAc) = 0.24.



355

The separation of the reaction mixture after the step 1 provided 2-bromopyridine **356** and 3-bromopyridine **357** as colorless solids.

356: Mp = 73.0 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* 4.36 (q, *J* = 7.2 Hz, 2H, CH_2), 3.08 (t, *J* = 7.5 Hz, 2H, CH_2), 2.91 (t, *J* = 7.6 Hz, 2H, CH_2), 2.07 (p, *J* = 7.7 Hz, 2H, CH_2), 1.38 (t, *J* = 7.2 Hz, 3H, CH_3), 0.31 (s, 9H, 3×CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) *δ* 167.79, 162.63, 154.78, 142.68, 139.69, 129.25, 62.15, 36.67, 32.82, 23.54, 14.18, 0.79. IR (drift KBr) υ_{max} 2983, 1732, 1522, 1304, 1282, 1256, 1241, 1168, 907, 851, 770 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{14}H_{21}NO_2BrSi$ (M+H) 342.0525, found 342.0524. R_f (20/1 hexane/EtOAc) = 0.15.



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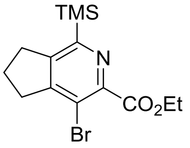
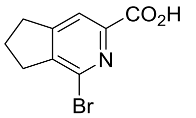
357: Mp = 33.2 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* 4.45 (q, *J* = 7.1 Hz, 2H, CH_2), 3.12 (t, *J* = 7.6 Hz, 2H, CH_2), 2.95 (t, *J* = 7.7 Hz, 2H, CH_2), 2.12 (p, *J* = 7.7 Hz, 2H, CH_2), 1.41 (t, *J* = 7.1 Hz, 3H, CH_3), 0.32 (s, 9H, 3×CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) *δ* 166.92, 161.10, 153.11, 148.46, 148.41, 116.03, 61.86, 34.27, 33.20, 23.71, 14.27, -1.33. IR (drift KBr) υ_{max} 2959, 1741, 1306, 1277, 1248, 1211, 1179, 1155, 929, 839 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{14}H_{21}NO_2BrSi$ (M+H) 342.0525, found 342.0528. R_f (20/1 hexane/EtOAc) = 0.21.



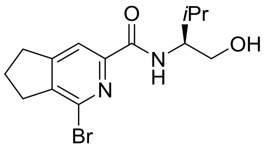
357

1-Bromo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-3-carboxylic acid (280).[232] LiOH·H_2O (37 mg, 0.87 mmol) was added to a solution of 2-bromopyridine **279** (118 mg, 0.44 mmol) in THF (2 mL) and water (0.5 mL). The reaction was stirred at 25 °C for 3 h and then the reaction mixture was acidified by HCl (1 M aq. sol.) to pH 7. The formed suspension was filtered, the solids were washed with water and dried under reduced pressure. This method provided 102 mg (97%) of the title compound as a colorless solid.



Mp = 163.3 °C. ^{1}H-NMR (300 MHz, d_6-Me_2CO) δ 8.11 (s, 1H, Ar-H), 3.28 (t, J = 7.6 Hz, 2H, CH_2), 3.12 (t, J = 7.7 Hz, 2H, CH_2), 2.32 (p, J = 7.7 Hz, 2H, CH_2). ^{13}C-NMR (75 MHz, d_6-Me_2CO) δ 166.08, 160.09, 148.84, 148.29, 139.71, 122.43, 35.39, 34.93, 25.20. IR (drift KBr) υ_{max} 3527, 2923, 1694, 1284, 1263, 1234, 1201, 940, 902 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_9H_9BrNO_2$ (M+H) 241.9817, found 241.9816. R_f (EtOAc) = 0.15.

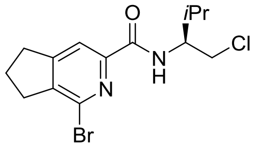
(*S*)-1-Bromo-*N*-(1-hydroxy-3-methylbutan-2-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-3-carboxamide (282). Step 1:[17] A solution of acid **280** (435 g, 1.80 mmol) in $SOCl_2$ (5.5 mL) was refluxed under condenser for 12 h. Then the excess of $SOCl_2$ was distilled off from the reaction mixture and the residue was subjected to the next step without any further purification.



Step 2:[233] A solution of the residue from step 1 in DCM (6.5 mL) was slowly added to a cooled (0 °C) solution of L-valinol (214 mg, 2.0 mmol) and Et_3N (0.5 mL, 3.6 mmol) in DCM (5 mL). After stirring for 18 h at 25 °C, the reaction was quenched by addition of NH_4Cl (sat. aq. sol., 10 mL) and extracted with DCM (3×30 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 3/2→1/1 cyclohexane/EtOAc) provided 556 mg (95%) of the title compound as a colorless oil.

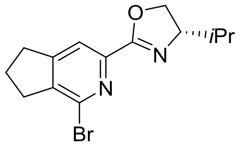
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04–7.89 (m, 2H, Ar-H, NH), 3.94–3.70 (m, 3H, CH, CH_2), 3.11–2.94 (m, 2H, CH_2), 2.40 (brs, 1H, OH), 2.24–2.11 (m, 2H, CH_2), 2.11–1.96 (m, 1H, CH), 1.07–0.97 (m, 6H, 2×CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.63, 158.44, 148.68, 146.11, 142.28, 118.22, 64.35, 58.03, 33.74, 31.60, 29.33, 23.96, 19.76, 19.00 . IR (drift KBr) υ_{max} 3390, 2965, 1655, 1533, 1308, 1269, 1066, 905 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{20}BrN_2O_2$ (M+H) 327.0708, found 327.0709. R_f (2/1 hexanes/EtOAc) = 0.18.

(*S*)-1-Bromo-*N*-(1-chloro-3-methylbutan-2-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-3-carboxamide (283).[233] $SOCl_2$ (0.35 mL, 4.8 mmol) was added to a solution of alcohol **282** (761 mg, 2.3 mmol) in dry DCM (13 mL). After refluxing for 15 h, the reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 20 mL) and extracted with DCM (3×60 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 7/1→5/1 hexanes/EtOAc) provided 792 mg (99%) of the title compound as a colorless solid.



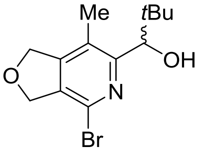
Mp = 59.2 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H, Ar-H), 7.94 (d, J = 9.12 Hz, 1H, NH), 4.18–4.07 (m, 1H, CH), 3.82–3.69 (m, 2H, CH_2), 3.12–2.93 (m, 4H, 2×CH_2), 2.66–2.02 (m, 3H, CH_2, CH), 1.03 (d, J = 6.7 Hz, 3H, CH_3), 1.00 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.56, 158.36, 148.58, 146.29, 142.36, 118.14, 55.52, 46.48, 33.73, 31.60, 29.55, 23.97, 19.56, 18.80. IR (drift KBr) υ_{max} 3393, 2965, 1679, 1533, 1518, 1434, 1308, 1296, 1269, 1186, 917 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{19}BrClN_2O$ (M+H) 345.0369, found 345.0372. R_f (2/1 hexanes/EtOAc) = 0.64.

(*S*)-2-(1-Bromo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-4-isopropyl-4,5-dihydrooxazole (284).[233] A solution of chloride **283** (497 mg, 1.44 mmol) in dry THF (12 mL) was slowly added to a suspension of NaH (60% w/w in mineral oil, 286 mg, 7.2 mmol) and *n*Bu_4NI (55 mg, 0.14 mmol) in dry THF (12 mL). After stirring for 17 h at 25 °C, the reaction was quenched by addition of NH_4Cl (sat. aq. sol., 10 mL) and extracted with DCM (3×30 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (4/1 cyclohexane/EtOAc) provided 358 mg (81%) of the title compound as a colorless solid.



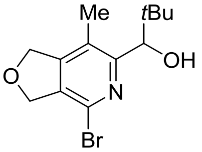
Mp = 60.7 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H, Ar-H), 4.53–4.42 (m, 1H, CH), 4.23–4.07 (m, 2H, CH_2), 3.09–2.92 (m, 2H, CH_2), 2.16 (p, J = 7.6 Hz, 2H, CH_2), 1.94–1.80 (m, 1H, CH), 1.03 (d, J = 6.8 Hz, 3H, CH_3), 0.92 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.25, 157.52, 147.66, 145.49, 141.80, 119.63, 73.05, 71.05, 33.67, 32.95, 31.72, 23.97, 19.25, 18.36. IR (drift KBr) υ_{max} 2953, 1646, 1347, 1314, 1272 1177, 1150, 1081, 976, 934, 908 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{18}BrN_2O$ (M+H) 309.0603, found 309.0603. R_f (2/1 hexanes/EtOAc) = 0.43.

5.3.6 Synthesis of analogues of Bolm's ligand



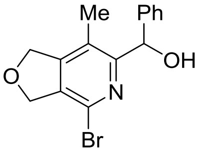
(*S*/*R*)-1-(4-Bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-ol (286).[236] BH_3·THF (1 M solution in THF, 100 µL, 0.1 mmol) was added to a cooled (0 °C) solution of ketone **244bb** (28 mg, 0.09 mmol) and (*R*)-2-methyl-CBS-oxazaborolidine (4 mg, 0.011 mmol) in THF (1 mL). After stirring at 0 °C for 18 h, the reaction was quenched by addition of water (2 mL) and extracted with DCM (3×5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→5/1 hexanes/EtOAc) furnished 9 mg (32%, 13% ee) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.16–5.12 (m, 2H, CH_2), 5.11–5.08 (m, 2H, CH_2), 4.57 (s, 1H, CH), 2.18 (s, 3H, CH_3), 0.94 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.90, 151.23, 135.14, 130.73, 124.35, 75.61, 74.15, 73.95, 37.98, 26.07, 15.39. IR (drift KBr) υ_{max} 2956, 1423, 1388, 1364, 1307, 1261, 1082, 1060, 1014, 924, 903 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{13}H_{19}BrNO_2$ (M+H) 300.0599, found 300.0598. R_f (5/1 hexane/EtOAc) = 0.21. HPLC: Daicel Chiralpak IA, *n*-heptane/IPA 95/5, 1 mL/min, 207 nm, t_1 = 6.3 min (major), t_2 = 8.3 min (minor).



(*RS*)-1-(4-Bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-ol ((*rac*)-286).[237] $NaBH_4$ (28 mg, 0.72 mmol) was added portionwise to a solution of ketone **244bb** (144 mg, 0.48 mmol) in MeOH (2 mL). After stirring at 25 °C for 2 h, the reaction was quenched by addition of water (3 mL) and extracted with EtOAc (3×10 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and dried under reduced pressure. This method provided 143 mg (99%) of the title compound as a colorless oil.

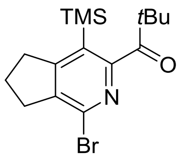
HPLC: Daicel Chiralpak IA, *n*-heptane/IPA 95/5, 1 mL/min, 207 nm, t_1 = 6.3 min, t_2 = 8.3 min. All spectral data were in agreement with the chiral product **286**.



(*RS*)-(4-Bromo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)(phenyl)methanol ((*rac*)-287).[237] $NaBH_4$ (6 mg, 0.16 mmol) was added portionwise to a solution of ketone **244bc** (30 mg, 0.09 mmol) in MeOH (1.2 mL). After stirring at 25 °C for 3 h, the reaction was quenched by addition of water (3 mL) and extracted with EtOAc (3×10 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and dried under reduced pressure. This method provided 29 mg (96%) of the title compound as a colorless oil.

Mp = 100.9 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H, 5×Ar-H), 5.13–5.08 (m, 4H, 2×CH_2), 5.76 (s, 1H, CH), 1.96 (s, 3H, CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.27, 151.92, 141.69, 135.93, 130.19, 128.69, 128.03, 127.57, 123.40, 73.70, 73.66, 72.35, 14.10. IR (drift KBr) υ_{max} 1453, 1410, 1376, 1259, 1058, 1062, 918, 903, 781, 704 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{15}H_{15}BrNO_2$ (M+H) 320.0286, found 320.0287. R_f (5/1 hexane/EtOAc) = 0.18.

1-(1-Bromo-4-(trimethylsilyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-one (288) and 1-(4-bromo-1-(trimethylsilyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-one (290). Following the general procedure for cyclotrimerization of halodiynes with nitriles, a solution of diyne **278** (700 g, 2.9 mmol) in DCE (18 mL) was added to a solution of Cp*RuCl(cod) (110 mg, 0.29 mmol) and nitrile **179b** (0.7 mL, 8.2 mmol) in DCE (14 mL) under Ar atmosphere during the course of 1 h. The reaction mixture was stirred at 25 °C for 17 h and then volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→2/1 hexanes/DCM) provided 566 mg (56%) of **288** and 151 mg (15%) of **290** as colorless solids.



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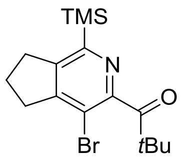
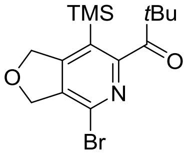


290

288: Mp = 65.7 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.09 (t, J = 7.5 Hz, 2H, CH_2), 2.92 (t, J = 7.6 Hz, 2H, CH_2), 2.06 (p, J = 7.6 Hz, 2H, CH_2), 1.41 (s, 9H, 3×CH_3), 0.28 (s, 9H, 3×CH_3).^{13}C-NMR (75 MHz, $CDCl_3$) δ 210.59, 162.76, 161.12, 141.90, 137.81, 130.33, 44.17, 36.91, 32.79, 28.31, 23.64, 1.69. IR (drift KBr) υ_{max} 2956, 1681, 1520, 1249, 1054, 919, 901, 845 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{14}H_{25}NOBrSi$ (M+H) 354.0889, found 354.0889. R_f (20/1 hexane/EtOAc) = 0.38.

290: Mp = 62.7 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.11 (t, J = 7.6 Hz, 2H, CH_2), 2.94 (t, J = 7.7 Hz, 2H, CH_2), 2.11 (p, J = 7.7 Hz, 2H, CH_2), 1.32 (s, 9H, 3×CH_3), 0.29 (s, 9H, 3×CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 210.58, 159.66, 154.91, 152.78, 147.24, 114.39, 44.44, 34.16, 33.10, 27.27, 23.64, -1.19. IR (drift KBr) υ_{max} 2954, 1705, 1248, 1053, 1004, 928, 895, 840, 754 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{14}H_{25}NOBrSi$ (M+H) 354.0889, found 354.0888. R_f (20/1 hexane/EtOAc) = 0.30.

1-(4-Bromo-7-(trimethylsilyl)-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-one (289) and 1-(7-bromo-4-(trimethylsilyl)-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-one (291). Following the general procedure for cyclotrimerization of halodiynes with nitriles, a solution of diyne **231f** (60 mg, 0.25 mmol) dissolved in DCE (2 mL) was added to a solution of Cp*RuCl(cod) (9 mg, 0.02 mmol), and nitrile **179b** (60 µL, 0.5 mmol) in DCE (1 mL) under Ar atmosphere during the course of 1 h. The reaction mixture was stirred at 25 °C for 15 h and then volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (gradient 50/1→40/1 cyclohexane/EtOAc) provided 52 mg (60%) of **289** and 10 mg (12%) of **291** as colorless oils.



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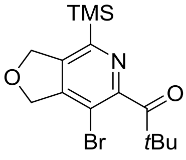
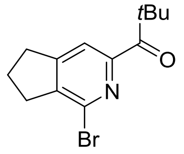


291

289: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 5.23–5.20 (m, 2H, CH$_2$), 5.06–5.03 (m, 2H, CH$_2$), 1.41 (s 9H, 3×CH$_3$), 0.27 (s, 9H, 3×CH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$) δ 208.84, 160.81, 156.96, 136.02, 132.71, 127.25, 74.99, 71.90, 43.26, 27.18, 0.29. IR (drift KBr) υ_{max} 2956, 1693, 1541, 1241, 1050, 1009, 931, 846 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{21}NO_2BrSi$ (M+H) 342.0525, found 342.0524. R$_f$ (10/1 hexane/EtOAc) = 0.40.

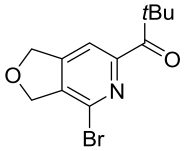
291: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 5.27 (t, *J* = 2.1 Hz, 2H, CH$_2$), 5.06 (t, *J* = 2.1 Hz, 2H, CH$_2$), 1.33 (s 9H, 3×CH$_3$), 0.29 (s, 9H, 3×CH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$) δ 211.31, 159.66, 157.34, 149.89, 143.85, 111.99, 75.90, 75.47, 46.16, 28.81, 0.00. IR (drift KBr) υ_{max} 2966, 1704, 1249, 1057, 1013, 942, 895, 845 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{21}NO_2BrSi$ (M+H) 342.0525, found 342.0524. R$_f$ (10/1 hexane/EtOAc) = 0.31.

1-(1-Bromo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-one (292).[235] TBAF (1 M solution in THF, 4.2 mL, 4.2 mmol) was added dropwise to a solution of **288** (1240 mg, 3.5 mmol) in THF (18 mL). After stirring at 25 °C for 1 h, the reaction was quenched by addition of water (20 mL) and extracted with EtOAc (3×70 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexanes/EtOAc) provided the 927 mg (94%) of the title compound as a colorless solid.



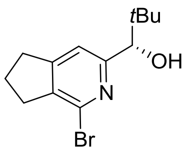
Mp = 53.2 °C. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.74 (s, 1H, Ar-H), 3.04 (t, *J* = 7.7 Hz, 2H, CH$_2$), 2.97 (t, *J* = 7.6 Hz, 2H, CH$_2$), 2.14 (p, *J* = 7.7 Hz, 2H, CH$_2$), 1.43 (s 9H, 3×CH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$) δ 205.51, 156.56, 153.12, 144.96, 136.85, 119.58, 44.38, 33.99, 33.37, 27.67, 23.50. IR (drift KBr) υ_{max} 2981, 2971, 1679, 1537, 1481, 1390, 1364, 1110, 898 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{13}H_{17}NOBr$ (M+H) 282.0494, found 282.0494. R_f (20/1 hexane/EtOAc) = 0.30.

1-(4-Bromo-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-one (293). K_2CO_3 (1.3 g, 9.4 mmol) was added to a solution of **289** (3.27 g, 9.24 mmol) in MeOH (80 mL). After stirring at 60 °C for 10 h, the reaction was quenched by addition of water (30 mL) and extracted with DCM (3×100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1→20/1) yielded 2.415 g (93%) of the title compound as colorless crystals.



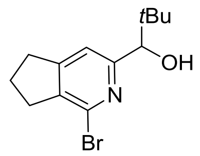
Mp = 112.9 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H, Ar-H), 5.23–5.19 (m, 2H, CH_2), 5.11–5.08 (m, 2H, CH_2), 1.44 (s, 9H, 3×CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.87, 154.44, 151.86, 139.84, 132.80, 116.21, 74.38, 73.41, 44.46, 27.59. IR (drift KBr) υ_{max} 2973, 2959, 1679, 1550, 1281, 1191, 1127, 1049, 996, 910, 855 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{12}H_{15}BrNO_2$ (M+H) 284.0286, found 284.0288. R_f (10/1 hexane/EtOAc) = 0.23.

(*S*)-1-(1-Bromo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-ol (294).[11] A mixture of Et_3N/HCOOH (2/1, 1.8 mL) was added to a solution of **292** (332 mg, 1.2 mmol) and RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) (40 mg, 0.06 mmol) in DCM (1 mL). After stirring at 25 °C for 3 d, the reaction was quenched by addition of water (10 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→7/1 hexanes/EtOAc) furnished 319 mg (96%, 94% ee) of the title compound as a colorless amorphous solid. Optically pure compound can be obtained by crystallization from $CHCl_3$ by slow evaporation of solvent.



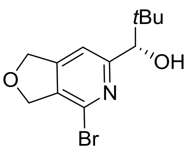
Mp = 65.9 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H, Ar-H), 4.27 (s, 1H, CH), 3.60 (brs, 1H, OH), 3.00 (t, J = 7.7 Hz, 2H, CH_2), 2.92 (t, J = 7.6 Hz, 2H, CH_2), 2.13 (p, J = 7.7 Hz, 2H, CH_2), 0.90 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.75, 155.84, 140.65, 137.61, 118.37, 80.47, 36.36, 33.91, 32.84, 26.01, 23.75. IR (drift KBr) υ_{max} 2956, 2903, 1598, 1541, 1453, 1415, 1364, 1238, 1108, 1063, 1016 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{13}H_{18}BrNO$ (M) 283.0572, found 283.0580. R_f (10/1 hexane/EtOAc) = 0.28. $[\alpha]_D^{20}$= +1.52° ($CHCl_3$, c = 2.6). Daicel Chiralpak IA, *n*-heptane/IPA 95/5, 1 mL/min, 210 nm, t_S = 7.7 min (major), t_R = 12.7 min (minor).

(*RS*)-1-(1-Bromo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-ol ((*rac*)-294).[237] NaBH$_4$ (6 mg, 0.16 mmol) was added to a solution of **292** (30 mg, 0.11 mmol) in dry MeOH (0.4 mL). After stirring at 25 °C for 2 h, the reaction was quenched by addition of water (2 mL) and extracted with Et$_2$O (3×5 mL). The combined organic fractions were washed with brine (5 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (15/1 hexanes/EtOAc) provided 30 mg (99%) of the title compound as an amorphous solid.



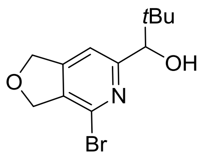
Daicel Chiralpak IA, *n*-heptane/IPA 95/5, 1 mL/min, 210 nm, t_S = 7.7 min, t_R = 12.9 min. All the spectral data were in agreement with the chiral product **294**.

(*S*)-1-(4-Bromo-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-ol (295).[11] A mixture of Et$_3$N/HCOOH (2/1, 1.5 mL) was added to a solution of **293** (270 mg, 0.95 mmol) and RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) (34 mg, 0.05 mmol) in DCM (2 mL). After stirring at 25 °C for 17 h, the reaction was quenched by addition of water (5 mL) and extracted with EtOAc (3×20 mL). The combined organic fractions were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 7/1→4/1 hexanes/EtOAc) furnished 270 mg (99%, 90% ee) of the title compound as an amorphous solid. Optically pure compound can be obtained by recrystallization from CHCl$_3$ by slow evaporation of solvent.



Mp = 49.2 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.08 (s, 1H, Ar-H), 5.18–5.16 (m, 2H, CH$_2$), 5.05 (t, J = 2.2 Hz, 2H, CH$_2$), 4.35 (s, 1H, CH), 0.92 (s, 9H, 3×CH$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$) δ 161.70, 151.05, 136.04, 133.60, 114.75, 80.77, 74.16, 73.15, 36.43, 25.97. IR (drift KBr) υ_{max} 2955, 2867, 1607, 1556, 1364, 1051, 1016, 906 cm^{-1}. HRMS (ESI) *m*/*z* calculated for C$_{12}$H$_{17}$BrNO$_2$ (M+H) 286.0437, found 286.0438. R$_f$ (4/1 hexane/EtOAc) = 0.30. $[\alpha]_D^{20}$ = +2.58° (CHCl$_3$, c = 2.7). HPLC: Daicel Chiralpak IA, *n*-heptane/IPA 98/2, 1 mL/min, 207 nm, t_S = 17.8 min (major), t_R = 18.8 min (minor).

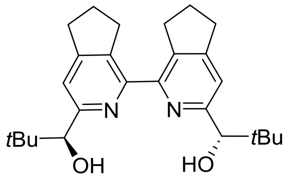
(*RS*)-1-(4-Bromo-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-ol ((*rac*)-295).[237] NaBH$_4$ (3 mg, 0.08 mmol) was added to a solution of **293** (16 mg, 0.06 mmol) in dry MeOH (0.4 mL). After stirring at 25 °C for 3 h, the reaction was quenched by addition of water (2 mL) and extracted with Et$_2$O (3×5 mL). The combined organic fractions were washed with brine (5 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the



residue on silica gel (5/1 hexanes/EtOAc) provided 15 mg (93%) of the title compound as an amorphous solid.

HPLC: Daicel Chiralpak IA, *n*-heptane/IPA 98/2, 1 mL/min, 207 nm, t_S = 17.7 min, t_R = 18.7 min. All the spectral data were in agreement with the chiral product **295**.

(*S*,*S*)-1,1'-(6,6',7,7'-Tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)]-3,3'-diyl)bis(2,2-dimethylpropan-1-ol) (296). Method A: Following the general method A for dimerization of 2-bromopyridines, PPh_3 (244 mg, 0.93 mmol) and Zn (17 mg, 0.25 mmol) were added to a warmed (70 °C) solution of $NiCl_2$ (31 mg, 0.23 mmol) in dry DMF (1 mL). The solution was sonicated while being bubbled through by Ar for 10 min and then stirred at 70 °C for 1 h. Then 2-bromopyridine **294** (55 mg, 0.19 mmol) in DMF (0.7 mL) was added and reaction was stirred at 70 °C for 15 h. After DMF was distilled off from the reaction mixture under reduced pressure, water (3 mL) was added and the reaction mixture was extracted with Et_2O (3×10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 100/1→2/1 hexanes, EtOAc; 4/1 PhMe/EtOAc) provided 14 mg (35%) of the title compound as a colorless solid.

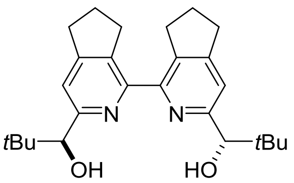


Method B:[11] A mixture of Et_3N/HCOOH (2/1, 0.5 mL) was added to a solution of **305** (60 mg, 0.15 mmol) and RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) (10 mg, 0.015 mmol) in DCM (0.3 mL). After stirring at 60 °C for 96 h, the reaction was quenched by addition of water (2 mL) and extracted with EtOAc (3×6 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 5/1→7/2 hexanes/EtOAc) furnished 22 mg (37%) of **313** and 29 mg (48%, 97% ee) of the title compound as a colorless solid.

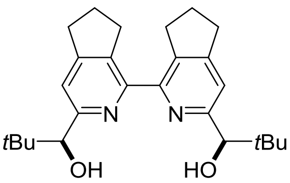
Method C:[238] K_2CO_3 (675 mg, 4.9 mmol) was added to a solution of **317** (321 mg, 0.65 mmol) in MeOH (5 mL). After stirring at 25 °C for 5 h, the reaction was quenched by addition of water (10 mL) and extracted with DCM (4×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 5/1→3/1 hexanes/EtOAc) provided 254 mg (96%, >99% ee) of the title compound as colorless crystals.

Mp = 214.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 2H, 2×Ar-H), 4.71 (brs, 2H, 2×OH), 4.38 (s, 2H, 2×CH), 3.37–3.27 (m, 2H, 2×CH), 3.25–3.15 (m, 2H, 2×CH), 2.97 (t, *J* = 7.6 Hz, 4H, $2\times CH_2$), 2.16–2.05 (m, 4H, $2\times CH_2$), 0.97 (s, 18H, $6\times CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$)

δ 156.47, 155.68, 151.06, 138.76, 118.74, 80.50, 36.66, 33.10, 32.89, 26.29, 25.40. IR (drift KBr) υ_{max} 2969, 2870, 1588, 1558, 1435, 1363, 1226, 1066, 1051, 1014 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{26}H_{37}N_2O_2$ (M+H) 409.2850, found 409.2852. R_f (3/1 hexanes/EtOAc) = 0.33. $[\alpha]_D^{20}$ = -20.5° ($CHCl_3$, *c* = 0.37). HPLC: Daicel Chiralpak IA, *n*-heptane/IPA 80/20, 1 mL/min, 215 nm, $t_{R,R}$ = 6.2 min (minor), $t_{S,S}$ = 8.0 min (major).



(*rac*)-**296**



(*meso*)-**296**

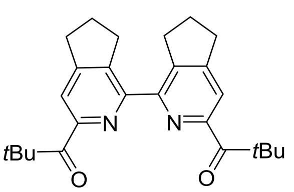
(*RS,RS*)-1,1'-(6,6',7,7'-Tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)]-3,3'-diyl)bis(2,2-dimethylpropan-1-ol) ((*rac*)-296) and (*RS,SR*)-1,1'-(6,6',7,7'-tetrahydro-5H,5'H-[1,1'-bi(cyclopenta[*c*]pyridine)]-3,3'-diyl)bis(2,2-dimethylpropan-1-ol) ((*meso*)-296).[237] $NaBH_4$ (8 mg, 0.2 mmol) was added to a solution of **305** (20 mg, 0.05 mmol) in MeOH (0.2 mL). After stirring at 25 °C for 7 h, the reaction was quenched by addition of water (0.5 mL) and extracted with DCM (3×2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→5/1 hexanes/EtOAc) furnished 9 mg (45%) of (*rac*)-**296** and 9 mg (45%) of (*meso*)-**296** as colorless solids.

(*rac*)-**296**: Daicel Chiralpak IA, *n*-heptane/IPA 80/20, 1 mL/min, 215 nm, $t_{R,R}$ = 6.1 min, $t_{S,S}$ = 8.0 min. All spectral data with agreement with chiral compound **296**.

(*meso*)-**296**: Mp = 203.7 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 7.08 (s, 2H, 2×Ar-H), 4.72 (brs, 2H, 2×OH), 4.37 (s, 2H, 2×CH), 3.35–3.19 (m, 4H, 2×CH_2), 2.97 (td, *J* = 7.4, 2.4 Hz, 4H, 2×CH_2), 2.10 (p, *J* = 7.5 Hz, 4H, 2×CH_2), 0.96 (s, 18H, 6×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 156.41, 155.63, 151.14, 138.73, 118.72, 80.54, 36.63, 33.20, 32.88, 26.29, 25.44.

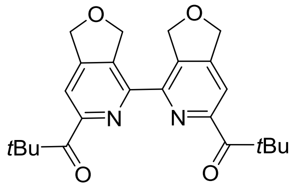
IR (drift KBr) υ_{max} 2958, 2924, 2860, 1588, 1561, 1433, 1408, 1363, 1067, 1014 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{26}H_{37}N_2O_2$ (M+H) 409.2850, found 409.2853. R_f (10/1 hexanes/EtOAc) = 0.25.

1,1'-(6,6',7,7'-Tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)]-3,3'-diyl)bis(2,2-dimethylpropan-1-one) (305). Following the general method A for dimerization of 2-bromopyridines, PPh$_3$ (446 mg, 1.70 mmol) and Zn (31 mg, 0.46 mmol) were added to a warmed (70 °C) solution of NiCl$_2$ (56 mg, 0.43 mmol) in dry DMF (1.5 mL). The solution was sonicated while being bubbled through by Ar for 10 min and then stirred at 70 °C for 1 h. Then 2-bromopyridine **292** (100 mg, 0.35 mmol) in DMF (1.5 mL) was added and reaction was stirred at 70 °C for 15 h. After DMF was distilled off from the reaction mixture under reduced pressure, water (5 mL) was added and the reaction mixture was extracted with Et$_2$O (3×15 mL). The combined organic fractions were washed with brine (15 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 20/1→5/1 hexanes/EtOAc) furnished 47 mg (66%) of the title compound as a colorless solid.



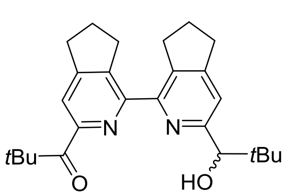
Mp = 109.2 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.77 (s, 2H, 2×Ar-H), 3.10 (t, J = 7.4 Hz, 4H, 2×CH$_2$), 3.02 (t, J = 7.5 Hz, 4H, 2×CH$_2$), 2.09 (t, J = 7.5 Hz, 4H, 2×CH$_2$), 1.43 (s, 18H, 6×CH$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$) δ 207.90, 156.01, 153.07, 151.58, 142.11, 119.74, 44.17, 33.04, 32.58, 27.72, 25.22. IR (drift KBr) υ_{max} 2955, 1677, 1557, 1482, 1430, 1388, 1127, 1115, 890 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{26}H_{33}N_2O_2$ (M+H) 405.2537, found 405.2539. R$_f$ (10/1 hexanes/EtOAc) = 0.50.

1,1'-(1,1',3,3'-Tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine]-6,6'-diyl)bis(2,2-dimethylpropan-1-one) (306). Following the general method A for dimerization of 2-bromopyridines, PPh$_3$ (256 mg, 0.98 mmol) and Zn (18 mg, 0.28 mmol) were added to a warmed (70 °C) solution of NiCl$_2$ (34 mg, 0.25 mmol) in dry DMF (0.8 mL). The solution was sonicated while being bubbled through by Ar for 10 min and then stirred at 70 °C for 1 h. Then 2-bromopyridine **293** (60 mg, 0.21 mmol) in DMF (1.0 mL) was added and reaction was stirred at 70 °C for 13 h. After DMF was distilled off from the reaction mixture under reduced pressure, water (3 mL) was added and the reaction mixture was extracted with Et$_2$O (3×10 mL). The combined organic fractions were washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexanes/EtOAc) furnished 20 mg (46%) of the title compound as a colorless solid.



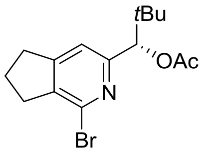
Mp = 189.7 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 2H, 2×Ar-H), 5.56 (t, J = 1.9 Hz, 4H, 2×CH_2), 5.19–5.16 (m, 4H, 2×CH_2), 1.44 (s, 18H, 6×CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.01, 155.43, 151.88, 148.76, 136.78, 116.54, 74.87, 72.62, 44.05, 27.52. IR (drift KBr) υ_{max} 2961, 2855, 1678, 1566, 1272, 1128, 1048, 1030, 999, 907, 895 cm^{-1}. HRMS (CI) *m*/*z* calculated for $C_{24}H_{29}N_2O_4$ (M+H) 409.2127, found 409.2127. R_f (5/1 hexanes/EtOAc) = 0.36.

(*S*/*R*)-1-(3'-(1-Hydroxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridin)]-3-yl)-2,2-dimethylpropan-1-one (313).[11] A solution of **305** (38 mg, 0.09 mmol) and RuCl[(*S,S*)-Tsdpen](*p*-cymene) (3 mg, 0.005 mmol) in a mixture of $Et_3N/HCOOH$ (2/1, 2 mL) was stirred at 25 °C for 48 h. Reaction was then quenched by addition of water (1 mL) and extracted with DCM (3×5 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 40/1→10/1 hexanes/EtOAc) furnished 26 mg (63%) of the starting compound **305** and 7 mg (18%) of the title compound as an amorphous solid.



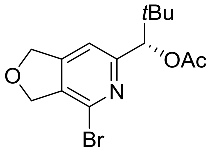
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H, Ar-H), 7.11 (s, H, Ar-H), 4.66 (brs, 1H, OH), 4.38 (s, 1H, CH), 3.28–3.15 (m, 2H, 2×CH), 3.14–3.05 (m, 2H, 2×CH), 3.04–2.95 (m, 4H, 2×CH_2), 2.19–2.03 (m, 4H, 2×CH_2), 1.44 (s, 9H, 3×CH_3), 0.97 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.04, 156.56, 156.13, 155.47, 153.09, 151.57, 151.20, 142.34, 138.58, 119.17, 118.83, 80.51, 44.14, 36.67, 33.23, 33.01, 32.98, 32.33, 27.73, 26.31, 25.57, 25.14. IR (drift KBr) υ_{max} 2953, 2860, 1679, 1219, 1129, 1111, 1072, 1015, 997 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{26}H_{35}N_2O_2$ (M+H) 407.2693, found 407.2694. R_f (10/1 hexane/EtOAc) = 0.30.

(*S*)-1-(1-Bromo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropyl acetate (315).[19] Acetic anhydride (0.8 mL, 7.5 mmol) was added dropwise to a cooled (0 °C) solution of **294** (790 mg, 2.8 mmol) in pyridine (0.6 mL, 7.5 mmol). After stirring at 25 °C for 10 h, the reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 10 mL) and extracted with DCM (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→7/1 hexanes/EtOAc) furnished 893 mg (99%) of the title compound as colorless crystals.



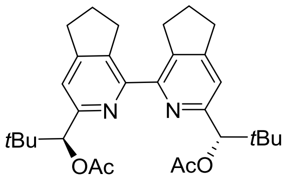
M.p. = 111.0 °C ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H, Ar-H), 5.47 (s, 1H, CH), 3.02–2.97 (m, 2H, CH_2), 2.90 (t, J = 7.4 Hz, 2H, CH_2), 2.14–2.06 (m, 5H, CH_2, CH_3), 0.95 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.34, 157.53, 155.80, 140.72, 137.91, 117.36, 82.98, 35.09, 34.00, 32.95, 36.23, 23.63, 21.21. IR (drift KBr) υ_{max} 2967, 1737, 1595, 1541, 1372, 1242, 1052, 1026, 911 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{15}H_{21}BrNO_2$ (M+H) 326.0750, found 326.0751. R_f (10/1 hexanes/EtOAc) = 0.35.

(*S*)-1-(4-Bromo-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropyl acetate (316).[19]



Acetic anhydride (0.2 mL, 1.9 mmol) was added dropwise to a cooled (0 °C) solution of **295** (198 mg, 0.69 mmol) in pyridine (0.15 mL, 1.7 mmol). After stirring at 25 °C for 16 h, the reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 5 mL) and extracted with DCM (3×15 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 6/1→5/1 hexanes/EtOAc) furnished 225 mg (99%) of the title compound as a colorless oil.

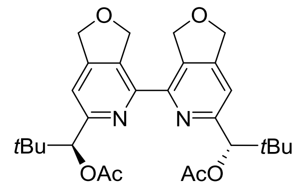
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 1H, Ar-H), 5.52 (s, 1H, CH), 5.19–5.14 (m, 2H, CH_2), 5.06–5.01 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 0.97 (s, 9H, 3×CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.34, 159.36, 151.07, 136.10, 133.85, 114.10, 82.89, 74.24, 73.27, 35.17, 26.22. IR (drift KBr) υ_{max} 2968, 1371, 1240, 1201, 1051, 1027, 911 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{19}BrNO_3$ (M+H) 328.0548, found 328.0552. R_f (3/1 hexane/EtOAc) = 0.50.



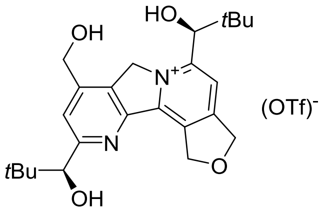
(*S*,*S*)-(6,6',7,7'-Tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)]-3,3'-diyl)bis(2,2-dimethylpropane-1,1-diyl) diacetate (317). Following the general method A for dimerization of 2-bromopyridines, PPh_3 (2.4 g, 9.24 mmol) and Zn (166 mg, 2.5 mmol) were added to a warmed (70 °C) solution of $NiCl_2$ (305 mg, 2.3 mmol) in dry DMF (13.5 mL). The solution was sonicated while bubbling Ar through for 10 min and then stirred at 70 °C for 1 h. Then 2-bromopyridine **315** (628 mg, 1.9 mmol) in DMF (13.5 mL) was added and reaction was stirred at 70 °C for 14 h. After DMF was distilled off from the reaction mixture under reduced pressure, water (25 mL) was added and the reaction mixture was extracted with Et_2O (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 20/1→5/1 hexanes/EtOAc) furnished 321 mg (68%) of the title compound as a colorless solid.

Mp = 173.6 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H, 2×Ar-H), 5.56 (s, 2H, 2×CH), 3.49–3.38 (m, 2H, 2×CH), 3.14–3.03 (m, 2H, 2×CH), 2.92 (t, J = 7.6 Hz, 4H, 2×CH_2), 2.12 (s, 6H, 2×CH_3), 2.11–1.94 (m, 4H, 2×CH_2), 1.00 (s, 18H, 6×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.43, 154.99, 154.63, 152.27, 138.88, 117.76, 84.08, 35.16, 33.01, 32.99, 26.53, 24.99, 21.32. IR (drift KBr) υ_{max} 2959, 2905, 2870, 1735, 1585, 1558, 1427, 1396, 1370, 1244, 1023, 972 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{30}H_{41}N_2O_4$ (M+H) 493.3061, found 493.3060. R_f (10/1 hexane/EtOAc) = 0.23.

(*S*,*S*)-(1,1',3,3'-Tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine]-6,6'-diyl)bis(2,2-dimethylpropane-1,1-diyl) diacetate (318). Following the general method A for dimerization of 2-bromopyridines, PPh_3 (1.53 g, 5.8 mmol) and Zn (105 mg, 1.6 mmol) were added to a warmed (70 °C) solution of $NiCl_2$ (193 mg, 1.5 mmol) in dry DMF (5 mL). The solution was sonicated while being bubbled through by Ar for 10 min and then stirred at 70 °C for 1 h. Then 2-bromopyridine **316** (400 mg, 1.2 mmol) in DMF (4 mL) was added and reaction was stirred at 70 °C for 13 h. After DMF was distilled off from the reaction mixture under reduced pressure, water (10 mL) was added and the reaction mixture was extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 4/1→3/1 hexanes/EtOAc) furnished 187 mg (62%) of the title compound as a colorless solid.

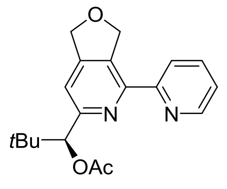


Mp = 176.4 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 2H, 2×Ar-H), 5.75 (dt, J = 14.6, 1.9 Hz, 2H, CH_2), 5.62–5.53 (m, 2H, CH_2), 5.55 (s, 2H, 2×CH), 5.14–5.09 (m, 4H, 2×CH_2), 2.15 (s, 6H, 2×CH_3), 1.01 (s, 18H, 6×CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.47, 156.58, 150.72, 149.45, 133.95, 114.74, 83.76, 75.18, 72.36, 35.23, 26.46, 21.24. IR (drift KBr) υ_{max} 2959, 2929, 2869, 1739, 1592, 1568, 1371, 1242. 1042, 1024, 902 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{28}H_{37}N_2O_6$ (M+H) 497.2652, found 497.2654. R_f (3/1 hexane/EtOAc) = 0.34.



5,10-Bis((*S*)-1-hydroxy-2,2-dimethylpropyl)-8-(hydroxymethyl)-3,7-dihydro-1*H*-furo[3,4-*g*]pyrido[2,3-*a*]indolizin-6-ium triflate (325). K_2CO_3 (156 mg, 1.13 mmol) was added to a solution of **318** (75 mg, 0.15 mmol) in MeOH (3 mL). After stirring at 25 °C for 6 h, the reaction was quenched by addition of water (5 mL) and extracted with DCM (3×15 mL). The combined organic layers were dried over $MgSO_{4,}$ filtered, and dried under reduced pressure. This method provided 58 mg of colorless solid, which was mixed with $Bi(OTf)_3$ (98 mg, 0.15 mmol) and THF (1 mL) and stirred at 60 °C for 1 h. The slow evaporation of the solvent at 25 °C resulted in the formation of red crystals in red oil. The crystals were mechanically separated from the oil and washed with THF.

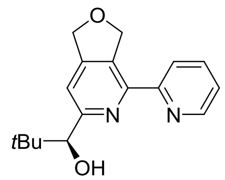
Mp = 235.2 °C. ^{1}H-NMR (600 MHz, *d₃*-MeCN) δ 8.00 (s, 1H, Ar-H), 7.66 (s, 1H, Ar-H), 6.04 (d, *J* = 20.0 Hz, 1H, CH), 5.85 (d, *J* = 19.9 Hz, 1H, CH), 5.68–5.56 (m, 2H, CH_2), 5.36 (d, *J* = 16.1 Hz, 1H, CH), 5.32 (d, *J* = 16.1 Hz, 1H, CH), 5.06 (s, 1H, CH), 4.91 (s, 2H, CH_2), 4.55 (s, 1H, CH), 1.08 (s, 9H, 3×CH_3), 0.95 (s, 9H, 3×CH_3). ^{13}C-NMR (150 MHz, d_3-MeCN) δ 166.59, 161.01, 158.23, 149.21, 148.62, 146.70, 134.56, 131.11, 123.06, 120.07, 81.75, 76.23, 74.00, 72.35, 62.18, 60.29, 38.54, 36.92, 26.27, 25.97. ^{19}F-NMR (400 MHz, d_3-MeCN) δ -79.34 (s, 3F). IR (drift KBr) υ_{max} 3485, 3443, 2962, 2872, 1658, 1371, 1260, 1171, 1063, 1036, 644 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{24}H_{33}N_2O_4^+$ (M-OTf) 413.2435, found 413.2433. R_f (EtOAc) = 0.44.



(*S*)-2,2-Dimethyl-1-(4-(pyridin-2-yl)-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)propyl acetate (326).[239] 2-(Tributylstannyl)pyridine (300 µL, 0.91 mmol) was added to a solution of 2-bromopyridine **316** (250 mg, 0.76 mmol) and $Pd(PPh_3)_4$ (88 mg, 0.076 mmol) in PhMe (3.5 mL). After refluxing for 4 h, the reaction was quenched by addition of $NaHCO_3$ (5 mL) and extracted with DCM (3×15 mL). The combined organic fractions were washed with NaF (20% aq. sol., 15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 8/1→6/1 hexanes/EtOAc) furnished 115 mg (46%) of the title compound as a colorless solid.

Mp = 114.3 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, Ar-H), 8.52 (dt, *J* = 8.0, 1.1 Hz, 1H, Ar-H), 7.79 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H, Ar-H), 7.25 (ddd, 7.5, 4.8, 1.3 Hz, ovelapping with $CHCl_3$, Ar-H), 7.17 (s, 1H, Ar-H), 7.68 (s, 1H, CH), 5.59 (t, *J* = 2.0 Hz, 2H, CH_2), 5.13–5.09 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 1.02 (s, 9H, 3×CH_3).

^{13}C-NMR (100 MHz, CDCl$_3$) δ 170.49, 156.88, 156.78, 150.91, 148.89, 148.65, 136.54, 133.05, 123.29, 122.07, 114.33, 83.63, 74.85, 72.39, 35.13, 26.38, 21.30. IR (drift KBr) υ_{max} 2971, 2875, 1733, 1583, 1374, 1248, 1225, 1048, 1030, 997, 902 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{22}N_2O_3Na$ (M+Na) 349.1523, found 349.1521. R$_f$ (4/1 hexanes/EtOAc) = 0.44.



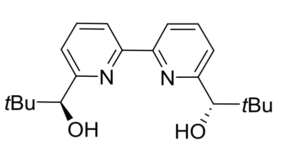
(*S*)-2,2-Dimethyl-1-(4-(pyridin-2-yl)-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)propan-1-ol (327).[238] K_2CO_3 (173 mg, 1.25 mmol) was added to a solution of **326** (102 mg, 0.31 mmol) in MeOH (4 mL). After stirring at 25 °C for 1 h, the reaction was quenched by addition of water (5 mL) and extracted with DCM (3×15 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (5/1 hexanes/EtOAc) provided 76 mg (86%) of the title compound as pinky solid.

Mp = 124.7 °C. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.64 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, Ar-H), 8.41 (dt, *J* = 8.0, 1.0 Hz), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H, Ar-H), 7.25 (ddd, *J* = 7.5, 4.7, 1.2 Hz, overlapping with CDCl$_3$), 7.09 (s, 1H, Ar-H), 5.63–5.50 (m, 2H, CH$_2$), 5.16–5.03 (m, 2H, CH$_2$), 4.41 (s, 1H, CH), 4.36 (s, 1H, OH), 0.96 (s, 9H, 3×CH$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$) δ 158.61, 156.21, 150.97, 149.03, 148.16, 136.61, 133.34, 123.43, 121.61, 115.39, 80.62, 74.63, 72.17, 36.34, 26.05. IR (drift KBr) υ_{max} 3431, 2965, 2869, 1586, 1574, 1428, 1392, 1359, 1254, 1120, 1069, 1036, 1015, 905, 863, 749 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{21}N_2O_2$ (M+H) 285.1598, found 285.1596. R$_f$ (4/1 hexanes/EtOAc) = 0.28.

5.4 Application of bipyridines

5.4.1 Synthesis of Bolm's ligand (*S,S*)-8

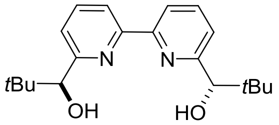
(1*S*,1'*S*)-1,1'-([2,2'-Bipyridine]-6,6'-diyl)bis(2,2-dimethylpropan-1-ol) ((*S,S*)-8).[11]



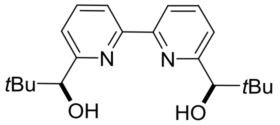
Following the general method E for dimerization of 2-bromopyridines, TDAE (4.2 mL, 18 mmol) was added to a solution of 2-bromopyridine (*S*)-**11** (2.18 g, 9.0 mmol) and $PdCl_2(PhCN)_2$ (175 mg, 0.46 mmol) in dry DMF (42 mL). After stirring at 50 °C for 28 h, the reaction was quenched by addition of water (20 mL) and extracted with Et_2O (3×100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (4/1 hexanes/EtOAc) furnished 1.28 g (86%, >99% ee) of the title compound (*S,S*)-**8** as a colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (dd, J = 7.8, 1.0 Hz, 2H, 2×Ar-H), 7.79 (t, J = 7.8 Hz, 2H, 2×Ar-H), 7.23 (dd, J = 7.8, 1.0 Hz, 2H, 2×Ar-H), 4.48–4.30 (m, 4H, 2×CH, 2×OH), 0.97 (s, 18H, 6×CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.48, 153.84, 136.92, 123.28, 119.87, 80.34, 36.43, 26.06.HRMS (ESI) *m/z* calculated for $C_{20}H_{28}N_2O_2Na$ (M+Na) 351.2043, found 351.2043. R_f (2/1 hexane/EtOAc) = 0.63. HPLC: Daicel Chiralpak OD-H, *n*-heptane/IPA 95/5, 1 mL/min, 290 nm, $t_{S,S}$ = 28.7 min. The recorded values were in agreement with the published data.[11]

(1*RS*,1'*RS*)-1,1'-([2,2'-Bipyridine]-6,6'-diyl)bis(2,2-dimethylpropan-1-ol) ((*rac*)-8) and (1*RS*,1'*SR*)-1,1'-([2,2'-bipyridine]-6,6'-diyl)bis(2,2-dimethylpropan-1-ol) ((*meso*)-8).



(*rac*)-**8**



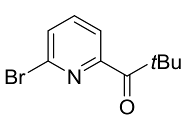
(*meso*)-**8**

Following the same procedure starting from (*rac*)-**11** (372 mg, 1.54 mmol), column chromatography on silica gel (4/1 hexanes/EtOAc) furnished 222 mg (88%) of a mixture of the title compounds as a colorless solid.

(*rac*)-**8**+(*meso*)-**8**: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.30 (dd, J = 7.7, 3.3 Hz, 4H, 4×Ar-H), 7.78 (t, J = 7.7 Hz, 4H, 4×Ar-H), 7.23 (d, J = 7.7 Hz, 4H, 4×Ar-H), 4.55–4.17 (m, 8H, 4×CH, 4×OH), 0.97 (s, 18H, 6×CH_3), 0.96 (s, 18H, 6×CH_3).^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.39, 159.37, 153.99, 153.95, 136.78 (2×C), 123.22, 123.18, 119.72 (2×C), 80.35, 80.34, 36.44 (2×C), 26.06 (2×C). HPLC: Daicel Chiralpak OD-H, *n*-heptane/IPA 95/5, 1 mL/min, 290 nm, t_{meso} = 13.0 min, $t_{R,R}$ = 23.3 min, $t_{S,S}$ = 29.2 min.

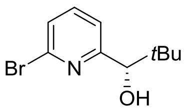
(*meso*)-**8**: R_f (2/1 hexane/EtOAc) = 0.55.

1-(6-Bromopyridin-2-yl)-2,2-dimethylpropan-1-one (10).[19] *n*-BuLi (1.6 M solution in hexane, 14.5 mL, 23.2 mmol) was added dropwise to a cooled (-78 °C) solution of 2,6-dibromopyridine **9** (5.00 g, 21.1 mmol) in dry Et_2O (83 mL). The reaction mixture was stirred at -78 °C for 30 min, then pivalonitrile (2.8 mL, 25.3 mmol) was added and the mixture was stirred for 1 h at the same temperature. Then, H_2SO_4 (2 M aq. sol., 70 mL, 152 mmol) was added, the mixture was stirred at 60 °C for 2 h and then allowed to cool down to 25 °C. The phases were separated and the aqueous phase was extracted with Et_2O (3×150 mL). The combined organic layers were washed with K_2CO_3 (sat. aq. sol., 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The Kugelrohr distillation (160 °C, 2 mbar) of the oily residue yielded 4.36 g (85%) of the title compound as a colorless oil.



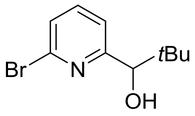
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.7, 1.1 Hz, 1H, Ar-H), 7.65 (t, J = 7.7 Hz, 1H, Ar-H), 7.57 (dd, J = 7.7, 1.1 Hz, 1H, Ar-H), 1.44 (s, 9H, 3×CH_3).^{13}C-NMR (100 MHz, $CDCl_3$) δ 205.07, 154.89, 139.82, 139.14, 130.66, 122.64, 44.37, 27.53.HRMS (ESI) *m*/*z* calculated for $C_{10}H_{13}NOBr$ (M+H) 242.0175, found 242.0175. R_f (5/1 hexanes/EtOAc) = 0.63. The recorded values were in agreement with the published data.[19]

(*S*)-1-(6-Bromopyridin-2-yl)-2,2-dimethylpropan-1-ol ((*S*)-11).[11] A solution of **10** (984 mg, 4.1 mmol) and RuCl[(*S,S*)-Tsdpen](*p*-cymene) (29 mg, 0.04 mmol) in mixture of Et_3N/HCOOH (2/1, 2 mL) was stirred at 25 °C for 20 h. The reaction was then quenched by addition of water (10 mL) and extracted with EtOAc (3×20 mL). The combined organic fractions were washed with $NaHCO_3$ (sat. aq. sol., 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (6/1 hexanes/EtOAc) furnished 808 mg (81%, 90% ee) of the title compound (*S*)-**11** as a colorless solid. Further crystallization from hexane gave rise to 630 mg (64%, 98% ee) of (*S*)-**11** as colorless crystals.



^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.47 (t, J = 7.7 Hz, 1H, Ar-H), 7.36 (d, J = 7.7 Hz, 1H, Ar-H), 7.15 (d, J = 7.7 Hz, 1H, Ar-H), 4.31 (s, 1H, CH), 0.90 (s, 9H, 3×CH_3).^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.08, 140.83, 138.05, 126.81, 121.64, 80.52, 36.42, 25.95.HRMS (ESI) *m*/*z* calculated for $C_{10}H_{15}NOBr$ (M+H) 244.0332, found 244.0331. R_f (3/1 hexanes/EtOAc) = 0.56. HPLC: Lux Columns – Lux Cellulose-3, *n*-heptane/IPA 99/1, 0.6 mL/min, 254 nm, t_R = 14.5 min (minor), t_S = 18.3 min (major). The recorded values were in agreement with the published data.[11]

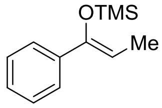
(*RS*)-1-(6-Bromopyridin-2-yl)-2,2-dimethylpropan-1-ol ((*rac*)-11).[237] $NaBH_4$ (120 mg, 3 mmol) was portionwise added to a solution of **10** (486 mg, 2 mmol) in MeOH (8.5 mL). The mixture was stirred for at 25 °C for 2 h and then the reaction was quenched by addition of water (10 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (6/1 hexanes/EtOAc) furnished 398 mg (81%) of the title compound as a colorless solid.



Lux Columns – Lux Cellulose-3, *n*-heptane/IPA 99/1, 0.6 mL/min, 254 nm, t_R = 14.5 min, t_S = 18.6 min. All spectral data were in agreement with the chiral form of (*S*)-**11**.

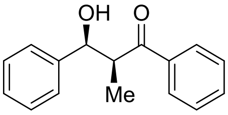
5.4.2 Mukaiyama aldol reaction

(*Z*)-Trimethyl((1-phenylprop-1-en-1-yl)oxy)silane (44).[240] *n*-BuLi (2 M solution in pentane, 7.0 mL, 14.2 mmol) was added to a cooled (-78 °C) solution of (*i*-Pr)$_2$NH (2.1 mL, 14.9 mmol) in THF (45 mL) with 3Å molecular sieves during the course of 10 min. The mixture was stirred at -78 °C for 1 h, and then solution of propiophenone (1.0 mL, 7.5 mmol) in THF (45 mL) was added dropwise. After stirring at -78 °C for 1 h, the formed enolate was treated with TMSCl (1.9 mL, 14.9 mmol). The reaction mixture was stirred at -78 °C for 1 h, then allowed to warm up to 25 °C and stirred for 30 min. Reaction was quenched by addition of cold NH$_4$Cl (sat. aq. sol., 20 mL). The phases were separated and the aqueous phase was extracted with Et$_2$O (2×50 mL). The combined organic fractions were washed with cold brine (30 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Fitration of the residue through silica gel pad (70/1 cyclohexane/EtOAc) furnished 1.25 g (82%) of the title compound as a colorless oil.



^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.49–7.42 (m, 2H, 2×Ar-H), 7.33–7.19 (m, overlapping with CDCl$_3$, 3×Ar-H), 5.33 (q, J = 6.9 Hz, 1H, CH), 1.74 (d, J = 6.9 Hz, 3H, CH$_3$), 0.14 (s, 9H, 3×CH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$) δ 150.03, 128.12, 125.31, 127.40, 139.34, 105.38, 11.78, 0.67. R$_f$ (50/1 hexanes/Et$_2$O) = 0.58. The recorded values were in agreement with the published data.[240]

(2*S*,3*S*)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (45).



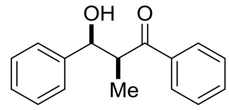
General method - conditions A:[51] A solution of Fe(OTf)$_2$ (3.1 mg, 0.009 mmol), pyridine (1.7 µl, 0.021 mmol) and bipyridine (0.011 mmol) in degassed DME (0.5 ml) was stirred under the Ar atmosphere at 25 °C for 30 min. Then degassed water (220 µL) was added and solution was stirred at 0 °C for additional 30 min. Then benzaldehyde (30 µL, 0.29 mmol) and **44** (72 mg, 0.35 mmol) were added and the reaction mixture was stirred at 0 °C until the benzaldehyde was fully consumed (disappearance of the respective spot on the TLC). Reaction was quenched by addition of NaHCO$_3$ (sat. aq. sol., 2 mL) and extracted with DCM (4×5 mL). The combined organic phases were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. ^{1}H-NMR was used for determination of diastereomeric ratio. Column chromatography of the residue on silica gel (gradient 20/1→10/1 cyclohexane/EtOAc) furnished the title compound as a colorless oil.

General method - conditions B:[51] A solution of $Fe(ClO_4)_2 \cdot 7.25\ H_2O$ (3.4 mg, 0.009 mmol), benzoic acid (1.3 mg, 0.011 mmol) and bipyridine (0.011 mmol) in degassed DME (0.5 ml) was stirred under the Ar atmosphere at 25 °C for 30 min. Then degassed water (220 μL) was added and solution was stirred at 0 °C for 30 min. Then benzaldehyde (30 μL, 0.29 mmol) and **44** (72 mg, 0.35 mmol) were added and the reaction mixture was stirred at 0 °C until the benzaldehyde was fully consumed (disappearance of the respective spot on the TLC). Reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 2 mL) and extracted with DCM (4×5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H-NMR was used for determination of diastereomeric ratio. Column chromatography of the residue on silica gel (gradient 20/1→10/1 cyclohexane/EtOAc) furnished the title compound as a colorless oil.

General method - conditions C:[64] A suspension of bipyridine (0.044 mmol) and $Fe(DS)_2$ (8.6 mg, 0.015 mmol) in degassed water (1 mL) was stirred under the Ar atmosphere at 25 °C for 1 h. Then benzaldehyde (30 μL, 0.29 mmol), benzoic acid (2.1 mg, 0.015 mmol) and **44** (72 mg, 0.35 mmol) were added. Reaction was stirred at 25 °C until the benzaldehyde was fully consumed (disappearance of the respective spot on the TLC). The reaction mixture was extracted with DCM (3×5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H-NMR was used for determination of diastereomeric ratio. Column chromatography of the residue on silica gel (gradient 20/1→10/1 cyclohexane/EtOAc) furnished the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96–7.91 (m, 2H, 2×Ar-H), 7.63–7.56 (m, 1H, Ar-H), 7.52–7.44 (m, 2H, 2×Ar-H), 7.44–7.34 (m, 4H, 4×Ar-H), 7.30–7.23 (m, overlapping with $CDCl_3$, Ar-H), 5.25 (d, J = 3.0 Hz, 1H, CH), 3.71 (qd, J = 7.2, 3.1 Hz, 1H, CH), 3.64 (brs, 1H, OH), 1.20 (d, J = 7.2 Hz, 3H, CH_3).^{13}C-NMR (150 MHz, $CDCl_3$) δ 205.90, 141.96, 135.81, 133.71, 128.93, 128.62, 128.40, 127.46, 126.18, 73.23, 47.19, 11.30. R_f (5/1 hexanes/EtOAc) = 0.35. HPLC: Daicel Chiralpak AD-H *n*-hexane/IPA 97/3, 1 mL/min, 244 nm, $t_{R,R}$ = 21.0 min (minor), $t_{S,S}$ = 27.4 min (major). The recorded values were in agreement with the published data.[51]

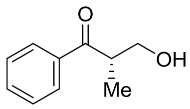
(2*RS*,3*RS*)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one ((*rac*)-45). The racemic mixture of products was prepared by method using conditions B without any bipyridine ligand.



HPLC: Daicel Chiralpak AD-H *n*-hexane/IPA 97/3, 1 mL/min, 244 nm, $t_{R,R}$ = 20.9 min, $t_{S,S}$ = 27.2 min. All spectral data were in agreement with the chiral product **45**.

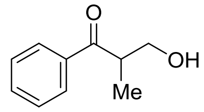
5.4.3 Hydroxymethylation

(*S*)-3-Hydroxy-2-methyl-1-phenylpropan-1-one (47).[26] A solution of Bi(OTf)$_3$ (2.0 mg, 0.003 mmol) and bipyridine (0.009 mmol) in DME (150 µL) was stirred at 25 °C for 30 min under Ar atmosphere, the mixture was then cooled down to 0 °C and a solution of 2,2'-bipyridine (2.4 mg, 0.015 mmol) in degassed DME (190 µL) was added. After stirring at 0 °C for 5 min, formaldehyde (37% w/w in water, 115 µL, 1.5 mmol) and **44** (62 mg, 0.30 mmol) were added. The mixture was stirred at 0 °C until **44** was fully consumed (disappearance of the respective spot on the TLC). The reaction was quenched by addition of NaHCO$_3$ (sat. aq. sol., 2 mL) and extracted with DCM (3×5 mL). The combined organic phases were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→2/1 cyclohexane/EtOAc) provided the title compound as a colorless oil.



^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.98–7.93 (m, 2H, 2×Ar-H), 7.61–7.53 (m, 1H, Ar-H), 7.51–7.43 (m, 2H, 2×Ar-H), 3.93 (dd, J = 11.1, 7.0 Hz, 1H, CH), 3.79 (dd, J = 11.1, 4.2 Hz, 1H, CH), 3.73–3.60 (m, 1H, CH), 2.50 (brs 1H, OH), 1.23 (d, J = 7.2 Hz, 3H, CH$_3$).^{13}C-NMR (75 MHz, CDCl$_3$) δ 204.55, 136.25, 133.44, 128.83, 128.58, 64.69, 43.04, 14.70. R$_f$ (3/1 hexanes/EtOAc) = 0.20. HPLC: Daicel Chiralpak AD-H *n*-hexane/IPA 97/3, 1 mL/min, 242 nm, t_S = 19.2 min (major), t_R = 21.5 min(minor). The recorded values were in agreement with the published data.[26]

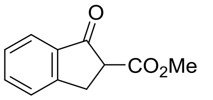
(*RS*)-3-Hydroxy-2-methyl-1-phenylpropan-1-one ((*rac*)-47).[241] Formaldehyde (37% w/w aq. sol., 125 µL, 1.67 mmol) and **44** (69 mg, 0.33 mmol) were added to a solution of Sc(OTf)$_3$ (16 mg, 0.033 mmol) in a mixture of THF/H$_2$O (6/1, 1.4 mL). After stirring at 25 °C for 16 h, the reaction was quenched by addition of water (2 mL) and extracted with DCM (3×7 mL). The combined organic fractions were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→2/1 cyclohexane/EtOAc) provided 52 mg (96%) of the title compound as a colorless oil.



HPLC: Daicel Chiralpak AD-H *n*-hexane/IPA 97/3, 1 mL/min, 242 nm, t_S = 19.3 min, t_R = 21.7 min.All spectral data were in agreement with the chiral product **47**.

5.4.4 Conjugated addition

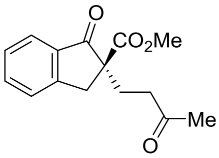
Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (21).[242] Dimethyl carbonate (3.2 mL, 37.8 mmol) and a solution of indanone (1.0 g, 7.6 mmol) in THF (8 mL) were slowly added to a vigorously stirred suspension of NaH (60% w/w in mineral oil, 638 mg, 15.9 mmol) in THF (16 mL). After refluxing for 18 h, the reaction was quenched by addition of HCl (1 M aq. sol., 15 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic fractions were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→7/1 cyclohexane/EtOAc) furnished 1.26 g (88%) of the mixture of keto/enol form (95/5) of the title compound as colorless crystals.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.6 Hz, 1H, Ar-H), 7.66–7.58 (m, 1H, Ar-H), 7.50 (d, J = 7.6 Hz, 1H, Ar-H), 7.39 (t, J = 7.6 Hz, 1H, Ar-H), 3.79 (s, 3H, CH_3), 3.73 (dd, J = 8.3, 4.0 Hz, 1H, CH), 3.56 (dd, J = 17.3, 4.0 Hz, 1H, CH), 3.37 (dd, J = 17.3, 8.3 Hz, 1H, CH).

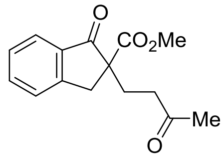
^{13}C-NMR (75 MHz, $CDCl_3$) δ 199.53, 169.67, 153.71, 135.58, 135.34, 127.95, 126.67, 124.83, 53.26, 52.90, 30.39. R_f (10/1 hexane/EtOAc) = 0.33. The recorded values were in agreement with the published data.[242]

(*R*)-Methyl 1-oxo-2-(3-oxobutyl)-2,3-dihydro-1*H*-indene-2-carboxylate (23).[40] A solution of Sc(OTf)$_3$ (7.5 mg, 0.015 mmol) and bipyridine (0.018 mmol) in dry DCE (2.4 mL) was stirred at 60 °C for 1 h. The mixture was allowed to cool down to 40 °C and DCE (9.5 mL) was added and stirring continued at 40 °C for 20 min. Then **21** (57 mg, 0.3 mmol) in DCE (1.5 mL) and methyl vinyl ketone **22** (50 µL, 0.6 mmol) in DCE (0.8 mL) were added subsequently. After stirring at 40 °C for the corresponding time, the reaction was quenched by addition of water (5 mL) and extracted with DCM (3×10 mL). The combined organic phases were washed with HCl (1 M aq. sol., 5 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 5/1→1/1 cyclohexane/EtOAc) furnished the title compound as colorless crystals.



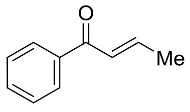
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H, Ar-H), 7.65–7.58 (m, 1H, Ar-H), 7.45 (d, J = 7.6 Hz, 1H, Ar-H), 7.38 (t, J = 7.6 Hz, 1H, Ar-H), 3.66 (s, 3H, CH_3), 3.65 (d, J = 17.2 Hz, 1H, CH), 3.02 (d, J = 17.2 Hz, 1H, CH), 2.68–2.41 (m, 2H, CH_2), 2.26–2.17 (m, 2H, CH_2), 2.10 (s, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 207.51, 202.32, 171.65, 152.61, 135.63, 135.12, 128.06, 126.50, 124.93, 59.19, 52.81, 38.85, 37.90, 29.99, 28.64. R_f (3/1 hexanes/EtOAc) = 0.15. HPLC: Daicel Chiralpak AD-H *n*-hexane/IPA 90/10, 1 mL/min, (244 nm, t_S = 13.7 min (minor), t_R = 15.6 min (major). The recorded values were in agreement with the published data. [40]

(*RS*)-Methyl 1-oxo-2-(3-oxobutyl)-2,3-dihydro-1*H*-indene-2-carboxylate ((*rac*)-23). The racemic product **23** was prepared by the same procedure without using any bipyridine ligand.



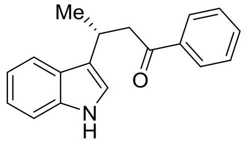
HPLC: Daicel Chiralpak AD-H *n*-hexane/IPA 90/10, 1 mL/min, 244 nm, t_S = 13.8 min, t_R = 15.7 min. All spectral data were in agreement with the chiral product **23**.

5.4.5 C–H activation of indole



1-Phenylbut-2-en-1-one (50). *t*-BuOOH (5.5 M solution in nonane, 560 µL, 3 mmol) was added by a syringe pump (15 µL/h) to a warmed (60 °C) suspension of CuO (4.1 mg, 0.05 mmol) and **330** (148 mg, 1 mmol) in dry MeCN (1.3 mL). The reaction mixture was quenched by addition of water (5 mL) and extracted with EtOAc (3×10 mL). The combined organic fractions were washed with HCl (0.1 M aq. sol., 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (5/1 cyclohexane/EtOAc) provided 117 mg (80%) of the title compound as a yellowish oil.

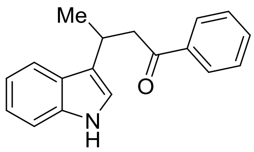
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96–7.88 (m, 2H, 2×Ar-H), 7.59–7.52 (m, 1H, Ar-H), 7.50–7.43 (m, 2H, 2×Ar-H), 7.08 (dq, *J* = 15.2, 6.7 Hz, 1H, CH), 6.95–6.87 (m, 1H, CH), 2.00 (dd, *J* = 6.7, 1.4 Hz, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.80, 145.09, 137.98, 132.65, 128.56 (2×C), 127.60, 18.65. R_f (5/1 cyclohexane/EtOAc) = 0.48. The recorded values were in agreement with the published data.[243]



(*R*)-3-(1*H*-Indol-3-yl)-1-phenylbutan-1-one (51).[69] $PhNMe_2$ (4.5 µL, 0.036 mmol) was added to a suspension of $PdCl_2$ (2.7 mg, 0.015 mmol), NaDS (8.8 mg, 0.03 mmol), and bipyridine (0.018 mmol) in degassed water (0.6 mL). After vigorous stirring at 25 °C for 1 h, indole **42** (42 mg, 0.36 mmol) and **50** (44 mg, 0.3 mmol) were added. After stirring at 25 °C for the corresponding time, the reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 5 mL) and extracted with DCM (3×15 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→6/1 cyclohexane/EtOAc) furnished the title compound as a colorless solid.

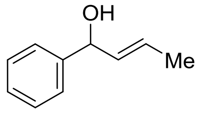
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (brs, 1H, NH), 8.00–7.94 (m, 2H, Ar-H), 7.73–7.67 (m, 1H, Ar-H), 7.59–7.52 (m, 1H, Ar-H), 7.49–7.41 (m, 2H, 2×Ar-H), 7.39–7.34 (m, 1H, Ar-H), 7.25–7.18 (m, 1H, Ar-H), 7.17–7.10 (m, 1H, Ar-H), 7.02 (d, *J* = 2.2 Hz, 1H, Ar-H), 3.92–3.79 (m, 1H, CH), 3.50 (dd, *J* = 16.4, 4.9 Hz, 1H, CH), 3.26 (dd, *J* = 16.4, 8.9 Hz, 1H, CH), 1.48 (d, *J* = 6.9 Hz, 3H, CH_3).^{13}C-NMR (75 MHz, $CDCl_3$) δ 199.92, 137.44, 136.68, 133.06, 128.67, 128.23, 126.42, 122.14, 121.63, 120.33, 119.37, 119.35, 111.41, 46.59, 27.28, 21.13. R_f (5/1 hexane/EtOAc) = 0.28. Daicel Chiralpak OD-H *n*-hexane/IPA 90/10, 1 mL/min, 214 nm, t_S = 17.2 min (minor), t_R = 23.2 min (major). The recorded values were in agreement with the published data.[69]

(*RS*)-3-(1*H*-Indol-3-yl)-1-phenylbutan-1-one ((*rac*)-51). The racemic product was prepared by the same procedure without using any bipyridine ligand.



Daicel Chiralpak OD-H *n*-hexane/IPA 90/10, 1 mL/min, 214 nm, t_S = 17.5 min, t_R = 23.6 min. All spectral data were in agreement with the chiral product **51**.

1-Phenylbut-2-en-1-ol (330).[244] A solution of 2 crystals of iodine in dry THF (2.5 mL) were added to dried vigorously stirred magnesium (465 mg, 19.1 mmol) under Ar atmosphere. After cooling down (0 °C) the suspension, bromobenzene (1.36 mL, 12.7 mmol) in dry THF (10.5 mL) was added dropwise. The mixture was stirred at 25 °C for 1.5 h and then a solution of crotonaldehyde (1.07 mL, 12.7 mmol) in dry THF (5 mL) was added slowly to the cooled (0 °C) reaction mixture. After stirring for 2 h at 25 °C, the reaction was quenched by pouring into NH_4Cl (sat. aq. sol., 30 mL) and extracted with Et_2O (3×100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (cyclohexane/EtOAc 5/1) furnished 1.351 g (72%) of the title compound as a yellowish oil.

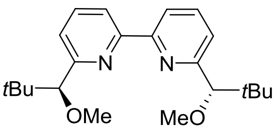


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40–7.33 (m, 4H, 4×Ar-H), 7.30–7.25 (m, overlapping with $CHCl_3$, Ar-H), 5.82–5.64 (m, 2H, 2×CH), 5.16 (dd, *J* = 6.4, 3.0 Hz, 1H, CH), 1.74–1.71 (m, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.51, 133.77, 128.61, 127.64, 127.62, 126.26, 75.35, 17.82.R_f (5/1 cyclohexane/EtOAc) = 0.31. The recorded values were in agreement with the published data.[243]

5.5 Synthesis of 2,2'-bipyridine *N*,*N'*-dioxides

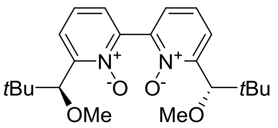
5.5.1 Synthesis of 2,2'-bipyridine *N*,*N'*-dioxide (*S*,*S*)-125

6,6'-Bis((*S*)-1-Methoxy-2,2-dimethylpropyl)-2,2'-bipyridine (72).[110] A solution of (*S*,*S*)-**8** (399 mg, 1.2 mmol) in THF (10 mL) was slowly added to a suspension of NaH (60% w/w in mineral oil, 146 mg, 3.7 mmol) in THF (5 mL). After stirring at 25 °C for 1 h, MeI (0.30 mL, 4.9 mmol) was added slowly. After stirring at 25 °C for 16 h, the reaction was quenched by addition of water (10 mL) and extracted with DCM (3×30 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 25/1→20/1 hexanes/EtOAc) yielded 384 mg (88%) of the title compound as a colorless solid.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, J = 7.8, 1.1 Hz, 2H, 2×Ar-H), 7.79 (t, J = 7.8 Hz, 2H, 2×Ar-H), 7.38 (dd, J = 7.7, 1.1 Hz, 2H, 2×Ar-H), 4.07 (s, 2H, 2×CH), 3.27 (s, 6H, $2\times CH_3$), 0.98 (s, 18H, $6\times CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.00, 155.24, 136.77, 121.73, 119.17, 93.01, 57.96, 35.70, 26.45. HRMS (ESI) *m/z* calculated for $C_{22}H_{33}N_2O_2$ (M+H) 357.2537, found 357.2534. R_f (5/1 hexanes/EtOAc) = 0.79. The recorded values were in agreement with the published data.[55]

6,6'-Bis((*S*)-1-methoxy-2,2-dimethylpropyl)-[2,2'-bipyridine] 1,1'-dioxide ((*S*,*S*)-125).[122] MCPBA (724 mg, 3.2 mmol) was added to a cooled (0 °C) solution of **72** (384 mg, 1.1 mmol) in DCM (20 mL). After stirring at 25 °C for 2 h, a second portion of MCPBA (727 mg, 3.2 mmol) was added to the cooled (0 °C) reaction mixture. After stirring at 25 °C for 19 h, the reaction mixture was quenched by addition of NaOH (40% aq. sol., 5 mL) and stirred for 1 h. The phases were separated and the aqueous phase was washed with DCM (3×20 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 40/1→10/1 $CHCl_3/Me_2CO$) and recrystallization from hexanes furnished 294 mg (70%) of title compound as a colorless solid.

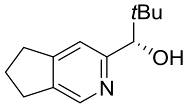


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.9, 2.2 Hz, 2H, 2×Ar-H), 7.44 (dd, J = 7.8, 2.2 Hz, 2H, 2×Ar-H), 7.29 (t, J = 7.8 Hz, 2H, 2×Ar-H), 5.04 (s, 2H, 2×CH), 3.24 (s, 6H, $2\times CH_3$), 0.99 (s, 18H, $6\times CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.01, 143.87, 126.28, 125.87, 123.45, 82.71, 58.33, 37.57, 25.86. HRMS (ESI) *m/z* calculated for $C_{22}H_{32}N_2O_4Na$

(M+Na) 411.2254, found 411.2249. R_f (60/1 DCM/MeOH) = 0.17. The recorded values were in agreement with the published data.[129]

5.5.2 Synthesis of 2,2'-bipyridine *N*,*N'*-dioxides 333 and 334

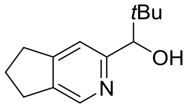
(*S*)-1-(6,7-Dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-ol (298).[11]



A mixture of $Et_3N/HCOOH$ (2/1, 4 mL) was added to a solution of **307** (498 mg, 2.45 mmol) and RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) (86 mg, 0.12 mmol) in DCM (5 mL). After stirring at 40 °C for 6 days, the reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 5 mL) and extracted with DCM (3×15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 5/2→2/1 hexanes/EtOAc) furnished 442 mg (88%, 74% ee) of the title compound as a colorless solid. Recrystallization of the product from excess of hexanes provided 240 mg (48%, >99% ee) of the title compound.

Mp = 93.2 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H, Ar-H), 7.05 (s, 1H, Ar-H), 4.40 (brs, 1H, OH), 4.29 (s, 1H, CH), 2.98–2.84 (m, 4H, 2×CH_2), 2.19–2.03 (m, 2H, CH_2), 0.90 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.48, 153.68, 143.46, 139.11, 119.03, 80.44, 36.40, 32.71, 30.02, 26.07, 25.27. IR (drift KBr) υ_{max} 3264, 3246, 3210, 2974, 2953, 2902, 2872, 1344, 1296, 1072, 1018, 884 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{20}NO$ (M+H) 206.1539, found 206.1540. R_f (2/1 hexanes/EtOAc) = 0.32. $[\alpha]_D^{20}$ = -30.1° ($CHCl_3$, c = 0.38). HPLC: Daicel Chiralpak IA, *n*-heptane/IPA 80/20, 1 mL/min, 208 nm, t_S = 6.3 min, t_R = ND.

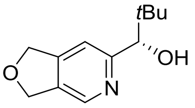
(*RS*)-1-(6,7-Dihydro-5H-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-ol ((*rac*)-298).[237]



NaBH$_4$ (43 mg, 1.1 mmol) was added to a solution of **307** (153 mg, 0.75 mmol) in dry MeOH (3 mL). After stirring at 25 °C for 1 h, the reaction was quenched by addition of water (5 mL) and extracted with DCM (3×15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Filtration of the residue through silica gel pad (1/1 hexanes/EtOAc) provided 152 mg (99%) of the title compound as an amorphous solid.

HPLC: Daicel Chiralpak IA, *n*-heptane/IPA 80/20, 1 mL/min, 208 nm, t_S = 6.3 min, t_R = 7.7 min. All the spectral data were in agreement with the chiral product **298**.

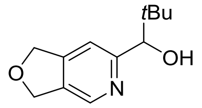
(*S*)-1-(1,3-Dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-ol (299).[11]



A mixture of $Et_3N/HCOOH$ (2/1, 10 mL) was added to a solution of **308** (1.327 g, 6.47 mmol) and RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) (227 mg, 0.32 mmol) in DCM (7 mL). After stirring for at 40 °C for 44 h, the reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 10 mL) and extracted with DCM (3×30 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1→2/3 hexanes/EtOAc) furnished 1317 mg (98%, 89% ee) of the title compound as an amorphous solid. Recrystallization from excess of hexanes provided 909 mg (68%, >99% ee) of the title compound.

Mp = 101.9 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.45, (s, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 5.18–5.03 (m, 4H, 2×CH_2), 4.36 (s, 1H, CH), 4.21 (brs, 1H, OH), 0.91 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.09, 148.82, 140.77, 134.34, 115.49, 80.69, 72.90, 71.59, 36.43, 26.00. IR (drift KBr) υ_{max} 3249, 2959, 2932, 2869, 1341, 1075, 1048, 1021, 902, 878 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{18}NO_2$ (M+H) 208.1332, found 208.1332. R_f (2/1 hexanes/EtOAc) = 0.11. $[\alpha]_D^{20}$ = -20.9° ($CHCl_3$, c = 0.31). HPLC: Daicel Chiralpak IC, *n*-heptane/IPA 80/20, 1 mL/min, 207 nm, t_S = 7.4 min, t_R = ND.

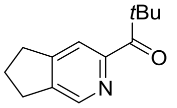
(***RS***)-1-(1,3-Dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-ol ((*rac*)-299).[237]



$NaBH_4$ (41 mg, 1.1 mmol) was added to a solution of **308** (150 mg, 0.73 mmol) in dry MeOH (4 mL). After stirring at 25 °C for 2 h, the reaction was quenched by addition of water (5 mL) and extracted with DCM (3×15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Filtration of the residue through silica gel pad (1/2 hexanes/EtOAc) provided 145 mg (96%) of the title compound as an amorphous solid.

HPLC: Daicel Chiralpak IC, *n*-heptane/IPA 80/20, 1 mL/min, 207 nm, t_S = 7.5 min, t_R = 11.0 min. All the spectral data were in agreement with the chiral product **299**.

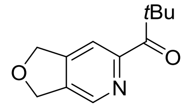
1-(6,7-Dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-one (307).



A solution of hepta-1,6-diyne **239** (310 mg, 3.3 mmol) in DCE (18 mL) was added slowly by a syringe pump to a solution of Cp*RuCl(cod) (126 mg, 0.33 mmol) and pivaloyl cyanide **179b** (90% purity, 0.60 mL, 4.9 mmol) in DCE (12 mL) under Ar atmosphere during the course of 10 h. After stirring at 25 °C for 3 h, volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (gradient 50/1→40/1 hexanes/EtOAc) provided 499 mg (75%) of the title compound as colorless crystals.

Mp = 25.7 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 2.99–2.90 (m, 4H, 2×CH_2), 2.12 (p, J = 7.5 Hz, 2H, CH_2), 1.44 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 207.35, 154.32, 153.06, 143.68, 142.82, 120.01, 44.26, 32.77, 30.55, 27.75, 24.98. IR (drift KBr) υ_{max} 3446, 3416, 2956, 2863, 1679, 1231, 1111, 985, 899, 884 cm^{-1}. HRMS (EI) m/z calculated for $C_{13}H_{17}NO$ (M) 203.1310, found 203.1306. R_f (10/1 hexanes/EtOAc) = 0.61.

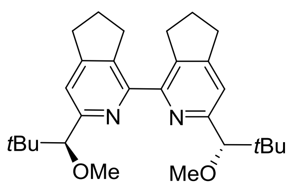
1-(6,7-Dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-one (308).



A solution of propargyl ether **234** (770 µL, 7.3 mmol) in DCE (20 mL) was added slowly by a syringe pump to a solution of Cp*RuCl(cod) (282 mg, 0.73 mmol) and pivaloyl cyanide **179b** (90% purity, 1.35 mL, 10.9 mmol) in DCE (50 mL) under Ar atmosphere during the course of 10 h. After stirring at 25 °C for 5 h, volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (gradient 20/1→8/1 hexanes/EtOAc) provided 1.327 g (89%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 0.8 Hz, 1H, Ar-H), 7.82 (d, J = 0.8, 1H, Ar-H), 5.19–5.15 (m, 2H, CH_2), 5.13–5.09 (m, 2H, CH_2), 1.44 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 206.64, 153.92, 149.60, 140.77, 137.57, 116.71, 73.08, 71.86, 44.31, 27.63. IR (drift KBr) υ_{max} 3482, 3422, 3402, 2968, 2956, 2926, 2863, 1688, 1272, 1189, 1147, 1123, 1048, 1003, 985, 899, 881 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{15}NO_2$ (M) 205.1103, found 205.1105. R_f (5/1 hexanes/EtOAc) = 0.46.

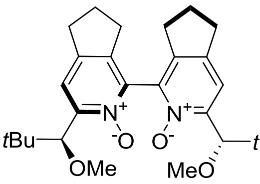
3,3'-Bis((*S*)-1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-1,1'-bi(cyclopenta[*c*]pyridine) (332). Method A:[110] A solution of **296** (100 mg, 0.25 mmol) in THF (4 mL) was added slowly to a suspension of NaH (60% w/w in mineral oil, 30 mg, 0.73 mmol) in THF (1 mL). After stirring at 25 °C for 30 min, MeI (124 µL, 3.0 mmol) was added slowly. After stirring at 50 °C for 24 h, the reaction was quenched by addition of water (2 mL) and extracted with DCM (3×10 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1→20/1) yielded 89 mg (83%) of the title compound as a colorless solid.



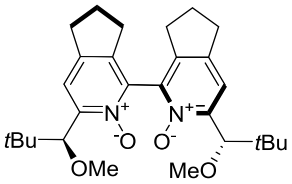
Method B: Following general method A for dimerization of 2-bromopyridines, PPh_3 (380 mg, 1.45 mmol) and Zn (26 mg, 0.39 mmol) were added to a warmed (70 °C) solution of $NiCl_2$ (48 mg, 0.36 mmol) in dry DMF (2 mL). The solution was sonicated while being bubbled through by Ar for 10 min and then stirred at 70 °C for 1 h. Then 2-bromopyridine **335** (90 mg, 0.30 mmol) in DMF (2 mL) was added and reaction was stirred at 70 °C for 12 h. After DMF was distilled off from the reaction mixture under reduced pressure, the residue was suspended in DCM (10 mL) and filtered through Celite®. The filtrate was washed with $NaHCO_3$ (sat. aq. sol., 5 mL) and the aqueous phase was then washed with DCM (2×15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 100/1→12/1 hexanes/EtOAc) furnished 45 mg (68%) of the title compound as colorless crystals.

Mp = 199.2 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27 (s, overlapping with $CDCl_3$), 4.05 (s, 2H, 2×CH), 3.44–3.33 (m, 2H, 2×CH), 3.18 (s, 6H, 2×CH_3), 3.01–2.93 (m, 4H, 2×CH_2), 2.75–2.65 (m, 2H, 2×CH), 2.23–2.11 (m, 2H, 2×CH), 2.05–1.19 (m, 2H, 2×CH), 0.96 (s, 18H, 9×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.67, 155.51, 152.50, 138.13, 117.66, 92.93, 57.77, 35.80, 33.13, 31.92, 26.66, 25.06. IR (drift KBr) υ_{max} 2983, 2962, 2926, 2869, 2815, 1248, 1231, 1183, 1105, 973 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{28}H_{41}N_2O_2$ (M+H) 437.3163, found 437.3157. R_f (5/1 hexanes/EtOAc) = 0.48.

(a*S*)-3,3'-Bis((*S*)-1-Methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*S*,*S*,a*S*)-333) and (a*R*)-3,3'-bis((*S*)-1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5H,5'H-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*S*,*S*,a*R*)-333). Method A:[122] MCPBA (90 mg, 0.41 mmol) was added in 6 portions during 5 h to a cooled (0 °C) solution of **332** (60 mg, 0.14 mmol) in DCM (4.5 mL). After stirring at 25 °C for 2 h, the reaction was quenched by addition of NaOH (40% aq. sol., 3 mL) and stirred at 25 °C for 1 h. The phases were separated and the aqueous phase was washed with DCM (3×15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 20/1→5/1 $CHCl_3$/Me_2CO) furnished 60 mg (93%) of (*S*,*S*,a*R*)-**333** as a colorless solid.



(*S*,*S*,a*S*)-**333**



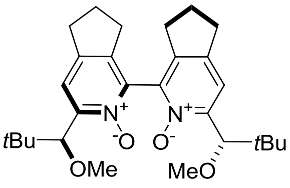
(*S*,*S*,a*R*)-**333**

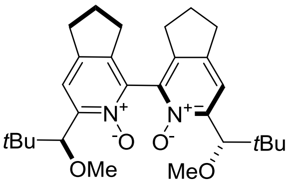
Method B:[110] A freshly prepared solution of LiTMP (1.27 mmol) in THF (3.5 mL) was dropwise added to a cooled (-73 °C) solution of **346** (273 mg, 1.16 mmol) in Et_2O (5 mL). After stirring at -73 °C for 16 h, a solution of I_2 (330 mg, 1.3 mmol) in THF (2.5 mL) was added in two portions in 1 h. The reaction was allowed to warm up to 25 °C during the period of 3 h, then it was quenched by addition of $Na_2S_2O_3$ (sat. aq. sol., 5 mL) and extracted with DCM (5×15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 90/1/1→90/30/1 DCM/Me_2CO/EtOH) furnished 75 mg (28%) of (*S*,*S*,a*S*)-**333** and 160 mg (59%) of (*S*,*S*,a*R*)-**333** as yellowish solids.

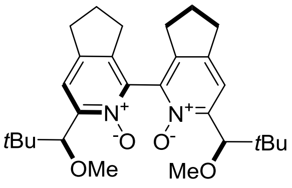
(*S*,*S*,a*S*)-**333**: Mp = 210.6 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2H, 2×Ar-H), 4.98 (s, 2H, 2×CH), 3.21 (s, 6H, 2×CH_3), 3.01 (ddd, *J* = 15.8, 8.6, 6.8 Hz, 2H, 2×CH), 2.96 (t, *J* = 7.4 Hz, 4H, 2×CH_2), 2.54 (ddd, *J* = 16.5, 8.8, 5.7 Hz, 2H, 2×CH), 2.26–2.03 (m, 4H, 2×CH_2), 0.96 (s, 18H, 6×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.88, 142.36, 141.31, 139.17, 120.49, 83.35, 58.05, 37.29, 32.67, 30.90, 25.85, 25.19. IR (drift KBr) υ_{max} 2965, 1290, 1263, 1248, 1225, 1174, 1096, 1066 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{28}H_{40}N_2O_4Na$ (M+Na) 491.2880, found 491.2878. R_f (60/1 DCM/MeOH) = 0.17. $[\alpha]_D^{20}$ = -315.6° ($CHCl_3$, *c* = 0.48). HPLC: Lux Columns – Lux Cellulose-1, *n*-heptane/IPA 99.5/0.5, 1 mL/min, 254 nm, $t_{S,S,aS}$ = 13.2 min, $t_{R,R,aR}$ = ND.

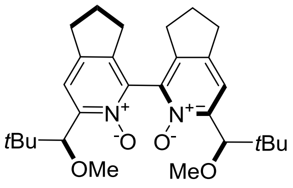
(*S*,*S*,a*R*)-**333**: Mp = 112.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 2H, 2×Ar-H), 5.04 (s, 2H, 2×CH), 3.22 (s, 6H, 2×CH_3), 3.07–2.95 (m, 4H, 2×CH_2), 2.90 (dt, *J* = 16.5, 8.3 Hz, 2H, 2×CH), 2.45 (ddd, *J* = 16.5, 9.1, 5.0 Hz, 2H, 2×CH), 2.28–2.15 (m, 2H, 2×CH), 2.15–2.02 (m, 2H, 2×CH), 0.98 (s, 18H, 6×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.19, 142.30, 142.15, 139.35, 120.73, 82.68, 58.34, 37.23, 32.72, 30.68, 25.89, 24.86. IR (drift KBr) υ_{max} 2971, 2953, 2926, 2908, 1392, 1293, 1248, 1210, 1102, 1072 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{28}H_{41}N_2O_4$ (M+H) 469.3061, found 469.3060. R_f (30/1 DCM/MeOH) = 0.36. $[\alpha]_D^{20}$ = +36.7° ($CHCl_3$, *c* = 0.15). HPLC: Lux Columns – Lux Cellulose-1, *n*-heptane/IPA 95/5, 1 mL/min, 254 nm, $t_{S,S,aR}$ = 4.1 min, $t_{R,R,aS}$ = ND.

(*RS*,*RS*,a*RS*)-3,3'-Bis(1-Methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5H,5'H-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*rac*)-333$_A$, $C_{28}H_{41}N_2O_4$), (*RS*,*RS*,a*SR*)-3,3'-bis(1-Methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5H,5'H-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*rac*)-333$_B$, $C_{28}H_{41}N_2O_4$), (*RS*,*SR*,a*RS*)-3,3'-bis(1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5H,5'H-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*rac*)-333$_C$, $C_{28}H_{41}N_2O_4$), and (*RS*,*SR*,a*SR*)-3,3'-bis(1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5H,5'H-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*rac*)-333$_D$, $C_{28}H_{41}N_2O_4$).


(*rac*)-**333$_A$**


(*rac*)-**333$_B$**


(*rac*)-**333$_C$**


(*rac*)-**333$_D$**

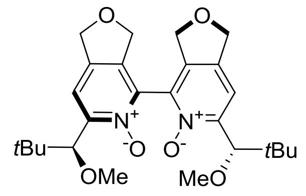
Products (*rac*)-**333$_A$** and (*rac*)-**333$_B$** and as well 50/50 mixture of (*rac*)-**333$_C$** and (*rac*)-**333$_D$** were prepared *via* oxidative dimerization approach using racemic alcohol (*rac*)-**298**.

(*rac*)-**333$_A$**: HPLC: Lux Columns – Lux Cellulose-1, *n*-heptane/IPA 99.5/0.5, 1 mL/min, 254 nm, $t_{S,S,aS}$ = 13.6 min, $t_{R,R,aR}$ = 16.1 min. All spectral data were in agreement with the chiral product (*S*,*S*,a*S*)-**333**

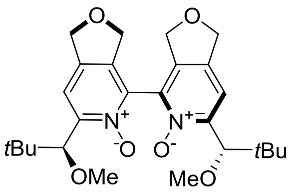
(*rac*)-**333$_B$**: HPLC: Lux Columns – Lux Cellulose-1, *n*-heptane/IPA 95/5, 1 mL/min, 254 nm, $t_{S,S,aR}$ = 4.1 min, $t_{R,R,aS}$ = 5.4 min. All spectral data were in agreement with the chiral product (*S*,*S*,a*R*)-**333**

(*rac*)-**333$_C$**+(*rac*)-**333$_D$**: Mp = 234.7 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 2H, 2×Ar-H), 7.29 (s, 2H, 2×Ar-H), 5.02 (s, 2H, 2×CH), 5.01 (s, 2H, 2×CH), 3.26 (s, 6H, 2×CH_3), 3.20 (s, 6H, 2×CH_3), 3.13–2.89 (m, 12H, 6×CH_2), 2.49–2.33 (m, 4H, 4×CH), 2.27–2.13 (m, 4H, 4×CH), 2.13–1.99 (m, 4H, 4×CH), 0.98 (s, 36H, 12×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.05 (2×C), 142.78, 142.71, 142.00, 141.44, 139.22, 139.15, 120.66 (2×C), 83.11, 82.79, 58.61, 57.97, 37.36, 37.12, 32.69, 32.64, 30.89, 30.76, 25.93, 25.92, 25.03, 24.99. IR (drift KBr) υ_{max} 2965, 1296, 1251, 1225, 1210, 1180, 1150, 1093, 1069, 970, 937, 923 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{28}H_{41}N_2O_4$ (M+H) 469.3061, found 469.3063. R_f (30/1 DCM/MeOH) = 0.49.

(a*S*)-3,3'-6,6'-Bis((*S*)-1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*S*,*S*,a*S*)-334) and (a*R*)-3,3'-6,6'-Bis((*S*)-1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*S*,*S*,a*R*)-334).[110] A freshly prepared solution of LiTMP (0.76 mmol) in THF (1.4 mL) was dropwise added to a cooled (-73 °C) solution of **347** (163 mg, 0.7 mmol) in Et_2O (4 mL). After stirring at -73 °C for 16 h, a solution of I_2 (191 mg, 1.3 mmol) in THF (2 mL) was added in two portions in 2 h. The reaction mixture was allowed to warm up to 25 °C during the period of 3 h, then it was quenched by addition of $Na_2S_2O_3$ (sat. aq. sol., 5 mL) and extracted with DCM (5×15 mL). The combined organic franctions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 90/1/1→100/20/1 DCM/Me_2CO/EtOH) furnished 18 mg (11%) of (*S*,*S*,a*S*)-**334** and 97 mg (60%) of (*S*,*S*,a*R*)-**334** as yellowish solids.



(*S*,*S*,a*S*)-**334**

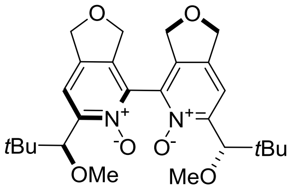


(*S*,*S*,a*R*)-**334**

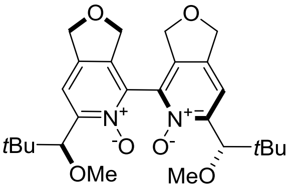
(*S*,*S*,a*S*)-**334**: Mp = 205.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 2H, 2×Ar-H), 5.29–5.22 (m, 2H, 2×CH), 5.13–5.08 (m, 4H, 2×CH_2), 4.97 (s, 2H, 2×CH), 4.73–4.66 (m, 2H, 2×CH), 3.21 (s, 6H, 2×CH_3), 0.96, (s, 18H, 6×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.82, 139.00, 136.31, 135.85, 118.14, 83.35, 73.13, 72.18, 58.21, 37.41, 25.79. IR (drift KBr) υ_{max} 1260, 1198, 1186, 1099, 1075, 1048, 1033, 908 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{26}H_{36}N_2O_6Na$ (M+Na) 495.2466, found 495.2465. R_f (60/1 DCM/MeOH) = 0.20. $[\alpha]_D^{20}$ = -393.4° ($CHCl_3$, *c* = 0.24). HPLC: Lux Columns – Lux Cellulose-2, *n*-heptane/IPA 80/20, 1 mL/min, 254 nm, $t_{S,S,aS}$ = 7.1 min, $t_{R,R,aR}$ = ND.

(*S*,*S*,a*R*)-**334**: Mp = 180.7 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.36 (s, 2H, Ar-H), 5.25–5.20 (m, 2H, 2×CH), 5.14–5.09 (m, 4H, 2×CH_2), 4.98 (s, 2H, 2×CH), 4.64–4.60 (m, 2H, 2×CH), 3.21 (s, 6H, 2×CH_3), 0.99 (s, 18H, 6×CH_3). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 150.84, 139.15, 136.46, 135.92, 118.14, 82.95, 73.17, 72.25, 58.48, 37.41, 25.79. IR (drift KBr) υ_{max} 1260, 1201, 1183, 1102, 1096, 1078, 1048, 1033, 973, 914, 899 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{26}H_{37}N_2O_6$ (M+H) 473.2646, found 473.2646. R_f (60/1 DCM/MeOH) = 0.17. $[\alpha]_D^{20}$ = +296.3° ($CHCl_3$, *c* = 0.37). HPLC: Lux Columns – Lux Cellulose-4, *n*-heptane/IPA 90/10, 1 mL/min, 254 nm, $t_{R,R,aS}$ = ND, $t_{S,S,aR}$ = 20.4 min.

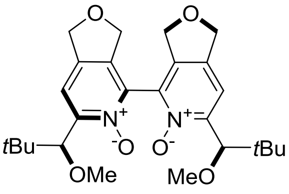
(*RS*,*RS*,a*RS*)-3,3'-6,6'-Bis(1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*rac*)-334$_\mathrm{A}$), (*RS*,*RS*,a*SR*)-3,3'-6,6'-bis(1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*rac*)-334$_\mathrm{B}$), (*RS*,*SR*,a*RS*)-3,3'-6,6'-bis(1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*rac*)-334$_\mathrm{C}$), and (*RS*,*SR*,a*SR*)-3,3'-6,6'-bis(1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*rac*)-334$_\mathrm{D}$).



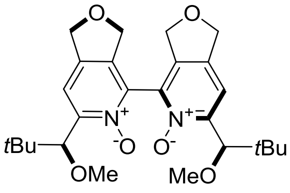
(*rac*)-**334**$_\mathbf{A}$



(*rac*)-**334**$_\mathbf{B}$



(*rac*)-**334**$_\mathbf{C}$



(*rac*)-**334**$_\mathbf{D}$

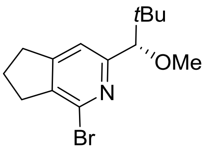
Products (*rac*)-**334**$_\mathbf{A}$ and (*rac*)-**334**$_\mathbf{B}$ and as well 50/50 mixture of (*rac*)-**334**$_\mathbf{C}$ and (*rac*)-**334**$_\mathbf{D}$ were prepared *via* oxidative dimerization approach using racemic alcohol (*rac*)-**299**.

(*rac*)-**334**$_\mathbf{A}$: HPLC: Lux Columns – Lux Cellulose-2, *n*-heptane/IPA 80/20, 1 mL/min, 254 nm, $t_{S,S,aS}$ = 7.0 min, $t_{R,R,aR}$ = 28.2 min. All spectral data were in agreement with (*S*,*S*,a*S*)-**334**.

(*rac*)-**334**$_\mathbf{B}$: HPLC: Lux Columns – Lux Cellulose-4, *n*-heptane/IPA 90/10, 1 mL/min, 254 nm, $t_{R,R,aS}$ = 9.7 min, $t_{S,S,aR}$ = 20.5 min. All spectral data were in agreement with (*S*,*S*,a*R*)-**334**.

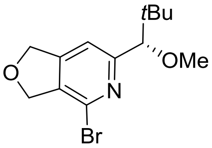
(*rac*)-**334**$_\mathbf{C}$+(*rac*)-**334**$_\mathbf{D}$: Mp = 232.8 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 2H, 2×Ar-H), 7.36 (s, 2H, 2×Ar-H), 5.36–5.30 (m, 2H, 2×CH), 5.29–5.23 (m, 2H, 2×CH), 5.13–5.08 (8H, 4×CH_2), 5.01 (s, 2H, 2×CH), 4.95 (s, 2H, 2×CH), 4.65–4.61 (m, 2H, 2×CH), 4.61–4.57 (m, 2H, 2×CH), 3.26 (s, 6H, 2×CH_3), 3.20 (s, 6H, 2×CH_3), 0.99 (s, 18H, 6×CH_3), 0.97 (s, 18H, 6×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.89, 150.87, 139.41, 139.35, 136.63, 136.30, 135.89, 135.87, 118.18, 118.16, 83.19, 83.01, 73.09, 73.07, 72.48, 72.21, 58.74, 58.16, 37.52, 37.29, 25.83, 25.82. IR (drift KBr) $\upsilon_{\max}$ 1263, 1231, 1183, 1093, 1078, 1051, 1036, 1024, 970, 943, 899 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{26}H_{36}N_2O_6Na$ (M+Na) 495.2466, found 495.2461. R_f (30/1 DCM/MeOH) = 0.53.

(*S*)-1-Bromo-3-(1-methoxy-2,2-dimethylpropyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (335).[110] A solution of **294** (131 mg, 0.46 mmol) in THF (4 mL) was slowly added to a cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 28 mg, 0.70 mmol) in THF (2 mL). After stirring at 25 °C for 30 min, MeI (58 µL, 0.92 mmol) was added slowly to the cooled (0 °C) reaction mixture. After stirring at 25 °C for 2 h, the reaction mixture was quenched by addition of water (5 mL) and extracted with DCM (3×15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1→20/1 hexanes/EtOAc) yielded 119 mg (87%) of the title compound as a colorless solid.



Mp = 113.4 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H, Ar-H), 3.96 (s, 1H, CH), 3.22 (s, 3H, CH_3), 3.02 (t, J = 7.6 Hz, 2H, CH_2), 2.93 (t, J = 7.6 Hz, 2H, CH_2), 2.13 (p, J = 7.7 Hz, 2H, CH_2), 0.89 (s, 9H, 3×CH_3).^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.07, 155.97, 140.32, 137.63, 117.47, 92.01, 58.00, 35.72, 34.04, 32.94, 26.24, 23.73. IR (drift KBr) υ_{max} 2956, 2923, 2821, 1592, 1539, 1368, 1242, 1180, 1099, 976, 967, 917 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{14}H_{20}NOBrNa$ (M+Na) 320.0621, found 320.0620. R_f (20/1 hexanes/EtOAc) = 0.47.

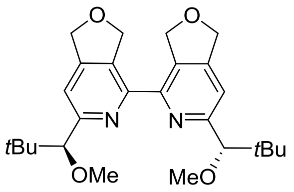
(*S*)-4-Bromo-6-(1-methoxy-2,2-dimethylpropyl)-1,3-dihydrofuro[3,4-*c*]pyridine (336).[110]



A solution of **295** (630 mg, 2.14 mmol) in THF (17 mL) was slowly added to a cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 130 mg, 3.2 mmol) in THF (9 mL). After stirring at 25 °C for 30 min, MeI (270 µL, 4.3 mmol) was added slowly to the cooled (0 °C) reaction mixture. After stirring at 25 °C for 2 h, the reaction mixture was quenched by addition of water (10 mL) and extracted with DCM (3×30 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1→20/1 hexanes/EtOAc) yielded 622 mg (97%) of the title compound as a colorless solid.

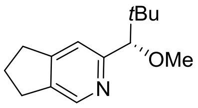
Mp = 47.3 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H, Ar-H), 5.21–5.17 (m, 2H, CH_2), 5.08–5.04 (m, 2H, CH_2), 4.00 (s, 1H, CH), 3.23 (s, 3H, CH_3), 0.90 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.08, 151.17, 135.68, 133.52, 113.93, 91.95, 74.34, 73.24, 58.16, 35.85, 26.20. IR (drift KBr) υ_{max} 2974, 2959, 1380, 1242, 1189, 1099, 1054, 908, 860 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{13}H_{18}NO_2BrNa$ (M+Na) 322.0413, found 322.0414. R_f (5/1 hexanes/EtOAc) = 0.42.

6,6'-Bis((*S*)-1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro-4,4'-bifuro[3,4-*c*]pyridine (337). Following general method A for dimerization of 2-bromopyridines, PPh_3 (630 mg, 2.4 mmol) and Zn (43 mg, 0.65 mmol) were added to a warmed (70 °C) solution of $NiCl_2$ (80 mg, 0.6 mmol) in dry DMF (1.5 mL). The solution was sonicated while being bubbled through by Ar for 10 min and then stirred at 70 °C for 1 h. Then 2-bromopyridine **336** (150 mg, 0.50 mmol) in DMF (2 mL) was added and reaction was stirred at 70 °C for 12 h. After DMF was distilled off from the reaction mixture under reduced pressure, the residue was suspended in DCM (15 mL) and filtered through Celite®. Filtrate was washed with $NaHCO_3$ (sat. aq. sol., 10 mL) and the aqueous phase was then washed with DCM (2×30 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1→18/1 hexanes/EtOAc) furnished 86 mg (78%) of the title compound as colorless crystals.

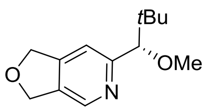


Mp = 215.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (s, overlapping with $CDCl_3$, 2×Ar-H), 5.73 (dt, J = 14.5, 2.0 Hz, 2H, 2×CH), 5.61 (dt, J =14.6, 1.9 Hz, 2H, 2×CH), 5.17–5.13 (m, 4H, $2\times CH_2$), 4.05 (s, 2H, 2×CH), 3.23 (s, 6H, $2\times CH_3$), 0.96 (s, 18H, $6\times CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.11, 150.72, 149.31, 133.49, 114.14, 92.98, 75.17, 72.49, 57.95, 35.25, 26.51. IR (drift KBr) υ_{max} 2986, 2962, 2926, 2866, 1180, 1099, 1048, 964, 908 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{26}H_{37}N_2O_4$ (M+H) 441.2748, found 441.2746. R_f (10/1 hexanes/EtOAc) = 0.35.

(*S*)-3-(1-Methoxy-2,2-dimethylpropyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (344).[110] A solution of **298** (259 mg, 1.26 mmol) in THF (8 mL) was added slowly to a cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 80 mg, 2.0 mmol) in THF (8 mL). After stirring at 25 °C for 30 min, MeI (160 µL, 2.5 mmol) was added slowly to the cooled (0 °C) reaction mixture. After stirring at 25 °C for 1 h, the reaction was quenched by addition of water (10 mL) and extracted with DCM (3×30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexanes/EtOAc) yielded 259 mg (94%) of the title compound as a colorless solid.

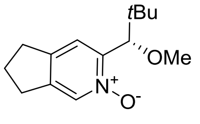


Mp = 38.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 3.92 (s, 1H, CH), 3.19 (s, 3H, CH_3), 2.89 (t, J = 7.5 Hz, 4H, $2\times CH_2$), 2.08 (p, J = 7.5 Hz, 2H, CH_2), 0.88 (s, 9H, $3\times CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.79, 153.66, 144.11, 138.76, 118.16, 92.87, 57.80, 35.60, 32.81, 30.08, 26.36, 25.16. IR (drift KBr) υ_{max} 2974, 2955, 2904, 1366, 1359, 1233, 1198, 1179, 1154, 1097, 1103, 1046, 973, 951, 900 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{22}NO$ (M+H) 220.1696, found 220.1698. R_f (3/1 hexanes/EtOAc) = 0.43.



(*S*)-6-(1-Methoxy-2,2-dimethylpropyl)-1,3-dihydrofuro[3,4-*c*]pyridine (345).[110] A solution of **299** (145 mg, 0.7 mmol) in THF (6 mL) was added slowly to a cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 42 mg, 1.1 mmol) in THF (3 mL). After stirring at 25 °C for 20 min, MeI (90 μL, 1.4 mmol) was added slowly to the cooled (0 °C) reaction mixture. After stirring at 25 °C for 2 h, the reaction was quenched by addition of water (6 mL) and extracted with DCM (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 3/1→2/1 hexanes/EtOAc) yielded 150 mg (97%) of the title compound as a colorless solid.

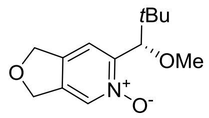
Mp = 81.6 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H, Ar-H), 7.26 s, overlapping with $CDCl_3$, Ar-H), 5.15–5.11 (m, 2H, CH_2), 5.11–5.07 (m, 2H, CH_2), 3.99 (s, 1H, CH), 3.21 (s, 3H, CH_3), 0.89 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.54, 148.92, 141.27, 134.04, 114.71, 92.70, 73.07, 71.69, 57.96, 35.71, 26.30. IR (drift KBr) υ_{max} 2977, 2953, 2923, 2869, 1180, 1114, 1087, 1048, 970, 905, 881 cm^{-1}. HRMS (EI) m/z calculated for $C_{13}H_{19}NO_2$ (M) 221.1416, found 221.1418. R_f (3/1 hexanes/EtOAc) = 0.20.



(*S*)-3-(1-Methoxy-2,2-dimethylpropyl)-6,7-dihydro-5H-cyclopenta[*c*]pyridine 2-oxide (346).[122] MCPBA (408 mg, 1.8 mmol) was added to a cooled (0 °C) solution of **344** (262 mg, 1.2 mmol) in DCM (15 mL). After stirring at 25 °C for 1 h, the reaction was quenched by addition of K_2CO_3 (sat. aq. sol., 10 mL) and stirred for 10 min. The phases were separated and the aqueous phase was washed with DCM (3×30 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1→1/1 $CHCl_3$/Me_2CO) furnished 278 mg (99%) of title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 4.98 (s, 1H, CH), 3.17 (s, 3H, CH_3), 2.90 (t, J = 7.5 Hz, 4H, 2×CH_2), 2.16 (p, J = 7.6 Hz, 2H, CH_2), 0.97 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.93, 143.70, 141.47, 135.14, 120.59, 82.69, 58.11, 37.23, 32.29, 30.61, 25.78, 25.55. IR (drift KBr) υ_{max} 2968, 2953, 1305, 1263, 1248, 1219, 1189, 1147, 1096, 1066, 967 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{21}NO_2$ (M) 235.1572, found 235.1570. R_f (50/1 DCM/MeOH) = 0.35.

(*S*)-6-(1-Methoxy-2,2-dimethylpropyl)-1,3-dihydrofuro[3,4-*c*]pyridine 5-oxide (347).[122]

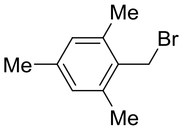


MCPBA (225 mg, 1.0 mmol) was added to a cooled (0 °C) solution of **345** (147 mg, 0.66 mmol) in DCM (9 mL). After stirring at 25 °C for 1 h, the reaction was quenched by addition of K_2CO_3 (sat. aq. sol., 6 mL) and stirred for 10 min. The phases were separated and the aqueous phase was washed with DCM (3×20 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1→3/2 $CHCl_3/Me_2CO$) furnished 156 mg (99%) of title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 5.07 (s, 4H, 2×CH_2), 4.97 (s, 1H, CH), 3.18 (s, 3H, CH_3), 0.96 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.61, 137.95, 137.07, 133.45, 117.77, 82.72, 72.86, 71.29, 58.25, 37.37, 25.70. IR (drift KBr) υ_{max} 2968, 2956, 1272, 1245, 1195, 1180, 1153, 1096, 1051, 1033, 902 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{19}NO_3$ (M) 237.1365, found 237.1366. R_f (50/1 DCM/MeOH) = 0.33.

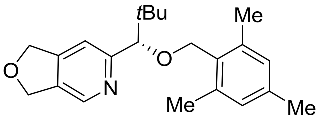
5.5.3 Synthesis of 2,2'-bipyridine *N*,*N'*-dioxide 352

2-(Bromomethyl)-1,3,5-trimethylbenzene (349).[245] PBr_3 (0.25 mL, 2.6 mmol) was added slowly to a cooled (0 °C) solution of 2,4,6-trimethylbenzyl alcohol **348** (998 mg, 6.6 mmol) in THF (45 mL). After stirring at 25 °C for 2 h, the reaction was quenched by addition of water (20 mL) and extracted with DCM (3×60 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient pure hexanes→20/1 hexanes/EtOAc) provided 1.103 g (78%) of the title compound as a colorless solid.



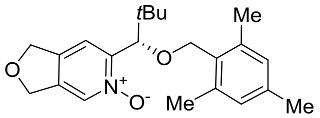
^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 2H, 2×Ar-H), 4.59 (s, 2H, CH_2), 2.40 (s, 6H, 2×CH_3), 2.29 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.62, 137.54, 131.20, 129.40, 29.82, 21.19, 19.29. R_f (hexanes) = 0.50. The recorded values were in agreement with the published data.[245]

(*S*)-6-(2,2-Dimethyl-1-((2,4,6-trimethylbenzyl)oxy)propyl)-1,3-dihydrofuro[3,4-*c*]pyridine (350). A solution of **299** (50 mg, 0.24 mmol) in THF (1.5 mL) was added slowly to a suspension of NaH (60% w/w in mineral oil, 15 mg, 0.36 mmol) and NaI (37 mg, 0.25 mmol) in THF (1.5 mL). After stirring at 25 °C for 30 min, **349** (107 mg, 0.50 mmol) was added slowly. After stirring at 25 °C for 20 h, the reaction was quenched by addition of water (3 mL) and extracted with DCM (3×10 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→5/1 hexanes/EtOAc) yielded 39 mg (48%) of the title compound as a colorless oil.



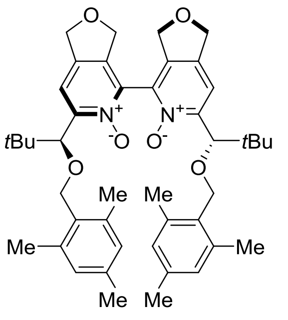
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 6.84 (s, 2H, 2×Ar-H), 5.20–5.16 (m, 2H, CH_2), 5.16–5.04 (m, 2H, CH_2), 4.33 (d, J = 10.5 Hz, 1H, CH), 4.29 (d, J = 10.5 Hz, 1H, CH), 4.24 (s, 1H, CH), 2.28–2.24 (m, 9H, 3×CH_3), 0.91 (s, 9H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.32, 148.33, 141.19, 138.06, 137.66, 134.09, 131.74, 128.96, 114.89, 90.78, 73.09, 71.76, 66.27, 35.79, 36.48, 21.12, 19.70. IR (drift KBr) υ_{max} 2950, 2917, 2860, 1610, 1574, 1395, 1362, 1335, 1078, 1048, 902, 881, 851 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{30}NO_2$ (M+H) 340.2277, found 340.2274. R_f (5/1 hexanes/EtOAc) = 0.29.

(*S*)-6-(2,2-Dimethyl-1-((2,4,6-trimethylbenzyl)oxy)propyl)-1,3-dihydrofuro[3,4-*c*]pyridine 5-oxide (351).[122] MCPBA (140 mg, 0.63 mmol) was added to a cooled (0 °C) solution of **350** (141 mg, 0.42 mmol) in DCM (7 mL). After stirring at 25 °C for 2 h, the reaction mixture was quenched by addition of K_2CO_3 (sat. aq. sol., 5 mL) and stirred for 10 min. The phases were separated and the aqueous phase was washed with DCM (3×15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1→3/2 $CHCl_3/Me_2CO$) furnished 146 mg (99%) of title compound as a colorless oil.

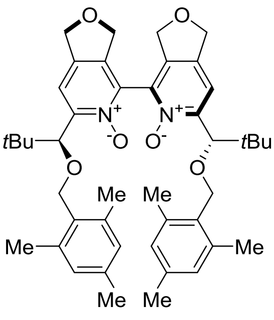


^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 6.83 (s, 2H, 2×Ar-H), 5.24 (s, 1H, CH), 5.16–4.97 (m, 4H, 2×CH_2), 4.38 (d, J = 10.4 Hz, 1H, CH), 4.25 (d, J = 10.4 Hz, 1H, CH), 2.25 (s, 9H, 3×CH_3), 0.99 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.18, 137.97, 137.92, 137.38, 137.09, 133.45, 131.34, 129.02, 118.11, 81.00, 72.86, 71.37, 66.85, 37.50, 25.89, 21.12, 19.68. IR (drift KBr) υ_{max} 2950, 2920, 2869, 1416, 1272, 1153, 1081, 1045, 899, 581, 770 cm^{-1}. HRMS (CI) *m*/*z* calculated for $C_{22}H_{33}NO_3$ (M+H) 356.2226, found 356.2228. R_f (30/1 DCM/MeOH) = 0.29.

(a*S*)-6,6'-Bis((*S*)-2,2-dimethyl-1-((2,4,6-trimethylbenzyl)oxy)propyl)-1,1',3,3'-tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*S*,*S*,a*S*)-352) and (a*R*)-6,6'-bis((*S*)-2,2-dimethyl-1-((2,4,6-trimethylbenzyl)oxy)propyl)-1,1',3,3'-tetrahydro-[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*S*,*S*,a*R*)-352).[110] A freshly prepared solution of LiTMP (0.46 mmol) in THF (0.9 mL) was dropwise added to a cooled (-73 °C) solution of **351** (150 mg, 0.42 mmol) in Et_2O (1.7 mL). After stirring at -73 °C for 16 h, a solution of I_2 (119 mg, 0.46 mmol) in THF (1 mL) was added in two portions in 2 h. The reaction mixture was allowed to warm up to 25 °C during the period of 3 h, then it was quenched by addition of $Na_2S_2O_3$ (sat. aq. sol., 5 mL) and extracted with DCM (5×15 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1→3/1 hexanes/EtOAc) furnished 19 mg (13%) of (*S*,*S*,a*S*)-**352** as an amorphous solid and 63 mg (42%) of (*S*,*S*,a*R*)-**352** as yellowish crystals.



(*S*,*S*,a*S*)-**352**



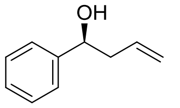
(*S*,*S*,a*R*)-**352**

(*S*,*S*,a*S*)-**352**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 2H, 2×Ar-H), 6.86 (s, 4H, 4×Ar-H), 5.32–5.25 (m, 2H, CH_2), 5.21 (s, 2H, 2×CH), 5.18–5.04 (m, 4H, 2×CH_2), 4.80–4.70 (m, 2H, CH_2), 4.44 (d, *J* = 10.8 Hz, 2H, 2×CH), 4.33 (d, *J* = 10.8 Hz, 2H, 2×CH), 2.31 (s, 12H, 6×CH_3), 2.28 (s, 6H, 2×CH_3), 0.97 (s, 9H, 3×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.41, 138.99, 137.94, 137.88, 136.02, 135.76, 131.20, 139.07, 118.58, 81.13, 73.14, 72.22, 66.64, 37.58, 25.88, 21.13, 19.73. IR (drift KBr) υ_{max} 2953, 2920, 2872, 2860, 1613, 1395, 359, 1263, 1219, 1192, 1087, 1042, 908, 854, 785 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{44}H_{57}N_2O_6$ (M+H) 709.4211, found 709.4212. R_f (3/1 hexanes/EtOAc) = 0.33. $[\alpha]_D^{20}$ = -135.0° ($CHCl_3$, *c* = 0.34).

(*S*,*S*,a*R*)-**352**: Mp = 143.7 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 2H, 2×Ar-H), 6.85 (s, 4H, 4×Ar-H), 5.38–5.31 (m, 2H, CH_2), 5.25 (s, 2H, 2×CH), 5.18–5.07 (m, 4H, 2×CH_2), 4.67–4.61 (m. 2H, CH_2), 4.35 (s, 4H, 2×CH_2), 2.29 (s, 12H, 4×CH_3), 2.27 (s, 6H, 2×CH_3), 1.01 (s, 18H, 6×CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.30, 139.97, 138.07, 137.87, 136.25, 136.10, 131.27, 129.02, 118.32, 81.00, 73.10, 72.49, 66.76, 37.51, 25.96, 21.13, 19.73. IR (drift KBr) υ_{max} 2953, 2917, 2869, 1616, 1392, 1356, 1263, 1219, 1189, 1090, 1045, 908, 857, 785 cm^{-1}. HRMS (ESI) *m*/*z* calculated for $C_{44}H_{56}N_2O_6Na$ (M+Na) 731.4031, found 731.4031. R_f (3/1 hexanes/EtOAc) = 0.53. $[\alpha]_D^{20}$ = +301.6° ($CHCl_3$, *c* = 0.32).

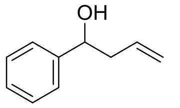
5.6 Application of bipyridine *N,N′*-dioxides

5.6.1 Allylation of benzaldehyde



(*S*)-1-Phenylbut-3-en-1-ol (161).[111] Allyltrichlorosilane (115 µL, 0.75 mmol) was added to a cooled (-78 °C) solution of benzaldehyde **14** (50 µL, 0.50 mmol), *N,N′*-dioxide (0.0025 mmol), and (*i*Pr)$_2$NEt (130 µL, 0.75 mmol) in DCM (2 mL). After stirring at -78 °C for 15.5 h, the reaction was quenched by addition of NaHCO$_3$ (sat. aq. sol., 1 mL) and extracted with DCM (3×5 mL). The combined organic fractions were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The yield was determined by ^{1}H-NMR analysis. Analytically pure product **161** was obtained by column chromatography on silica gel (gradient 30/1→20/1 hexanes/EtOAc). (*S*)-configuration was determined by comparison of data with literature.[111]

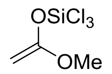
^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.40–7.32 (m, 4H, 4×Ar-H), 7.32–7.27 (m, 1H, Ar-H), 5.88–5.75 (m, 1H, CH), 5.21–5.10 (m, 2H, CH$_2$), 4.74 (dd, *J* = 7.5, 5.3 Hz, 1H, CH), 2.58–2.43 (m, 2H, CH$_2$), 2.11 (brs, 1H, OH). ^{13}C-NMR (100 MHz, CDCl$_3$) δ 143.99, 134.58, 128.53, 127.66, 125.94, 118.53, 73.42, 43.96. R$_f$ (5/1 hexanes/EtOAc) = 0.37. HPLC: Lux Columns – Lux Cellulose-1, *n*-heptane/IPA 100/1, 1 mL/min, 215 nm, t_S = 19.5 min (major), t_R = 20.6 min (minor). The recorded values were in agreement with the published data.[246]



(*RS*)-1-Phenylbut-3-en-1-ol ((*rac*)-161).[37] Allylboronic acid pinacol ester (100 µL, 0.52 mmol) and benzaldehyde **14** (35 µL, 0.35 mmol) were added to a solution of Fe(ClO$_4$)$_2$·6H$_2$O (13 mg, 0.035 mmol) in MeCN (10 mL). After stirring at 25 °C for 5 h, the reaction was quenched by addition of water (3 mL) and extracted with DCM (3×10 mL). The combined organic fractions were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1→20/1 hexanes/EtOAc) furnished 50 mg (97%) of the title compound as a colorless oil.

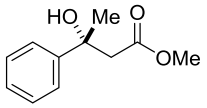
HPLC: Lux Columns – Lux Cellulose-1, *n*-heptane/IPA 100/1, 1 mL/min, 215 nm, t_S = 19.3 min, t_R = 20.3 min. All spectral data were in agreement with the chiral product **161**.

5.6.2 Aldol reaction



Trichloro((1-methoxyvinyl)oxy)silane (163).[130] Acetate **354** (4.1 g, 11.3 mmol) followed by $(Bu_3Sn)_2O$ (0.6 mL, 1.1 mmol) were slowly added to a vigorously stirred $SiCl_4$ (10.0 mL, 85 mmol). Mixture was stirred until the starting **354** was fully consumed (12 h, determined by ^{1}H-NMR) and then the mixture of $SiCl_4$ and product **163** was distilled to receiving flask connected with dry-ice condenser (50 °C, 2-5 mbar). Then $SiCl_4$ was from the distillate slowly distilled off (25 °C, 80 mbar) to another flask using the vacuum regulator. The purity of the title compound was determined by ^{1}H-NMR analysis based on the amount of created aldol product in a reaction of a small sample of the oily residue with the excess of benzaldehyde **14** in d_2-DCM.

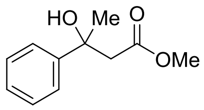
^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.65 (d, J = 3.9 Hz, 1H, CH), 3.64 (s, 3H, CH_3), 3.41 (d, J = 3.9 Hz, 1H, CH). The recorded values were in agreement with published data.[130]



(*S*/*R*)-Methyl 3-hydroxy-3-phenylbutanoate (164).[130] Trichlorosilyl ketene acetal **163** (48% purity, 100 µL, 0.3 mmol) was added to a cooled (-20 °C) solution of acetophenone **162** (23 µL, 0.20 mmol) and *N*,*N'*-dioxide (0.02 mmol) in DCM (1 mL). After stirring at -20 °C for 18 h, the reaction was quenched by addition of $NaHCO_3$ (sat. aq. sol., 1 mL), filtered throuh Celite®, and extracted with DCM (3×5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The yield was determined by ^{1}H-NMR analysis. Analytically pure product **164** was obtained by column chromatography on silica gel (gradient 20/1→7/1 cyclohexane/EtOAc) (*S*/*R*)-configuration was determined by comparison of data with literature.[130]

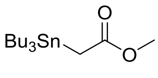
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2H, 2×Ar-H), 7.38–7.30 (m, 2H, 2×Ar-H), 7.28–7.21 (m, overlapping with $CDCl_3$, Ar-H), 4.32 (brs, 1H, OH, 3.61 (s, 3H, CH_3), 3.00 (d, J = 16,0 Hz, 1H, CH), 2.81 (d, J = 16.0 Hz, 1H, CH), 1.55 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.28, 146.96, 128.43, 127.03, 124.53, 72.81, 51.91, 46.30, 30.78. R_f (10/1 hexanes/EtOAc) = 0.27. HPLC: Lux Columns – Lux Cellulose-3, *n*-heptane/IPA 75/1, 1 mL/min, 220 nm, t_R = 15.3 min, t_S = 19.5 min. The recorded values were in agreement with published data.[130]

(*RS*)-Methyl 3-hydroxy-3-phenylbutanoate ((*rac*)-164). The racemic product was prepared by the same procedure as chiral product **164** using trimethylamine *N*-oxide as catalyst.



HPLC: Lux Columns – Lux Cellulose-3, *n*-heptane/IPA 75/1, 1 mL/min, 220 nm, t_R = 15.3 min, t_S = 19.6 min. All spectral data were in agreement with the chiral product **164**.

Methyl 2-(tributylstannyl)acetate (354).[130] *n*-BuLi (1.6 M solution in hexane, 27 mL, 42.8 mmol) was slowly added to a cooled (0 °C) solution of (iPr)$_2$NH (6 mL, 42.4 mmol) in THF (150 mL). After stirring at 0 °C for 20 min the reaction was cooled down to -78 °C. Then MeOAc (3.4 mL, 42.9 mmol) was added slowly and the mixture was stirred at -78 °C for 1 h. The solution was then transferred *via* cannula to a cooled (-78 °C) solution of Bu$_3$SnCl (10 mL, 35.4 mmol) in THF (50 mL) during the course of 30 min. The reaction mixture was stirred at -78 °C for 10 min, then it was allowed to warm up to 25 °C during the course of 3 h, and then stirred at 25 °C for 30 min. Volatiles were evaporated under reduced pressure, then hexanes (150 mL) were added. White precipitate was removed by filtration through Celite® and the filtrate was concentrated under reduce pressure. Filtration through the short silica gel column (90/10/1 hexanes/EtOAc/Et$_3$N) and Kugelrohr distillation (175 °C, 2 mbar) provided 11.9 g (93%) of the title compound as a colorless oil.



^{1}H-NMR (300 MHz, CDCl$_3$) δ 3.60 (s, 3H, CH$_3$), 1.93 (s, 2H, CH$_2$), 1.58–1.43 (m, 6H, 3×CH$_2$), 1.38–1.24 (m, 6H, 3×CH$_2$), 1.01–0.93 (m, 6H, 3×CH$_2$), 0.90 (t, J = 7.2 Hz, 9H, 3×CH$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$) δ 175.94, 50.96, 18.84, 27.31, 16.42, 13.75, 10.49. R$_f$ (20/1 hexanes/Et$_2$O) = 0.47. The recorded values were in agreement with published data.[130]

5.7 Preparation of metal salts and catalysts

Iron (II) trifluoromethanesulfonate ($Fe(OTf)_2$).[247] Trifluoromethanesulfonic acid (0.3 mL, 3.4 mmol) was slowly added to a cooled (0 °C) suspension of iron(0) (106 mg, 1.9 mmol) in water (3 mL) under Ar atmosphere. The mixture was vigorously stirred at 100 °C until all iron particles were dissolved. After evaporation to dryness, the colorless solid was dried under reduced pressure at 150 °C for 24 h.

Iron (II) dodecyl sulfate ($Fe(DS)_2$).[64] $Fe(ClO_4)_2 \cdot 7.25\ H_2O$ (1.00 g, 2.6 mmol) dissolved in a minimal amount of degassed water and sodium(I) dodecyl sulfate (1.52 g, 5.2 mmol) also dissolved in a minimal amount of degassed water were mixed and stirred under Ar atmosphere at 25 °C for 1 h. The solution was then cooled down to 0 °C which resulted in formation of suspension that was recrystallized from water and dried under reduced pressure.

Bis(benzonitrile)palladium(II) dichloride ($PdCl_2(PnCN)_2$).[248] Palladium(II) acetate (502 mg, 2.2 mmol) was stirred at 90 °C for 30 min in the mixture of HCl (37% aq. solution, 0.7 mL, 8.5 mmol) and benzonitrile (15 mL). After cooling down to 25 °C, hexane (8 mL) was added. The mixture was filtered through Celite® and washed with hexane. Filtrate was cooled down to 4 °C, which caused the formation of orange crystals. Crystals were filtered, washed with hexane and dried under reduced pressure.

5.8 Crystallographic data

All single crystal X-ray analyses were performed by RNDr. Ivana Císařová CSc. and their data can be found in the corresponding article or in CSD database under appropriate CCDC number. The only exception is crystal of triflate **325** which is presented herein.

Ethyl 4-iodo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (**244aa**, CCDC 1442030). Compound **244aa** (32 mg) was dissolved in a minimal amount of MeOH at 50 °C. The mixture was allowed to cool down to 25 °C, which resulted in the formation of colorless crystals.

Ethyl 4-chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (**245aa**, CCDC 1442031). Compound **245aa** (36 mg) was dissolved in a minimal amount of MeOH at 50 °C. The mixture was allowed to cool down to 25 °C, which resulted in the formation of colorless crystals.

(*S*)-1-(1-Bromo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-ol (**294**, CCDC 1834253). Compound **294** (50 mg) was dissolved in a minimal amount of boiling $CHCl_3$. The mixture was allowed to cool down to 25 °C, which resulted in the formation of colorless crystals.

(*S*)-1-(4-Bromo-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-ol (**295**, CCDC 1855477). Compound **295** (41 mg) was dissolved in a minimal amount of boiling $CHCl_3$. The mixture was to cool down to -20 °C, which resulted in the formation of colorless crystals.

(*S*,*S*)-1,1'-(6,6',7,7'-Tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)]-3,3'-diyl)bis(2,2-dimethylpropan-1-ol) (**296**, CCDC 1834254). Compound **296** (15 mg) was dissolved in THF (0.3 mL). Slow evaporation of the solvent resulted in the formation of colorless crystals.

Complex $[Cu_4296_2(OH)_2Cl_4]$ (CCDC 1834255). Compound **296** (10 mg, 0.025 mmol) and $[CuCl(cod)]_2$ (5 mg, 0.012 mmol) were dissolved in a minimal amount of MeOH at 50 °C. The yellow solution first changed its color to green after 1 h and then to blue after 1 d. Slow evaporation of the solvent resulted in the formation of blue and green crystals from which only green crystals were suitable for X-ray analysis.

Complex $[Cu_4296_2Cl_5(MeOH)_4]Cl$. Compound **296** (20 mg, 0.05 mmol) and $CuCl_2$ (7 mg, 0.05 mmol) were dissolved in minimal amount of MeOH at 50 °C. Slow evaporation of the solvent caused the formation of green crystals.

This crystallization method provided crystals with highly disordered arrangement of chloride and PF_6 anions and solvating methanol molecules in their unit cells, which did not allow to determine exactly the structures of these complexes.

Complex $[Cu_2296_2](PF_6)_2$. Compound **296** (10 mg, 0.025 mmol) and $Cu(MeCN)_4PF_6$ (9 mg, 0.025 mmol) were dissolved in a minimal amount of MeOH at 50 °C. The green solution slowly changed its color to blue. Slow evaporation of the solvent caused the formation of blue crystals.

This crystallization method provided crystals with highly disordered arrangement of chloride and PF_6 anions and solvating methanol molecules in their unit cells, which did not allow to determine exactly the structures of these complexes.

(*S*)-1-(6,7-Dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)-2,2-dimethylpropan-1-ol (**298**, CCDC 1855478). Compound **298** (60 mg) was dissolved in a minimal amount of $CHCl_3$. Slow evaporation of solvent resulted in the formation of colorless crystals.

(a*R*)-3,3'-Bis((*S*)-1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((***S*,*S*,a*R***)**-333**, CCDC 1855479). Compound (*S*,*S*,a*R*)-**333** was dissolved in minimal amount of boiling cyclohexane. Slow evaporation of the solvent caused the formation of colorless crystals.

5,10-Bis((*S*)-1-hydroxy-2,2-dimethylpropyl)-8-(hydroxymethyl)-3,7-dihydro-1*H*-furo[3,4-*g*]pyrido[2,3-*a*]indolizin-6-ium triflate (**325**). Colorless solid (58 mg) obtained by deacetylation of **318** was mixed with Bi(OTf)$_3$ (98 mg, 0.15 mmol) and THF (1 mL) and stirred at 60 °C for 1 h. The slow evaporation of the solvent at 25 °C resulted in the formation of red crystals in red oil. The crystals were mechanically separated from the oil and washed with THF.

Chemical formula	$C_{24}H_{33}N_2O_4 \cdot CF_3O_3S$
M_r	562.59
Crystal system, space group	Triclinic, *P*1
Temperature (K)	150
a, *b*, *c* (Å)	6.4464 (4), 8.8305 (6), 13.6458 (9)
a, b, g (°)	101.839 (2), 96.282 (2), 95.834 (2)
V (Å^3)	749.52 (9)
Z	1
Radiation type	Mo *K*a
m (mm^{-1})	0.17
Crystal size (mm)	0.27 × 0.20 × 0.06
Data collection	
Diffractometer	Bruker D8 VENTURE Kappa Duo PHOTON 100 CMOS
Absorption correction	Multi-scan *SADABS2016*/2 - Bruker AXS area detector scaling and absorption correction
T_{min}, T_{max}	0.92, 0.99
No. of measured, independent and observed [I > 2s(I)] reflections	17890, 6456, 5481
R_{int}	0.036
(sin q/l)$_{max}$ (Å^{-1})	0.650
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.042, 0.104, 1.02
No. of reflections	6456
No. of parameters	359
No. of restraints	3
H-atom treatment	H-atom parameters constrained
Dρ$_{max}$, Dρ$_{min}$ (e Å^{-3})	0.24, -0.22
Absolute structure	Flack x determined using 2172 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.05 (2)

6 ABBREVIATIONS

Ac	acetyl
acac	acetylacetone
Ad	adamantyl
AFIR	Artificial Force-Induced Reaction
aq.	aqueous
BDE	bond-dissociation energy
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1'-binaphtol
BipyMOX	bis(oxazolinyl)bipyridine
BM	ball-mill
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bis(oxazoline)
Bu	butyl
c	*cyclo*
CBS	Corey–Bakshi–Shibata catalyst
CCDC	The Cambridge Crystallographic Data Centre
CI	chemical ionization
cod	cyclooctadiene
cond.	conditions
cot	cyclooctatriene
Cp	cyclopentadienyl
CPME	cyclopentyl methyl ether
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DFT	Density Functional theory
DME	dimethoxyethane
DMF	*N*,*N*'-dimethylformamide
dmfu	dimethyl fumarate
DMP	2,2'-dimethoxypropane
DMSO	dimethyl sulfoxide

dpen	diphenylethylenediamine
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DS	dodecyl sulfate
DTBP	2,6-di-*tert*-butylpyridine
EDG	electron-donating group
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron ionization
ent	enantiomer
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
GC	gas chromatography
Hep	heptyl
HMDS	hexamethyldisilamide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
i	*iso*
IOCB	Institute of Organic Chemistry and Biochemistry
Ipc	isopinocampheyl
IR	infrared spectrometry
LA	Lewis acid
LASC	Lewis acid surfactant catalysts
LB	Lewis base
LDA	lithium diisopropylamine
LSD	lysergic acid diethylamide
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Mp	melting point

ms	minimal-salt
MS	molecular sieves
MVK	methyl vinyl ketone
MW	microwave
n	*normal*
Naphth	naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge Thermal-Ellipsoid Plot
p	*para*
PEG	polyethylene glycol
PG	protecting group
Ph	phenyl
pin	pinacol
Pr	propyl
PyBOX	bis(oxazolinyl)pyridine
PyMOX	mono(oxazolinyl)pyridine
quant.	quantitative
r.t.	room temperature
rac	racemic
s	*sec*
sat.	saturated
sol.	solution
t	*tert*
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TDAE	tetrakis(dimethylamino)ethylene
TFA	trifluoroacetic acid
TfO	triflate, trifluoromethanesulfonate
THF	tetrahydrofuran

TMB	2,4,6-trimethylbenzyl
TMP	tetramethylpiperidide
TMS	trimethylsilyl
TOF	time-of-flight
TPP	triphenylphosphine
TPPO	triphenylphosphine oxide
Ts	tosyl, *p*-toluenesulfonyl
UDST	undecyl sulfonate
UHP	urea hydroperoxide
US	ultrasound

7 RÉSUMÉ

7.1 Etat de l'art

7.1.1 Bipyridines

Les bipyridines sont des composés hétérocycliques possédant 2 cycles pyridiniques. Bien qu'il existe généralement 6 types de bipyridines, chacun dépendant de la position où se situe le lien entre les 2 pyridines, les plus étudiées restent les 2,2'-bipyridines, reliées par une liaison chimique entre les 2 atomes de carbone voisins de l'atome d'azote de chaque pyridine (Figure 1).[1]

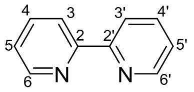
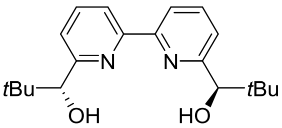


Figure 1. Numérotation des atomes de la 2,2'-bipyridine.

Diverses applications ont été trouvées pour ces 2,2'-bipyridines dans plusieurs domaines de la chimie tels que les chimies macro-[2] et supra-moléculaires[3] ainsi qu'en chimie des matériaux,[4] en photochimie[5] et en électrochimie.[6] Cela est dû aux excellentes propriétés de coordination de ces ligands dans des réactions métallo-catalysées.[7] L'insertion d'un élément de chiralité permet le contrôle de la stéréochimie du centre métallique et ainsi permet d'agrandir le champs d'application en catalyse asymétrique.[8]

Un des ligands chiraux de type 2,2'-bipyridine les plus utilisés dans des réactions asymétriques catalysées par des métaux de transition est le ligand de Bolm **8** (Figure 2).[18,19] Ce diol possédant une symétrie de type C_2 a trouvé beaucoup d'applications en tant que ligand chiral dans des réactions d'alkylation et d'allylation asymétriques d'aldéhydes,[18,36] d'addition conjuguée,[38] d'ouverture d'époxydes *meso*,[56] d'aldolisation de Mukaiyama[23] et dans l'activation C–H d'indoles[69] ou encore dans des réactions de Diels–Alder,[71] etc.

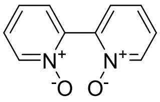


(*R*,*R*)-**8**

Figure 2. Ligand de Bolm (*R,R*)-**8**.

7.1.2 Les 2,2'-bipyridine *N,N'*-dioxydes

Les 2,2'-bipyridines *N,N'*-dioxydes font partie d'une classe de composés très intéressante dérivée des 2,2'-bipyridines, qui portent des atomes d'oxygène sur chaque atome d'azote (Figure 3).[100] Grâce à la polarisation de la liaison *N–O*, elles possèdent des propriétés chimiques et réactionnelles uniques. Les oxygènes présents sur les azotes des pyridines sont considérés comme des bases de Lewis et ont ainsi la capacité de coordiner et activer les nucléophiles comportant un caractère acide de Lewis dans des réactions avec des électrophiles.[101]



2,2'-bipyridine *N,N'*-dioxyde

Figure 3. Structure de la 2,2'-bipyridine *N,N'*-dioxyde.

Bien que les *N,N'*-dioxydes puissent être utilisés comme ligands dans des réactions métallo-catalysées, ils aussi ont montré un grand intérêt en tant qu'organocatalyseur. Durant ces vingt dernières années, les *N,N'*-dioxydes chiraux ont été utilisés dans des réactions d'allylation/de propargylation/d'allénylation avec des aldéhydes, d'aldolisation, d'ouverture d'époxydes, de cyanosilylation d'aldéhydes, etc.[102]

7.1.3 Réaction de cocyclotrimérisation [2+2+2] catalytique d’alcynes et de nitriles

De nombreuses méthodes existent pour construire le squelette pyridine. Cependant l’une d’entre elles s’est révélée être la plus puissante : la réaction de cocyclotrimérisation métallo-catalysée d’alcynes avec des dérivés nitriles (Schéma 1).[132]

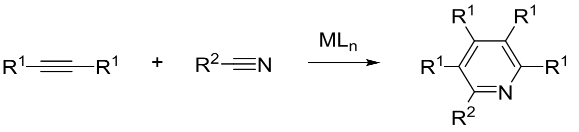


Schéma 1. Cocyclotrimérisation métallo-catalysée d’alcynes avec des dérivés nitriles.

Les principaux avantages de cette réaction sont : l’utilisation de “conditions douces”, l’économie d’atome, la tolérance à un large panel de groupements fonctionnels et l’accessibilité des produits de départ.[133] Néanmoins les autres méthodes synthétiques, impliquant trois réactifs, peuvent poser des problèmes de chimiosélectivité. De plus, dans le cas des substrats non symétriques, la régiosélectivité peut aussi poser problème. Tous ces problèmes peuvent être résolus par (a) un choix méticuleux du catalyseur métallique et du ligand, (b) une connexion entre au moins deux des substrats et (c) une optimisation des conditions réactionnelles.

7.2 Les objectifs du sujet

1) Développer une nouvelle méthodologie de synthèse de 2,2'-bipyridines énantiopures et les utiliser en tant que ligand dans des réactions métallo-catalysées asymétriques.

La conception de nouveaux ligands de type 2,2'-bipyridine est basée sur l'hypothèse que les substituants en position 3 et 3' pourraient affecter la rotation de la liaison *C*2–*C*2'. De plus la présence de groupements électrodonneurs sur la pyridine pourrait améliorer les effets chélatant de ces ligands. Tous ces critères ont été réunis afin d'avoir une influence positive sur l'induction asymétrique dans les réactions métallo-catalysées.

2) Synthétiser de nouvelles 2,2'-bipyridines *N*,*N'*-dioxydes et tester ces catalyseurs en tant que base de Lewis dans des réactions asymétriques.

Une séquence réactionnelle similaire a été proposée pour la synthèse de chacun de ces composés, les 2,2'-bipyridines et les 2,2'-bipyridines *N*,*N'*-dioxydes. Rétrosynthétiquement parlant, les 2,2'-bipyridines *N*,*N'*-dioxydes pourraient être obtenues grâce à une réaction d'oxydation des 2,2'-bipyridines chirales (Etape a, Schéma 2), qui pourraient être synthétisées par une dimérisation réductrice de la 2-halogéno-pyridine chirale (Etape b). La chiralité présente sur les 2-halogéno-pyridines sera installée par une modification asymétrique de la chaîne latérale portée par la position 6 de 2-halogéno-pyridines non chirales (e.g. réaction énantiosélective, Etape c). Une réaction de cocyclotrimérisation catalytique [2+2+2] des diynes halogénés en présence de dérivés nitriles nous permettrait de préparer les 2-halogéno-pyridines bicycliques (Etape d).

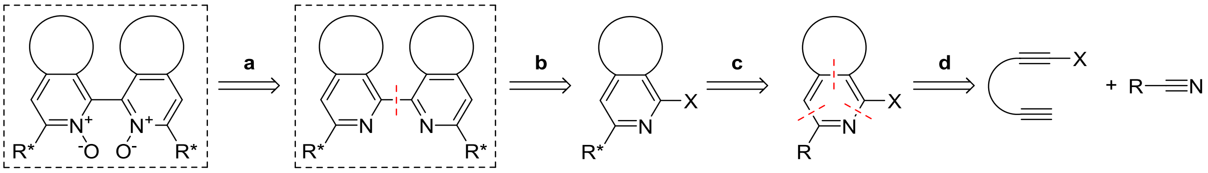


Schéma 2. Conception rétrosynthétique des composés 2,2'-bipyridines.

3) La réaction de cocyclotrimérisation des diynes halogénés avec les nitriles n'était pas connue au moment du démarrage de ce travail de thèse. Le troisième but de cette étude a été de développer et étudier cette nouvelle réaction de cyclotrimérisation.

7.3 Résultats et Discussion

7.3.1 Cocyclotrimérisation catalytique [2+2+2] des diynes halogénés avec des dérivés nitriles

La cocyclotrimérisation de l'iododiyne **231a** en présence de nitrile portant un substituant électro-attracteur (cyanoformate d'éthyle **179a**) permet l'obtention, dans des conditions réactionnelles optimisées (10 mol% of Cp*RuCl(cod), 2 éq. de nitrile, DCE, 25 °C), de deux régioisomères, la 2-iodopyridine **244aa** et la 3-iodopyridine **245aa** avec 29% et 45% de rendements (Schéma 3). L'analyse du milieu réactionnel a révélé la formation, à hauteur de 5%, d'un sous-produit **246aa** comportant un atome de chlore à la place de l'iode en position 2.

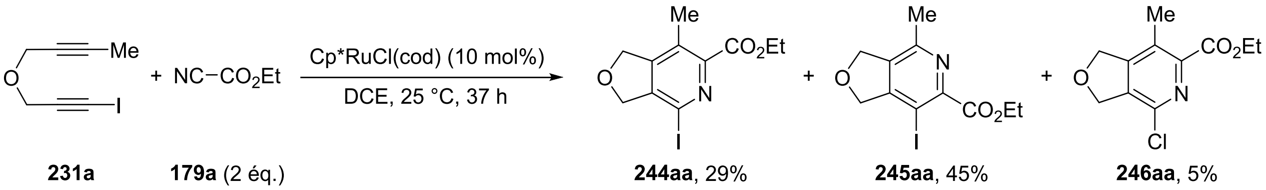


Schéma 3. Cocyclotrimérisation du diyne halogéné **231a** avec le nitrile **179a** sous des conditions réactionnelles optimales.

L'origine de ce composé a été élucidée par la réaction de la 2-iodopyridine **244aa** (produit de cyclotrimérisation) avec le catalyseur à base de ruthénium. Une étude RMN ^{1}H a été réalisée afin de suivre la réaction et d'élucider la formation du sous-produit (Schéma 4). Plus tard, il a été révélé expérimentalement que cette réaction se déroule même sur les simples 2-iodopyridines. Néanmoins, les essais pour mettre en place la réaction de façon catalytique ont échoué.

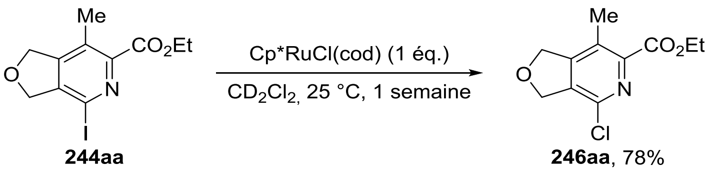


Schéma 4. Réaction d'échange d'halogène.

L'exemplification de la réaction a ensuite été étudiée avec différents diynes halogénés et dérivés nitriles. La structure des diynes est modifiable en trois positions – le substituant halogéné (vert, Figure 4), le substituant porté par la deuxième triple liaison (rouge), et l'espaceur entre les deux triples liaisons (bleu). Au regard des dérivés nitriles, seulement ceux portant des substituants électro-attracteurs se sont avérés réactifs dans les conditions réactionnelles mises en place (orange).

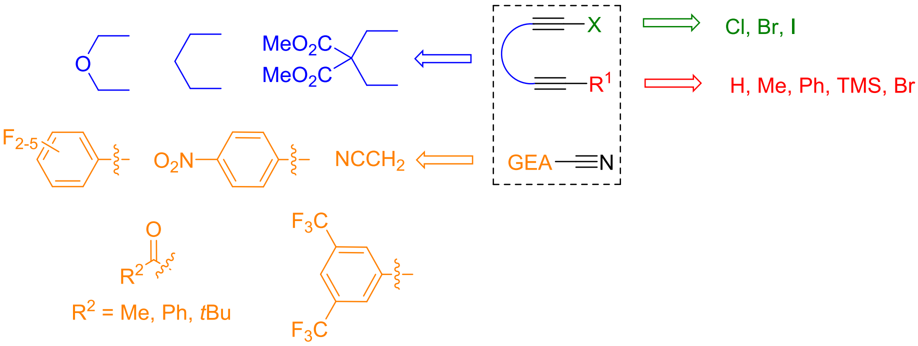
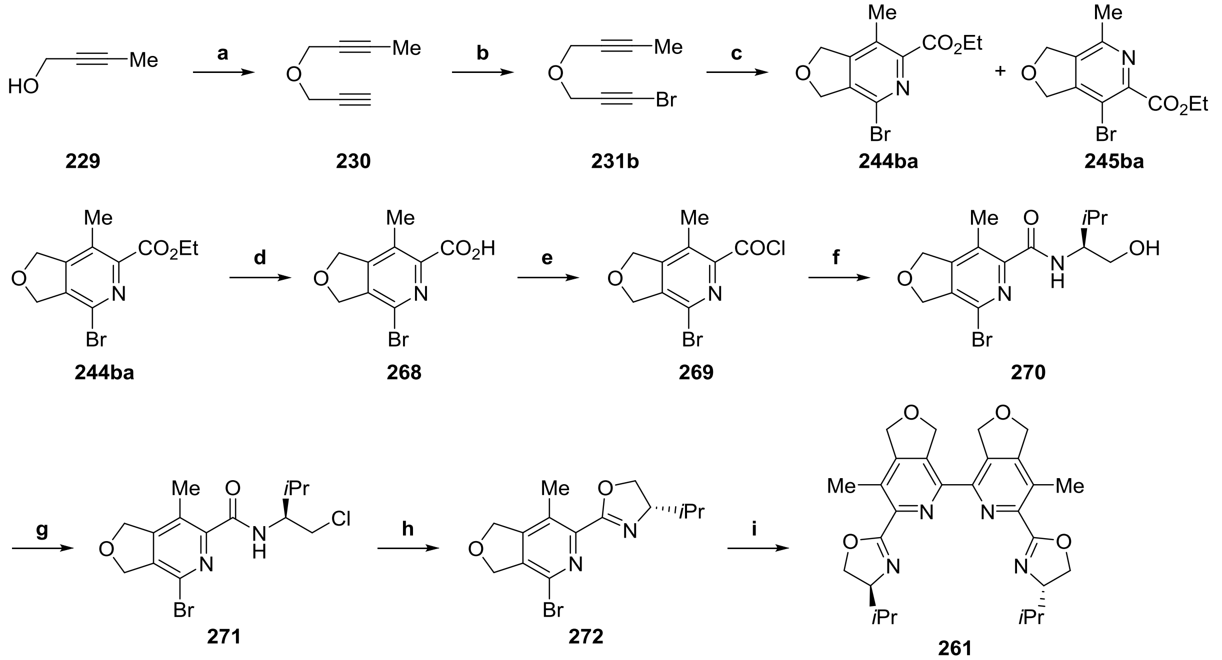


Figure 4. Modification des diynes halogénés et dérivés nitriles de départ dans la réaction de cocyclotrimérisation.

7.3.2 Synthèse et application des 2,2'-bipyridines

Ayant la méthode de cyclotrimérisation des diynes halogénés en présence de dérivés nitriles en main, la synthèse de nouveaux ligands de type 2,2'-bipyridine a été envisagée.

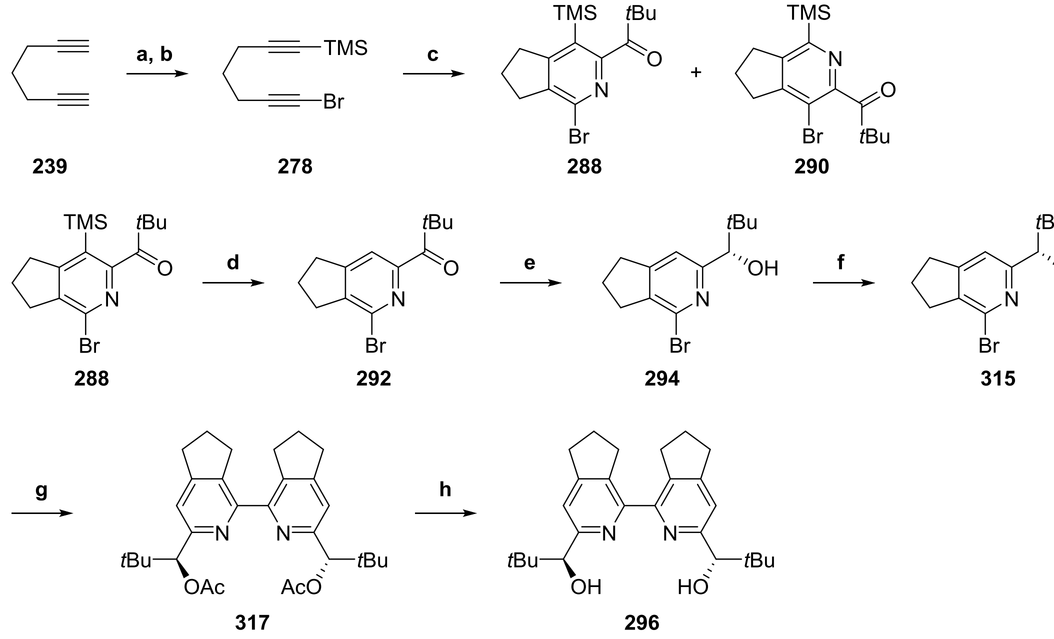
Tout d'abord, le ligand 2,2'-bipyridine **261** portant deux cycles oxazoline en positions 6 et 6' du squelette de la bipyridine a été synthetisé en neuf étapes avec un rendement global de 8% (Schéma 5). La synthèse démarre avec la préparation du diyne halogéné **231b** (Etape a et b), la cocyclotrimérisation du cyanoformate d'éthyle **179a** a donné les cycloadduits **244ba** et **245ba** avec des rendements de 40% et 48% respectivement (Etape c). Ensuite le régioisomère **244aa** a été converti en 2-bromopyridine **272** avec un cycle oxazoline grâce à des réactions standards (Etape d à h). L'étape cruciale de cette synthèse a été la réaction de dimérisation réductrice (Etape i). La bipyridine cible **261** a été obtenue avec un rendement global de 51%.



a) I) NaH (1,2 éq.), THF, de 0 à 25 °C, 30 min; II) bromure de propargyle (1,8 éq.), THF, de 0 à 25 °C, 2 h (74%)
b) NBS (1,2 éq.), $AgNO_3$ (12,5 mol%), Me_2CO, 25 °C, 2 h (78%)
c) NC-CO_2Et **179a** (2 éq.), Cp*RuCl(cod) (10 mol%), DCE, 25 °C, 21 h (40% (**244ba**), 48% (**245ba**))
d) $LiOH{\cdot}H_2O$ (2 éq.), THF/H_2O 3/1, 25 °C, 3 h (99%)
e) $SOCl_2$, reflux, 12 h
f) L-valinol (1,1 éq.), Et_3N (2 éq.), DCM, de 0 à 25 °C, 23 h (87% en 2 étapes)
g) $SOCl_2$ (2 éq.), DCM, reflux, 21 h (>96%)
h) NaH (5 éq.), $n Bu_4NI$ (10 mol%), THF, 25 °C, 12 h (93%)
i) $NiBr_2(PPh_3)_2$ (1 éq.), Zn (5 éq.), $n Bu_4NI$ (5 éq.), THF, 60 °C, 18 h (51%)

Schéma 5. Synthèse de la bipyridine **261**.

L'analogue du ligand de Bolm, la 2,2'-bipyridine **296**, a été synthétisé en huit étapes de synthèse avec 16% de rendement global. La séquence réactionnelle consiste en trois étapes clé: (a) cocylotrimérisation du diyne halogéné **278** avec le cyanure de pivaloyle **179b** donnant accès aux bromopyridines **288** et **290** avec 56% et 15% de rendement, respectivement (Etape c, Schéma 6); (b) hydrogénation énantiosélective de la cétone **292**, permettant l'obtention du alcool **294** avec 96% de rendement et 94% d'excès énantiomérique (Etape e); et (c) dimérisation réductrice de la 2-bromopyridine **315** en bipyridine **317** (66%, Etape g).



a) I) LiHMDS (1 éq.), THF, -78 °C, 1 h; II) TMSCl (1 éq.), -78 °C, 1 h
b) I) *n*BuLi (1 éq.), THF, -78 °C, 30 min; II) NBS (1,2 éq.), de -78 à 25 °C, 12 h (52% en 2 étapes)
c) NC-CO*t*Bu **179b** (2 éq.), Cp*RuCl(cod) (10 mol%), DCE, 25 °C, 17 h (56% (**288**), 15% (**290**))
d) TBAF (1,2 éq.), THF, 25 °C, 1 h (94%)
e) RuCl[(*S*,*S*)-Tsdpen](*p*-cymène) (5 mol%), HCO_2H (13 éq.), Et_3N (7,5 éq.), DCM, 25 °C, 3 jrs (96%, 94% ee)
f) Ac_2O (2,5 éq.), pyridine (2,5 éq.), 25 °C, 10 h (>96%)
g) $NiCl_2$ (1,2 éq.), Zn (1,3 éq.), PPh_3 (4,8 éq.), DMF, 70 °C, 14 h (66%)
h) K_2CO_3 (7,5 éq.), MeOH, 25 °C, 5 h (>96%, 99% ee)

Schéma 6. Synthèse de la bipyridine **296**.

La bipyridine **277** a été synthétisée utilisant la même séquence réactionnelle que pour le composé **261** avec 9% de rendement global (Figure 5). Malheureusement la synthèse de la bipyridine **297** a, elle, échoué à la dernière étape de déprotection.

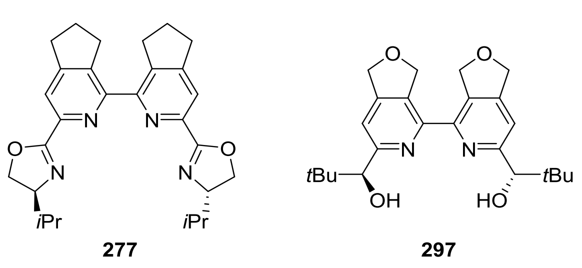
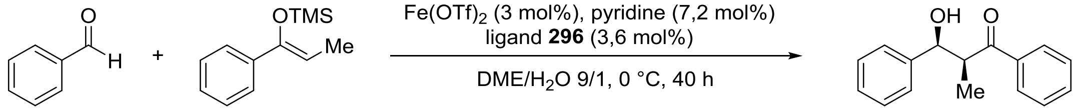


Figure 5. Structures des bipyridines **277** et **297**.

La conformation et les propriétés de chélation du composé **296** ont ensuite été examinées grâce à une étude RMN, des calculs DFT de la bipyridine **296**, ainsi que des analyses par diffraction des rayons X des complexes de cuivre. Cette étude a révélé que la conformation périplanaire du ligand bipyridine **296** était énergétiquement défavorable, la complexation du centre métallique impliquant une légère rotation des deux cycles pyridine rend cet arrangement stable.

La bipyridine **296** a également été testé dans des réactions asymétriques métallo-catalysées. Un haut niveau d'induction asymétrique a été observé dans le cas de la réaction d'aldolisation de Mukaiyama catalysée au Fe(II) (92% ee, Schéma 7) et la réaction d'ouverture d'époxydes catalysée au Sc(III) (98% ee, Schéma 8). De plus, les complexes métalliques **296** démontrent une meilleure robustesse que les complexes précédemment reportés, qui résulte de sa faible sensibilité à la pureté des réactifs dans les réactions catalysées par le complexe métallique **296**.



14 **44** **45**, >96%, dr 99/1, 92% ee

Schéma 7. Aldolisation asymétrique de Mukaiyama catalysée par le complexe Fe(II)-**296**.

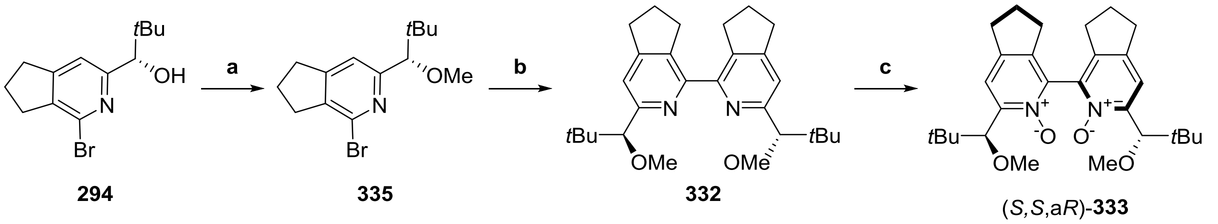
38

319: X = OCH_2, R = OMe, 82%, 98% ee
99: X = NH, R = H, 82%, 98% ee

Schéma 8. Ouverture asymétrique d'époxydes *meso* catalysée par le complexe de Sc(III)-**296**.

8.3.3 Synthèse et application des 2,2'-bipyridines *N,N'*-dioxydes

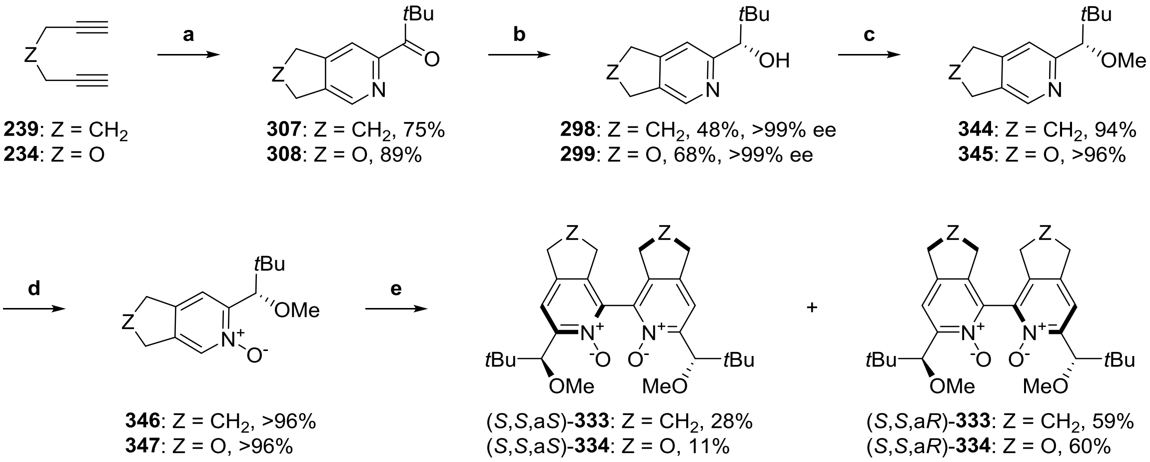
Les 2,2'-Bipyridines *N,N'*-dioxydes ont été préparés par deux approches basés sur des réactions de dimérisation différentes. La première approche utilise une réaction de dimérisation réductrice de 2-halogéno-pyridines en bipyridines. Grâce à cette réaction, la bipyridine **332** a pu être préparé puis oxydé en présence de MCPBA pour former sélectivement l'atropoisomère (a*R*), (*S*,*S*,a*R*)-**333** (Schéma 9).



a) I) NaH (1,5 éq.), THF, de 0 à 25 °C, 30 min; II) MeI (2 éq.), THF, 25 °C, 2 h (87%)
b) $NiCl_2$ (1,2 éq.), Zn (1,3 éq.), PPh_3 (4,8 éq.), DMF, 70 °C, 12 h (68%)
c) MCPBA (3 éq.), DCM, de 0 à 25 °C, 7 h (93%)

Schéma 9. Synthèse du 2,2'-bipyridine *N,N'*-dioxyde (*S*,*S*,a*R*)-**333** *via* une dimérisation réductrice.

La seconde approche basée sur une réaction de dimérisation oxydante de la pyridine-*N*-oxyde a été utilisée pour la synthèse des dioxydes **333** et **334** (Schéma 10). L'hepta-1,6-diyne **239** et l'éther de propargyle **234** ont été cocyclotrimérisés avec le cyanure de pivaloyle **179b** avec 75% et 89% de rendement (Etape a). Le transfert énantiosélectif d'hydrogène a permis de fournir les alcools chiraux **298** et **299** avec 48% et 68% de rendements respectifs en tant que composés optiquement purs après recristallisation (Etape b). Après la protection des groupements hydroxyles (Etape c), les pyridines **344** et **345** ont été oxydées en *N*-oxydes **346** et **347** avec des rendements quantitatifs (Etape d). La réaction de dimérisation oxydante permet l'obtention des *N,N'*-dioxydes **333** et **334** possédant une chiralité axiale avec la formation préférentielle d'un seul atropoisomère, (a*R*) (Etape e).



239: Z = CH_2
234: Z = O

307: Z = CH_2, 75%
308: Z = O, 89%

298: Z = CH_2, 48%, >99% ee
299: Z = O, 68%, >99% ee

344: Z = CH_2, 94%
345: Z = O, >96%

346: Z = CH_2, >96%
347: Z = O, >96%

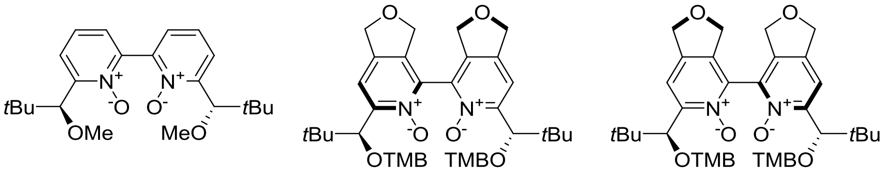
(*S*,*S*,a*S*)-**333**: Z = CH_2, 28%
(*S*,*S*,a*S*)-**334**: Z = O, 11%

(*S*,*S*,a*R*)-**333**: Z = CH_2, 59%
(*S*,*S*,a*R*)-**334**: Z = O, 60%

a) NC-CO*t*Bu **179b** (1,5 éq.), Cp*RuCl(cod) (10 mol%), DCE, 25 °C, 13 h
b) RuCl[(*S*,*S*)-Tsdpen](*p*-cymène) (5 mol%), HCO_2H (13 éq.), Et_3N (7,5 éq.), 40 °C, 6 jrs (**307**) ou 44 h (**308**)
c) I) NaH (1,6 éq.), THF, 25 °C, de 20 à 30 min ; II) MeI (2 éq.), THF, de 0 à 25 °C, de 1 à 2 h
d) MCPBA (1,5 éq.), DCM, de 0 à 25 °C, 1 h
e) I) LiTMP (1,1 éq.), Et_2O, THF, -73 °C, 16 h; II) I_2 (1,1 (**346**) ou 2 (**347**) éq.), Et_2O, THF, de -73 à 25 °C, de 4 à 5 h

Schéma 10. Synthèses des 2,2'-bipyridines *N*,*N'*-dioxydes **333** et **334** *via* une dimérisation oxydante.

L'unique élément de chiralité centrale du *N*,*N'*-dioxyde (*S*,*S*)-**125** a aussi été synthétisé par l'approche de dimérisation réductrice tandis que les *N*,*N'*-dioxydes (*S*,*S*,a*S*)-**352** and (*S*,*S*,a*R*)-**352** possédant une chiralité axiale ont été synthétisés par une approche comportant une dimérisation oxydante (Figure 6).



(*S*,*S*)-**125**

(*S*,*S*,a*S*)-**352**

(*S*,*S*,a*R*)-**352**

Figure 6. Structures des *N*,*N'*-dioxydes (*S*,*S*)-**125**, (*S*,*S*,a*S*)-**352** et (*S*,*S*,a*R*)-**352**.

Les *N*,*N'*-dioxydes préparés ont été ensuite examinés en tant qu'organocatalyseurs dans la réaction d'allylation du benzaldéhyde **14** et dans la réaction d'aldolisation de l'acétophénone en présence de l'acétal de cétène de trichlorosilylé **163**. Tandis que les meilleurs résultats dans la réaction d'allylation ont été obtenus avec le *N*,*N'*-dioxyde (*S*,*S*)-**125** (76%, 82% ee, Schéma 11), le meilleur catalyseur dans la réaction d'aldolisation s'est avéré être le composé (*S*,*S*,a*R*)-**334** (>95%, 78% ee, Schéma 12).

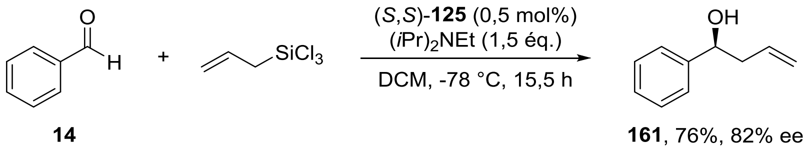


Schéma 11. Allylation du benzaldéhyde **14** catalysée par le *N*,*N′*-dioxyde (*S*,*S*)-**125**.

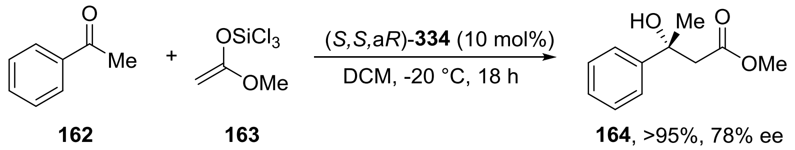


Schéma 12. Aldolisation de l'acétophénone **162** avec l'acétal de cétène de trichlorosilylé **163** catalysée par le *N*,*N′*-dioxyde (*S*,*S*,a*R*)-**334**.

7.4 Conclusion

Une variante de la cyclotrimérisation, la cocyclotrimérisation des diynes halogénés avec les dérivés nitriles, a été développée et étudiée. La formation d'un produit non désiré, issu d'un échange d'halogène, a été observée et son origine a été élucidée par des analyses expérimentales.

Trois nouveaux ligands de type 2,2'-bipyridine ont été synthétisés utilisant la réaction de cocyclotrimérisation développée en tant qu'étape clé de la séquence réactionnelle. La conformation et les propriétés de chélation d'une des nouvelles bipyridines ont été examinées par analyse RMN, des calculs DFT et analyses par diffraction des rayons X de ces complexes. L'activité des nouvelles bipyridines a ensuite été testée dans des réactions métallo-catalysées. Les meilleurs résultats ont été obtenus dans la réaction d'aldolisation de Mukaiyama et d'ouverture d'époxydes.

Six nouvelles 2,2'-bipyridines *N*,*N'*-dioxydes ont été préparées grâce à l'utilisation d'une réaction de dimérisation soit réductrice soit oxydante. Les *N*,*N'*-dioxydes ont ensuite été utilisés en tant qu'organocatalyseurs dans les réactions d'allylation et d'aldolisation.

8 REFERENCES

(1) Summers, L. A. The Bipyridines. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press, 1984; Vol. 35, pp 281–374.

(2) Liu, B.; Yu, W.-L.; Pei, J.; Liu, S.-Y.; Lai, Y.-H.; Huang, W. Design and Synthesis of Bipyridyl-Containing Conjugated Polymers: Effects of Polymer Rigidity on Metal Ion Sensing. *Macromolecules* **2001**, *34*, 7932–7940.

(3) Mathieu, J.; Fraisse, B.; Lacour, D.; Ghermani, N.; Montaigne, F.; Marsura, A. An Original Supramolecular Helicate from a Bipyridine–Bipyrazine Ligand Strand and Ni^{II} by Self-Assembly. *Eur. J. Inorg. Chem.* **2006**, 133–136.

(4) Schubert, U. S.; Kersten, J. L.; Pemp, A. E.; Eisenbach, C. D.; Newkome, G. R. A New Generation of 6,6′-Disubstituted 2,2′-Bipyridines: Towards Novel Oligo(Bipyridine) Building Blocks for Potential Applications in Materials Science and Supramolecular Chemistry. *Eur. J. Org. Chem.* **1998**, 2573–2581.

(5) Balzani, V.; Juris, A. Photochemistry and Photophysics of Ru(II)-Polypyridine Complexes in the Bologna Group. From Early Studies to Recent Developments. *Coord. Chem. Rev.* **2001**, *211*, 97–115.

(6) Margel, S.; Smith, W.; Anson, F. C. Electrochemistry of 2,2′-Bipyridine Complexes of Cobalt in the Presence of Acrylonitrile. *J. Electrochem. Soc.* **1978**, *125*, 241–246.

(7) Smith, A. P.; Fraser, C. L. Bipyridine Ligands. In *Comprehensive Coordination Chemistry II*; McCleverty, J. A., Meyer, T. J., Eds.; Pergamon: Oxford, 2003; pp 1–23.

(8) C. Fletcher, N. Chiral 2,2′-Bipyridines: Ligands for Asymmetric Induction. *J. Chem. Soc. Perkin 1* **2002**, 1831–1842.

(9) A. V. Malkov; Kočovský, P. Chiral Bipyridine Derivatives in Asymmetric Catalysis. *Curr. Org. Chem.* **2003**, *17*, 1737–1757.

(10) MacBride, J. A. H.; Wright, P. H.; Wakefield, B. J. Synthesis of 1,6-Diazabiphenylene by Flash Vacuum Pyrolysis of 2,5,9,10-Tetra-azaphenanthrene; NMR Evidence for Rehybridisation in Biphenylenes. *Tetrahedron Lett.* **1981**, *22*, 4545–4548.

(11) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. New Efficient Method for the Synthesis of Chiral 2,2′-Bipyridyl Ligands. *Synthesis* **2005**, 2176–2182.

(12) Nelson, T. D.; Crouch, R. D. Cu, Ni, and Pd Mediated Homocoupling Reactions in Biaryl Syntheses: The Ullmann Reaction. In *Organic Reactions*; Denmark, S. E., Overman, L. E., Eds.; American Cancer Society, 2004; pp 265–555.

(13) Kröhnke, F.; Zecher, W.; Curtze, J.; Drechsler, D.; Pfleghar, K.; Schnalke, K. E.; Weis, W. Syntheses Using the Michael Adddition of Pyridinium Salts. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 626–632.

(14) Domínguez, G.; Pérez-Castells, J. Recent Advances in [2+2+2] Cycloaddition Reactions. *Chem. Soc. Rev.* **2011**, *40*, 3430–3444.

(15) Kolp, B.; Abeln, D.; Stoeckli-Evans, H.; von Zelewsky, A. Platinum(II) Compounds with Enantiomerically Pure Bis(pinene)-Fused Bipyridine Ligands − Diimine-Dichloro Complexes and Their Substitution Reactions. *Eur. J. Inorg. Chem.* **2001**, 1207–1220.

(16) Hrdina, R.; Dračínský, M.; Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. New Pathway to C_2-Symmetric Atropoisomeric Bipyridine *N,N′*-Dioxides and Solvent Effect in Enantioselective Allylation of Aldehydes. *Adv. Synth. Catal.* **2008**, *350*, 1449–1456.

(17) Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K. New Chiral Bis(oxazolinyl)bipyridine Ligand (Bipymox): Enantioselection in the Asymmetric Hydrosilylation of Ketones. *Tetrahedron Asymmetry* **1993**, *4*, 143–150.

(18) Bolm, C.; Zehnder, M.; Bur, D. Optically Active Bipyridines in Asymmetric Catalysis. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 205–207.

(19) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. Enantioselective Synthesis of Optically Active Pyridine Derivatives and C_2-Symmetric 2,2′-Bipyridines. *Chem. Ber.* **1992**, *125*, 1169–1190.

(20) Kobayashi, S.; Endo, T.; Yoshino, T.; Schneider, U.; Ueno, M. Allylation Reactions of Aldehydes with Allylboronates in Aqueous Media: Unique Reactivity and Selectivity That Are Only Observed in the Presence of Water. *Chem. – Asian J.* **2013**, *8*, 2033–2045.

(21) Kokubo, M.; Naito, T.; Kobayashi, S. Chiral Zinc(II) and Copper(II)-Catalyzed Asymmetric Ring-Opening Reactions of *meso*-Epoxides with Aniline and Indole Derivatives. *Tetrahedron* **2010**, *66*, 1111–1118.

(22) Plancq, B.; Lafantaisie, M.; Companys, S.; Maroun, C.; Ollevier, T. Highly Enantioselective Iron(II)-Catalyzed Opening Reaction of Aromatic *meso*-Epoxides with Indoles. *Org. Biomol. Chem.* **2013**, *11*, 7463–7466.

(23) Ollevier, T.; Plancq, B. Highly Enantioselective Mukaiyama Aldol Reaction in Aqueous Conditions Using a Chiral Iron(II) Bipyridine Catalyst. *Chem. Commun.* **2012**, *48*, 2289–2291.

(24) Plancq, B.; Ollevier, T. Iron(II)-Catalyzed Enantioselective *meso*-Epoxide-Opening with Anilines. *Chem. Commun.* **2012**, *48*, 3806–3808.

(25) Kokubo, M.; Naito, T.; Kobayashi, S. Metal-Controlled Reversal of Enantioselectivity in Catalyzed Asymmetric Ring-Opening Reactions of *meso*-Epoxides in Water. *Chem. Lett.* **2009**, *38*, 904–905.

(26) Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. Bismuth Triflate−Chiral Bipyridine Complexes as Water-Compatible Chiral Lewis Acids. *Org. Lett.* **2005**, *7*, 4729–4731.

(27) Nandakumar, M. V.; Tschöp, A.; Krautscheid, H.; Schneider, C. Indium–Bipyridine-Catalyzed, Enantioselective Thiolysis of *meso*-Epoxides. *Chem. Commun.* **2007**, 2756–2758.

(28) Sheldon, R. A.; Arends, I. W. C. E.; Hanefeld, U. Introduction: Green Chemistry and Catalysis. In *Green Chemistry and Catalysis*; Wiley-Blackwell, 2007; pp 1–47.

(29) Egorova, K. S.; Ananikov, V. P. Which Metals Are Green for Catalysis? Comparison of the Toxicities of Ni, Cu, Fe, Pd, Pt, Rh, and Au Salts. *Angew. Chem. Int. Ed.* **2016**, *55*, 12150–12162.

(30) Jiménez-González, C.; Curzons, A. D.; Constable, D. J. C.; Cunningham, V. L. Cradle-to-Gate Life Cycle Inventory and Assessment of Pharmaceutical Compounds. *Int. J. Life Cycle Assess.* **2004**, *9*, 114–121.

(31) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. CHEM21 Selection Guide of Classical- and Less Classical-Solvents. *Green Chem.* **2015**, *18*, 288–296.

(32) Lipshutz, B. H.; Gallou, F.; Handa, S. Evolution of Solvents in Organic Chemistry. *ACS Sustain. Chem. Eng.* **2016**, *4*, 5838–5849.

(33) Sorella, G. L.; Strukul, G.; Scarso, A. Recent Advances in Catalysis in Micellar Media. *Green Chem.* **2015**, *17*, 644–683.

(34) Kobayashi, S.; Nagayama, S.; Busujima, T. Lewis Acid Catalysts Stable in Water. Correlation between Catalytic Activity in Water and Hydrolysis Constants and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands. *J. Am. Chem. Soc.* **1998**, *120*, 8287–8288.

(35) Bolm, C.; Schlingloff, G.; Harms, K. Catalyzed Enantioselective Alkylation of Aldehydes. *Chem. Ber.* **1992**, *125*, 1191–1203.

(36) Kobayashi, S.; Endo, T.; Schneider, U.; Ueno, M. Aldehyde Allylation with Allylboronates Providing α-Addition Products. *Chem. Commun.* **2010**, *46*, 1260–1262.

(37) Kobayashi, S.; Endo, T.; Ueno, M. Chiral Zinc-Catalyzed Asymmetric α-Alkylallylation and α-Chloroallylation of Aldehydes. *Angew. Chem. Int. Ed.* **2011**, *50*, 12262–12265.

(38) Bolm, C.; Ewald, M. Optically Active Bipyridines in Nickel Catalyzed Enantioselective Conjugate Addition to Enones. *Tetrahedron Lett.* **1990**, *31*, 5011–5012.

(39) Bolm, C.; Ewald, M.; Felder, M. Catalytic Enantioselective Conjugate Addition of Dialkylzinc Compounds to Chalcones. *Chem. Ber.* **1992**, *125*, 1205–1215.

(40) Ogawa, C.; Kizu, K.; Shimizu, H.; Takeuchi, M.; Kobayashi, S. Chiral Scandium Catalysts for Enantioselective Michael Reactions of β-Ketoesters. *Chem. – Asian J.* **2006**, *1* , 121–124.

(41) Bonollo, S.; Lanari, D.; Pizzo, F.; Vaccaro, L. Sc(III)-Catalyzed Enantioselective Addition of Thiols to α,β-Unsaturated Ketones in Neutral Water. *Org. Lett.* **2011**, *13*, 2150–2152.

(42) Ueno, M.; Kitanosono, T.; Sakai, M.; Kobayashi, S. Chiral Sc-Catalyzed Asymmetric Michael Reactions of Thiols with Enones in Water. *Org. Biomol. Chem.* **2011**, *9*, 3619–3621.

(43) Lauzon, S.; Keipour, H.; Gandon, V.; Ollevier, T. Asymmetric Fe^{II}-Catalyzed Thia-Michael Addition Reaction to α,β-Unsaturated Oxazolidin-2-One Derivatives. *Org. Lett.* **2017**, *19*, 6324–6327.

(44) Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T. Chiral Copper(II)-Catalyzed Enantioselective Boron Conjugate Additions to α,β-Unsaturated Carbonyl Compounds in Water. *Angew. Chem. Int. Ed.* **2012**, *51*, 12763–12766.

(45) Zhu, L.; Kitanosono, T.; Xu, P.; Kobayashi, S. A Cu(II)-Based Strategy for Catalytic Enantioselective β-Borylation of α,β-Unsaturated Acceptors. *Chem. Commun.* **2015**, *51*, 11685–11688.

(46) Kitanosono, T.; Kobayashi, S. Asymmetric Boron Conjugate Additions to Enones in Water Catalyzed by Copper(0). *Asian J. Org. Chem.* **2013**, *2*, 961–966.

(47) Kitanosono, T.; Xu, P.; Isshiki, S.; Zhu, L.; Kobayashi, S. Cu(II)-Catalyzed Asymmetric Boron Conjugate Addition to α,β-Unsaturated Imines in Water. *Chem. Commun.* **2014**, *50*, 9336–9339.

(48) Zhu, L.; Kitanosono, T.; Xu, P.; Kobayashi, S. Chiral Cu(II)-Catalyzed Enantioselective β-Borylation of α,β-Unsaturated Nitriles in Water. *Beilstein J. Org. Chem.* **2015**, *11*, 2007–2011.

(49) Kitanosono, T.; Xu, P.; Kobayashi, S. Heterogeneous and Homogeneous Chiral Cu(II) Catalysis in Water: Enantioselective Boron Conjugate Additions to Dienones and Dienoesters. *Chem. Commun.* **2013**, *49*, 8184–8186.

(50) Bergmeier, S. C. The Synthesis of Vicinal Amino Alcohols. *Tetrahedron* **2000**, *56*, 2561–2576.

(51) Kitanosono, T.; Ollevier, T.; Kobayashi, S. Iron- and Bismuth-Catalyzed Asymmetric Mukaiyama Aldol Reactions in Aqueous Media. *Chem. – Asian J.* **2013**, *8*, 3051–3062.

(52) Mai, E.; Schneider, C. Catalytic, Enantioselective Synthesis of Boc-Protected 1,2-Amino Alcohols through Aminolysis of *meso*-Epoxides with Benzophenone Imine. *ARKIVOC* **2008**, 216–222.

(53) Singh, T. P.; Singh, O. M. Recent Progress in Biological Activities of Indole and Indole Alkaloids. *Mini Rev. Med. Chem.* **2018**, *18*, 9–25.

(54) Schneider, C.; Sreekanth, A. R.; Mai, E. Scandium–Bipyridine-Catalyzed Enantioselective Addition of Alcohols and Amines to *meso*-Epoxides. *Angew. Chem. Int. Ed.* **2004**, *43*, 5691–5694.

(55) Mai, E.; Schneider, C. Scandium–Bipyridine-Catalyzed Enantioselective Aminolysis of *meso*-Epoxides. *Chem. – Eur. J.* **2007**, *13*, 2729–2741.

(56) Azoulay, S.; Manabe, K.; Kobayashi, S. Catalytic Asymmetric Ring Opening of *meso*-Epoxides with Aromatic Amines in Water. *Org. Lett.* **2005**, *7*, 4593–4595.

(57) Bonollo, S.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. Zn(II)-Catalyzed Desymmetrization of *meso*-Epoxides by Aromatic Amines in Water. *Synlett* **2008**, 1574–1578.

(58) Bonollo, S.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. $Zr(DS)_4$ as an Efficient Catalyst for the Aminolysis of Epoxides in Water. *Synlett* **2007**, 2683–2686.

(59) Mai, E.; Schneider, C. Indium-Bipyridine Catalyzed, Enantioselective Aminolysis of *meso*-Epoxides. *Synlett* **2007**, 2136–2138.

(60) Tschöp, A.; Marx, A.; Sreekanth, A. R.; Schneider, C. Scandium-Bipyridine-Catalyzed, Enantioselective Alcoholysis of *meso*-Epoxides. *Eur. J. Org. Chem.* **2007**, 2318–2327.

(61) Boudou, M.; Ogawa, C.; Kobayashi, S. Chiral Scandium-Catalysed Enantioselective Ring-Opening of *meso*-Epoxides with *N*-Heterocycle, Alcohol and Thiol Derivatives in Water. *Adv. Synth. Catal.* **2006**, *348*, 2585–2589.

(62) Ogawa, C.; Wang, N.; Kobayashi, S. Chiral Scandium-Catalyzed Highly Stereoselective Ring-Opening of *meso*-Epoxides with Thiols. *Chem. Lett.* **2007**, *36*, 34–35.

(63) Tschöp, A.; Nandakumar, M. V.; Pavlyuk, O.; Schneider, C. Scandium–Bipyridine-Catalyzed, Enantioselective Selenol Addition to Aromatic *meso*-Epoxides. *Tetrahedron Lett.* **2008**, *49*, 1030–1033.

(64) Lafantaisie, M.; Mirabaud, A.; Plancq, B.; Ollevier, T. Iron(II)-Derived Lewis Acid/Surfactant Combined Catalysis for the Enantioselective Mukaiyama Aldol Reaction in Pure Water. *ChemCatChem* **2014**, *6*, 2244–2247.

(65) Sameera, W. M. C.; Hatanaka, M.; Kitanosono, T.; Kobayashi, S.; Morokuma, K. The Mechanism of Iron(II)-Catalyzed Asymmetric Mukaiyama Aldol Reaction in Aqueous Media: Density Functional Theory and Artificial Force-Induced Reaction Study. *J. Am. Chem. Soc.* **2015**, *137*, 11085–11094.

(66) Hodgson, D. R. W.; Sanderson, J. M. The Synthesis of Peptides and Proteins Containing Non-Natural Amino Acids. *Chem. Soc. Rev.* **2004**, *33*, 422–430.

(67) de Graaf, A. J.; Kooijman, M.; Hennink, W. E.; Mastrobattista, E. Nonnatural Amino Acids for Site-Specific Protein Conjugation. *Bioconjug. Chem.* **2009**, *20*, 1281–1295.

(68) Ghosh, S.; Nandakumar, M. V.; Krautscheid, H.; Schneider, C. Copper–Bipyridine-Catalyzed Enantioselective α-Amination of β-Keto Esters. *Tetrahedron Lett.* **2010**, *51*, 1860–1862.

(69) Kitanosono, T.; Miyo, M.; Kobayashi, S. Surfactant-Aided Chiral Palladium(II) Catalysis Exerted Exclusively in Water for the C–H Functionalization of Indoles. *ACS Sustain. Chem. Eng.* **2016**, *4*, 6101–6106.

(70) Zhou, W.; Xu, L.-W.; Li, L.; Yang, L.; Xia, C.-G. Enantioselective Michael-Type Friedel–Crafts Reactions of Indoles to Enones Catalyzed by a Chiral Camphor-Based Brønsted Acid. *Eur. J. Org. Chem.* **2006**, 5225–5227.

(71) Li, M.; Carreras, V.; Jalba, A.; Ollevier, T. Asymmetric Diels–Alder Reaction of α,β-Unsaturated Oxazolidin-2-One Derivatives Catalyzed by a Chiral Fe(III)-Bipyridine Diol Complex. *Org. Lett.* **2018**, *20*, 995–998.

(72) Lee, W.-S.; Yeung, C.-T.; Sham, K.-C.; Wong, W.-T.; Kwong, H.-L. Chiral Copper–Bipyridine Complexes: Synthesis, Characterization and Mechanistic Studies on Asymmetric Cyclopropanation. *Polyhedron* **2011**, *30*, 178–186.

(73) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. Catalytic Asymmetric Hydroxymethylation of Silicon Enolates Using an Aqueous Solution of Formaldehyde with a Chiral Scandium Complex. *J. Am. Chem. Soc.* **2004**, *126*, 12236–12237.

(74) Kokubo, M.; Ogawa, C.; Kobayashi, S. Lewis Acid Catalysis in Water with a Hydrophilic Substrate: Scandium-Catalyzed Hydroxymethylation with Aqueous Formaldehyde in Water. *Angew. Chem. Int. Ed.* **2008**, *47*, 6909–6911.

(75) Rahm, F.; Fischer, A.; Moberg, C. Pyridyl Phosphinites and Pyridyl Phosphites from Chiral Pyridyl Alcohols — A Modular Approach. *Eur. J. Org. Chem.* **2003**, 4205–4215.

(76) Kwong, H.-L.; Lee, W.-S. New Chiral 2,2′-Bipyridine Diols as Catalysts for Enantioselective Addition of Diethylzinc to Benzaldehyde. *Tetrahedron Asymmetry* **1999**, *10*, 3791–3801.

(77) Huang, H.; Chen, H.; Hu, X.; Bai, C.; Zheng, Z. Structural Probing of D-Fructose Derived Ligands for Asymmetric Addition of Diethylzinc to Aldehydes. *Tetrahedron Asymmetry* **2003**, *14*, 297–304.

(78) Lin, R.-X.; Chen, C. Chiral 8-Substituted 10,10-Dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-8-ols as Enantioselective Catalysts in the Addition of Diethylzinc to Substituted Benzaldehydes. *J. Mol. Catal. Chem.* **2006**, *243*, 89–98.

(79) Kwong, H.-L.; Lau, K.-M.; Lee, W.-S.; Wong, W.-T. Chiral Zinc(II) Bipyridine Complex. Crystal Structure and Catalytic Activity in Asymmetric Allylation Reaction. *New J. Chem.* **1999**, *23*, 629–632.

(80) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. Enantioselective Friedel−Crafts Alkylation Reactions Catalyzed by a Chiral Nonracemic C_2-Symmetric 2,2‘-Bipyridyl Copper(II) Complex. *Org. Lett.* **2005**, *7*, 901–904.

(81) R. Boyd, D.; D. Sharma, N.; Sbircea, L.; Murphy, D.; F. Malone, J.; L. James, S.; R. Allen, C. C.; G. Hamilton, J. T. Chemoenzymatic Synthesis of Chiral 2,2′-Bipyridine Ligands and Their *N*-Oxide Derivatives: Applications in the Asymmetric Aminolysis of Epoxides and Asymmetric Allylation of Aldehydes. *Org. Biomol. Chem.* **2010**, *8*, 1081–1090.

(82) R. Boyd, D.; D. Sharma, N.; Sbircea, L.; Murphy, D.; Belhocine, T.; F. Malone, J.; L. James, S.; R. Allen, C. C.; G. Hamilton, J. T. Azaarene *cis*-Dihydrodiol-Derived 2,2′-Bipyridine Ligands for Asymmetric Allylic Oxidation and Cyclopropanation. *Chem. Commun.* **2008**, 5535–5537.

(83) Lyle, M. P. A.; Wilson, P. D. Synthesis of a New Chiral Nonracemic C_2-Symmetric 2,2‘-Bipyridyl Ligand and Its Application in Copper(I)-Catalyzed Enantioselective Cyclopropanation Reactions. *Org. Lett.* **2004**, *6*, 855–857.

(84) Bouet, A.; Heller, B.; Papamicaël, C.; Dupas, G.; Oudeyer, S.; Marsais, F.; Levacher, V. Preparation of New Axially Chiral Bridged 2,2′-Bipyridines and Pyridyl Monooxazolines (Pymox). Evaluation in Copper(I)-Catalyzed Enantioselective Cyclopropanation. *Org. Biomol. Chem.* **2007**, *5*, 1397–1404.

(85) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. Synthesis and Evaluation of New Chiral Nonracemic C_2-Symmetric and Unsymmetric 2,2′-Bipyridyl Ligands. *Org. Biomol. Chem.* **2006**, *4*, 877–885.

(86) Kokubo, M.; Kobayashi, S. Nazarov-Type Reactions in Water. *Chem. – Asian J.* **2009**, *4*, 526–528.

(87) Tsuji, M.; Sakai, R.; Satoh, T.; Kaga, H.; Kakuchi, T. Enantiomer-Selective Radical Cyclopolymerization of *rac*-2,4-Pentanediyl Dimethacrylate Using ATRP Initiating System with Chiral Amine Ligand. *Macromolecules* **2002**, *35*, 8255–8257.

(88) Tsuji, M.; Sakai, R.; Satoh, T.; Kaga, H.; Kakuchi, T. Enantiomer-Selective Radical Polymerization of *rac*-2,4-Pentanediyl Dimethacrylate by 2,2’-Azobisisobutyronitrile/Copper(II) Trifluoromethanesulfonate/Chiral Diamine as

Asymmetric Reverse Atom Transfer Radical Polymerization Initiating System. *Polym. J.* **2003**, *35*, 84–87.

(89) Lee, W.-S.; Kwong, H.-L.; Chan, H.-L.; Choi, W.-W.; Ng, L.-Y. Chiral Bipyridine–Copper(I) Complex-Catalyzed Enantioselective Allylic Oxidation of Cyclic Alkenes. *Tetrahedron Asymmetry* **2001**, *12*, 1007–1013.

(90) Lyle, M. P. A.; Wilson, P. D. Asymmetric Allylic Oxidation Reactions Catalyzed by a Chiral Nonracemic and C_2-Symmetric 2,2′-Bipyridyl Copper(I) Complex. *Org. Biomol. Chem.* **2006**, *4*, 41–43.

(91) Lowenthal, R. E.; Abiko, A.; Masamune, S. Asymmetric Catalytic Cyclopropanation of Olefins: Bis-Oxazoline Copper Complexes. *Tetrahedron Lett.* **1990**, *31*, 6005–6008.

(92) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. Bis(oxazolines) as Chiral Ligands in Metal-Catalyzed Asymmetric Reactions. Catalytic, Asymmetric Cyclopropanation of Olefins. *J. Am. Chem. Soc.* **1991**, *113*, 726–728.

(93) Corey, E. J.; Imai, N.; Zhang, H. Y. Designed Catalyst for Enantioselective Diels-Alder Addition from a C_2-Symmetric Chiral Bis(oxazoline)-Iron(III) Complex. *J. Am. Chem. Soc.* **1991**, *113*, 728–729.

(94) Desimoni, G.; Faita, G.; Jørgensen, K. A. C_2-Symmetric Chiral Bis(oxazoline) Ligands in Asymmetric Catalysis. *Chem. Rev.* **2006**, *106*, 3561–3651.

(95) Hargaden, G. C.; Guiry, P. J. Recent Applications of Oxazoline-Containing Ligands in Asymmetric Catalysis. *Chem. Rev.* **2009**, *109*, 2505–2550.

(96) Yang, G.; Zhang, W. Renaissance of Pyridine-Oxazolines as Chiral Ligands for Asymmetric Catalysis. *Chem. Soc. Rev.* **2018**, *47*, 1783–1810.

(97) Nishiyama, H.; Park, S.-B.; Haga, M.; Aoki, K.; Itoh, K. Ruthenium(II)Cl_2-Bis(oxazolinyl)bipyridine Complex. Its Structure and Reactivity. *Chem. Lett.* **1994**, *23*, 1111–1114.

(98) Qian, C.; Wang, L. Asymmetric Hetero-Diels–Alder Reaction of Glyoxylate Esters and Danishefsky's Diene Catalyzed by Chiral Bis(oxazoline)–Lanthanide Complexes. *Tetrahedron Lett.* **2000**, *41*, 2203–2206.

(99) Jalba, A.; Régnier, N.; Ollevier, T. Enantioselective Aromatic Sulfide Oxidation and Tandem Kinetic Resolution Using Aqueous H_2O_2 and Chiral Iron–Bis(oxazolinyl)bipyridine Catalysts. *Eur. J. Org. Chem.* **2017**, 1628–1637.

(100) Kočovský, P.; Malkov, A. V. From Transition Metals to Organocatalysis. *Russ. Chem. Bull.* **2004**, *53*, 1806–1812.

(101) Nakajima, M. Chiral *N*-Oxides as Catalysts or Ligands in Enantioselective Reactions. *J. Synth. Org. Chem.* **2003**, *61*, 1081–1087.

(102) Koukal, P.; Ulč, J.; Nečas, D.; Kotora, M. Pyridine *N*-Oxides and Derivatives Thereof in Organocatalysis. In *Heterocyclic N-Oxides*; Larionov, O. V., Ed.; Topics in Heterocyclic Chemistry; Springer, Cham, 2017; pp 29–58.

(103) Shaker, Y. Recent Trends in Chemistry of Pyridine *N*-Oxides. *ARKIVOC* **2001**, 242–268.

(104) Barton, D. H. R.; Ozbalik, N.; Vacher, B. An Unusual Reaction between the Esters of *N*-Hydroxy-2-thiopyridone and Activated Azo Compounds. *Tetrahedron* **1988**, *44*, 7385–7392.

(105) Chucholowski, A. W.; Uhlendorf, S. Base Catalyzed Rearrangement of 5-Cyanomethyl-2-isoxazolines; Novel Pathway for the Formation of 2-Aminopyridine *N*-Oxides. *Tetrahedron Lett.* **1990**, *31*, 1949–1952.

(106) Nesi, R.; Giomi, D.; Papaleo, S.; Turchi, S. Polyfunctionalized 3-Nitropyridine Derivatives by [4 + 2] Cycloadditions of 4-Nitro-3-phenylisoxazole-5-carboxylates with Enamines: Applications and Limits. *J. Org. Chem.* **1992**, *57*, 3713–3716.

(107) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. A Novel Axially Chiral 2,2‘-Bipyridine *N*,*N*‘-Dioxide. Its Preparation and Use for Asymmetric Allylation of Aldehydes with Allyl(trichloro)silane as a Highly Efficient Catalyst. *Org. Lett.* **2002**, *4*, 2799–2801.

(108) Fujii, M.; Honda, A. Axially Chiral Heteroaromatics. 1. Preparation of Optically Active 1,1′-Biisoquinoline *N*,*N*′-Dioxide. *J. Heterocycl. Chem.* **1992**, *29*, 931–933.

(109) Deng, Y.; Pan, W.; Pei, Y.-N.; Li, J.-L.; Bai, B.; Zhu, H.-J. Addition of Aldehydes with Allyltrichlorosilane Catalyzed by Chiral Bis-N–O Secondary Amides. *Tetrahedron* **2013**, *69*, 10431–10437.

(110) Denmark, S. E.; Fan, Y. Preparation of Chiral Bipyridine Bis-*N*-Oxides by Oxidative Dimerization of Chiral Pyridine *N*-Oxides. *Tetrahedron Asymmetry* **2006**, *17*, 687–707.

(111) Ulč, J.; Nečas, D.; Koukal, P.; Havlíček, V.; Tošner, Z.; Hybelbauerová, S.; Kotora, M. Chiral Unsymmetrically Substituted Bipyridine *N*,*N*’-Dioxides as Catalysts for Allylation of Aldehydes. *Eur. J. Org. Chem.* **2018**, *in press*.

(112) O’Hora, P. S.; Incerti-Pradillos, C. A.; Kabeshov, M. A.; Shipilovskikh, S. A.; Rubtsov, A. E.; Elsegood, M. R. J.; Malkov, A. V. Catalytic Asymmetric Crotylation of Aldehydes: Application in Total Synthesis of (−)-Elisabethadione. *Chem. – Eur. J.* **2015**, *21*, 4551–4555.

(113) Chelucci, G.; Murineddu, G.; Pinna, G. A. Chiral Pyridine *N*-Oxides: Useful Ligands for Asymmetric Catalysis. *Tetrahedron Asymmetry* **2004**, *15*, 1373–1389.

(114) Malkov, A. V.; Kočovský, P. Chiral *N*-Oxides in Asymmetric Catalysis. *Eur. J. Org. Chem.* **2007**, 29–36.

(115) Denmark, S. E.; Fu, J. Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones. *Chem. Rev.* **2003**, *103*, 2763–2794.

(116) Kobayashi, S.; Nishio, K. Facile and Highly Stereoselective Allylation of Aldehydes Using Allyltrichlorosilanes in DMF. *Tetrahedron Lett.* **1993**, *34*, 3453–3456.

(117) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. Asymmetric Allylation of Aldehydes with Chiral Lewis Bases. *J. Org. Chem.* **1994**, *59*, 6161–6163.

(118) Malkov, A. V.; Kočovský, P. Lewis Base-Catalyzed Reactions of SiX_3-Based Reagents with C=O, C=N (N→σ*). In *Lewis Base Catalysis in Organic Synthesis*; Vedejs, E., Denmark, S. E., Eds.; Wiley-Blackwell, 2016; pp 1011–1038.

(119) Hrdina, R.; Opekar, F.; Roithová, J.; Kotora, M. Neutral and Ionic Reaction Mechanisms for the Allylation of Aldehydes by Bipyridine *N*,*N*′-Dioxides. *Chem. Commun.* **2009**, 2314–2316.

(120) Ducháčková, L.; Kadlčíková, A.; Kotora, M.; Roithová, J. Oxygen Superbases as Polar Binding Pockets in Nonpolar Solvents. *J. Am. Chem. Soc.* **2010**, *132*, 12660–12667.

(121) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. (*S*)-3,3‘-Dimethyl-2,2‘-biquinoline *N*,*N*‘-Dioxide as an Efficient Catalyst for Enantioselective Addition of Allyltrichlorosilanes to Aldehydes. *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420.

(122) Hrdina, R.; Kadlčíková, A.; Valterová, I.; Hodačová, J.; Kotora, M. An Easy Route to Atropoisomeric Bipyridine *N*,*N*′-Dioxides and Allylation of Aldehydes. *Tetrahedron Asymmetry* **2006**, *17*, 3185–3191.

(123) Hrdina, R.; Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. A Simple Approach to Unsymmetric Atropoisomeric Bipyridine *N*,*N*′-Dioxides and Their Application in Enantioselective Allylation of Aldehydes. *Adv. Synth. Catal.* **2007**, *349*, 822–826.

(124) Hrdina, R.; Dračínský, M.; Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. New Pathway to C_2-Symmetric Atropoisomeric Bipyridine *N*,*N*′-Dioxides and Solvent Effect in Enantioselective Allylation of Aldehydes. *Adv. Synth. Catal.* **2008**, *350*, 1449–1456.

(125) Bai, B.; Shen, L.; Zhu, H.-J. Chiral Biscarboline *N*,*N*′-Dioxide Derivatives: Highly Enantioselective Addition of Allyltrichlorosilane to Aldehydes. *Adv. Synth. Catal.* **2012**, *354*, 354–358.

(126) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. Chiral 2,2‘-Bipyridine-Type *N*-Monoxides as Organocatalysts in the Enantioselective Allylation of Aldehydes with Allyltrichlorosilane. *Org. Lett.* **2002**, *4*, 1047–1049.

(127) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. New Lewis-Basic *N*-Oxides as Chiral Organocatalysts in Asymmetric Allylation of Aldehydes. *J. Org. Chem.* **2003**, *68*, 9659–9668.

(128) Kadlčíková, A.; Hrdina, R.; Valterová, I.; Kotora, M. Simple and Fast Synthesis of New Axially Chiral Bipyridine *N,N′*-Dioxides for Highly Enantioselective Allylation of Aldehydes. *Adv. Synth. Catal.* **2009**, *351*, 1279–1283.

(129) Denmark, S. E.; Fan, Y. Catalytic, Enantioselective Aldol Additions to Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235.

(130) Denmark, S. E.; Fan, Y.; Eastgate, M. D. Lewis Base Catalyzed, Enantioselective Aldol Addition of Methyl Trichlorosilyl Ketene Acetal to Ketones. *J. Org. Chem.* **2005**, *70*, 5235–5248.

(131) Ramsay, W. On Picoline and Its Derivatives. *Lond. Edinb. Dublin Philos. Mag. J. Sci.* **1876**, *2*, 269–281.

(132) Heller, B.; Hapke, M. The Fascinating Construction of Pyridine Ring Systems by Transition Metal-Catalysed [2 + 2 + 2] Cycloaddition Reactions. *Chem. Soc. Rev.* **2007**, *36*, 1085–1094.

(133) Turek, P.; Kotora, M. Synthesis of Pyridines by [2+2+2]-Cyclotrimerization of Alkynes with Nitriles. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; RSC Publishing, 2010; Vol. 13, pp 175–202.

(134) Varela, J. A.; Saá, C. Construction of Pyridine Rings by Metal-Mediated [2 + 2 + 2] Cycloaddition. *Chem. Rev.* **2003**, *103*, 3787–3802.

(135) Broere, D. L. J.; Ruijter, E. Recent Advances in Transition-Metal-Catalyzed [2+2+2]-Cyclo(co)trimerization Reactions. *Synthesis* **2012**, *44*, 2639–2672.

(136) Dazinger, G.; Torres-Rodrigues, M.; Kirchner, K.; Calhorda, M. J.; Costa, P. J. Formation of Pyridine from Acetylenes and Nitriles Catalyzed by RuCpCl, CoCp, and RhCp Derivatives – A Computational Mechanistic Study. *J. Organomet. Chem.* **2006**, *691*, 4434–4445.

(137) Orian, L.; van Stralen, J. N. P.; Bickelhaupt, F. M. Cyclotrimerization Reactions Catalyzed by Rhodium(I) Half-Sandwich Complexes: A Mechanistic Density Functional Study. *Organometallics* **2007**, *26*, 3816–3830.

(138) Yamamoto, Y. Syntheses of Heterocycles via Alkyne Cycloadditions Catalyzed by Cyclopentadienylruthenium-Type Complexes. *Heterocycles* **2013**, *87*, 2459.

(139) Gesing, E. R. F.; Groth, U.; Vollhardt, K. P. C. Iron-Catalyzed Cocyclization of Adiponitriles with Nitriles: A New Synthesis of Fused 1,2,4-Triazines. *Synthesis* **1984**, 351–353.

(140) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. Cp*RuCl-Catalyzed [2 + 2 + 2] Cycloadditions of α,ω-Diynes with Electron-Deficient Carbon−Heteroatom Multiple Bonds Leading to Heterocycles. *J. Am. Chem. Soc.* **2005**, *127*, 605–613.

(141) Young, D. D.; Teske, J. A.; Deiters, A. Open-Vessel Microwave-Mediated [2+2+2]-Cyclotrimerization Reactions. *Synthesis* **2009**, 3785–3790.

(142) Varela, J. A.; Castedo, L.; Maestro, M.; Mahía, J.; Saá, C. Regiocontrolled One-Step Synthesis of 3,3′-Disubstituted 2,2′-bipyridine Ligands by Cobalt(I)-Catalyzed Cyclotrimerization. *Chem. – Eur. J.* **2001**, *7*, 5203–5213.

(143) Weding, N.; Hapke, M. Preparation and Synthetic Applications of Alkene Complexes of Group 9 Transition Metals in [2+2+2] Cycloaddition Reactions. *Chem. Soc. Rev.* **2011**, *40*, 4525–4538.
(144) Shaaban, M. R.; El-Sayed, R.; Elwahy, A. H. M. Construction of Fused Heterocycles by Metal-Mediated [2+2+2] Cyclotrimerization of Alkynes and/or Nitriles. *Tetrahedron* **2011**, *67*, 6095–6130.
(145) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. Selective Preparation of Pyridines, Pyridones, and Iminopyridines from Two Different Alkynes *via* Azazirconacycles. *J. Am. Chem. Soc.* **2002**, *124*, 5059–5067.
(146) Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. The Chemistry of Titanacyclopentadiene Rings Supported by 2,6-Diphenylphenoxide Ligation: Stoichiometric and Catalytic Reactivity. *Organometallics* **1993**, *12*, 2911–2924.
(147) Sugiyama, Y.; Okamoto, S. Regioselective Syntheses of Substituted Pyridines and 2,2′-Bipyridines by Cobalt-Catalyzed [2+2+2] Cycloaddition of α,ω-Diynes with Nitriles. *Synthesis* **2011**, 2247–2254.
(148) Tanaka, K. Rhodium-Catalyzed [2+2+2] Cycloaddition for the Synthesis of Substituted Pyridines, Pyridones, and Thiopyranimines. *Heterocycles* **2012**, *85*, 1017.
(149) Hashimoto, T.; Ishii, S.; Yano, R.; Miura, H.; Sakata, K.; Takeuchi, R. Iridium-Catalyzed [2+2+2] Cycloaddition of α,ω-Diynes with Cyanamides. *Adv. Synth. Catal.* **2015**, *357*, 3901–3916.
(150) Thakur, A.; Louie, J. Advances in Nickel-Catalyzed Cycloaddition Reactions To Construct Carbocycles and Heterocycles. *Acc. Chem. Res.* **2015**, *48*, 2354–2365.
(151) Mulcahy, S. P.; Varelas, J. G. Three-Step Synthesis of an Annulated β-Carboline *via* Palladium Catalysis. *Tetrahedron Lett.* **2013**, *54*, 6599–6601.
(152) Wang, C.; Li, X.; Wu, F.; Wan, B. A Simple and Highly Efficient Iron Catalyst for a [2+2+2] Cycloaddition to Form Pyridines. *Angew. Chem. Int. Ed.* **2011**, *50*, 7162–7166.
(153) Chen, Y.-L.; Sharma, P.; Liu, R.-S. Sulfonamide-Directed Gold-Catalyzed [2+2+2]-Cycloadditions of Nitriles with Two Discrete Ynamides to Construct 2,4-Diaminopyridine Cores. *Chem. Commun.* **2016**, *52*, 3187–3190.
(154) Satoh, Y.; Obora, Y. Low-Valent Niobium-Catalyzed Intermolecular [2 + 2 + 2] Cycloaddition of *tert*-Butylacetylene and Arylnitriles to Form 2,3,6-Trisubstituted Pyridine Derivatives. *J. Org. Chem.* **2013**, *78*, 7771–7776.
(155) Takai, K.; Yamada, M.; Utimoto, K. Selective Cyclotrimerization of Acetylenes *via* Tantalum-Alkyne Complexes. *Chem. Lett.* **1995**, *24*, 851–852.
(156) Piper, T. S.; Cotton, F. A.; Wilkinson, G. Cyclopentadienyl-Carbon Monoxide and Related Compounds of Some Transitional Metals. *J. Inorg. Nucl. Chem.* **1955**, *1*, 165–174.
(157) Parnell, C. A.; Peter, K.; Vollhardt, C. The Cobalt Way to Vitamin B_6: Regioselective Construction of the Tetrasubstituted Pyridine Nucleus by Cobalt-Catalyzed Alkyne-Nitrile Cooligomerizations. *Tetrahedron* **1985**, *41*, 5791–5796.
(158) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. A Cobalt-Catalyzed Entry Into the Ergot Alkaloids: Total Syntheses of (±)-Lysergene and (±)-LSD. *Synlett* **1994**, 487–489.
(159) McIver, A.; Young, D. D.; Deiters, A. A General Approach to Triphenylenes and Azatriphenylenes: Total Synthesis of Dehydrotylophorine and Tylophorine. *Chem. Commun.* **2008**, 4750–4752.
(160) Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. Synthesis of (+)-Complanadine A, an Inducer of Neurotrophic Factor Excretion. *J. Am. Chem. Soc.* **2010**, *132*, 5924–5925.

(161) Yuan, C.; Chang, C.-T.; Siegel, D. Syntheses of (+)-Complanadine A and Lycodine Derivatives by Regioselective [2 + 2 + 2] Cycloadditions. *J. Org. Chem.* **2013**, *78*, 5647–5668.

(162) Pauson, P. L. Dicarbonyl(cyclopentadienyl)cobalt(I). In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; American Cancer Society, 2001.

(163) Geny, A.; Agenet, N.; Iannazzo, L.; Malacria, M.; Aubert, C.; Gandon, V. Air-Stable {$(C_5H_5)Co$} Catalysts for [2+2+2] Cycloadditions. *Angew. Chem. Int. Ed.* **2009**, *48*, 1810–1813.

(164) Thiel, I.; Spannenberg, A.; Hapke, M. Synthesis of Air-Stable and Recyclable $CpCo^I$-Complexes. *ChemCatChem* **2013**, *5*, 2865–2868.

(165) Bönnemann, H.; Brijoux, W.; Brinkmann, R.; Meurers, W.; Mynott, R.; Von Philipsborn, W.; Egolf, T. A Correlation between ^{13}C and ^{59}Co NMR Data and the Catalytic Activity of Organocobalt Complexes in the Synthesis of Pyridine Derivatives. *J. Organomet. Chem.* **1984**, *272*, 231–249.

(166) Fatland, A. W.; Eaton, B. E. Cobalt-Catalyzed Alkyne−Nitrile Cyclotrimerization To Form Pyridines in Aqueous Solution. *Org. Lett.* **2000**, *2*, 3131–3133.

(167) Hapke, M.; Kral, K.; Fischer, C.; Spannenberg, A.; Gutnov, A.; Redkin, D.; Heller, B. Asymmetric Synthesis of Axially Chiral 1-Aryl-5,6,7,8-tetrahydroquinolines by Cobalt-Catalyzed [2 + 2 + 2] Cycloaddition Reaction of 1-Aryl-1,7-octadiynes and Nitriles. *J. Org. Chem.* **2010**, *75*, 3993–4003.

(168) Yamamoto, Y. Chloro[(1,2,5,6-η)-1,5-cyclooctadiene][(1,2,3,4,5-η)-1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-Yl]ruthenium. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; American Cancer Society, 2009.

(169) Yamamoto, Y.; Okuda, S.; Itoh, K. Ruthenium(II)-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes with Electron-Deficient Nitriles. *Chem. Commun.* **2001**, 1102–1103.

(170) Adriaenssens, L.; Severa, L.; Vávra, J.; Šálová, T.; Hývl, J.; Čížková, M.; Pohl, R.; Šaman, D.; Teplý, F. Bio- and Air-Tolerant Carbon–Carbon Bond Formations *via* Organometallic Ruthenium Catalysis. *Collect. Czechoslov. Chem. Commun.* **2009**, *74*, 1023–1034.

(171) Xu, F.; Wang, C.; Li, X.; Wan, B. Ruthenium-Catalyzed [2+2+2] Cycloaddition of Diynes with Nitriles in Pure Water. *ChemSusChem* **2012**, *5*, 854–857.

(172) Chowdhury, H.; Goswami, A. A Quick Access to 1-(2-Pyridyl)indoles via Solvent-Free Ruthenium(II)-Catalyzed Chemo- and Regioselective [2+2+2] Cycloaddition of α,ω-Diynes and *N*-Cyanoindoles. *Adv. Synth. Catal.* **2017**, *359*, 314–322.

(173) Bhatt, D.; Patel, N.; Chowdhury, H.; Bharatam, P. V.; Goswami, A. Additive-Controlled Switchable Selectivity from Cyanobenzenes to 2-Alkynylpyridines: Ruthenium(II)-Catalyzed [2+2+2] Cycloadditions of Diynes and Alkynylnitriles. *Adv. Synth. Catal.* **2018**, *360*, 1876–1882.

(174) Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P. Rhodium-Catalyzed Synthesis of Pyridines from Alkynes and Nitriles. *J. Mol. Catal.* **1987**, *40*, 337–357.

(175) Tanaka, K.; Suzuki, N.; Nishida, G. Cationic Rhodium(I)/Modified-BINAP Catalyzed [2+2+2] Cycloaddition of Alkynes with Nitriles. *Eur. J. Org. Chem.* **2006**, 3917–3922.

(176) Komine, Y.; Kamisawa, A.; Tanaka, K. Flexible Synthesis of Fused Benzofuran Derivatives by Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition with Phenol-Linked 1,6-Diynes. *Org. Lett.* **2009**, *11*, 2361–2364.

(177) Nishida, G.; Suzuki, N.; Noguchi, K.; Tanaka, K. Enantioselective Synthesis of Tetra-Ortho-Substituted Axially Chiral Biaryls through Rhodium-Catalyzed Double [2 + 2 + 2] Cycloaddition. *Org. Lett.* **2006**, *8*, 3489–3492.

(178) Shibata, T.; Uchiyama, T.; Endo, K. Enantioselective Synthesis of Chiral Tripodal Cage Compounds by [2 + 2 + 2] Cycloaddition of Branched Triynes. *Org. Lett.* **2009**, *11*, 3906–3908.

(179) Shibata, T.; Miyoshi, M.; Uchiyama, T.; Endo, K.; Miura, N.; Monde, K. Enantioselective Synthesis of Tripodal Cyclophanes and Pyridinophanes by Intramolecular [2+2+2] Cycloaddition. *Tetrahedron* **2012**, *68*, 2679–2686.

(180) Okamoto, S. Synthesis of 2,2'-Bipyridines by Transition Metal-Catalyzed Alkyne/Nitrile [2 + 2 + 2] Cycloaddition Reactions. *Heterocycles* **2012**, *85*, 1579.

(181) Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. Regioselective Cobalt-Catalyzed Formation of Bicyclic 3- and 4-Aminopyridines. *Org. Lett.* **2011**, *13*, 2030–2033.

(182) Bönnemann, H.; Brinkmann, R. Eine kobalt-katalysierte Einstufen-Synthese von Dipyridinen. *Synthesis* **1975**, *1975*, 600–602.

(183) Botteghi, C.; Caccia, G.; Chelucci, G.; Soccolini, F. Optically Active Nitrogen Ligands. 1. Synthesis of Two Optically Active Monoalkyl-Substituted 2-(2'-Pyridyl)Pyridines. *J. Org. Chem.* **1984**, *49*, 4290–4293.

(184) Botteghi, C.; Chelucci, C.; Chessa, G.; Delogu, G.; Gladiali, S.; Soccolini, F. Optically Active Nitrogen Ligans: III. Enantioface-Discriminating Transfer Hydrogenation of Acetophenone Catalyzed by Rhodium(I) Complexes with Chiral 2-(2′-Pyridyl)pyridines. *J. Organomet. Chem.* **1986**, *304*, 217–225.

(185) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Obermann, U. Asymmetrische Katalysen: XLVI. Enantioselektive Hydrosilylierung von Ketonen mit $[Rh(COD)Cl]_2$ Und Optisch Aktiven Stickstoff-Liganden. *J. Organomet. Chem.* **1989**, *370*, 17–31.

(186) Goswami, A.; Ohtaki, K.; Kase, K.; Ito, T.; Okamoto, S. Synthesis of Substituted 2,2′-Bipyridines and 2,2′:6′,2″-Terpyridines by Cobalt-Catalyzed Cycloaddition Reactions of Nitriles and α,ω-Diynes with Exclusive Regioselectivity. *Adv. Synth. Catal.* **2008**, *350*, 143–152.

(187) Nissen, F.; Detert, H. Total Synthesis of Lavendamycin by a [2+2+2] Cycloaddition. *Eur. J. Org. Chem.* **2011**, 2845–2853.

(188) Garcia, L.; Pla-Quintana, A.; Roglans, A.; Parella, T. Microwave-Enhanced Rhodium-Catalyzed [2+2+2] Cycloaddition Reactions To Afford Highly Functionalized Pyridines and Bipyridines. *Eur. J. Org. Chem.* **2010**, 3407–3415.

(189) Varela, J. A.; Castedo, L.; Saá, C. One-Step Synthesis of Symmetrical 3,3‘-Substituted 2,2‘-Bipyridine Ligands by Cobalt(I)-Catalyzed [2 + 2 + 2] Cycloadditions. *J. Am. Chem. Soc.* **1998**, *120*, 12147–12148.

(190) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. Ruthenium-Catalyzed Cycloaddition of 1,6-Diynes and Nitriles under Mild Conditions: Role of the Coordinating Group of Nitriles. *Chem. – Eur. J.* **2006**, *12*, 5618–5631.

(191) Ye, F.; Haddad, M.; Ratovelomanana-Vidal, V.; Michelet, V. Ruthenium-Catalyzed [2 + 2 + 2] Cycloaddition Reaction Forming 2-Aminopyridine Derivatives from α,ω-Diynes and Cyanamides. *Org. Lett.* **2017**, *19*, 1104–1107.

(192) Ye, F.; Boukattaya, F.; Haddad, M.; Ratovelomanana-Vidal, V.; Michelet, V. Synthesis of 2-Aminopyridines via Ruthenium-Catalyzed [2+2+2] Cycloaddition of 1,6- and 1,7-Diynes with Cyanamides: Scope and Limitations. *New J. Chem.* **2018**, *42*, 3222–3235.

(193) Iannazzo, L.; Kotera, N.; Malacria, M.; Aubert, C.; Gandon, V. Co(I)- versus Ru(II)-Catalyzed [2+2+2] Cycloadditions Involving Alkynyl Halides. *J. Organomet. Chem.* **2011**, *696*, 3906–3908.

(194) Yamamoto, Y.; Hashimoto, T.; Hattori, K.; Kikuchi, M.; Nishiyama, H. Synthesis of Spirocyclic *C*-Arylribosides via Cyclotrimerization. *Org. Lett.* **2006**, *8*, 3565–3568.

(195) Melnes, S.; Bayer, A.; Gautun, O. R. Cyclotrimerization of Unsymmetrically Bromo-Substituted Diynes: Toward the Synthesis of Potential Selective Inhibitors of Tyrosine Kinase 2. *Tetrahedron* **2012**, *68*, 8463–8471.

(196) Kuniyasu, H.; Sanagawa, A.; Nakajima, T.; Iwasaki, T.; Kambe, N.; Bobuatong, K.; Ehara, M. Halogen Exchange by Reaction of $CpRu(Cl)(PPh_3)_2$ with MeC(O)X (X = Br, I) and Its Mechanistic Study. *J. Organomet. Chem.* **2014**, *769*, 34–37.

(197) Shirakawa, E.; Imazaki, Y.; Hayashi, T. Ruthenium-Catalyzed Transformation of Alkenyl Triflates to Alkenyl Halides. *Chem. Commun.* **2009**, 5088–5090.

(198) Imazaki, Y.; Shirakawa, E.; Ueno, R.; Hayashi, T. Ruthenium-Catalyzed Transformation of Aryl and Alkenyl Triflates to Halides. *J. Am. Chem. Soc.* **2012**, *134*, 14760–14763.

(199) Froese, R. D. J.; Whiteker, G. T.; Peterson, T. H.; Arriola, D. J.; Renga, J. M.; Shearer, J. W. Computational and Experimental Studies of Regioselective S_NAr Halide Exchange (Halex) Reactions of Pentachloropyridine. *J. Org. Chem.* **2016**, *81*, 10672–10682.

(200) Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. Theoretical Bond Dissociation Energies of Halo-Heterocycles: Trends and Relationships to Regioselectivity in Palladium-Catalyzed Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 6632–6639.

(201) Vice, S.; Bara, T.; Bauer, A.; Evans, C. A.; Ford, J.; Josien, H.; McCombie, S.; Miller, M.; Nazareno, D.; Palani, A.; Tagat, J. Concise Formation of 4-Benzyl Piperidines and Related Derivatives Using a Suzuki Protocol. *J. Org. Chem.* **2001**, *66*, 2487–2492.

(202) Yamamoto, Y.; Ogawa, R.; Itoh, K. Significant Chemo- and Regioselectivies in the Ru(II)-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes with Dicyanides. *J. Am. Chem. Soc.* **2001**, *123*, 6189–6190.

(203) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359.

(204) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457–2483.

(205) Wong, H. L.; Tian, Y.; Chan, K. S. Electronically Controlled Asymmetric Cyclopropanation Catalyzed by a New Type of Chiral 2,2′-Bipyridine. *Tetrahedron Lett.* **2000**, *41*, 7723–7726.

(206) Liao, L.-Y.; Kong, X.-R.; Duan, X.-F. Reductive Couplings of 2-Halopyridines without External Ligand: Phosphine-Free Nickel-Catalyzed Synthesis of Symmetrical and Unsymmetrical 2,2′-Bipyridines. *J. Org. Chem.* **2014**, *79*, 777–782.

(207) Schultz, D. M.; Sawicki, J. W.; Yoon, T. P. An Improved Procedure for the Preparation of $Ru(Bpz)_3(PF_6)_2$ *via* a High-Yielding Synthesis of 2,2'-Bipyrazine. *Beilstein J. Org. Chem.* **2015**, *11*, 61–65.

(208) Barolo, C.; Yum, J.-H.; Artuso, E.; Barbero, N.; Di Censo, D.; Lobello, M. G.; Fantacci, S.; De Angelis, F.; Grätzel, M.; Nazeeruddin, M. K.; Viscardi, G. A Simple Synthetic Route to Obtain Pure *trans*-Ruthenium(II) Complexes for Dye-Sensitized Solar Cell Applications. *ChemSusChem* **2013**, *6* , 2170–2180.

(209) Batesky, D. C.; Goldfogel, M. J.; Weix, D. J. Removal of Triphenylphosphine Oxide by Precipitation with Zinc Chloride in Polar Solvents. *J. Org. Chem.* **2017**, *82*, 9931–9936.

(210) Macgregor, S. A. Transition Metal-Mediated P–C/X Exchange at Bound Phosphine Ligands (X = Aryl, Alkyl, NR_2, OR and F): Scope and Mechanisms. *Chem. Soc. Rev.* **2006**, *36*, 67–76.

(211) Theilacker, W.; Böhm, H. Optically Active 2,2′-Dimethylbiphenyl, the Simplest Atropisomeric Hydrocarbon. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 251–251.

(212) Lutsenko, I. F.; Baukov, Y. I.; Burlachenko, G. S.; Khasapov, B. N. The Synthesis and the Rearrangement of *O*-Silyl-*O*-alkyl Keteneacetals into Esters of Silylacetic Acid. *J. Organomet. Chem.* **1966**, *5*, 20–28.

(213) Denmark, S. E.; Fan, Y. Methyl Trichlorosilyl Ketene Acetal. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; American Cancer Society, 2008.

(214) Matoušová, E.; Gyepes, R.; Císařová, I.; Kotora, M. [2+2+2]-Cyclotrimerization of 1-Cyclopropyl-1,6-diynes with Alkynes: Formation of Cyclopropylarenes. *Adv. Synth. Catal.* **2016**, *358*, 254–267.

(215) Bednářová, E.; Dračínský, M.; Malatinec, Š.; Císařová, I.; Lamaty, F.; Kotora, M. Synthesis of a Bolm's 2,2′-Bipyridine Ligand Analogue and Its Applications. *Adv. Synth. Catal.* **2018**, *360*, 2869–2878.

(216) Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. Cobalt-Catalyzed Intramolecular [2 + 2 + 2] Cocyclotrimerization of Nitrilediynes: An Efficient Route to Tetra- and Pentacyclic Pyridine Derivatives. *Org. Lett.* **2007**, *9*, 505–508.

(217) Trost, B. M.; Rudd, M. T. Ruthenium-Catalyzed Cycloisomerizations of Diynols. *J. Am. Chem. Soc.* **2005**, *127*, 4763–4776.

(218) Yamamoto, Y.; Hattori, K.; Nishiyama, H. Synthesis of Bicyclic *p*-Diiodobenzenes *via* Silver-Catalyzed C*sp*-H Iodination and Ruthenium-Catalyzed Cycloaddition. *J. Am. Chem. Soc.* **2006**, *128*, 8336–8340.

(219) Maleczka, Robert E.; Terrell, L. R.; Clark, D. H.; Whitehead, S. L.; Gallagher, W. P.; Terstiege, I. Application of Fluoride-Catalyzed Silane Reductions of Tin Halides to the in Situ Preparation of Vinylstannanes. *J. Org. Chem.* **1999**, *64*, 5958–5965.

(220) Nicolai, S.; Sedigh-Zadeh, R.; Waser, J. Pd(0)-Catalyzed Alkene Oxy- and Aminoalkynylation with Aliphatic Bromoacetylenes. *J. Org. Chem.* **2013**, *78*, 3783–3801.

(221) Geiger, R. E.; Lalonde, M.; Stoller, H.; Schleich, K. Kobalt-Katalysiert Cycloadditionen von Alkinen Und Nitrilen Zu Pyridinen: Ein Neuer Zugang Zu Pyridoxin (Vitamin B_6). *Helv. Chim. Acta* **1984**, *67*, 1274–1282.

(222) Llerena, D.; Buisine, O.; Aubert, C.; Malacria, M. Synthesis of Variously Substituted Allenediynes and Their Cobalt (I)-Mediated [2+2+2] Cycloaddition Reactions. *Tetrahedron* **1998**, *54*, 9373–9392.

(223) Shimamoto, T.; Chimori, M.; Sogawa, H.; Yamamoto, K. Cationic Palladium-Catalyzed Hydrosilylative Cross-Coupling of Alkynes with Alkenes. *J. Am. Chem. Soc.* **2005**, *127*, 16410–16411.

(224) Sperber, N.; Fricano, R. The Reaction of Tributylacetyl Chloride and Anhydrous Cuprous Cyanide. *J. Am. Chem. Soc.* **1950**, *72*, 2792–2793.

(225) Lundgren, S.; Wingstrand, E.; Moberg, C. Lewis Acid–Lewis Base-Catalysed Enantioselective Addition of α-Ketonitriles to Aldehydes. *Adv. Synth. Catal.* **2007**, *349*, 364–372.

(226) Urgoitia, G.; SanMartin, R.; Herrero, M. T.; Domínguez, E. An Outstanding Catalyst for the Oxygen-Mediated Oxidation of Arylcarbinols, Arylmethylene and Arylacetylene Compounds. *Chem. Commun.* **2015**, *51*, 4799–4802.

(227) Wang, S.; Li, X.; Liu, H.; Xu, L.; Zhuang, J.; Li, J.; Li, H.; Wang, W. Organocatalytic Enantioselective Direct Additions of Aldehydes to 4-Vinylpyridines and Electron-Deficient Vinylarenes and Their Synthetic Applications. *J. Am. Chem. Soc.* **2015**, *137*, 2303–2310.

(228) Ushijima, S.; Moriyama, K.; Togo, H. Facile Preparation of Aromatic Esters from Aromatic Bromides with Ethyl Formate or DMF and Molecular Iodine *via* Aryllithium. *Tetrahedron* **2012**, *68*, 4701–4709.

(229) Declerck, V.; Colacino, E.; Bantreil, X.; Martinez, J.; Lamaty, F. Poly(Ethylene Glycol) as Reaction Medium for Mild Mizoroki–Heck Reaction in a Ball-Mill. *Chem. Commun.* **2012**, *48*, 11778–11780.

(230) Chelucci, G.; Addis, D.; Baldino, S. A New Approach to the 1,10-Phenanthroline Core. *Tetrahedron Lett.* **2007**, *48*, 3359–3362.

(231) Conifer, C. M.; Law, D. J.; Sunley, G. J.; Haynes, A.; Wells, J. R.; White, A. J. P.; Britovsek, G. J. P. Dicarbonylrhodium(I) Complexes of Bipyridine Ligands with Proximate H-Bonding Substituents and Their Application in Methyl Acetate Carbonylation. *Eur. J. Inorg. Chem.* **2011**, 3511–3522.

(232) Schlosser, M.; Bobbio, C. Creating Structural Manifolds from a Common Precursor: Basicity Gradient-Driven Isomerization of Halopyridines. *Eur. J. Org. Chem.* **2002**, *2002*, 4174–4180.

(233) Aranda, C.; Cornejo, A.; Fraile, J. M.; García-Verdugo, E.; Gil, M. J.; Luis, S. V.; Mayoral, J. A.; Martinez-Merino, V.; Ochoa, Z. Efficient Enhancement of Copper-Pyridineoxazoline Catalysts through Immobilization and Process Design. *Green Chem.* **2011**, *13*, 983–990.

(234) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. Copper-Catalyzed 1,2-Double Amination of 1-Halo-1-Alkynes. Concise Synthesis of Protected Tetrahydropyrazines and Related Heterocyclic Compounds. *J. Am. Chem. Soc.* **2008**, *130*, 1820–1821.

(235) Manteau, B.; Genix, P.; Brelot, L.; Vors, J.-P.; Pazenok, S.; Giornal, F.; Leuenberger, C.; Leroux, F. R. A General Approach to (Trifluoromethoxy)pyridines: First X-Ray Structure Determinations and Quantum Chemistry Studies. *Eur. J. Org. Chem.* **2010**, 6043–6066.

(236) Corey, E. J.; Shibata, S.; Bakshi, R. K. An Efficient and Catalytically Enantioselective Route to (S)-(–)-Phenyloxirane. *J. Org. Chem.* **1988**, *53*, 2861–2863.

(237) Gomtsyan, A.; Schmidt, R. G.; Bayburt, E. K.; Gfesser, G. A.; Voight, E. A.; Daanen, J. F.; Schmidt, D. L.; Cowart, M. D.; Liu, H.; Altenbach, R. J.; et al. Synthesis and Pharmacology of (Pyridin-2-yl)methanol Derivatives as Novel and Selective Transient Receptor Potential Vanilloid 3 Antagonists. *J. Med. Chem.* **2016**, *59*, 4926–4947.

(238) Uenishi, J.; Aburatani, S.; Takami, T. Stereocomplexity and Stereoselective Synthesis of Triamine Molecules Bearing Four Chiral Carbon Centers: Stereodifferentiated Preparation of All 10 Stereoisomers of 2,6-Bis[1-(1-phenylethylamino)ethyl]pyridines. *J. Org. Chem.* **2007**, *72*, 132–138.

(239) Schubert, U. S.; Eschbaumer, C.; Heller, M. Stille-Type Cross-Coupling An Efficient Way to Various Symmetrically and Unsymmetrically Substituted Methyl-Bipyridines: Toward New ATRP Catalysts. *Org. Lett.* **2000**, *2*, 3373–3376.

(240) Malmedy, F.; Wirth, T. Stereoselective Ketone Rearrangements with Hypervalent Iodine Reagents. *Chem. – Eur. J.* **2016**, *22*, 16072–16077.

(241) Nicolle, S. M.; Lewis, W.; Hayes, C. J.; Moody, C. J. Stereoselective Synthesis of Highly Substituted Tetrahydrofurans through Diverted Carbene O-H Insertion Reaction. *Angew. Chem. Int. Ed.* **2015**, *54*, 8485–8489.

(242) Geibel, I.; Christoffers, J. Synthesis of 1,4-Diketones from β-Oxo Esters and Enol Acetates by -Cerium-Catalyzed Oxidative Umpolung Reaction. *Eur. J. Org. Chem.* **2016**, 918–920.

(243) Wu, D.; O’Shea, D. F. Synthesis and Properties of BF_2-3,3′-Dimethyldiarylazadipyrromethene Near-Infrared Fluorophores. *Org. Lett.* **2013**, *15*, 3392–3395.

(244) Onishi, Y.; Yoneda, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. $InCl_3/Me_3SiCl$-Catalyzed Direct Michael Addition of Enol Acetates to α,β-Unsaturated Ketones. *Org. Lett.* **2012**, *14*, 5788–5791.

(245) Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. Palladium-Catalyzed Cross Coupling Reaction of Benzyl Bromides with Diazoesters for Stereoselective Synthesis of (*E*)-α,β-Diarylacrylates. *Org. Lett.* **2009**, *11*, 469–472.

(246) Dey, P.; Koli, M.; Goswami, D.; Sharma, A.; Chattopadhyay, S. [bmim][Br] as an Inexpensive and Efficient Medium for the Barbier-Type Allylation Reaction Using a Catalytic Amount of Indium: Mechanistic Studies. *Eur. J. Org. Chem.* **2018**, 1333–1341.

(247) Seredyuk, M.; Gaspar, A. B.; Muñoz, M. C.; Verdaguer, M.; Villain, F.; Gütlich, P. Cooperative Spin-Crossover Behaviour in Polymeric 1D Fe^{II} Coordination Compounds: $[\{Fe(tba)_3\}X_2]\cdot nH_2O$. *Eur. J. Inorg. Chem.* **2007**, 4481–4491.

(248) Milani, B.; Marson, A.; Zangrando, E.; Mestroni, G.; Ernsting, J. M.; Elsevier, C. J. New Monocationic Methylpalladium(II) Compounds with Several Bidentate Nitrogen-Donor Ligands: Synthesis, Characterisation and Reactivity with CO. *Inorganica Chim. Acta* **2002**, *327*, 188–201.

9 AUTHOR’S PUBLICATIONS

1. Bednářová, E.; Colacino, E.; Lamaty, F.; Kotora, M. A Ruthenium Complex-Catalyzed Cyclotrimerization of Halodiynes with Nitriles. Synthesis of 2- and 3-Halopyridines. *Adv. Synth. Catal.* **2016**, *358*, 1916–1923.

2. Bednářová, E.; Dračínský, M.; Malatinec, Š.; Císařová, I.; Lamaty, F.; Kotora, M. Synthesis of a Bolm’s 2,2′-Bipyridine Ligand Analogue and Its Applications. *Adv. Synth. Catal.* **2018**, *360*, 2869–2878.

3. Bednářová, E.; Nečas, D.; Císařová, I.; Dušek, M.; Lamaty, F.; Kotora, M. Synthesis of New Bipyridine *N,N′*-Dioxides and Their Application in Asymmetric Allylation of Benzaldehyde and Aldol Addition to Acetophenone. *Monatsh. Chem.* **2018**, *in press.* (Invited paper)

10 ABSTRACTS

2,2'-Bipyridines and their appropriate *N*,*N'*-dioxides form a significant class of heteroaromatic compounds, which has found application in various fields of chemistry and predominantly in asymmetric catalysis. One of the most powerful methods for their synthesis is cocyclotrimerization of alkynes with nitriles.

A new variant of cyclotrimerization reaction – cocyclotrimerization of halodiynes with nitriles, which results in the formation of 2- and 3-halopyridines, has been developed. The reaction was studied on a wide range of substrates providing the pyridine products in good isolated yields. Formation of an unexpected product of halogen exchange reaction was observed during the course of the study and its origin was elucidated by experimental studies.

The prepared 2-halopyridines were used as starting materials for syntheses of new chiral 2,2'-bipyridine ligands. The crucial step of their synthesis turned out to be the reductive dimerization of 2-halopyridines to the corresponding 2,2'-bipyridines. Application of the formed bipyridine ligands was then tested in various metal-catalyzed asymmetric reactions, namely Mukaiyama aldol reaction, hydroxymethylation, conjugate addition, C–H activation of indole and desymmetrization of *meso*-epoxides, in which one of the bipyridine ligands showed extraordinary activity and robustness. The structural properties of this ligand were then studied based on the NMR analyses, DFT calculations and single crystal X-ray analyses.

New axially chiral 2,2'-bipyridine *N*,*N'*-dioxides were synthesized *via* two approaches, which differed in the type of the key dimerization step. While the first approach, based on the reductive dimerization of 2-halopyridines, furnished only one atropoisomer of the target *N*,*N'*-dioxide by an eight-step reaction sequence, the second approach, based on oxidative dimerization of pyridine-*N*-oxides, provided both atropoisomers in only five steps. The applicability of these novel *N*,*N'*-dioxides as Lewis base catalysts were then examined in the enantioselective allylation of benzaldehyde and aldol reaction of trichlorosilyl ketene acetal with acetophenone.

2,2'-Bipyridiny a od nich odvozené *N*,*N'*-dioxidy tvoří významnou skupinu heteroaromatických sloučenin, které našly uplatnění v různých odvětvích chemie, zvláště pak v asymetrické katalýze. Jednou z nejefektivnějších metod jejich přípravy je kocyklotrimerizace alkynů a nitrilů.

Tato práce se zabývá vývojem nové varianty cyklotrimerizace – kocyklotrimerizace halodiynů a nitrilů, která vede k tvorbě 2- a 3-halopyridinů. Tato reakce byla studována na velkém množství substrátů a produkty této reakce byly izolovány v dobrých výtěžcích. Během studie této reakce byla pozorována tvorba neočekávaného produktu halogenové výměny, jehož mechanismus vzniku byl objasněn pomocí jak spektroskopických metod, tak kinetických experimentů.

Připravené 2-halopyridiny byly použity jako výchozí látky pro syntézu chirálních 2,2'-bipyridinových ligandů. Klíčovou reakcí byla reduktivní dimerizace 2-halopyridinů na bipyridiny. Výsledné chirální bipyridiny byly poté testovány jako ligandy v několika enantioselektivních reakcích katalyzovaných komplexy kovů, konkrétně v Mukaiyamově aldolové reakci, hydroxymethylaci, konjugované adici, aktivaci C–H vazby indolu a otevírání epoxidového kruhu. V poslední uvedené reakci se komplex skandia s jedním z nově připravených ligandů ukázal být výjimečně aktivní a výsledné produkty byly získány s vysokou enantioselektivitou. Pomocí NMR, DFT výpočtů a rentgenové strukturní analýzy byly dále zkoumány strukturní vlastnosti tohoto ligandu.

Prostřednictvím dvou různých syntetických přístupů, které se liší v použitém dimerizačním kroku, byly také připraveny nové axiálně chirální 2,2'-bipyridin *N*,*N'*-dioxidy. Zatímco první osmikroková reakční cesta využívající reduktivní dimerizaci 2-halopyridinů poskytla pouze jediný atropoizomer kýženého *N*,*N'*-dioxidu, druhá cesta, v které se uplatňuje oxidativní dimerizace pyridin-*N*-oxidů, vedla pouze v pěti krocích ke vzniku směsi obou atropoizomerů. Připravené nové 2,2'-bipyridin *N*,*N'*-dioxidy (Lewisovy báze) byly testovány jako organokatalyzátory v enantioselektivní allylaci benzaldehydu a aldolové reakci trichlorsilylketenacetalu s acetofenonem.

Les 2,2´-bipyridines et leurs homologues, les *N*,*N*´-dioxydes, appartiennent à une classe de composés hétéroaromatiques très importante ayant montré de nombreuses applications dans le domaine de la chimie et principalement en synthèse asymétrique. Une des méthodes les plus performantes pour leurs synthèses s´est révélée être une réaction de cocyclotrimérisation d´alcynes en présence de dérivés nitriles.

Une nouvelle variante de la réaction de cyclotrimérisation – cocyclotrimérisation de diynes halogénés avec des dérivés nitriles – permettant la formation de composés 2- et 3-halogéno-pyridines a ainsi été développée. La réaction a été étudiée sur une large gamme de substrats permettant l´accès à une librairie de pyridines avec de bons rendements. La formation d´un sous-produit, issu d´un échange d´halogène, a été approfondie au cours de l´étude et son origine a été élucidée grâce à différentes expériences.

Les 2-halogéno-pyridines ont été utilisées comme réactifs de départ pour la synthèse de ligands chiraux de type 2,2´-bipyridines. L´étape problématique s´est avérée être la réaction de dimérisation réductrice des 2-halogéno-pyridines donnant accès aux 2,2-bipyridines correspondantes. L´efficacité de ces ligands chiraux de type 2,2´-bipyridine a été évaluée dans différentes réactions asymétriques catalysées par des métaux de transition telles que l´aldolisation de Mukaiyama, l´hydroxyméthylation, l´addition conjuguée, l´activation C–H d´indoles mais aussi la désymmétrisation d´époxydes *meso*, dans laquelle un des ligands bipyridines a montré une extraordinaire activité et robustesse. Ensuite, basées sur des analyses RMN, des calculs DFT et des analyses par diffraction des rayons X, les propriétés structurales de ce ligand ont été étudiées.

De plus, une nouvelle famille de catalyseurs à chiralité axiale de type 2,2´-bipyridines *N*,*N*´-dioxydes a pu être synthétisée *via* 2 différentes approches, où seule l´étape clé de dimérisation diffère. La première approche, basée sur la réaction de dimérisation réductrice des 2-halogéno-pyridines, permet l´obtention d´un seul atropoisomère du *N*,*N*´-dioxydes cible après une séquence réactionnelle de 8 étapes tandis que la seconde approche, basée sur la réaction de dimérisation oxydante de pyridines *N*-oxydes, donne l´accès aux 2 atropoisomères en seulement 5 étapes. Le champs d´application de ces nouveaux catalyseurs de type *N*,*N*´-dioxydes, en tant que base de Lewis, a été examiné dans l´allylation énantiosélective du benzaldéhyde ainsi que dans l´aldolisation de l´acétal de cétène trichlorosilylé en présence de l´acétophénone.