UNIVERZITA KARLOVA V PRAZE
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KATEDRA ANORGANICKÉ A ORGANICKÉ CHEMIE

DIPLOMA Thesis

Picolinamide Derivatives of *N*-Methyl Valine as New Possible Chiral Organocatalysts in the Enantioselective Reduction of Aromatic Ketimines with Trichlorosilane

Glasgow, 2007 **Petr BEŠŤÁK**

I would like to thank Dr. Sigitas Stončius for his intensive care, kind supervision, versatile and devoting help and assistance throughout my work on this Diploma Thesis.
For their valuable advice and plenty of useful comments I also thank to PharmDr. Marcel Špulák Ph.D., Ing. Jan Štambaský, Ph.D. and Mgr. Květoslava Vraňková.
Special thanks belong to Prof. Pavel Kočovský, Ph.D, DSc. and Prof. RNDr. Milan Pour, Ph.D. for giving me the opportunity and support to accomplish this job.

This Diploma Thesis is dedicated to my parents.

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ABBREVIATIONS

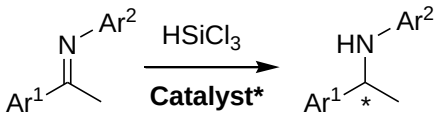
Ar	- aryl
BOC	- Tert-butyl carbonyl
$C_6H_5NO_2$	- Picolinic acid
$C_8H_{10}N$	- 3,5-dimethylaniline
DCM	- Dichlormethane
EDCI	- 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et	- Ethyl
Et_3N	- Triethylamine
$Et_3NH^+Cl^-$	- Triethylamonium chloride
GC	- Gas chromatography
HOBt	- 3-Hydroxybenzotriazole
HPLC	- High performance chromatography
$HSiCl_3$	- Trichlorosilane
i-Pr	- Isopropyl
IR	- Infrared spectroscopy
MCPBA	- Methachloroperoxybenzoic acid
Me	- Methyl
MeOCOCl	- Methylchloroformiate
MS	- Mass spectrometry
NMR	- Nuclear magnetic resonance
p-^{t}BuPh	- *tert*-butylphenyl
Ph	- Phenyl
*p*Ka	- Acid dissociation constant
t-Bu	- Tert-butyl
TFA	- Trifluoracetic acid
THF	- Tetrahydrofurane
TLC	- Thin layer chromatography

1. INTRODUCTION

The significance of chiral substances has been rising[(1)] through the past two decades, mainly after 2001, when racemic mixtures of pharmaceutical compounds are virtually no longer registered[(2)]. The reason is simple – enantiomers usually differ in the level of their activity, selectivity and/or safety of using. Thus, optically pure substances have bigger chance to become the compounds of choice[(1)], used as valuable building blocks for pharmaceutical and other fine chemistry processes. Success of chiral substances nonetheless depends not only on their intrinsic power, which is limited, but rather on the commercial availability. The research and development chemists are in most cases inclined to use synthons and procedures due to their nature rather than their source, whereas the process chemists, pressed by more and more challenging time lines, have usually little initiative to design totally a novel route, especially if it uses building blocks that are readily available on large a scale at a reasonable cost. In the pharmaceutical industry for instance, high pressure hydrogenation[(3)(4)], hydrosilylation[(3)(5)] or transfer hydrogenation[(4)(6)], catalyzed by transition metals (Pd, Ti, Ir, etc.) are commonly used. These widespread methods allow processing various substrates in high amounts with fair yields and enantioselectivity, if required. The dark side of this methodology includes leaching of the metal catalyst in the final product. Considering the catalysts mostly use the heavy-metals, deadly to living organisms and dangerous to the environment, a number of safety procedures and high level clearance of catalysts from a product have to be admitted[(7)] , in order to avoid e.g. some side effects and increase the harmlessness of products made in this way. On the other hand, organocatalysis provides very similar results using small organic molecules instead of metals. Therefore only mild reaction conditions can be employed, avoiding catalysts' decomposition and/or changing reaction mechanism. Organocatalysis usually applies small-amount loading of a catalyst with its almost complete regeneration possibility. It is possible to modify a catalyst in various ways in order e.g. to support the characteristics shown above, whereas, due to the variability of the catalysts, there is the possibility that only small alterations of a structure might dramatically change either the reactions mechanism, or the characteristics already mentioned. For this particular reason, including also lower costs in comparison to metal catalysts, organocatalysis is still a developing field with a very large scope and future.

While enantioselective reduction of ketones is now well developed[3], synthetic transformations of ketones, leading to chiral amine substances via imines are still a developing field of organic synthesis.

Scheme 1



1 **2**

Asymmetric reduction of aromatic ketimines with trichlorosilane.

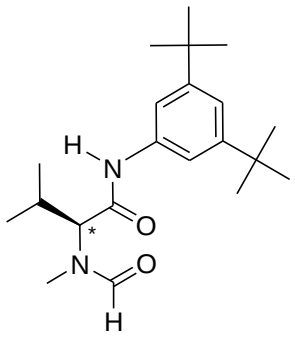
The initial publication by Iwasaki[8] reported enantioselective reduction of imines catalyzed by the with derivative of proline **A** (Figure 1). He also discovered the catalytic activity of the modified proline[9] **B** in the reduction of aromatic ketones.

Figure 1

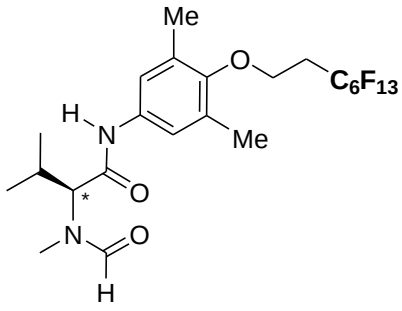
A **B**

Latter attempts, published by Kočovský and Malkov[10], use formamide and other derivatives[11] **C** of *N*-methylvaline for the reduction of imines, in order to increase enantioselectivity. Structures with an added fluorous tag **D**[12] for simplified isolation from reaction mixture with preserved high enantioselectivity and very low catalyst loading (1-5 mol %) are their extended derivatives. As shown below (Figure 2), a valine molecule used instead of proline, is supposed to decrease the rigidity of the catalyst structure, hence to have higher chiral relay on the substrate.

Figure 2



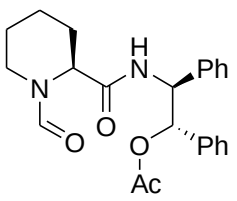
C



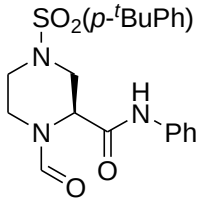
D

Wang and Sun[13][14] use formamide derivatives of pipecolinic-acid **E** (Figure 3) and piperazine-2-carboxylic acid **F** for the reduction of imines. Matsumura[15][16] has developed picolinic derivatives of proline **G**, used as new catalyst for imine reduction[17]. By extending a pyridine ring **H** , Kočovský[18] prepared the catalyst, capable of reducing both imines and aromatic ketones. His former approaches employed *N*-oxide structures **I**[19] capable of ketone reduction and aromatic aldehyde allylation as well. Appropriate mechanistic considerations[20] (Figure 6) led to comparison between formamide and pyridine type of bonding of silicon in the reaction.

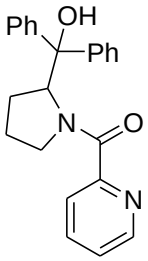
Figure 3



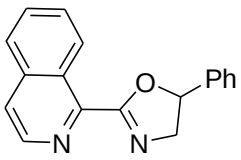
E



F



G



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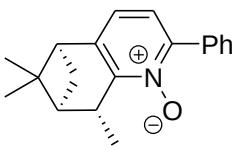
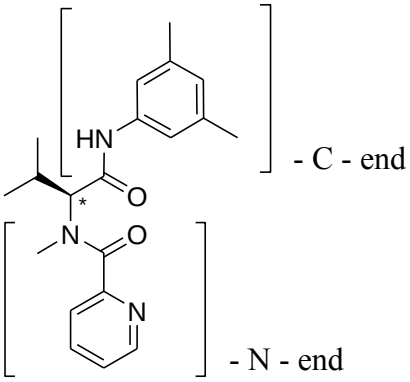


I

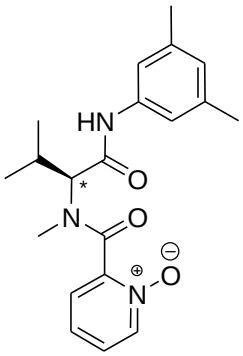
2. AIM OF THE WORK

The main objective of this project was to design catalyst **5** (Figure 4), that would combine the qualities of proline - picolinic derivatives[15] **G** with *N*-methylated valine scaffold ligands[11][18] **C** in order to expand the scope of the reduction to aromatic ketones and allylation of aromatic aldehydes. In this particular case, the objective was to combine *N*-methylated valine skeleton with a 3,5-dimethylanilide on its C-end and instead of using formamide at the N-end, to use a picolinamide as a probable silicon bonding part of the molecule[20].

Figure 4



catalyst 5



catalyst 5a

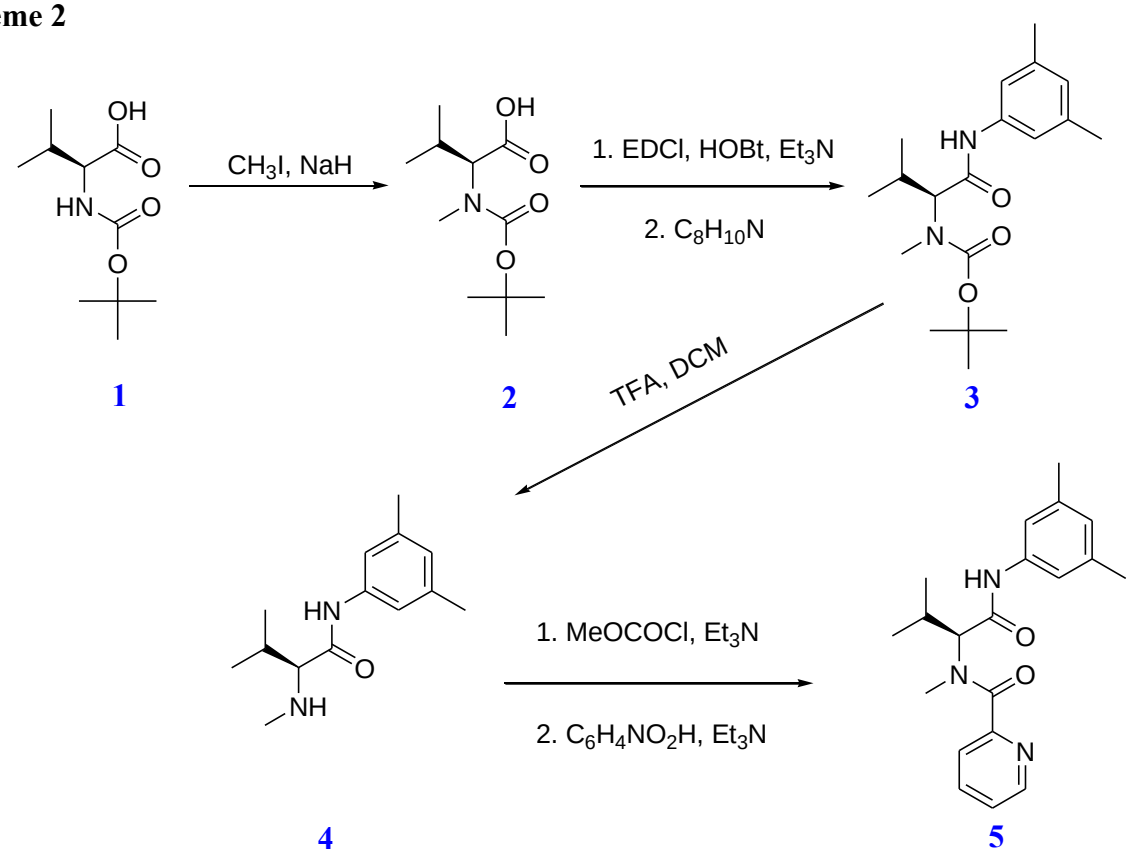
Further intentions with catalyst **5** were to explore the catalytic efficiency in ketone reduction with trichlorosilane and allylation of aromatic aldehydes as well as to explore the catalytic efficiency of the corresponding *N*-oxide **5a**.

3. RESULTS AND DISCUSSION

3.1. Catalyst design and synthesis

From the viewpoint of previous results[12][21], the best approach to the synthesis of the catalyst involves *N*-methylation of **1** with MeI in the presence of NaH (Scheme 2), which afforded the BOC-protected *N*-methyl valine[16] **2** (98 %). To obtain **2** in high yield, it is crucial to add NaH (in small portions) slowly to a mixture of BOC-valine **1** and MeI at 0 °C. If the deprotonation of **1** is carried out prior to the addition of MeI, the methylation becomes inefficient. Despite many expectations (*p*Ka difference between COOH and NH group is almost 7), only *N*-methyl moiety forms, instead of the methyl ester of the unprotected carboxylic group. This is probably caused by the combination of lower temperatures employed, very slow loading of NaH to the reaction mixture and its high loading – 1000 mol %.

Scheme 2



The next step uses the carbodiimide method[10] with EDCI and HOBt, to form **3**. HOBt is used in order to suppress possible racemisation of the amino acid, due to keeping stable chiral relay

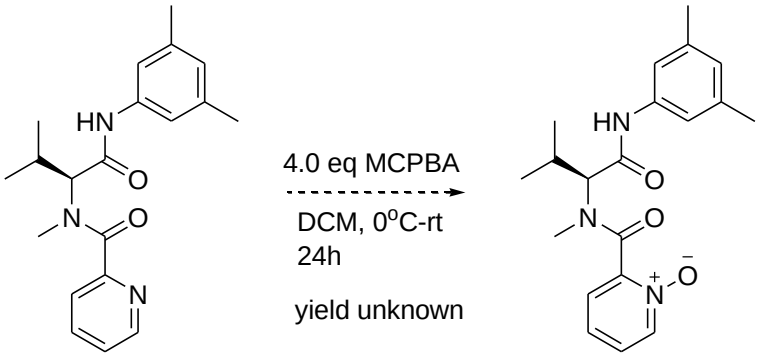
of the ligand. After deprotecting the BOC group with TFA, the coupling process, using the mixed-anhydride[23] method with crude **4,** led to the target catalyst **5.** This method was nonetheless used after a few modifications. The method involves the formation of a mixed anhydride *in-situ* and then filtration of the precipitate of $Et_3NH^+Cl^-$ at low temperature avoiding moisture and air access and then using the crude filtrate of the mixed anhydride of picolinic acid and methyl chloroformate. The standard procedure was modified by excluding the filtration step, trying to avoid any moisture in the reaction mixture and thus lowering risk of the decomposition of the mixed anhydride. The precipitate of $Et_3NH^+Cl^-$ was kept in the mixture until final washing. It did not not cause any damage to either the coupling process or its intermediates

Other alternative of the final step was to use the carbodiimide method using EDCI, which provided 80 % yield of **5**. However, following the modification of the mixed anhydride method, the isolated yield of **5** rose to 92 % and the purification according to TLC was remarkably easier.

The comparison of the carbodiimide method and the mixed anhydride method was performed on the reaction of picolinic acid and aniline. With same reaction conditions employed, the modified mixed anhydride method provided higher yield. The subsequent column chromatography purification also seemed to be easier to perform. While the only side-products in the reaction mixture were of inorganic origin, the elution mixture used was 1:1 ethylacetate and hexane.

It is known[19] that the chiral *N*-oxide structures are efficient organocatalysts for the asymmetric reduction of ketones and allylation of aldehydes. Therefore, we tried to convert the parent molecule of the catalyst **5** into the corresponding *N*-oxide **5a.** However, the initial attempts to oxidise **5** using the standard conditions,[24] i.e. using an equimolar amount of MCPBA for 1 hour resulted in complete recovery of the starting material. The general method for the oxidation of bipyridines[24] was then modified (Scheme 3), using not equimolar, but twofold molar excess of MCPBA. The reaction mixture was left to stir for 48 hours instead of 1 hour, while another 2 equivalents of MCPBA were added after 24 hours.

Scheme 3



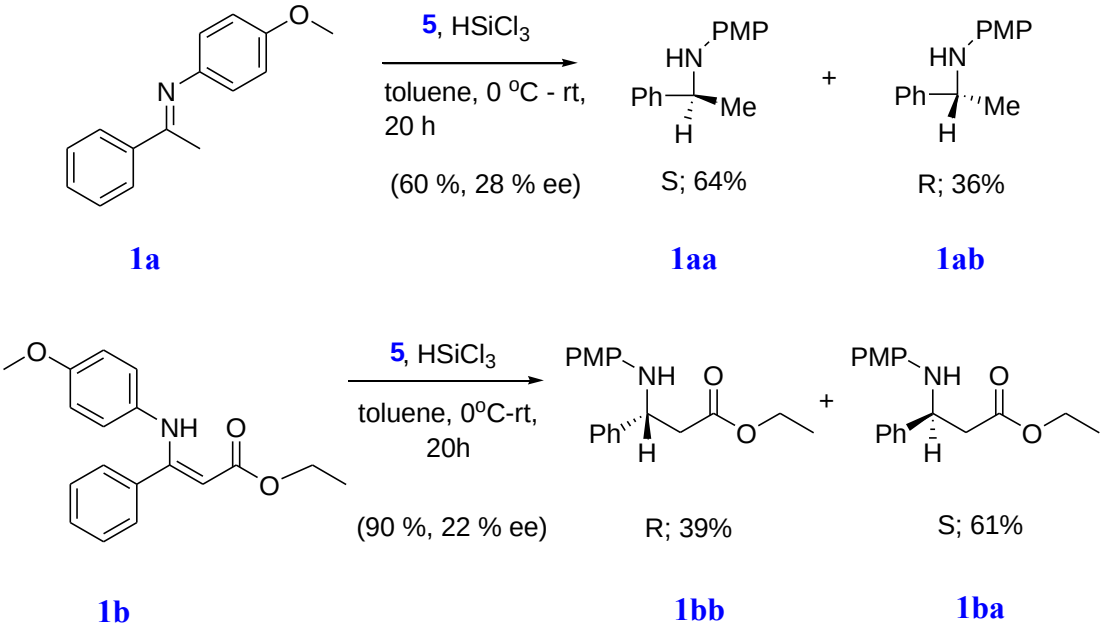
5 **5a**

Despite the prolonged time of the reaction, we were unable to isolate any *N*-oxide **5a** from the reaction mixture. Possible reason of this failure could have been some side reactions, as neither the starting material nor the product were obtained. Both aqueous (neutralised with HCl) and organic phase were checked by NMR, however, no signs of **5a** were detected.

3.2. Asymmetric reduction of imines with $HSiCl_3$, catalyzed by 5

In order to determine the efficiency of catalyst **5**, two types of imine structures (**1a** and **1b**) were used as test substrates (Scheme 4).

Scheme 4



1a **1aa** **1ab**

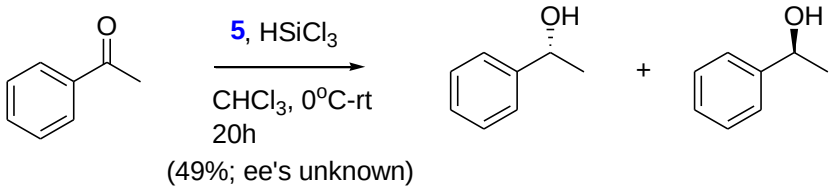
1b **1bb** **1ba**

For both reactions, 10 mol % of **5** as a catalyst and 2 eq. of $HSiCl_3$ in dry toluene were used. The reactions were carried out under argon athmosphere at 0 ^oC and left stirring overnight at room temperature.

3.3. Asymmetric reduction of ketones with $HSiCl_3$ in the presence of 5

Acetophenone was used as a model ketone, and the reaction was performed under the conditions for the asymmetric reduction of acetophenone with trichlorosilane published in the literature[10] (Scheme 5). To achieve a higher yield of the reduction, the reaction temperature was raised from -20 ^oC to 0 ^oC and, after the addition of $HSiCl_3$, left to reach room temperature and stirred overnight. General expectations were that a higher temperature should positively influence the yield, while a lower temperature is necessary for a higher asymmetric induction.

Scheme 5

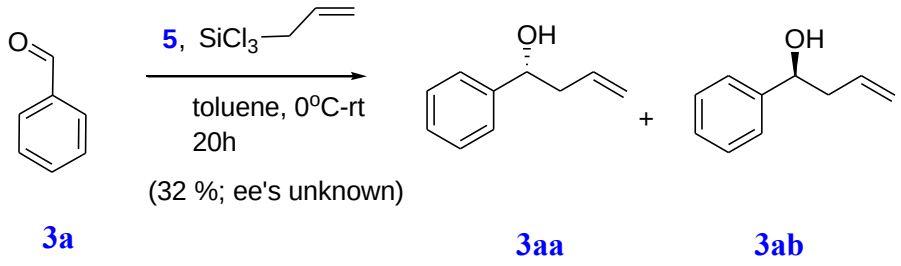


2a **2aa** **2ab**

3.4. Allylation of benzaldehyde with allyl trichlorosilane in the presence of 5

Benzaldehyde **3a**, as the simplest molecule possible, was used in this reaction. The same conditions as shown above for the asymmetric reduction of imines, were employed (Scheme 6). Catalyst was added in 10 mol % and the reaction was left to stir for 20 hr. In comparison with other, previously published catalysts[25], a very low enantioselectivity was observed in this case, and for this reason, the ee's were not specified.

Scheme 6



3.5. Mechanistic Considerations.

The *N*-methyl valine scaffold-based catalysts appear to act as Lewis bases in the imine reduction reaction. The basicity is afforded by two amide groups, and possibly the pyridine nitrogen as well. Taking **C** as the predecessor of **5**, the mechanism can be defined based on the measured data and evidence. In the ^{13}C NMR spectrum of a 1:1 mixture of **C** and $HSiCl_3$, shifts of ~ 0.1 and 0.2 ppm were observed for the corresponding signals of the formamide and anilide carbonyls relative to free **C**. Furthermore, the methyl groups at the aromatic ring became non-equivalent, suggesting a weak coordination (possibly bidentate) that restricts the rotation around the *N*-Ar bond. [10]

The aromatic substitution at the C-end is crucial for the reaction to occur. This is because of the essential arene-arene interactions with the substrate, which most likely coordinate the substrate to the activated $HSiCl_3$-catalyst complex. Substitution on the aromatic ring affects the Lewis basicity of the anilide carbonyl. On the assumption that the activation of $HSiCl_3$ begins with the coordination of Si to either one or both carbonyls, modulating of their basicity may appear crucial for the activity of various catalysts. The formamide moiety controls the electron density on the amide carbonyl in a constant way, unlike the 3,5-disubstitued anilide at the C-end, where electron-donating groups in 3,5-positions make the carbonyl a stronger Lewis base and electron-withdrawing groups weaken the basicity. Thus, the selectivity and efectivity were negatively regulated. After advanced research and testing,[10] the 3,5-dimethyl and 3,5-di-*tert*-butyl substitued anilides were proven to be the most effective and selective derivatives. Reasons for using the 3,5-dimethylanilide as a replacement for the most efficient and active, 3,5-di-*tert*-butyl anilide in a derivative **C** were following: a) in comparison between **C** and its 3,5-dimethylanilide derivative, only small differences in enantioselectivity and yields were observed. With only 5 mol %, both catalysts provided yields over 90 % and more than 92 % ee, b) prices of commercially available 3,5-dimethylaniline and 3,5-di-*tert*-

butyaniline differ by more than 40 EUR for a 1g amount, thus 3,5-dimethylaniline became the substitute of choice.

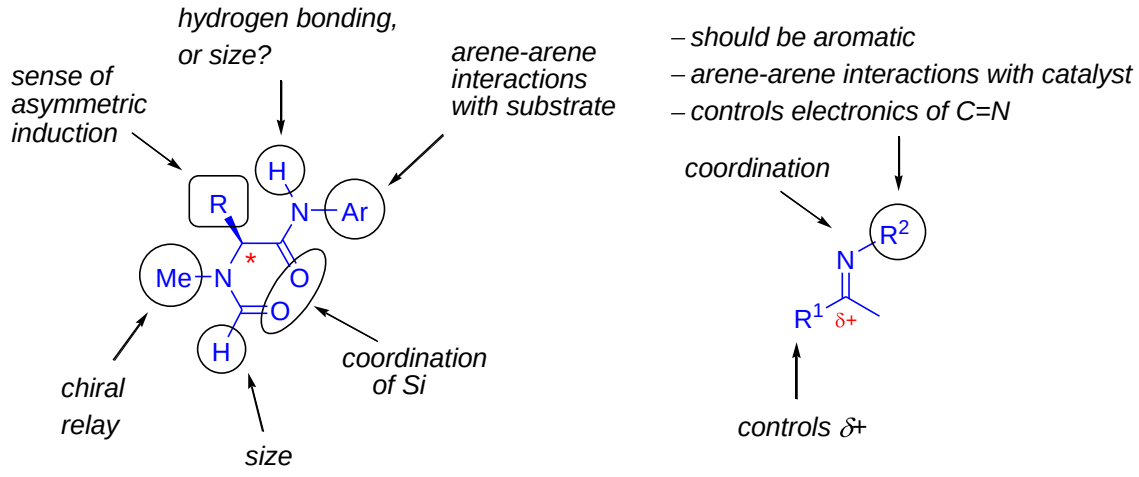
Unlike the tertiary one, a secondary anilide has most probably a decreased rigidity of the molecule, and possibly also provides the formation of the transition state by forming a hydrogene bond to the substrate's nitrogen.

The valine skeleton itself, determines the sense of assymetric reduction via the *i*-Pr group. *(S)*-proline based substances[(15)] provide mostly the *R* enantiomers, often in high yield, whereas *(S)*-valine derivatives catalyzed reduction results usually in high yields of *S* enantiomer. For instance, methyl and phenyl substitued amino-acids were observed to have moderate enantioselectivity.

The *N*-methyl group plays a role in the enantioselectivity as well as in the support of the Lewis basicity of the formamide, being sufficiently small so as not to interact with a substrate, though is not necessary for performing the reaction.

The formamide moiety is employed in order to stabilize and strongly coordinate Si and to be as small as possible to allow bulky and variable substrates to approach the ligand.

Figure 5



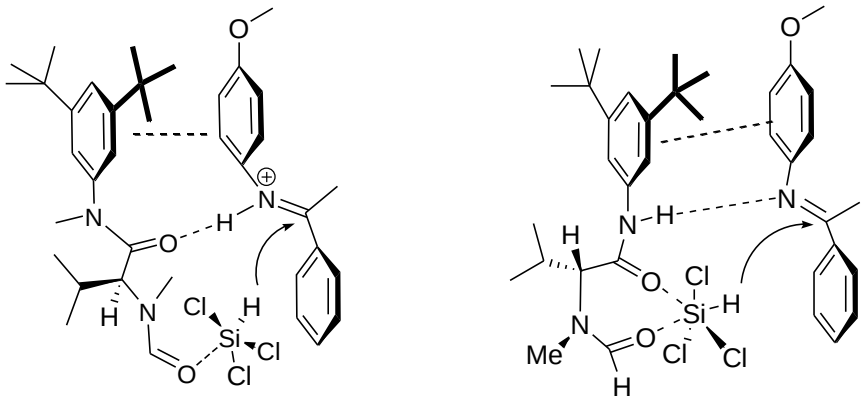
Catalyst **Imine**

The imine requirements include R^2 being strictly aromatic, being involved in arene-arene coordination to the ligand. This substitution provides the effectiveness as well as the enantioselectivity of the reaction. R^1 controls electronics of the imine carbon and hence the stability of the transition state.

For example (Scheme 7) catalyst **C** starts the activation of $HSiCl_3$ by binding Si via its two carbonyls, if bidentate Si coordination is assumed. Aromatic parts of both substrate and the

ligand molecule organize themselves via arene-arene interactions, therefore an aromatic anilide substitute is crucial for the reaction to occur. The eight-membered transition state is then formed allowing $HSiCl_3$ to donate its hydride to C=N bond, where the hydride is coordinated by the partial positive charge of the carbon. The subsequent process, not fully explored yet, sustains probably with falling the transition state apart, while Si is bound to the amine N atom. The regeneration of the ligand and its recovery possibility is obvious. Finally, the reaction is quenched by saturated $NaHCO_3$, while hydrolysis offers the new amine and and ($SiO_2.nH_2O$) via $Si(OH)_4$ is formed.

Scheme 7



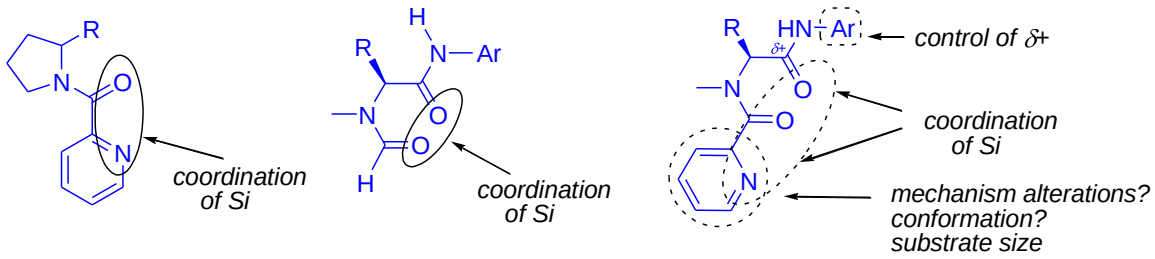
monodentate bidentate

U

nlike **C**, **G**[15] uses the N-end amide carbonyl and the nitrogen in the pyridine ring of the picolinic acid for the activation (Figure 6). The presence of all three of these binding groups in **5** might cause interactions and competition among them. Consequently, a change of mechanism was likely. The competition could be suppressed either by the substitution of the pyridine ring or by the substitution of the Ar-ring at the C-end of the valine scaffold. In the first case an electron donor groups, supporting the Lewis basicity of the picolinamide carbonyl could be employed. The latter approach, using 3,5-disubstitution of the aromatic part by electron-withdrawing groups (e.g. dinitro) might on the other hand lower the anilide carbonyl Lewis basicity. No doubt the new mechanism design is based on the picolinic substituent, whose involvement in Si activation is and steric interactions with the substrate are likely. Restricted rotation around the 2-pyridyl bond and a more rigid molecule can cause a difficult approach for bulky substrates. It is also questionable, whether the substrate can be attached to an activated $HSiCl_3$, coordinated between carbonyl and pyridine. It is also possible

that a monodentate Si is unavailable for a substrate bound by arene-arene interactions with the upper part of the ligand molecule.

Figure 6



Matsumura's catalyst **Kočovský / Malkov** **5**

4. CONCLUSIONS

Despite all expectations and previous considerations, catalyst **5** is not more catalytically active or enantioselective than previously used molecules **C**[11] and **G**[15] previously used in the reduction of imines. Matsumura proline derived catalyst worked up to ≤ 67 % in the yield and ≤ 80 % ee. Kočovský-Malkov – *N*-Methyl valine-derived Sigamide performed the imine reduction in the yield of ≤ 92 % and ≤ 96 % ee, while **5** catalyzed imine reduction with the yield of 60 % and the enantioselectivity of 28 % ee.

Moderate catalytic activity was observed also in the reduction of acetophenone and allylation of benzaldehyde with allyltrichlorosilane.

The possible causes lie in the mechanistic comparisons [20], between **5**, **G** and **C** (Scheme 13) and the structural nature of **5**. Most likely, the reaction mechanism is completely changed, using previous postulates in a new way, which is worth further exploration, using either new types of substrate, or new substituents on the aromatic part of the ligand.

5. EXPERIMENTAL

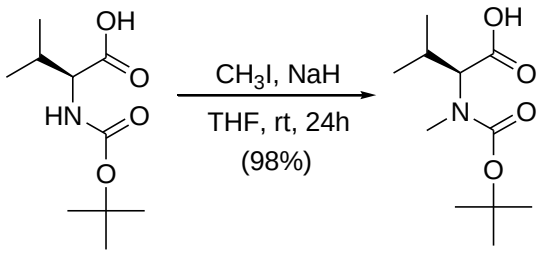
5.1. General Methods.

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated, with an error of ≤±0.1. The $[\alpha]_D$ values are given in 10^{-1} deg cm^3 g^{-1}. The NMR spectra were recorded in $CDCl_3$, ^1H at 400 MHz and ^{13}C at 100.6 MHz with chloroform-d_1 (δ 7.26, ^1H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for $CHCl_3$ solutions unless otherwise indicated. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware, twice evacuated and filled with inert gas. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use (dichloromethane from calcium hydride). Petroleum ether refers to the fraction boiling in the range of 60-80 ^oC. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures. The imines **1a**, **1b**, are known compounds and were prepared according to the procedures shown in appropriate literature[10][26]. Amines **1aa**, **1ab**, **1ba**, **1bb**, are all known compounds and their absolute configuration was established in reference to the literature data[10]. The ketone **2a** is known compound and was prepared according to the procedures shown in appropriate literature[18]. Secondary alcohols **2ab** and **2aa** are known compounds and their absolute configuration was established in reference to the literature data[18].

5.2. Synthesis of *N*-Methyl BOC-Protected Amino Acids 2.

Sodium hydride (60 % dispersion in mineral oil; 3.0 g, 138 mmol) was added in small portions to a stirred solution of the BOC-protected valine **1**, (2,99 g, 13.8 mmol) and methyl iodide (19.6 g, 138 mmol) in anhydrous THF (60 mL) at 0 ^oC. The mixture was allowed to reach room temperature and stirred for 24 h under an argon athmosphere, the reaction was

then quenched with water (15 mL), ethyl acetate (10 mL) was added and the mixture was evaporated in vacuo. The concentrate was diluted with water (300 mL) and washed with ethyl acetate (150 mL). The aqueous solution was acidified to pH 3.5 with a solution of 5% citric acid and extracted with ethyl acetate (200 mL). The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give the **2**;

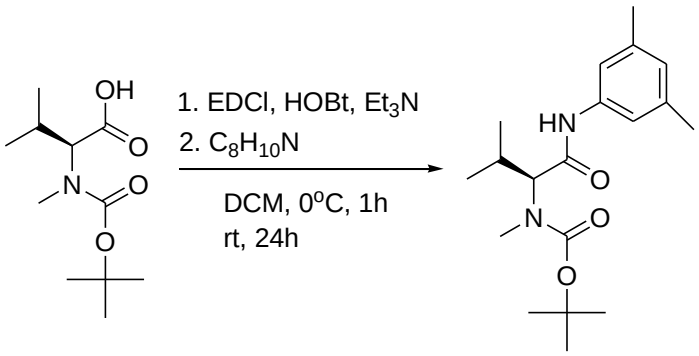


1 **2**

***(S)*-*N*-BOC-*N*-Methyl valine – *(S)*-2** : Obtained from *(S)*-**1** as an oil (2.87 g, 12.3 mmol, 89%) using protocol A; this product was used in the following step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ *4.01* (d, *J* = 10.4 Hz, 1H), 2.90 (s, 3H), 2.39 (m, 1H), 1.49 (s, 9H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H); in agreement with literature[(22)] data.

5.3. Synthesis of the *N*-BOC Protected Amides 3.

Triethylamine (1.44 mL, 10.3 mmol) was dropwise added to a solution of **2** (1.59 g; 6.87 mmol) in dry dichloromethane (60 mL) at 0 °C. To the resulting clear solution were consecutively added 3,5-dimethylaniline (1.00 g; 8.25 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 1.363 g ; 8.94 mmol) and 1-hydroxy-benzotriazole hydrate (HOBt; 1.421 g; 8.94 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (250 mL) and washed successively with water (60 mL), cold 0.5 M HCl (60 mL), saturated $NaHCO_3$ (2×60 mL), and brine (60 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. Purification by column chromatography on silicagel using petroleum ether-ethyl acetate 95:5 mixture afforded amide **3** in the yield of 1.98 g (86.1 %) as a white, crystalline solid.

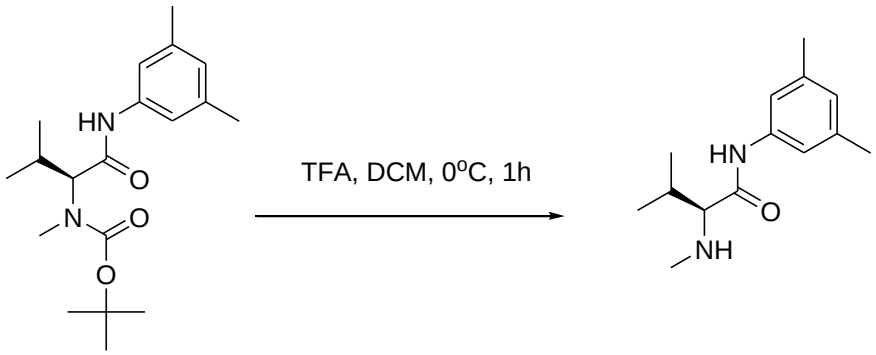


2 **3**

***(S)*-tert-butyl 1- (3,5-dimethylphenylamino)-3-methyl-1-oxobutan-2-yl (methyl) carbamate *(S)*-(-)-3**: Mp 103-104 °C; $[\alpha]_D$ -132.7 (*c* 1.0, $CHCl_3$); $_1H$ NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.6 Hz, 3H), 1.01 (d,*J* = 6.5 Hz, 3H), 1.48 (s, 9H), 2.28 (s, 6H), 2.31-2.41 (m, 1H), 2.82 (s, 3H), 4.11 (d, *J* = 11.0 Hz,1H), 6.73 (s, 1H), 7.15 (s, 2H), 8.14 (br s, 1H); in agreement with the literature data.[(11)]

5.4. Synthesis of Picolinamide 5.

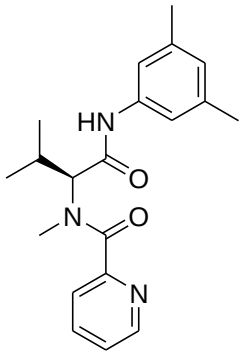
A trifluoroacetic acid (4.1 mL; 0.85 mmol) was slowly added to a solution of **3** (300 mg; 0.897 mmol) in dry DCM (4.1 mL) at 0 °C and left stirring for 1 hour. The reaction mixture was gently evaporated in vacuo, the residue then 3x co-evaporated with toluene, due to usage of TFA, dissolved in EtOAc, washed with sat. $NaHCO_3$, and the aqueous phase again with pure ethylacetate. Organic phase was evaporated in vacuo, dissolved in THF (20mL) and used in the next step without further purification.



3 **4**

Methyl chloroformate (70 μL ; 0.897 mmol) was slowly added to a solution of 2-picolinic acid (110.43 mg ; 0.897 mmol) and Et_3N (130 μL ; 1,0 mmol) in dry THF (20 mL) at 0 °C while stirring under an argon atmosphere and the resulting mixture was stirred in an ice bath for 30 min. The white precipitate of triethylammonium chloride was left in the reaction

mixture to which, a solution of crude **4** from former step in dry THF (20 mL) and Et_3N (110 μL, 0.897 mmol) was slowly added. The reaction mixture was observed to have a clear yellow color. After 20 hours stirring TLC (petroleum ether – ethyl acetate mixture (1:2) indicated that the starting material **4** had disappeared. The mixture was concentrated under vacuum to afford a viscous yellow oil, which was purified by chromatography on a column of degassed silica gel (30 g) with a petroleum ether – ethyl acetate mixture (7:3) to give pure ***(S)*-(+)-5** as a white crystalline solid. Yield of whole two-step reaction resulted in 0.259 g, 85.3 %.



5

***(S)*-N-(1-(3,5-dimethylphenylamino)-3-methyl-1-oxobutan-2-yl)-N-methylpicolinamide *(S)*-(+)-5**:

Mp 235-237 °C; $[\alpha]_D$ = + 47.3 (*c* = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (1H, bs, NH), 8.73 (1H, d, *J*=5.2 Hz, H6′), 8.00 (1H, td, J_1=7.8 Hz, J_2=2.0 Hz, H4′), 7.92 (1H, d, *J*=7.8 Hz, H3′), 7.57-7.54 (1H, m, H5′), 7.34 (2H, s, H2′′, H6′′), 6.80 (1H, s, H4′′), 4.17 (1H, d, *J*=10.4 Hz, NCH), 3.06 (3H, s, NCH_3), 2.54-2.48 (1H, m, CH), 2.35 (6H, s, CH_3), 0.92 (3H, d, *J*=6.6 Hz, CH_3), 0.78 (3H, d, *J*=6.6 Hz, CH_3)

$_{13}$C NMR (100 MHz, $CDCl_3$): δ 168.43 (C=O), 167.35 (C=O), 153.69, 146.98, 138.80, 138.66, 138.53, 125.74, 125.70, 117.51, 117.09, 67.81, 29.13, 25.79, 21.50, 20.01, 18.51.

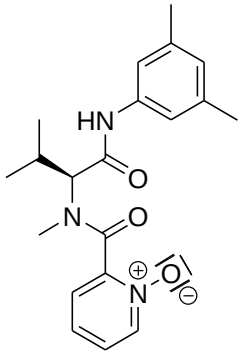
IR (KBr) ν 3276, 3018, 2964, 2923, 2399, 1693, 1628, 1569, 1454, 1426, 1403, 1334, 1287, 1217, 1073, 1046, 844, 771, 608 cm^{-1}.

MS (EI) *m/z*(%) 340(M^++H, 100), 277(2), 219(30), 206(4), 191(3), 122(5), 69(12).

5.5. Oxidation of Pyridine Ring.

A solution of **5** (560 mg, 1.66 mmol) in DCM (11 mL) was cooled to 0^{o}C. Then *metha*-chloroperoxybenzoic acid (MCPBA, 630 mg, 3.65 mmol) was added, the reaction mixture was allowed to reach room temperature and stirred overnight. After 20hrs of stirring, TLC (petroleum ether-ethyl acetate mixture 9:1) showed residues of starting material, according to which, next 2eq amount of MCPBA was added and left stirring overnight again.

The reaction mixture was quenched with brine (10 mL), due to huge amount of peroxides (tested by KI paper) then washed with Na_2SO_3 (2x10 mL) and saturated $NaHCO_3$. Combined aqueous phase was neutralised to pH 7 with 5% HCl and extracted with ethyl acetate (3x10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The mixture was used for NMR testing without further purification.

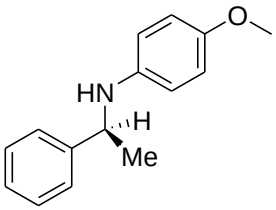


5a

(S)-2-[1-(3,5-dimethylphenylamino)-3-methyl-1-oxobutan-2-yl]-*N*-methyl carbamoyl) pyridine-2-yl-1-oxide: Both ^{1}H and ^{13}C NMR showed no sign of the *N*-oxide structures.

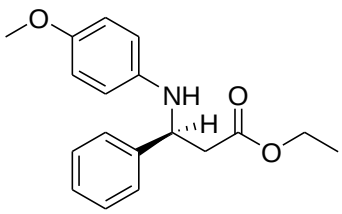
5.6. Imine Reduction in Presence of 5.

Tested imine (**1a**, **1b,** 0.2 mmol) and **5** (0.02 mmol, 6.23 mg) were dissolved in anhydrous toluene (2 mL) under argon atmosphere at 0 ^{o}C. Trichlorosilane (40 μL, 0.4 mmol) was added dropwise and the mixture left to stir overnight and allowed to reach room temperature. The reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL), washed with brine (5 mL) and extracted with ethyl acetate (2x10 mL). The extract was dried over anhydrous $MgSO_4$ and concetrated under vacuum. Purification using column chromatography on silica gel (20 g) with a petroleum ether–ethyl acetate mixture (9:1) afforded the products (**1aa**, **1 ab**, **1ba**, **1 bb**). The yields and ee‘s are given below:



1aa

***(S)*-*N*-(4-Methoxyphenyl)-*N*-(1-phenylethyl)amine *(S)*-1aa.** ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.43 (d, *J* = 6.8 Hz, 3H), 3.62 (s, 3H), 3.72 (bs, 1H), 4.34 (q, *J* = 6.8 Hz, 1H), 6.40 (m, 2H), 6.62 (m, 2H), 7.15 (m, 1H), 7.22-7.30 (m, 4H) in agreement with literature data [27]. Chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.75 mL/min) showed 28% ee at *t*R = 14.8 min, *t*S = 16.1 min (lit.[18] gives 85 % ee ; *t*R = 23.9 min, *t*S = 27.2 min). Yield 27.5 mg, 60 % as a yellow oil.



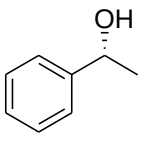
1ba

***(S)*-ethyl 3-(4-methoxyphenylamino)-3-phenylpropanoate, *(S)*-1ba**. $_1$H-NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.6 Hz, 3H), 1.01 (d,*J* = 6.5 Hz, 3H), 1.48 (s, 9H), 2.28 (s, 6H), 2.31-2.41 (m, 1H), 2.82 (s, 3H), 4.11 (d, *J* = 11.0 Hz,1H), 6.73 (s, 1H), 7.15 (s, 2H), 8.14 (br s, 1H) in agreement with literature data.

Chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.75 mL/min) showed 23 % ee at *t*R = 10.4 min, *t*S = 11.2 min. Yield was 27.5 mg, 90 % as a brown viscous oil.

5.7. Ketone Reduction in Presence of 5.

Trichlorosilane (50 μL, 0.4 mmol, 2.1 eq) was slowly added dropwise to a solution of **5** (21.9 mg, 0.08 mmol or 11.0 mg, 0.04 mmol) and the ketone **2a** (0.40 mmol, 1.0 eq) in $CHCl_3$ (2 mL) at 0 °C. The reaction mixture was stirred for 24 h at room temperature, after which time saturated aqueous $NaHCO_3$ (5 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were dried over $MgSO_4$. Concentration *in vacuo* followed by column chromatography on silica gel (15 g) with CH_2Cl_2 afforded *sec*-alcohols **2aa** and **2ab**.



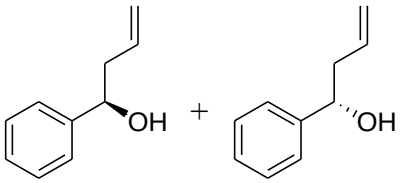
2ab

***(R)*-(+)-1-Phenylethanol – *(R)*-2ab.** $[\alpha]_D$ +45.2 (*c* 0.93, $CHCl_3$,), ee's unknown, [lit.[28] gives $[\alpha]_D$+49.0 (*c* 1.0, $CHCl_3$, 98 % *ee*)]; $_1$H NMR (400MHz, $CDCl_3$) δ_H 1.52 (d, *J* = 6.4 Hz, 3H),

2.21(bd, 1H), 4.92 (q, *J* = 6.4 Hz, 1H), 7.28-7.50 (m, 5H); in agreement with literature data [18]

5.8. Allylation of Benzaldehyde in Presence of 5.

Allyltrichlorosilane (0.4 mmol, 40 μL) was added to a solution of **5** (0.02 mmol, 6.23 mg) and benzaldehyde (0.2 mmol) in dry toluene (2 mL) under argon athmosphere at 0°C. After addition, the mixture was allowed to reach room temperature and stirred overnight. The reaction was quenched with solution of sat. $NaHCO_3$ (2 mL) and extracted with ethyl acetate (2 × 10 mL). The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The mixture was concentrated under vacuo and purified by column chromatography on silica gel (15 g) with a petroleum ether - ethyl acetate mixture (95:5).



3aa **3ab**

Phenyl-but-3-en-1-ol (3aa, 3ab):[29][30] ^{1}H-NMR δ 2.08 (s, 1H), 2.37-2.49 (m, 2H), 4.62-4.66 (m, 1H), 5.05-5.15 (m, 2H), 5.68-5.78 (m, 1H), 7.17-7.29 (m, 5H); in agreement with literature[25] data. Yield was 29 % (8.2 mg). Ee's weren't specified.

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