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Funkcionalizace pyrimidinových nukleobází přímými C-H arylacemi.
Functionalization of pyrimidine nucleobases by direct C-H arylations.

Disertační práce

Školitel: Prof. Ing. Michal Hocek, CSc., DSc.

Praha, 2015

Prohlášení:

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V Praze, 09.06.2015

Podpis

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Abstract

Within presented dissertation thesis Pd-catalyzed direct C-H arylation of 1,3-dimethyluracil to position 5 or 6 was developed. An interesting dichotomy in the regioselectivity and mechanism of reactions were observed. A reaction of 1,3-dimethyluracil with diverse aryl halides performed in the absence of CuI led preferentially to 5-aryl-1,3-dimethyluracils, while with the addition of CuI 6-aryl-1,3-dimethyluracils were formed as the major products. Reactions mediated only in the presence of copper(I) iodide (in the absence of a Pd-catalyst) proceeded with lower yields but led exclusively to 6-arylated derivatives. In order to prepare free 5- and 6 arylated uracils for biological activity screening, the developed methodologies for the direct C-H arylations were applied to various 1,3-protected uracils. Benzyl-protected uracil was selected as the best candidate both in terms of stability during the arylations, as well as facile cleavage of the benzyl groups during deprotection of arylated uracils. Synthesis of various substituted 5- and 6-aryl-1,3-dibenzyluracils proceeded with the same regioselectivity as with the model compound 1,3-dimethyluracil. For deprotection of synthesized derivatives either transfer hydrogenolysis over Pd/C or treatment with BBr_3 in case of uracils bearing bulky aromatic substituents was used. Furthermore, novel and efficient synthesis of 2,4-diarylpyrimidines was developed based on the use of phosphonium-mediated Suzuki coupling of 2-(methylsulfanyl)uracil at position 4 followed by the Liebeskind–Srogl cross-coupling at position 2 under microwave irradiation. The synthesized 2,4-diarylpyrimidines were tested *in vitro* for their cytostatic activity against human cancer cell lines. The possibility of subsequent direct arylation of 2,4-diarylpyrimidines was also investigated. Finally, diverse electrophilic, nucleophilic and radical direct trifluoromethylations of 1,3-dimethyluracil were systematically studied in order to prepare either 5- or 6-(trifluoromethyl)uracil derivatives and consequently explore possibilities of direct arylation to free 5 or 6 position. The radical trifluoromethylation by CF_3SO_2Na in presence of *t*-BuOOH gave 1,3-dimethyl-5-(trifluoromethyl)uracil in good yield. The 6-(trifluoromethyl)uracil derivative was only prepared in a mixture with 1,3-dimethyl-5-(trifluoromethyl)uracil by Ir-catalyzed borylation followed by treatment with the Togni's reagent. This isomer was isolated from the mixture only in a very low yield, therefore, the attempts of subsequent C-H arylation were performed only on 1,3-dimethyl-5-(trifluoromethyl)uracil. Its Pd-catalyzed arylation with various aryl halides proceeded successfully only with 4-iodotoluene, wherein in the presence of CsF as a base and copper iodide the desired 6-tolyl-5-trifluoromethyluracil derivative was successfully prepared.

Abstrakt

V rámci předložené dizertační práce byly navrženy metody přímé Pd-katalyzované C-H arylace 1,3-dimethyluracilů do pozice 5 nebo 6, přičemž byla pozorována zajímavá dichotomie v regioselektivitě a v mechanismu reakcí. Reakcemi 1,3-dimethyluracilu prováděnými bez přítomnosti CuI s různými aryl halogenidy vznikaly přednostně 5-aryl-1,3-dimethyluracily, přičemž reakce prováděné s přídavkem CuI poskytly jako hlavní produkt 6-aryl-1,3-dimethyluracily. Reakce pouze v přítomnosti jodidu měďného (bez přítomnosti Pd-katalyzátoru) probíhaly sice s nižším výtěžkem, ale vedly výhradně k 6-arylovaným derivátům. Vyvinuté metody pro přímé C-H arylace byly následně aplikovány na různě 1,3-chráněné uracily, s cílem získat volné 5- a 6-arylované uracily k prozkoumání jejich biologické aktivity. Uracil ochráněný benzylovou chránicí skupinou byl vybrán jako nejlepší kandidát a to z hlediska jak stability v průběhu arylací, tak i následného snadného odchránění benzylových skupin při deprotekci arylovaných uracilů. Syntéza různě substituovaných 5- a 6-aryl-1,3-dibenzyluracilů probíhala se stejnou regioselektivitou jako u modelové látky 1,3-dimethyluracilu. K odchránění syntetizovaných derivátů byla zvolena transfer hydrogenolýza v přítomnosti Pd/C případně reakce s BBr_3, která se osvědčila při odchránění derivátů uracilů nesoucích objemnější arylové substituenty. Dále byla navržena nová efektivní syntéza 2,4-diarylpyrimidinů, založená na použití fosfoniové varianty Suzukiho reakce 2-(methylsulfanyl)uracilu do pozice 4 a následnou Liebeskind-Šroglovou cross-couplingovou reakcí do pozice 2 působením mikrovlnného záření. Syntetizované 2,4-diarylpyrimidiny byly testovány *in vitro* na cytostatickou aktivitu proti vybraným nádorovým buněčným liniím. Prozkoumaná byla také možnost následné přímé arylace 2,4-diarylpyrimidinů. Nakonec byly studovány také různé elektrofilní, nukleofilní a radikálové přímé trifluormethylace 1,3-dimethyluracilu s cílem připravit buď 5-, nebo 6-(trifluormethyl)uracilové deriváty a následně prozkoumat možnosti jejich přímé arylace do volné pozice 5 nebo 6. Radikálová trifluormethylace použitím CF_3SO_2Na v přítomnosti *t*-BuOOH poskytla 1,3-dimethyl-5-(trifluormethyl)uracil v dobrém výtěžku. 6-(Trifluormethyl)uracilový derivát byl připraven jedině ve směsi s 1,3-dimethyl-5-(trifluormethyl)uracilem, a to použitím Ir-katalyzované borylace a následné reakce s Togniho činidlem. Separací ze směsi byl tento isomer získán jen ve velmi nízkém výtěžku, proto byly pokusy o následnou C-H arylaci provedeny jen na 1,3-dimethyl-5-(trifluormethyl)uracilu. Jeho palladiem katalyzovaná arylace s řadou arylhalogenidů proběhla úspěšně pouze s 4-jodtoluenem, kde v přítomnosti fluoridu cesného jako báze a jodidu měďného byl získán požadovaný 6-tolyl-5-trifluormethyluracilový derivát.

List of abbreviations

Ac = acetyl

Ar = aryl

API = active pharmaceutical ingredient

APT = attached proton test

aq = aqueous solution

ATR = attenuated total reflection

BOM = benzyloxymethyl

Bn = benzyl

BRAF = human gene that makes a protein B-Raf

B-Raf = amino acid, regulated signal transduction serine/threonine-protein kinase

Bz = benzoyl

cataCXium F Sulf = dicyclohexyl-{2-sulfo-9-[3-(4-sulfo-phenyl)propyl]-9-fluorenyl} phosphonium-hydrogensulfate

CCRF-CEM = T-lymphoblastic leukemia

CMD = concerted metalation-deprotonation

cod = 1,5-cyclooctadiene

CuTC = copper(I) thiophene-2-carboxylate

CuMeSal = copper(I) 3-methylsalycilate

Cy = cyclohexyl

dba = dibenzylideneacetone

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE = 1,2-dichloroethane

DCM = dichloromethane

DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DMA = *N,N*-dimethylacetamide

DME = dimethoxyethane

DMEDA = *N,N′*-dimethylethylenediamine

DMF = *N,N*-dimethylformamide

DMSO = dimethyl sulfoxide

DNA = deoxyribonucleic acid

dtbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl

EI = electron ionization
ESI = electrospray ionization
Et = ethyl
EtOAc = ethyl-acetate
EtOH = ethanol
equiv = equivalent
GnRH = gonadotropin-releasing hormone
HeLa S3 = cervical carcinoma
HepG2 = liver carcinoma
HIV = human immunodeficiency virus
HL-60 = promyelocytic leukemia
HMBC = heteronuclear multiple bond correlation
HMPT = hexamethylphosphoramide
HR MS = high-resolution mass spectrometry
HSQC = heteronuclear single quantum coherence
IR = infrared
Me = methyl
MeCN = acetonitrile
MEM = methoxyethoxymethyl
MeOH = methanol
mp = melting point
MS = mass spectrometry
MW = microwaves
*n*Bu = butyl
NMR = nuclear magnetic resonance spectroscopy
Ph = phenyl
PhDavePhos = 2-diphenylphosphino-2'-(*N,N*-dimethylamino)biphenyl (Buchwald's ligand)
phen = 1,10-phenantroline
pin = pinacolato
PivOH = pivalic acid
PMB = *p*-methoxybenzyl
PyBroP = bromotripyrrolidinophosphonium hexafluorophosphate
Pyr = pyridine

RNA = ribonucleic acid

r.t. = room temperature

TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy

TBDMS = *tert*-butyldimethylsilyl

*t*Bu = *tert*-butyl

*t*BuOOH = *tert*-butyl hydroperoxide

Tf = trifluoromethanesulfonyl

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TM = transition metal

TMS = trimethylsilyl

TMP = 2,2,6,6-tetramethylpiperidide

Tol = tolyl

List of publications of the author related to the thesis

Čerňová, M.; Pohl, R.; Hocek, M.: "Switching the Regioselectivity of Direct C–H Arylation of 1,3-Dimethyluracil" *Eur. J. Org. Chem.* **2009**, 3698-3701.

Čerňová, M.; Čerňa, I.; Pohl, R.; Hocek, M.: "Regioselective Direct C-H Arylations of Protected Uracils. Synthesis of 5- and 6-Aryluracil Bases" *J. Org. Chem.* **2011**, *76*, 5309-5319.

Čerňová, M.; Pohl, R.; Klepetářová, B.; Hocek, M.: "A General Regioselective Synthesis of 2,4-Diarylpyrimidines from 2-Thiouracil through Two Orthogonal Cross-Coupling Reactions" *Synlett* **2012**, *23*, 1305-1308.

Čerňová, M.; Pohl, R.; Klepetářová, B.; Hocek, M.: "C-H Trifluoromethylations of 1,3-Dimethyluracil and Reactivity of the Products in C-H Arylations" *Heterocycles* **2014**, *89*, 1159-1171.

Contents

1. Introduction

Pyrimidine is a nitrogen heterocyclic aromatic compound which oxo derivatives known as pyrimidine nucleobases are beside purine bases one of the key structural parts found in nucleotides, building blocks of nucleic acids. There are three major natural representatives of pyrimidine nucleobases - cytosine (in DNA and RNA), thymine (in DNA), and uracil (in RNA).

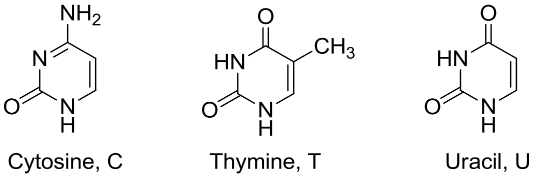


Figure 1 Natural pyrimidine nucleobases

Apart from primary pyrimidine nucleobases there are also other bases found in nucleic acids as a result of post modification of primary nucleobases. In DNA 5-methylcytosine (m^5C) could be found while in RNA pseudouridine (Ψ) and dihydrouridine (D) are present.

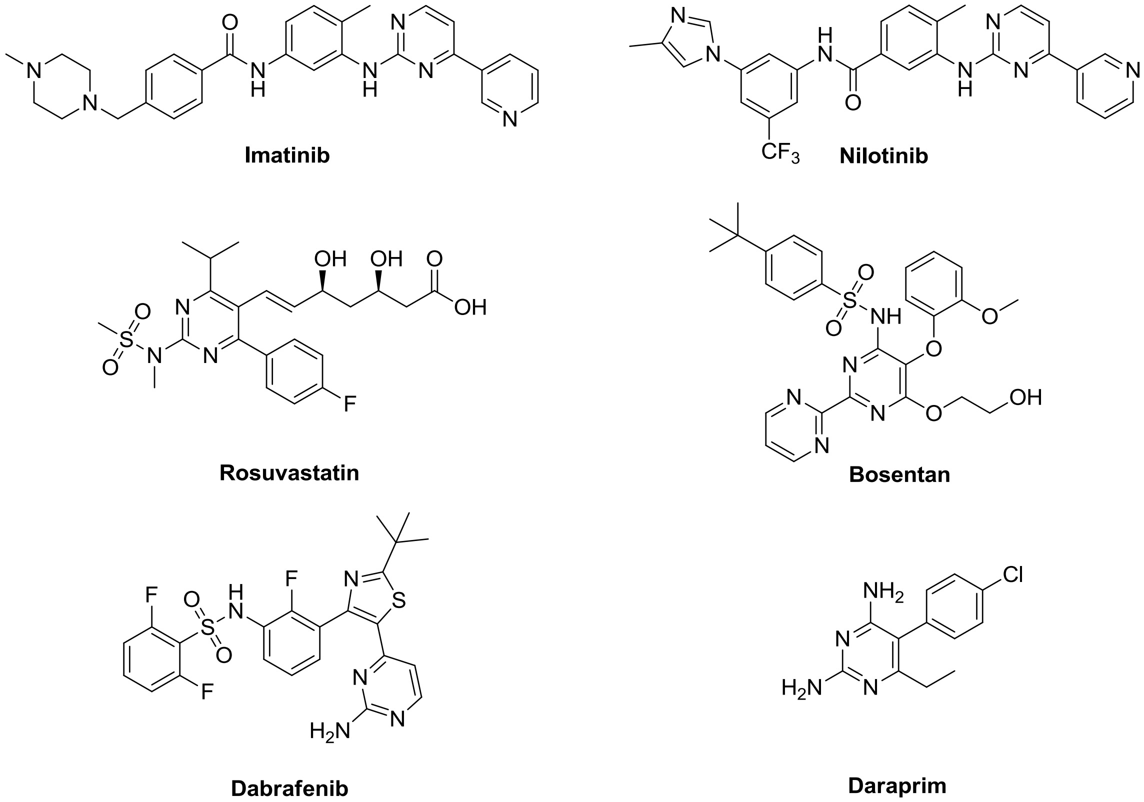
At the moment, many artificial modified nucleobases and nucleosides are known and have been applied in DNA or RNA research as labels, photosensitive or fluorescent probes. They also found their application in medicinal chemistry as biologically active compounds.

1.1. Utilization of arylated pyrimidines

1.1.1. Clinically used APIs based on arylated pyrimidines

Heterocycles containing pyrimidine scaffold are of a great interest because they constitute an important class of natural products (thiamine B1, riboflavin B2, folic acid etc.) and synthetic compounds, many of which exhibit useful biological activities and clinical applications. Pyrimidines are biologically very important and are represented by the essential building blocks of nucleic acids, such as uracil, thymine and cytosine. Various analogs of pyrimidines have been found to posses antibacterial,[1] antifungal,[2] antiinflammatory,[3] antihypertensive,[4] antiviral,[5] anticancer,[6] analgesic,[7,3a] antidiabetic,[8] antiallerggic activities,[9] and many of pyrimidines derivatives are reported to possess potential antioxidative[10] and central nervous system (CNS) depressant properties.[11] Additional biologically active substances include agents against hyperthyroidism, Parkinson's disease or even cardiovascular, antiepileptic, antihistaminic, anesthetic, antimalarial agents, and also act as calcium channel blockers.[3b,12] There are several available herbicides and insecticides that contain a pyrimidine skeleton.[2d]

In Figure 2 a five examples of commercially available drugs containing the pyrimidine skeleton to which (het)aryl moiety is directly bound through C-C bond are depicted. Imatinib, the trade names Gleevec (Canada, South Africa and the USA) or Glivec (Australia, Europe and Latin America), is an ATP-competitive inhibitor of the tyrosine-kinase used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs).[13] For the treatment of imatinib-resistant chronic myelogenous leukemia compound Nilotinib (trade name Tasigna) was approved.[14] Rosuvastatin, the trade names Crestor, in India Zyrova, is a member of the drug class of statins, used in combination with exercise, diet, and weight-loss to treat high cholesterol and related conditions, and to prevent cardiovascular disease.[15] Bosentan, the trade name Tracleer, is a dual endothelin receptor antagonist used in the treatment of pulmonary artery hypertension.[16] Dabrafenib, the trade name Tafinlar, is a drug for the treatment of cancers associated with a mutated version of the BRAF gene. Dabrafenib acts as an inhibitor of the associated enzyme B-Raf, which plays a role in the regulation of cell growth.[17] Pyrimethamine, the trade name Daraprim, is a medication used for protozoal infections. It is commonly used for treatment and prevention of malaria. Combined with the sulfonamide antibiotic sulfadiazine is also used in the treatment of *Toxoplasma gondii* infections in immunocompromised patients, such as HIV-positive individuals. It is also currently being evaluated in clinical trials as a treatment for amyotrophic lateral sclerosis.[18]



Imatinib Nilotinib

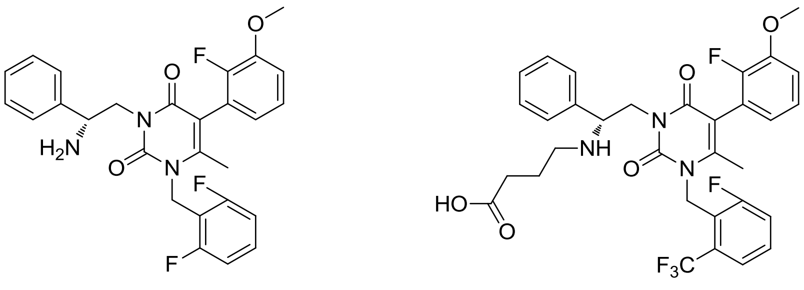
Rosuvastatin Bosentan

Dabrafenib Daraprim

Figure 2 Commercially available drugs containing a pyrimidine scaffold

Derivatives of pyrimidine nucleobase uracil have a wide range of applications and can be used for drug delivery, as pharmaceuticals, pesticides or as antiphotosynthetic herbicides. Uracil bases and nucleosides bearing aryl groups in positions 5 or 6 represent an important class of compounds displaying diverse biological activities (cytostatic, antiviral, antagonists of GnRH etc.).[19]

Several disease conditions, such as endometriosis and prostate cancer, can be treated by suppression of the pituitary-gonadal axis. Several peptide GnRH-R antagonists have become commercially available for clinical use. Non-peptide antagonists of GnRH-R represent an important new class of potential therapeutics for a range of indications, only some of which are currently addressed by peptide GnRH analogues. This field is still young and non-peptide GnRH-R antagonists are studied in recent years.[19a,19b,20] Currently, two different classes of non-peptide GnRH-R antagonists that present insurmountable antagonism have been examined in detail: uracils and thienopyrimidinediones.[21] Historically the first uracil GnRH-R antagonist was prepared by scientists from Neurocrine Biosciences.[22] The clinical development later reached compound 3-[(2*R*)-amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-5-(2-fluoro-3-methoxyphenyl)-6-methylpyrimidin-2,4-dione **I** synthetized by Struthers and co-workers, as a potent and orally active antagonist of the human gonadotropin-releasing hormone receptor (*h*GnRH-R).[23] This compound possesses a good *in vitro* profile and suppresses luteinizing hormone in serum of castrated macaques[24] and postmenopausal women after oral administration.[25] The potent and selective *h*GnRH-R antagonist (Elagolix) was discovered from a series of uracils bearing a carboxylic group. After appropriate preclinical and toxicological studies, this compound was advanced to clinical development in humans.[19c] In 2010, Abbott and Neurocrine Biosciences, Inc. announced regulatory approval for Elagolix for clinical use as a medicament of endometriosis-related pain. Elagolix thus became a novel, first-in-class oral gonadotropin-releasing hormone (GnRH) antagonist (Figure 3).



I, *h*GnRH-R antagonist

Elagolix

Figure 3 Uracil GnRH-R antagonists

1.1.2. Other applications of arylated pyrimidine nucleobases

In addition to the above mentioned biological activities, arylation in position 5 of nucleobases is often used for labeling of nucleotides, oligonucleotides, and DNA for applications in bioanalysis or chemical biology.[26]

Fluorescence labeling of biomolecules[27] and fluorescence analytical methods have recently become one of the most frequently used techniques in chemical biology.[28] The design of new fluorinated biaryl fluorescent labels and their attachment to uracil nucleosides $\mathrm{dU^R}$ and nucleoside triphosphates $\mathrm{dU^RTP}$ (Figure 4) was reported, in addition to other nucleosides and nucleoside triphosphates. All of the modified $\mathrm{dU^RTPs}$ were good substrates for KOD XL DNA polymerase and were enzymatically incorporated into DNA probes.[28] The fluorophores incorporated into DNA are able to sense the changes in the structure of the DNA strand by the increase of intensity of fluorescence during the transformation from hairpin to double strand, which has been confirmed simultaneously by ^{19}F NMR measurement. The fluorophores are also able to detect the site-specific single nucleotide mismatches in the G-rich sequence by decrease of intensity of fluorescence. However, the effects are sequencedependent.

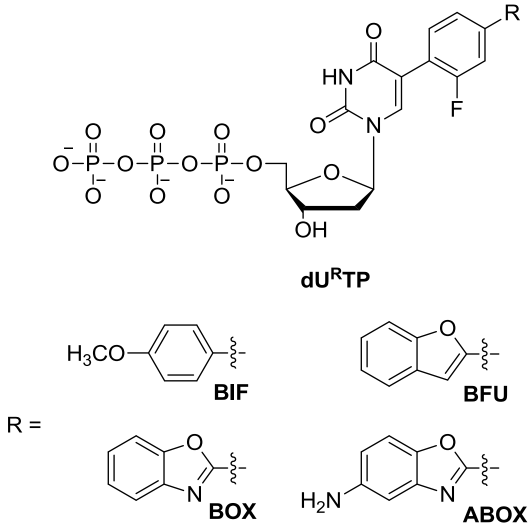
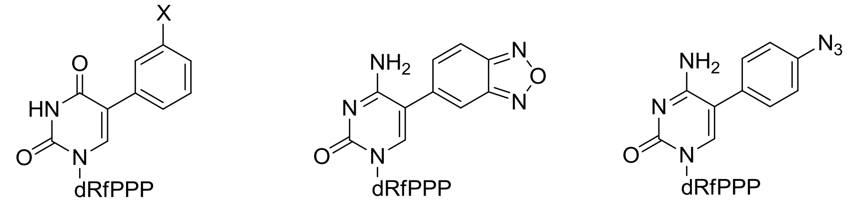


Figure 4 Fluorescent-labeled uracil nucleoside triphosphates $dU^{R}TP$

Electrochemical detection of redox-labeled DNA[29] is an alternative to fluorescence techniques for DNA sequencing and diagnostics. A single-step synthesis of aminophenyl- and nitrophenyl-containing nucleoside triphosphates (dNTPs) through cross-coupling reactions was developed, specifically also the $dU^{NH2}TP$ and $dU^{NO2}TP$ (Figure 5).[26a] The modified dNTPs were efficiently incorporated by DNA polymerases to form NH_2- or NO_2-modified oligonucleotides. Both types of modifications serve as excellent electrochemical labels detectable by either oxidation (NH_2) or reduction (NO_2), which allows perfect discrimination between the two tags incorporated in the same DNA molecule, which could be analytically useful.[26a] The benzofurazane[30] and azidophenyl group (Figure 5)[31] was also used as a reducible label for DNA. Voltammetric analysis of DNA labeled with combinations of benzofurazane, $PhNO_2$, and $PhNH_2$ as an oxidizable label revealed no significant interference between benzofurazane and $PhNO_2$ reductions and no effect of $PhNH_2$ on the signals of any of the reducible tags. The quantities of benzofurazane and $PhNO_2$ labels incorporated into a nucleotide sequence could be determined independently, and the relative intensities of their signals exhibited excellent correlation with the number of complementary bases in the template, making them applicable for ratiometric analysis of nucleotide sequences (such as electrochemical detection of mutations in a DNA stretch based on a change in the ratio of two nucleobases encoded by two different redox labels). On the other hand, $PhNH_2$ is suitable for qualitative but not (semi)quantitative ratiometric electrochemical probing of nucleotide sequences (at least when combined with benzofurazane and/or $PhNO_2$).[30]



dU^{X}TP, X = NH_2, NO_2 **dC^{BF}TP** **dC^{A}TP**

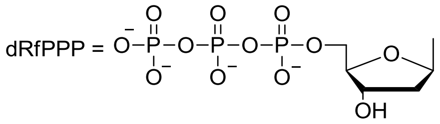


Figure 5 Redox-labeled uracil nucleoside triphosphates dU^{R}TP

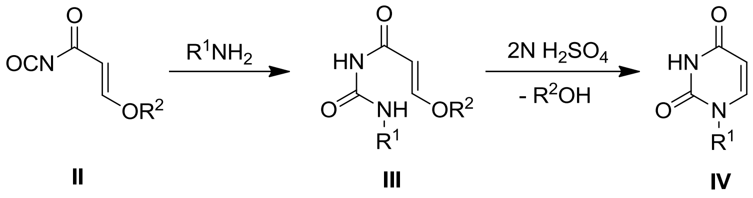
1.2. Synthesis of arylpyrimidines

1.2.1. Synthesis of pyrimidines by heterocyclization

Ring synthesis of derivatives of pyrimidine from acyclic compounds can be devided according to number of ring atoms which contribute to the formation of heterocycles. The pyrimidine ring is constructed by condensation of components bearing the desired substituents in appropriate locations. A lot of strategies of these ring syntheses have been published. Below some approaches for synthesis of derivatives of pyrimidine are mentioned.

1.2.1.1. Synthesis from the six ring atoms component

In most of these reactions the nitrogen of urea, thiourea, isothiourea, or amidine is a nucleophile for the addition to an appropriately situated electrophilic carbon. Conditions which enhance the electrophilic character of the carbon, or the nucleophilicity of the nitrogen, promote cyclization. Most commonly, this cyclization is effected by nitrogen addition to the electrophilic *β*-carbon of a Michael acceptor, and can be performed under acidic or basic conditions.[3b] This approach is commonly used for the synthesis of carbocyclic nucleosides and other N-1-substituted uracils **IV**, where the newly formed bond is between the uracil N-1 and C-6 positions.[32] The starting N-acylurea **III** is obtained by the reaction of an amine with 3-methoxy- or 3-ethoxy-2-propenyl isocyanate **II**[32a] and the overall synthesis from amine to uracil derivative can be achieved quite efficiently, when an improved synthesis of the isocyanate reagent **II** is used[32c]. Ring closure is normally performed using acid catalysis (Scheme 1).

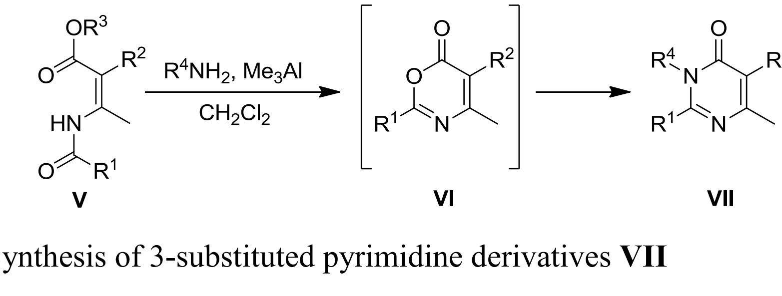


Scheme 1 Synthesis of N-1-substituted uracils **IV**

1.2.1.2. Synthesis from two components

1.2.1.2.1. Synthesis from two components of one and five ring atoms

In this type of reactions the most used one atom component is N-1, N-3, or C-2. When N-1 or N-3 is the one atom component then ring formation is effected using of reaction of a precursor with ammonia or a primary amine.[33] This synthetic strategy for preparation of 3-substituted 3*H*-pyrimidin-4-ones **VII** involves the cyclization of enamide esters **V**, derived from *β*-keto esters, with trimethylaluminium and primary amines.[34] During the reaction an oxazinone intermediate **VI** is formed, which undergoes ring opening and consecutive ring closure by reaction with the primary amine. In this synthesis aliphatic and also aromatic primary amines can be used (Scheme 2).[34]



Scheme 2 Synthesis of 3-substituted pyrimidine derivatives **VII**

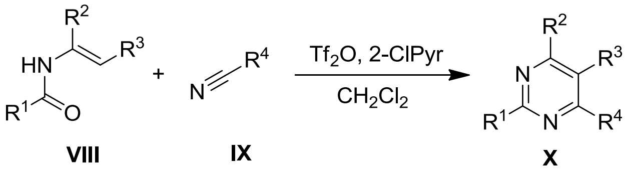
When C-2 is the one atom component in the synthetsis route, reduced pyrimidines are commonly prepared from urea and 1,3-propanediamines. Cyclic guanidines, cyclic ureas and cyclic thioureas represent frequent targets.[35]

1.2.1.2.2. Synthesis from two components of two and four ring atoms

The two-atom components usually consist from N-(C-2) or (N-3)-(C-4) or (C-4)-(C-5) atoms.

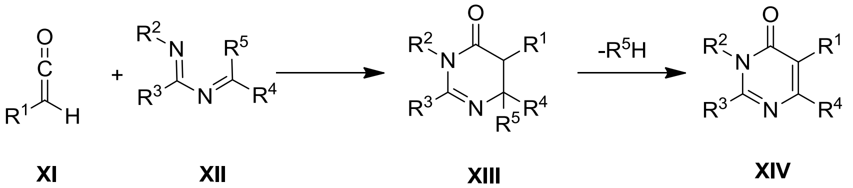
When two-atom component is consisted from N-(C-2) atoms the four-atom unit is an unsaturated *β*-amino ester, *β*-amino nitrile, *β*-amino amide, or an equivalent structure.[33a, 36]

Examples of two-atom component (N-3)-(C-4) are nitriles that condensate with wide range of secondary amides for synthesis of pyrimidine derivatives. Example of the synthesis which involves the condensation of nitriles **IX** with N-vinyl or N-aryl amides **VIII** activated by trifluoromethanesulfonic anhydride and 2-chloropyridine to form desired pyrimidine derivatives **X** is depicted in Scheme 3.[37]



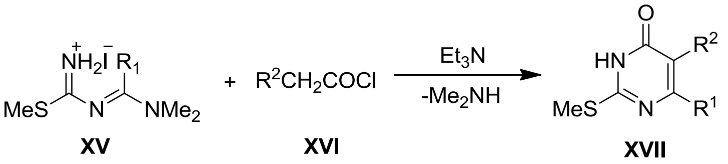
Scheme 3 Synthesis of pyrimidine derivatives **X**

When the two-atom component consists of (C-4)-(C-5) bonded carbons, the [4+2] cycloaddition of ketenes **XI** with 1,3-diazabutadienes **XII** is a well-established synthesis to 5,6-dihydro-4-pyrimidinones **XIII** and, when a leaving group is present, 4-pyrimidinones **XIV** are formed.[38]



Scheme 4 Synthesis of 4-pyrimidinones **XIV**

A variety of pyrimidine derivatives has been prepared from stable and versatile S-methyl aza- and diazadienium iodides, readily available by reaction of thioamides with methyl iodide.[39] For example, reaction of acyclic 1,3-diazadienium iodides **XV** with acyl chlorides **XVI** under [4+2] cycloaddition reaction conditions furnishes 2-methylsulfanyl-4-pyrimidinones **XVII** (Scheme 5).[39c]

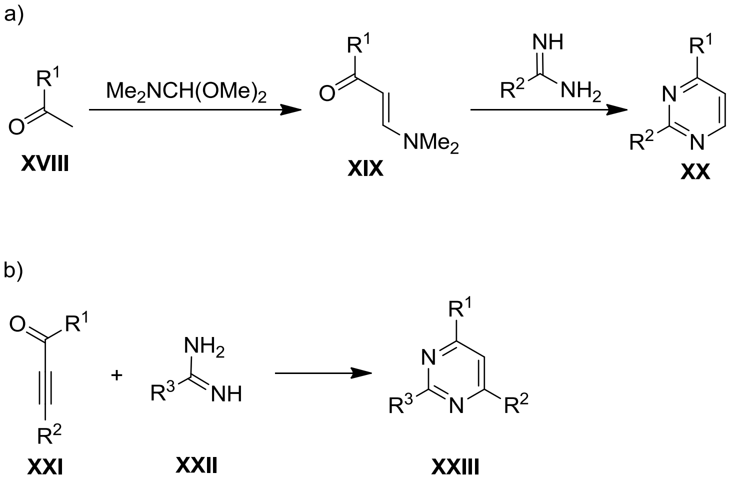


Scheme 5 [4+2] cycloaddition reaction for preparation of derivatives **XVII**

1.2.1.2.3. Synthesis from two components with three ring atoms

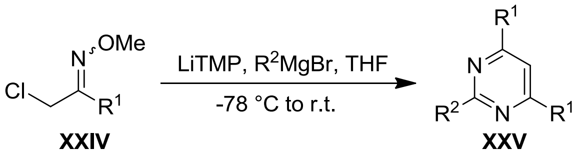
This approach represents the most important route for the preparation of pyrimidines and can be divided into two main classes: the combination of an (N-1)-(C-2)-(N-3) with a (C-4)-(C-5)–(C-6) component, and the combination of a (C-2)-(N-3)-(C-4) with a (C-5)-(C-6)-(N-l) component.

When the pyrimidine derivatives are prepared using the combination of an (N-1)-(C-2)-(N-3) with a (C-4)-(C-5)-(C-6) component, the ring atoms in the 3-carbon component are usually from a 1,3-dicarbonyl derivative (an aldehyde, a ketone, an ester, or equivalents such as an amide or a nitrile in any combination), but more recently the use of alkynyl ketones and propargylic compounds has become more common.[40, 41] The (N-1)-(C-2)-(N-3) component is most frequently an amidine, guanidine, urea, or thiourea or their equivalents. An example of this type of strategy is a commonly used procedure which involves the preparation of dimethylaminomethylene ketone **XIX** by reaction of methyl ketone **XVIII** with DMF dimethylacetal and subsequent reaction with an amidine or guanidine to form the target pyrimidine **XX** (Scheme 6a).[42] The next example of synthesis of substituted pyrimidines **XXIII** uses alkynyl ketones as a one component.[41 a-g,j] Alkyne groups can be formally considered as highly masked aldehyde or ketone equivalents. 2-Propynyl ketones **XXI** react readily with amidine derivatives **XXII** to give substituted pyrimidines **XXIII** in good yields (Scheme 6b). Recently, tandem oxidation/heterocyclocondensation of propargylic alcohols instead of alkynyl ketones were published.[40, 41h, 41i]



Scheme 6 Synthesis of substituted pyrimidines **XX** and **XXIII**

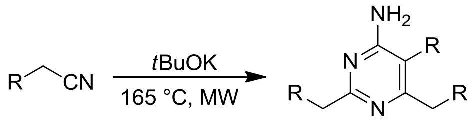
The second approach is preparation of the pyrimidine derivatives using the combination of an (C-2)-(N-3)-(C-4) component (i.a. acyl isothiocyanate) with a (C-5)-(C-6)-(N-1) component (i.a. an enamine). A newer approach to this synthetic strategy involves a dimerization of halogenated oxime ethers **XXIV** by a reaction with Grignard reagents, where the C-2 atom of the product **XXV** arises from a rearrangement that is proposed to proceed via azirene intermediates (Scheme 7).[3b, 43]



Scheme 7 Synthesis of substituted pyrimidines **XXV**

1.2.1.3. Synthesis from three components

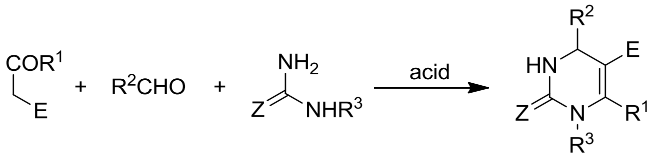
One of the possibilities of this synthetic strategy is use of a combination of (C-2)-(N-3), (C-4)-(C-5), and (C-6)-(N-1) components. In this approach the (C-2)-(N-3) and (C-6)-(N-1) components are usually the same. Formamide or nitriles represent common C-N components. A classical example is the trimerization of acetonitrile to give 2,6-dimethyl-4-pyrimidinamine,[33a] while a more recent example involves a similar trimerization of a variety of alkyl and benzylic nitriles **XXVI** under microwave conditions to form compounds **XXVII** (Scheme 8).[44]



XXVI **XXVII**

Scheme 8 Trimerization of nitriles **XXVI** to form compounds **XXVII**

The second possibility of tree components of ring atoms involves use of a combination of (N-1)-(C-2)-(N-3), (C-4)-(C-5), and C-6 components. Biginelli reaction is the most important multiple-component reaction within this subgroup, which involves reaction between methylene ketone **XXVIII**, aldehyde **XXIX**, and either urea (Z=O) or thiourea (Z=S) **XXX** to give a dihydro-2-pyrimidinone (Z=O) **XXXI** or dihydro-2-pyrimidinethione (Z=S) **XXXI**.[12, 45] Several microwave-assisted procedures have been also published (Scheme 9).[46]



XXVIII **XXIX** **XXX** **XXXI**

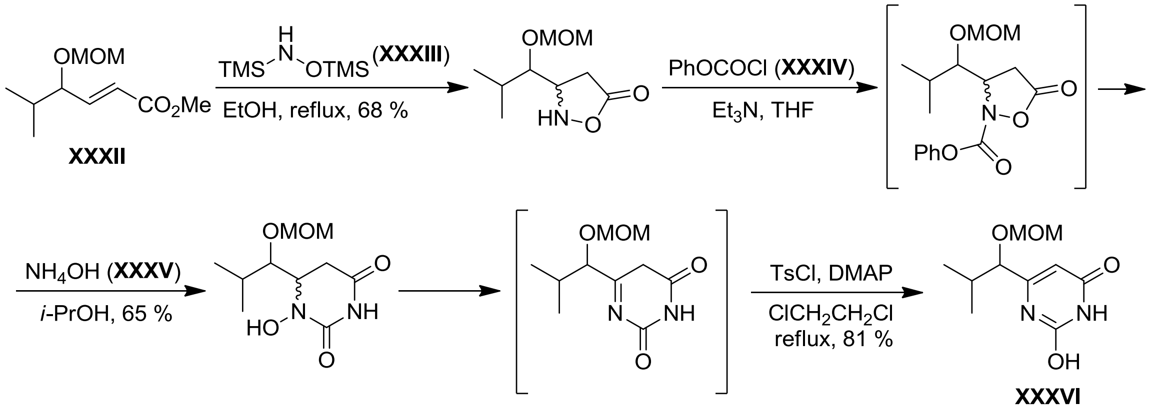
Z = O or S

Scheme 9 Biginelli reaction for preparation of derivatives **XXXI**

The third approach which utilizes tree components includes the combination of N-1, (C-2)-(N-3), (C-4)-(C-5)-(C-6) components. The three-carbon component in this subgroup is either a *β*-dicarbonyl compound or a *β*-keto nitrile. The N and C-N components in the reactions with *β*-dicarbonyl compounds come from formamide, a nitrile, a thiocyanate, or a cyanamide.[3b, 33a]

1.2.1.4. Synthesis by combination of four components

Derivatives of pyrimidine can also be formed in reactions involving multiple bond formations, and as an example the synthesis of a 6-substituted uracil derivative **XXXVI** is demonstrated. In this reaction *α*,*β*-unsaturated methyl ester **XXXII**, *N*,*O*-bis-(trimethylsilyl)hydroxylamine (**XXXIII**), phenyl chloroformate (**XXXIV**), and ammonia (**XXXV**) represent the four components of (C-4)-(C-5)-(C-6), N-1, C-2, and N-3, respectively (Scheme 10).[47] This procedure was successfully used as part of a total synthesis of the freshwater cyanobacterial hepatotoxins cylindrospermopsin and 7-epicylindrospermopsin.[48]



Scheme 10 Synthesis of 6-substituted uracil derivative **XXXVI**

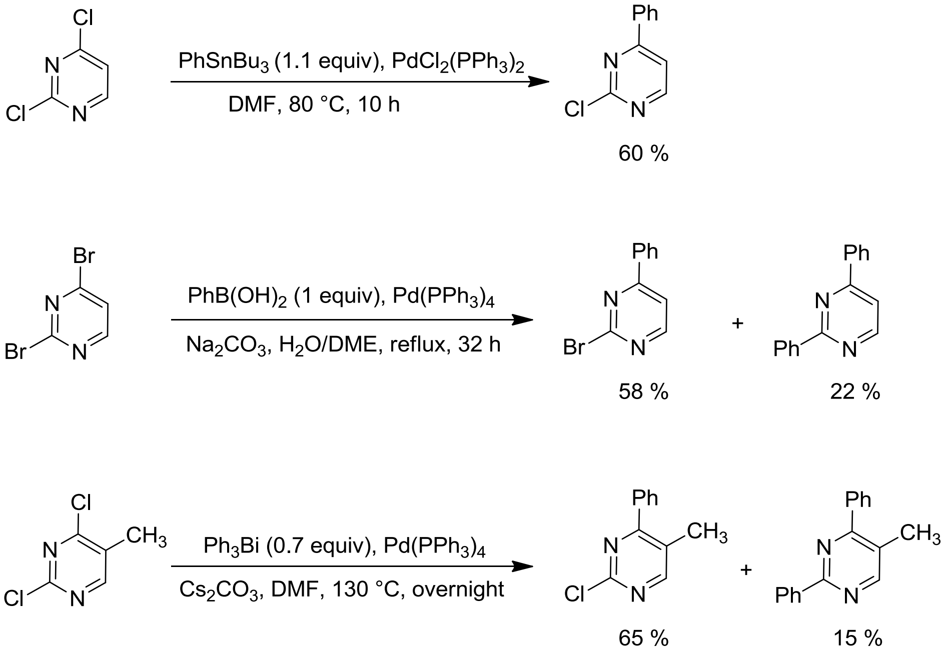
1.2.2. Synthesis of pyrimidines by cross-coupling reactions

Recently, a modification of existing substrates has become a much more feasible approach for preparation of derivatives of pyrimidine and pyrimidine nucleobases. In the last decade great advances have been done in metal catalyzed cross-coupling reactions which are utilized in this synthetic route. Since a number of pyrimidine reagents are commercially available (specially halogenated pyrimidine derivatives), this approach is particularly attractive for preparation of some types of compounds. A lot of recent studies have been interested in investigations of their selective functionalization under metal catalyzed cross-coupling procedures (such as carbonylation, acylation, cyanation, alkylation, alkenylation, alkynylation, arylation or heteroarylation), using both conventional and microwave-assisted conditions.[49] Due to the topic of my thesis, I focused on cross-coupling arylation reactions for preparation of 2,4-diarylpyrimidines and 5- or 6-arylated pyrimidine bases in this chapter.

The vast majority of transition metal catalyzed arylations of pyrimidine derivatives used palladium as the most effective catalyst in this type of reactions. A lot of different methods are available for the palladium catalyzed arylation and heteroarylation of pyrimidines including organoboron (Suzuki), organotin (Stille) and organozinc (Negishi) reaction procedures. The availability of starting materials is a determining factor for selection a suitable reaction for particular examples. Suzuki reactions are becoming more preferred in this chemistry.

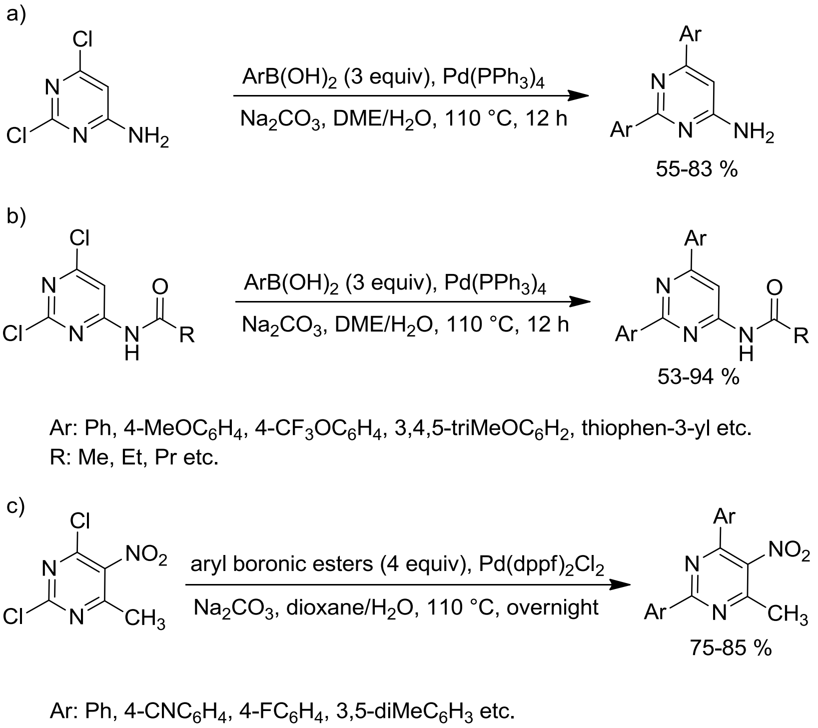
1.2.2.1. Synthesis of 2,4-diarylpyrimidines

Cross-coupling reactions between pyrimidine halides or pseudohalides and organometallic reagents are much more common than reactions of metallopyrimidines with (het)aryl halides, due to better availability of pyrimidine (pseudo)halides as starting materials. 2,4-Dihalopyrimidines undergo regioselective or chemoselective cross-coupling reactions. Many detailed studies of the selectivity of couplings at positions 2 or 4 of the pyrimidine ring have been examined. It has been found that the 4-position is more reactive than the 2-position resulting in the regioselective coupling of 2,4-dihalopyrimidines as depicted in examples in Scheme 11.[50, 51]



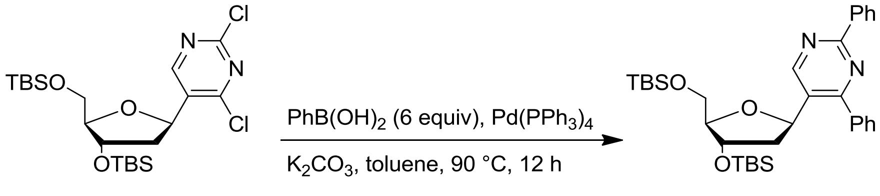
Scheme 11 Regioselective cross-couplings of 2,4-dihalopyrimidines with organometallic reagents

2,4-Diarylpyrimidine derivatives containing the same aryl substituents are synthesized easily using cross-couplings with the excess of organometallic compound as a coupling partner. Recently, the highly reliable and well-established Suzuki-Miyaura cross-coupling reactions have been generally used for preparation of 2,4-diarylated pyrimidine derivatives in order to afford library of derivatives for screening of their biological activities.[52] Examples of this approach exploit palladium catalyzed arylations using commercially available boronic acids (Scheme 12 a,b)[52b,c,d] or boronic esters (Scheme 12 c)[52e] as organometallic partners.



Scheme 12 Suzuki-Miyaura cross-couplings of 2,4-diarylpyrimidine derivatives

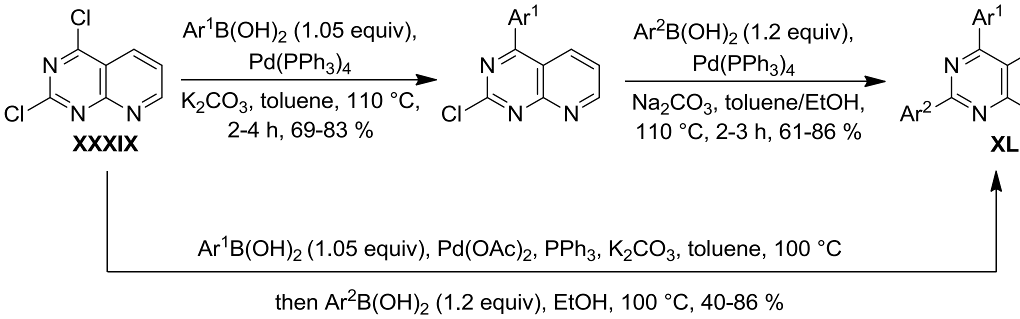
Suzuki-Miyaura cross-coupling was also successfully applied in nucleoside chemistry. For example, 2,6-dichloropyrimidin-5-yl *C*-nucleoside **XXXVII** in reaction with phenyl boronic acide afforded 2,4-diphenylpyrimidin-5-yl *C*-2′-deoxyribonucleoside **XXXVIII** in 61% yield (Scheme 13).[53]



XXXVII **XXXVIII**, 61 %

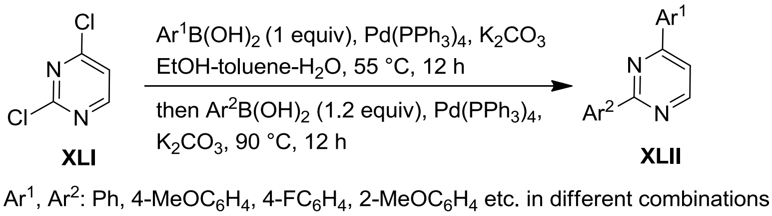
Scheme 13 Suzuki-Miyaura cross-coupling of 2,6-dichloropyrimidin-5-yl *C*-nucleoside **XXXVII**

The cross-coupling methods are less efficient if different substituents have to be installed to the pyrimidine ring. The selective and sequential palladium catalyzed reactions are usually used to prepare rare dissymmetrical 2,4-bis(het)arylpyrimidines. The regioselective C-4 arylation occurred using the Suzuki-Miyaura or Stille cross-couplings,[54] indicating the lack of reactivity of the 2-Cl versus the 4-Cl atom. The second chlorine at C-2 position can be repleaced by a new coupling reaction to form the carbon disubstituted pyrimidines containing different aryl substituents. Scheme 14 depicts two consecutive palladium catalyzed Suzuki-Miyaura couplings for designed 2,4-di(het)aryl-pyrido[3,2-*d*]pyrimidines **XL**.[54 b] The one-pot regioselective diarylation of 2,4-dichloro-pyrido[3,2-*d*]pyrimidine **XXXIX** by double Suzuki–Miyaura cross-coupling was also described for the introduction of two different (het)aryl groups to the pyrimidine ring and use sequentional addition of different boronic acides (Scheme 14).[55]



Scheme 14 Consecutive Suzuki-Miyaura couplings and the one-pot double Suzuki-Miyaura coupling of 2,4-dichloro-pyrido[3,2-*d*]pyrimidine **XLV**

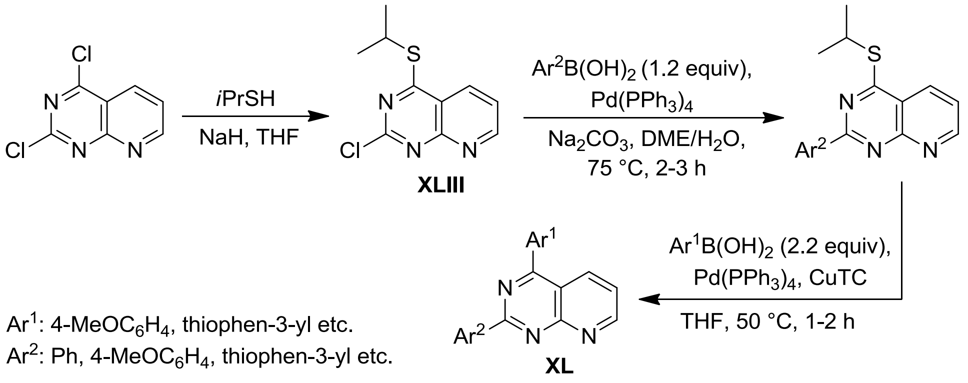
A regioselective double Suzuki coupling of 2,4-dichloropyrimidine **XLI** for preparation of compounds **XLII** was also described (Scheme 15).[56]



Scheme 15 One-pot double Suzuki-Miyaura coupling of 2,4-dichloropyrimidine **XLI**

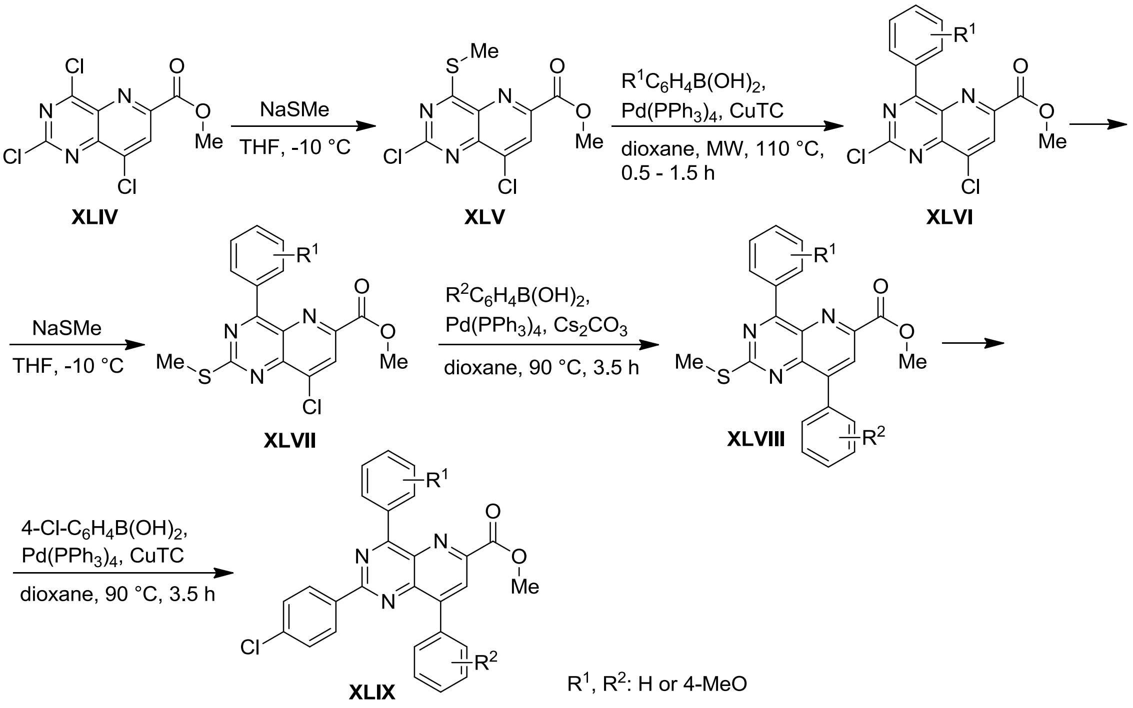
In many cases of synthesis of some 2,4-di(het)arylpyrimidines by consecutive double Suzuki reactions, the regioselectivities were not complete and/or yields were moderate.

In addition to halogens, methylthio, isopropylthio and phenylthio groups have also been shown to be replaceable under modified Stille or Suzuki-Miyaura conditions when a copper source such as copper(I) 3-methylsalicylate (CuMeSal) or copper(I) bromide-dimethyl sulfide was utilized in at least stoichiometric amounts.[57,3b] Therefore, the other approach to prepare dissymmetrical 2,4-bis(het)arylpyrimidines is based on the protection of the C-4 position with the isopropylsulfanyl group[54] and the synthesis involves two sequential (het)aryl transfers starting from the 2-chloro-4-isopropylsulfanylpyrimidine derivative by palladium insertion first into the C-Cl bond and then into the C-S bond. At first the Suzuki-Miyaura or Stille cross-couplings provide regioselective C-2 arylated compounds and subsequently the second palladium cross-coupling reaction requires the presence of copper(I) cofactors according to coupling conditions reported by Liebeskind. Scheme 16 depicts the sequential displacement of the C-2 chlorine atom of compound **XLIII** using Suzuki-Miyaura coupling followed by the elimination of the C-4 isopropylsulfanyl group using Liebeskind coupling for preparation of **XL**.[54b]



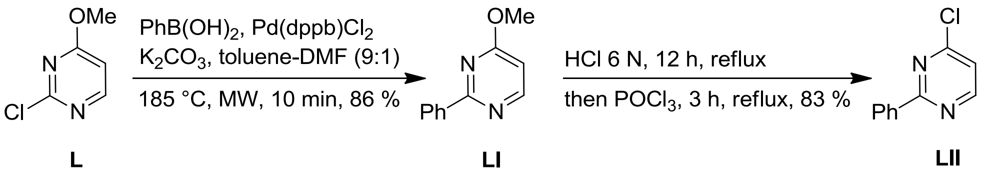
Scheme 16 Synthesis of dissymmetrical 2,4-bis(het)arylpyrimidine derivatives **XL**

Selective displacement of the different chlorides in compound **XLIV** using metal catalyzed cross-coupling reactions was also investigated (Scheme 17).[58] In this aproach Suzuki-Miyaura cross-coupling reaction, using various reaction conditions yielded either partial conversion or multiple product mixtures. Alternative cross-coupling reactions of derivative **XLIV** such as Stille cross-coupling reactions were not successful either. As a possible option Liebeskind-Srogl cross-coupling reaction has been shown. Sulfur nucleophilic addition was performed regioselectively at C-4 and led to compound **XLV**, which was subjected to arylation via Liebeskind-Srogl cross-coupling reaction with boronic acids. This two-step process, methylsulfanyl aromatic substitution followed by Liebeskind-Srogl cross-coupling reaction, yielded the selective arylation at position 4 to form compound **XLVI**. The consecutive arylation of derivative **XLVI** via metal catalyzed cross-coupling reactions provided either partial conversion or multiple side reactions. Therefore, the two remaining chlorides were differentiated by selective thiolation at C-2 to form compounds **XLVII**, wich were subsequently transformed by Suzuki−Miyaura reaction into **XLVIII**. Then, the Liebeskind−Srogl reaction was used for the introduction of an aryl at C-2 to form the final compounds **XLIX** (Scheme 17).



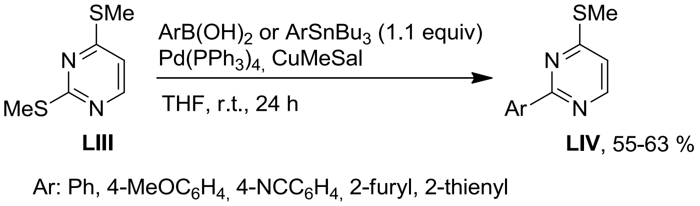
Scheme 17 Selective arylations of the different chlorides in compound **XLIV**

In order to reverse the order of reactivity, methoxy group can be used as masked chlorine atom in 4-C position and then the cross-coupling reaction proceeds at 2-C position. Palladium catalyzed cross-coupling of 2-chloro-4-methoxypyrimidine (**L**) with phenylboronic acid under microwave-assisted conditions gave 2-phenyl derivative **LI**, which was then converted to 4-chloro-2-phenylpyrimidine (**LII**) by hydrolysis and chlorination with $POCl_3$ (Scheme 18) and can be subsequently used in another cross-coupling reactions.[59]



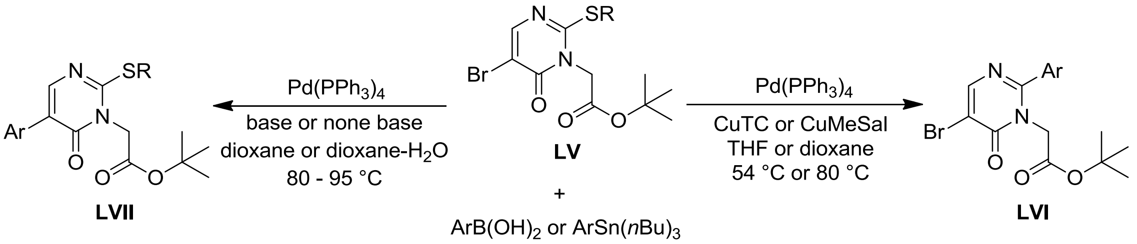
Scheme 18 Cross-coupling of 2-chloro-4-methoxypyrimidine (**L**)

Unusual regioselectivity was achieved under Pd-catalyzed Suzuki or Stille cross-coupling reactions of 2,4-bis(methylsulfanyl)pyrimidine (**LIII**) with aryl boronic acids or organostannanes in the presence of Liebeskind–Srogl Cu(I) cofactor.[60] 2-Aryl-4-(methylsulfanyl)pyrimidines **LIV** (55-63 %) were formed as the major products, so the opposite regioselectivity in comparison to 2,4-dichloropyrimidine derivatives was observed (Scheme 19). Under these conditions, small amounts (3-4 %) of products forming from coupling at the 4-position were isolated under Suzuki conditions with phenylboronic acid, 4-methoxyphenylboronic acid or 4-cyanophenylboronic acid. Also, no 4-arylated products were obtained using the Stille reaction with tributyl(2-furyl)stannane, tributyl(2-thienyl)stannane or tributyl(4-methoxyphenyl)stannane. Small amounts (2 - 6 %) of the disubstituted products were isolated using both Suzuki and Stille reactions.



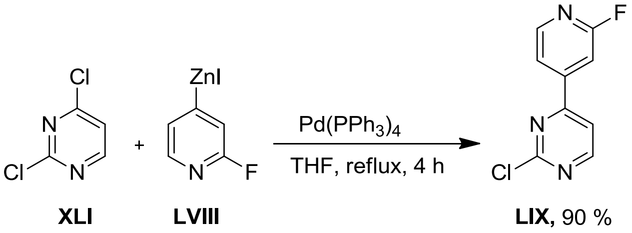
Scheme 19 Regioselective Suzuki or Stille cross-couplings of 2,4-bis(methylsulfanyl)pyrimidine (**LIII**)

The mechanistic differences between the Suzuki-Miyaura or Stille cross-coupling of halides compared to the Liebeskind-Srogl protocol for thioorganics were used for selective introducing the aryl group to 5-bromo-2-methylthiopyrimidinone **LV**. The selective palladium catalyzed replacement of the methylthio group furnished derivatives **LVI**, in the reaction with either arylboronic acids or arylstannanes in the presence of CuMeSal or copper(I) thiophene-2-carboxylate (CuTC). However, in the absence of the copper cofactor, standard Suzuki or Stille coupling reactions prevailed, with selective replacement of the bromine rather than the methylthio group leading to 5-aryl derivatives **LVII**. Therefore, coupling chemistry can be switched on and off between halide and methylthio positions by employing a base or a Cu(I) carboxylate cofactor according to needs (Scheme 20).[62a]



Scheme 20 Cross-coupling reactions of 5-bromo-2-methylthiopyrimidinone **LV**

Negishi cross-coupling reactions using organozinc reagents are the preferred procedure in those cases where Sukuki reactions cannot be used, or perform poorly, due to the nonavailability or instability of heteroaryl boronates.[61] Therefore, for example, the cross-coupling of 2,4-dichloropyrimidine (**XLI**) with (2-fluoropyridin-4-yl)zinc iodide (**LVIII**) gave a 90 % yield of the 4-substituted pyrimidine product **LIX** (Scheme 21).[61]



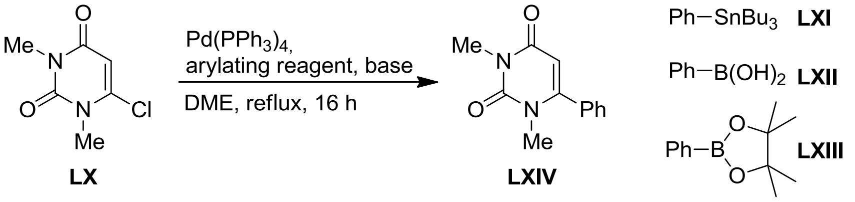
Scheme 21 Negishi cross-coupling of 2,4-dichloropyrimidine (**XLI**)

1.2.2.2. Synthesis of 5- or 6-aryluracils

5- Or 6-aryluracils can be prepared by cross-coupling reactions[62] of halouracils with organometallic reagents such as arylboronic acids or -stannanes or by cross-coupling reactions of metalated uracils with aryl halides. The first approach is much more feasible and more often used for preparation of arylated uracil derivatives.

1.2.2.2.1. Cross-couplings of halouracils with organometallic reagent

As an example of a cross-coupling reaction between halouracil and organometallic reagent a reaction of 6-chloro-1,3-dimethyluracil (**LX**) with tributylphenylstannane (**LXI**) can be mentioned. The reaction leads to formation of derivative **LXIV** (Scheme 22).[63] The C-C bond formation was investigated using $Pd(PPh_3)_4$ as a catalyst in a reaction with other two commercially available arylating reagents, including phenylboronic acid (**LXII**) and phenylboronic acid pinacol ester (**LXIII**) (Scheme 22) and were compared with tributylphenylstannane (**LXI**). The survey of reaction conditions showed that both Suzuki-Miyaura and Stille coupling reactions led to fomation of **LXIV** in excellent yields under various conditions.[63]

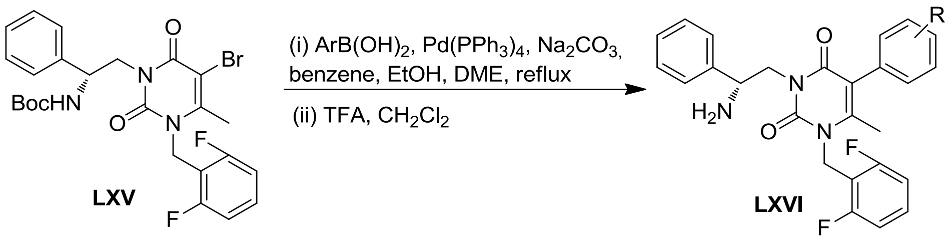


arylating reagent	base	yield (%)
LXI	2 M Na_2CO_3[a]	86
LXII	2 M Na_2CO_3[a]	73
LXII	DBU	59
LXIII	2 M Na_2CO_3[a]	94
LXIII	DBU	59

[a] 2 M in H_2O

Scheme 22 Cross-couplings of 6-chloro-1,3-dimethyluracil (**LX**)

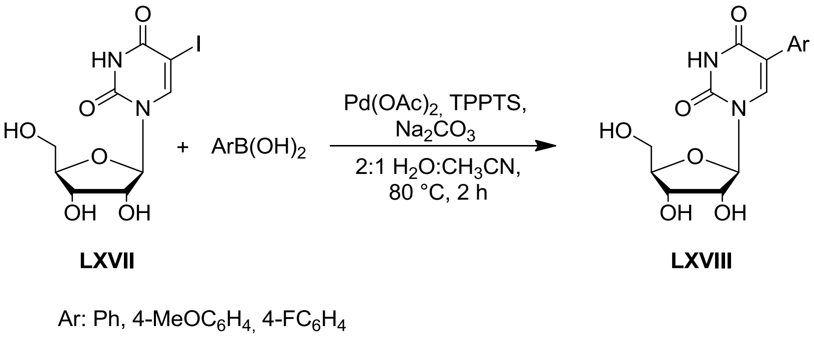
Suzuki-Myaura coupling between halouracils and boronic acids or boron pinacol esters is the most commmon process for the preparation of 5- or 6-arylated uracil derivatives.[23, 64] Syntesis of a series of 5-arylated compounds syntetized to explore the SAR of the compounds as potent antagonists of the hGnRHR was done.[23] 5-Bromouracil derivative **LXV** bearing a *R*-2-aminophenethyl side chain was subjected to Suzuki-Myaura coupling reactions with various substituted phenylboronic acids and after deprotection compounds **LXVI** were formed (Scheme 23).



R: 3-MeO, 3,4-OCH$_2$O, 2-Cl etc.

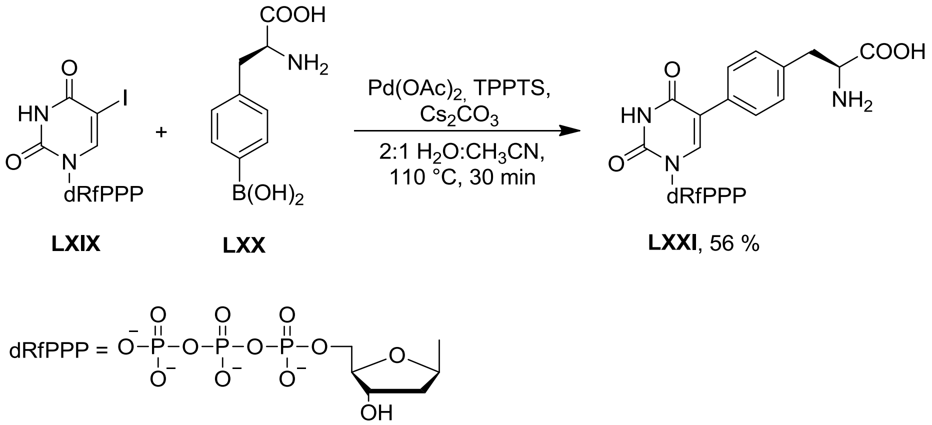
Scheme 23 Suzuki-Myaura cross-coupling reactions of 5-bromouracil **LXV**

Cross-coupling reaction is also efficient methodology for the introduction of carbon substituents into nucleosides.[65] The reactions were usually performed in organic solvents on protected nucleosides, but the development of Shaughnessy's[66] aqueous-phase cross-coupling reactions using the water-soluble P(*m*-$C_6H_4SO_3Na)_3$ (TPPTS) ligand enabled efficient direct modification of unprotected halonucleosides. For example, 5-iodo-2′-deoxyuridine (5-IdU) (**LXVII**) was coupled with arylboronic acids to give 5-aryl-2′-deoxyuridine adducts (5-ArdU) **LXVIII** in a 2:1 water:acetonitrile solvent mixture (Scheme 24).[66a]



Scheme 24 Suzuki-Miyaura cross-couplings of nucleoside 5-IdU (**LXVII**)

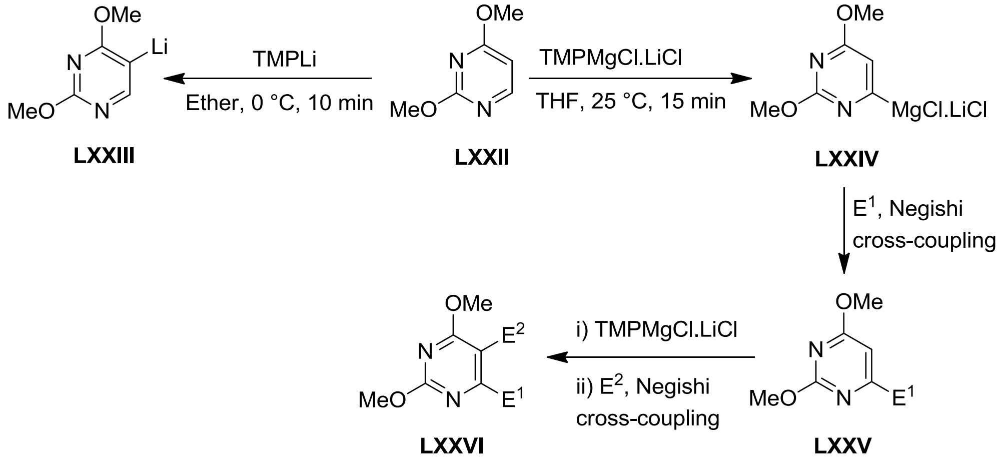
A single-step aqueous-phase Suzuki–Miyaura cross-coupling reaction was extended to functionalization of halogenated nucleoside triphosphates in reaction with boronophenylalanine **LXX**.[67] This method does not require protection of any of the reaction components and allows expeditious and simple modifications of triphosphates with functionalized aryl groups. The corresponding reaction of boronic acid **LXX** with 5-iodo-2′-deoxyuridine triphosphate (5-IdUTP) (**LXIX**) was carried out at 110 °C in the presence of Cs_2CO_3 as a base and gave the phenylalanine–dUTP conjugate **LXXI** (Scheme 25).



Scheme 25 Aqueous-phase Suzuki-Miyaura cross-coupling of 5-IdUTP (**LXIX**)

1.2.2.2.2. Cross-couplings of metalated uracils with aryl halides

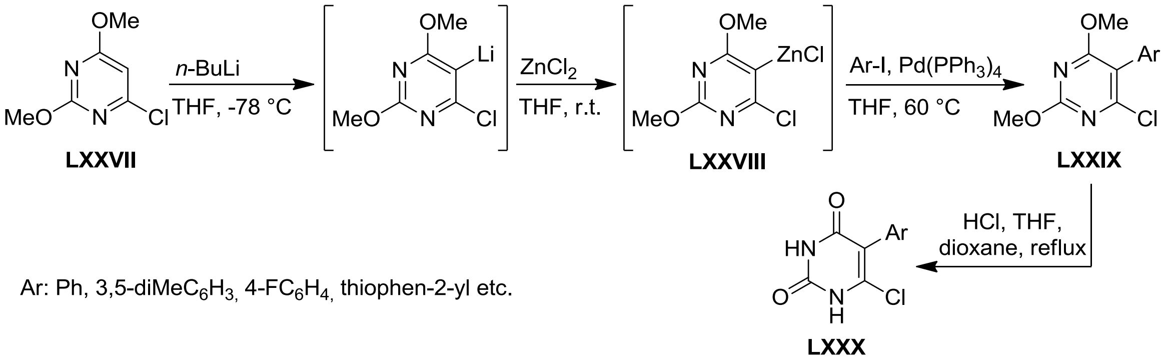
Negishi cross-coupling reactions of zincated uracils with various (het)aryl halides was described, wherein zinc reagents are formed by a transmetalation from lithiated or magnesiated compounds *in situ*. The regio- and chemoselective functionalization of protected uracils and thiouracils has been reported using magnesiations with TMPMgCl.LiCl and consequtive reaction with electrofiles.[62c] While the lithiation of 2,4-dimethoxypyrimidine (**LXXII**) with TMPLi[68] provided exclusively the 5-lithiated pyrimidine **LXXIII**, the treatment of **LXXII** with TMPMgCl.LiCl gave exclusively the 6-magnesiated uracil derivative **LXXIV** (Scheme 26). The consecutive formation of the 6-arylpyrimidines **LXXV** was readily performed by a Negishi cross-coupling reaction (transmetalation with $ZnCl_2$ followed by the addition of $Pd(dba)_2$ and P(*o*-furyl)$_3$ with various electrofiles (e.g. ethyl 4-iodobenzoate). Subsequent magnesiation of uracils **LXXV** allows further functionalization in position 5 providing 5,6-disubstituted uracils **LXXVI**.



Scheme 26 Metalations of 2,4-dimethoxypyrimidine (**LXXII**), transmetalation and consecutive Negishi cross-coupling reactions

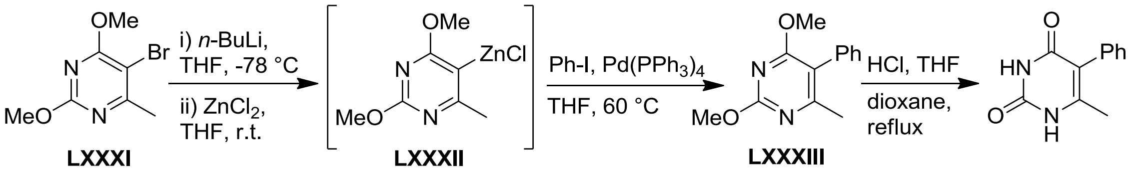
The direct lithiation step was utilized in the synthetic approach for preparation of 5-arylated-6-chlorouracils **LXXX** starting from commercially available 4-chloro-2,6-dimethoxypyrimidine (**LXXVII**).[62 b] The lithiation and consecutive transmetalation with zinc chloride in THF at room temperature gave the corresponding organozinc reagent **LXVIII**. Subsequent Negishi couplings with aryl halides using

$Pd(PPh_3)_4$ as a catalyst provided derivatives bearing aromatic substituents **LXXIX** at the C5-position (Scheme 27).



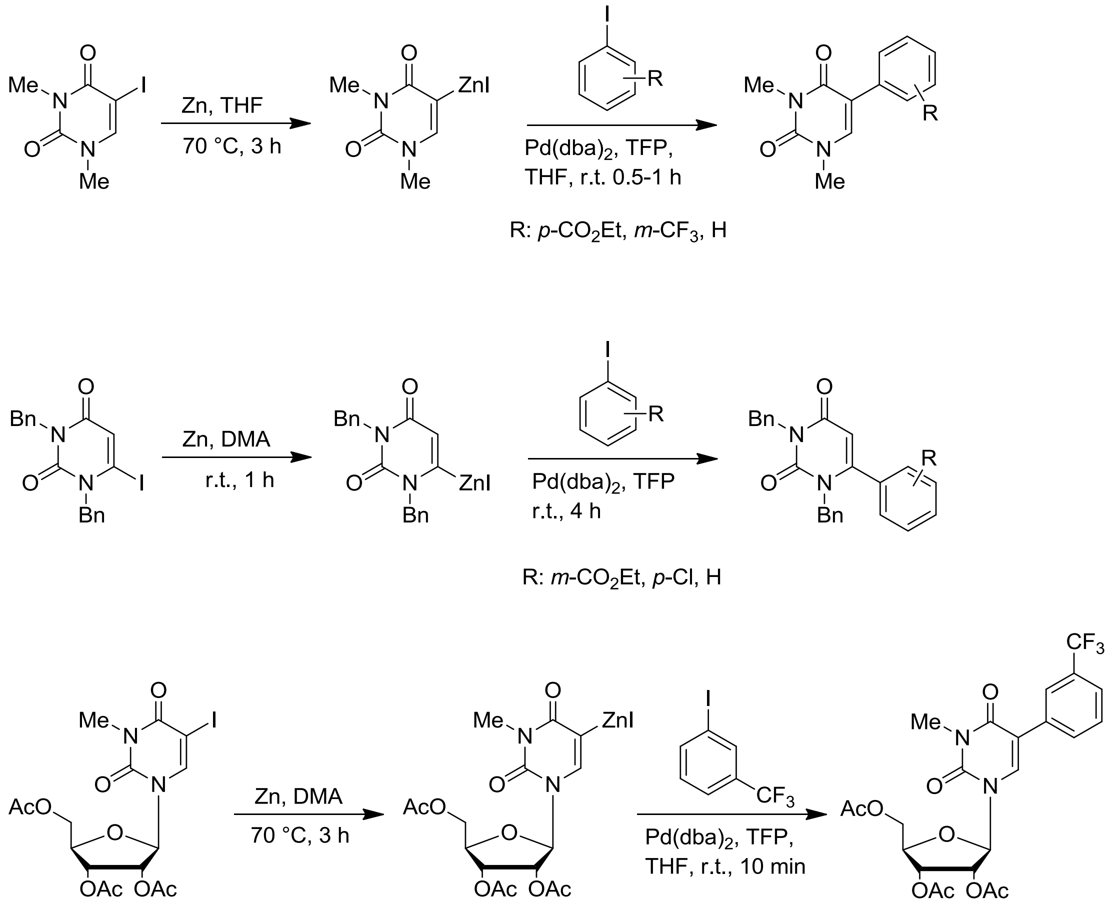
Scheme 27 Lithiation and transmetalation of 4-chloro-2,6-dimethoxypyrimidine (**LXXVII**) and consecutive Negishi cross-coupling reactions

Several 5- or 6-lithiated pyrimidines have been synthesized also via halogen–metal exchange reactions. For example, the 5-bromo-2,4-dimethoxy-6-methylpyrimidine (**LXXXI**) was lithiated and subsequently converted to organozinc reagent **LXXXII** which was subjected to Negishi coupling to form 6-methyl-5-phenyl derivative **LXXXIII** (Scheme 28).[62b]



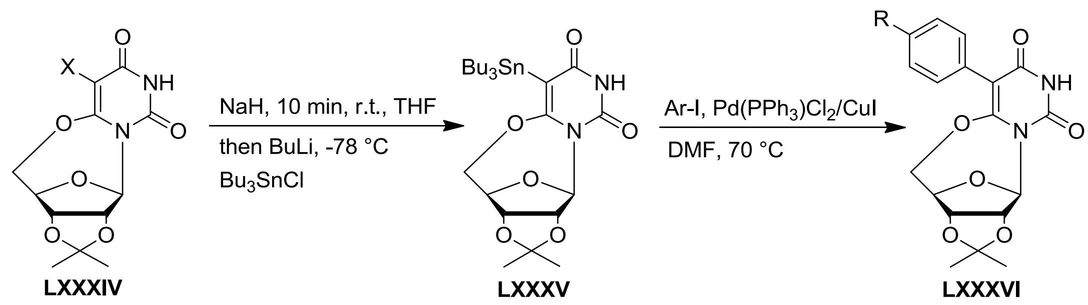
Scheme 28 Lithiation and transmetalation of 5-bromo-2,4-dimethoxy-6-methylpyrimidine (**LXXXI**) and consecutive Negishi cross-coupling

Zincated uracil bases and nucleosides can be formed from iodides using zinc dust in polar solvent like DMA or THF[69], and then readily undergo palladium catalyzed cross-coupling reactions with various aryl iodides in the presence of $Pd(dba)_2$ and tri(2-furyl)phosphine (Scheme 29).[69]



Scheme 29 Pd-catalyzed cross-coupling reactions of uracil derivatives

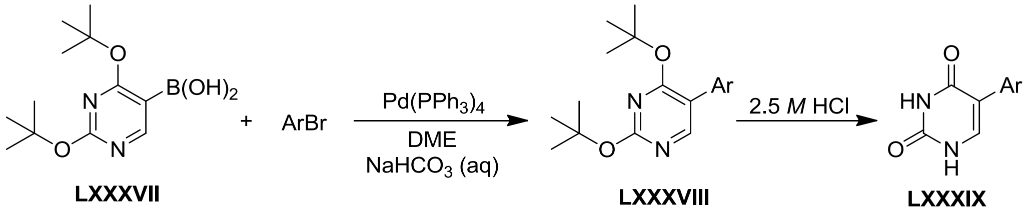
The next approach for preparation of arylated uracil derivatives **LXXXVI** uses organostannyl compounds which are subjected to the Stille coupling. The example of this type of synthesis started from 5-halogenated nucleosides **LXXXIV** which were converted by halogen–metal exchange to lithiated pyrimidine using n-butyllithium at -78 °C. Transmetalation with a large excess of tributylstannyl chloride gave 5-tri-(*n*-butylstannyl)-2',3'-isopropylidene-6,5'-*O*-anhydrouridine (**LXXXV**) which was subjected to the Stille coupling under Pd(0) conditions with several aryl iodides and finally desired C5-arylated cyclouridines **LXXXVI** were formed (Scheme 30).[70]



X: I, Br
R: H, OMe, F, CF_3

Scheme 30 Pd-catalyzed Stille coupling for preparation C5-arylated cyclouridines **LXXXVI**

2,4-Dialkoxypyrimidine-5-boronic acids represent examples of metalated uracils which can react with aryl halides in cross-coupling reactions. (2,4-Di-*tert*-butoxypyrimidin-5-yl)boronic acid (**LXXXVII**) represents an example of masked uracil derivative which can be used directly in Suzuki cross-coupling reactions to form compounds **LXXXVIII**. Subsequent hydrolyzis of **LXXXVIII** gives the dione form **LXXXXIX** (Scheme 31).[71]



Ar: 5-bromofuran-2-yl, 5-bromothiophen-2-yl, 3-bromophenyl, 6-bromopyridin-2-yl etc.

Scheme 31 Suzuki cross-coupling reactions of (2,4-di-*tert*-butoxypyrimidin-5-yl)boronic acid (**LXXXVII**)

1.3. Direct C-H arylations

1.3.1. Transition metal catalyzed direct arylations vs cross-couplings

Traditional cross-coupling reactions have contributed significantly to the formation of new carbon-carbon bonds and to the synthesis of biaryl compounds. Over the years, impressive improvements have been made in the discovery of transition metal catalyzed cross-coupling reactions, specially the Pd-catalyzed couplings between aryl halides or pseudohalides and organometallic reagents.[72] The most popular cross-couplings are known as the Suzuki-Miyaura (B),[73] Stille (Sn),[74] Hiyama (Si),[75] Negishi (Zn),[76] Corriu–Kumada (Mg)[77] coupling for preparation of bi(hetero)aryl compounds. Cross-coupling reactions require prefunctionalization of both coupling partners and typically involve the coupling of an aryl(pseudo)halide with stoichiometric amount of organometallic reagent (Figure 6, Pathway A). Furthermore, pre-activation of reagents usually involves a number of synthetic operations, which can be time consuming and expensive.

Direct C-H arylations[78] have recently emerged as an alternative to traditional cross-couplings, and our group[79] and also others[80] have repeatedly shown that they are complementary and could be used for multiple substitutions of diverse (hetero)arenes. Transition metal catalyzed direct arylation can be divided according to the character of the coupling partners into direct arylations with aryl (pseudo)halides as one coupling partner (Figure 6, Pathway B) and oxidative arylations (Figure 6, Pathway C). Oxidative arylations can be achieved either with organometallic reagents (Figure 6, Pathway Ca) or directly with (hetero)arene (Figure 6, Pathway Cb), however in this dehydrogenative arylation the regioselectivity could be difficult to obtain and often requires presence of a directing group. Therefore, the direct arylations with easily accessible aryl (pseudo)halides have become the most popular approach in bi(hetero)aryl synthesis so far.

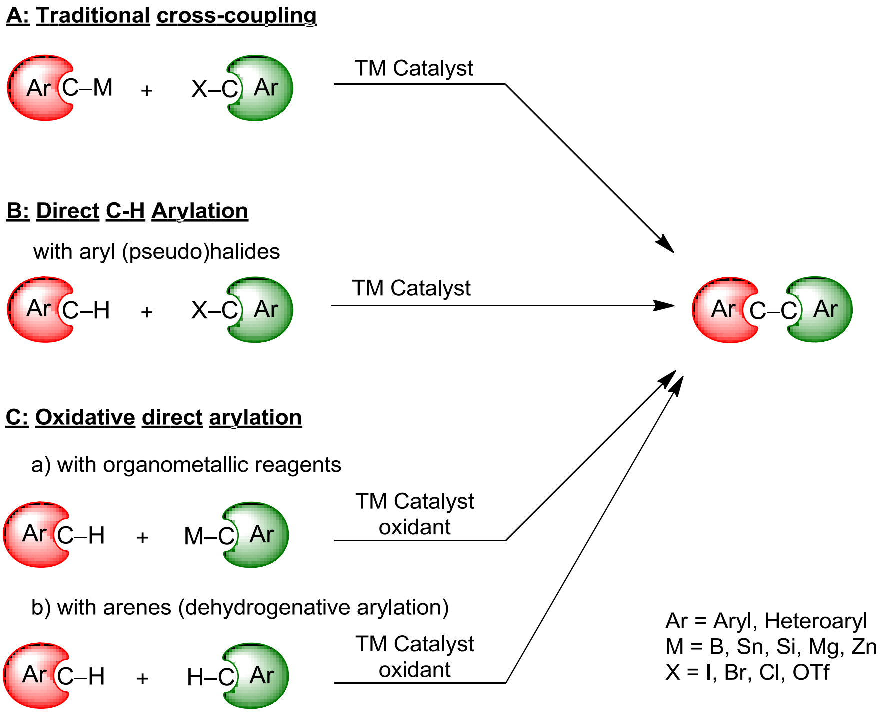


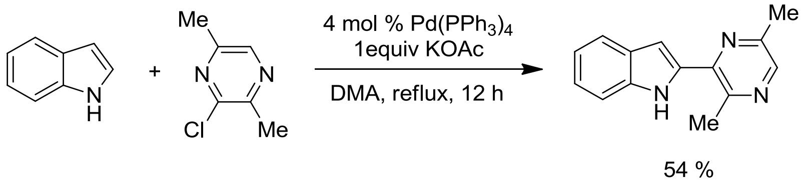
Figure 6 Possible pathways in bi(hetero)aryl bond formation

Major challenges associated with C-H functionalization reactions include: (*i*) the need for developing regioselective activation of specific C-H bonds in the presence of other C-H bonds; (*ii*) low chemoselectivity which means it is necessary to protect sensitive functional groups before performing the coupling; and (*iii*) the necessity to work at high temperature that is needed to activate C-H bonds with intrinsic low activity, which often causes decomposition of the substrates.[81]

1.3.1.1. Direct arylations with aryl(pseudo)halides

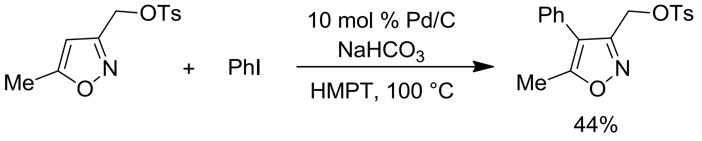
Extensive research has resulted in the development of efficient methodologies for C-H arylation of diverse aromatics and heterocycles.[78a, 101, 82, 94, 97]. Although a number of transition metal complexes were used as catalysts, the second-row transition metals palladium[82c,d], rhodium[83, 821] and ruthenium[84] are most commonly used catalysts. Also copper, iron, and nickel complexes are effective in direct arylation. These methodologies eliminate the use of organometallic substrates and require only one activated substrate and C-H activation at the second substrate. Homogenous Pd complexes (i.e. $PdCl_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$), are the most versatile catalysts, successful in most cases in combination with ligand (i.e. PPh_3, Buchwald's biphenylphosphines, *N*-heterocyclic carbene ligands), a base (i.e. K_2CO_3, Cs_2CO_3, KOAc, *t*-BuOK, CsOPiv), and high-boiling point polar aprotic solvent (i.e. DMF, DMA, CH_3CN, NMP, DMSO). High reaction temperatures (>100°C), Pd loading (5-20 mol %) and heating for several hours to days are usually required because of relative inertness of the C-H bonds caused by their high dissociation energy. Reactions at room temperature[85] or at low catalyst loading (0.1-1mol %)[86] have also been described. In some cases the microwave heating was applied as a time-saving alternative.[87]

The first C-H arylation of a heterocycles using homogenous Pd catalysis was published by Akita and Ohta utilizing tetrakis(triphenylphosphine)palladium as catalyst (Scheme 32).[88]



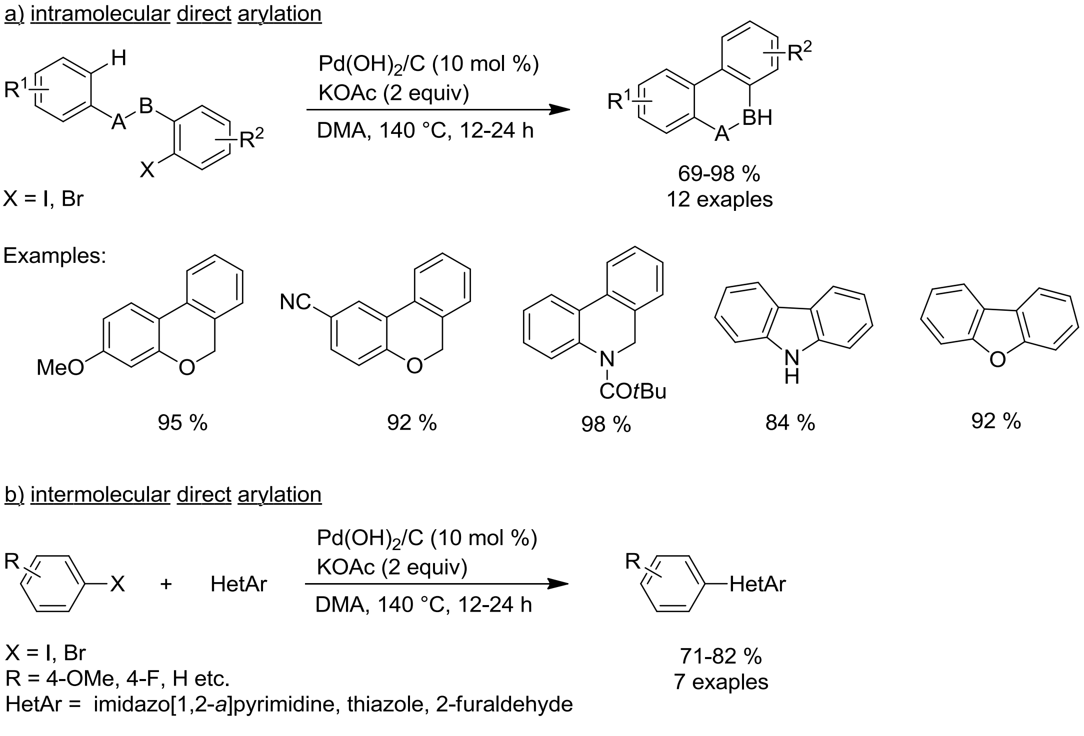
Scheme 32 Homogenous Pd-catalyzed C-H arylation

In recent literature of heterogenous catalysts are also likely to be used.[89] The first example of heterogenous arylation of heterocycles was published by Nakamura and co-workers and it was performed on substituted electron-rich isoxazoles with iodobenzene using Pd/C as the catalyst in HMPT at 120 °C (Scheme 33).[90]



Scheme 33 Heterogenous Pd-catalyzed C-H arylation

The group of Fagnou introduced palladium hydroxide on carbon (Pearlman's catalyst), as an efficient heterogenous catalyst for the intra- and intermolecular direct arylation reaction of arenes and heteroarenes, respectively (Scheme 34).[82e] It was discovered that a homogeneous catalyst species are generated under the reaction conditions and that these species are responsible for the observed catalysis. The use of heterogenous catalysts gives the advantage that the catalyst can be removed by simple filtration allowing product isolation without traces of transition metal and ligand, which are challenging to remove. These attributes make use of these catalysts interesting mainly in the pharmaceutical industry.



Scheme 34 Intra- and intermolecular direct arylations of arenes and heteroarenes

1.3.1.2. Reaction mechanisms of direct arylations

A lot of mechanistic investigations of the direct arylation have been carried out. The generally accepted mechanism for palladium catalyzed direct arylation of aryl halides with simple arenes is depicted in Figure 7. The active Pd(0) catalyst undergoes oxidative insertion into the aryl halide, followed by C-H bond cleavage of arene. Reductive elimination provides the desired biaryl product and regenerates the active Pd(0) catalyst.[91]

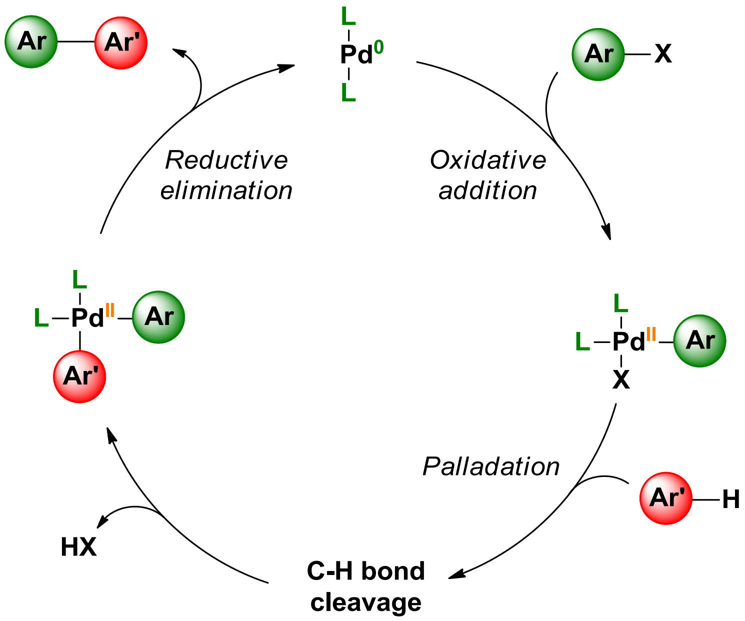
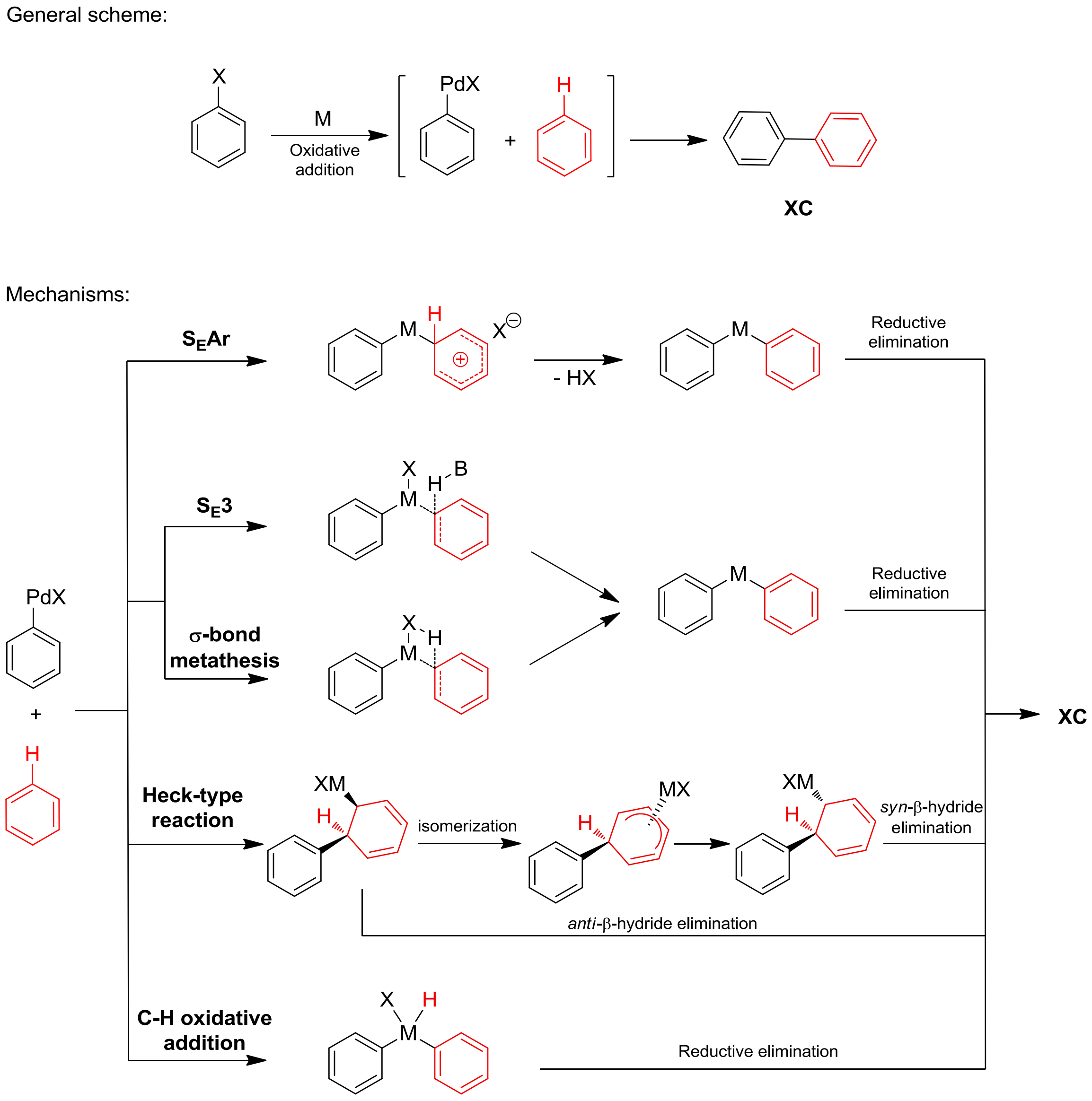


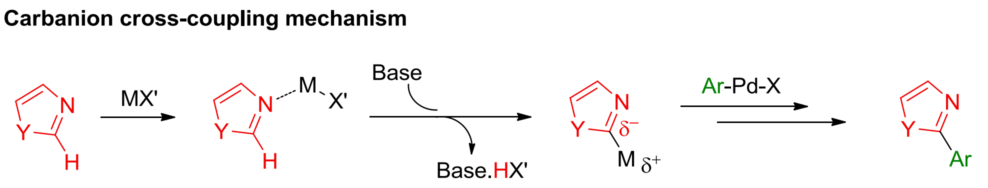
Figure 7

The C-H bond cleavage can be performed by one of the proposed mechanisms: 1) an electrophilic aromatic substitution (S_EAr), 2) a concerted S_E3 process, 3) a σ-bond metathesis, 4) a Heck-type reaction, and 5) an oxidative addition, which are depicted for benzene to form biphenyl (**XC**) (Scheme 35). However, a number of important recent experimental and computational mechanistical studies supported concerted S_E3 or σ-bond metathesis mechanisms, which were recently termed as concerted metalation-deprotonation processes (CMD).[92]



Scheme 35 Proposed mechanisms for the catalytic C-H direct arylation reactions

In addition to the above mentioned mechanisms, the carbanion cross-coupling mechanism with *in situ* formation of organometallic species has been also described for direct arylation of heterocycles (Scheme 36).[93]



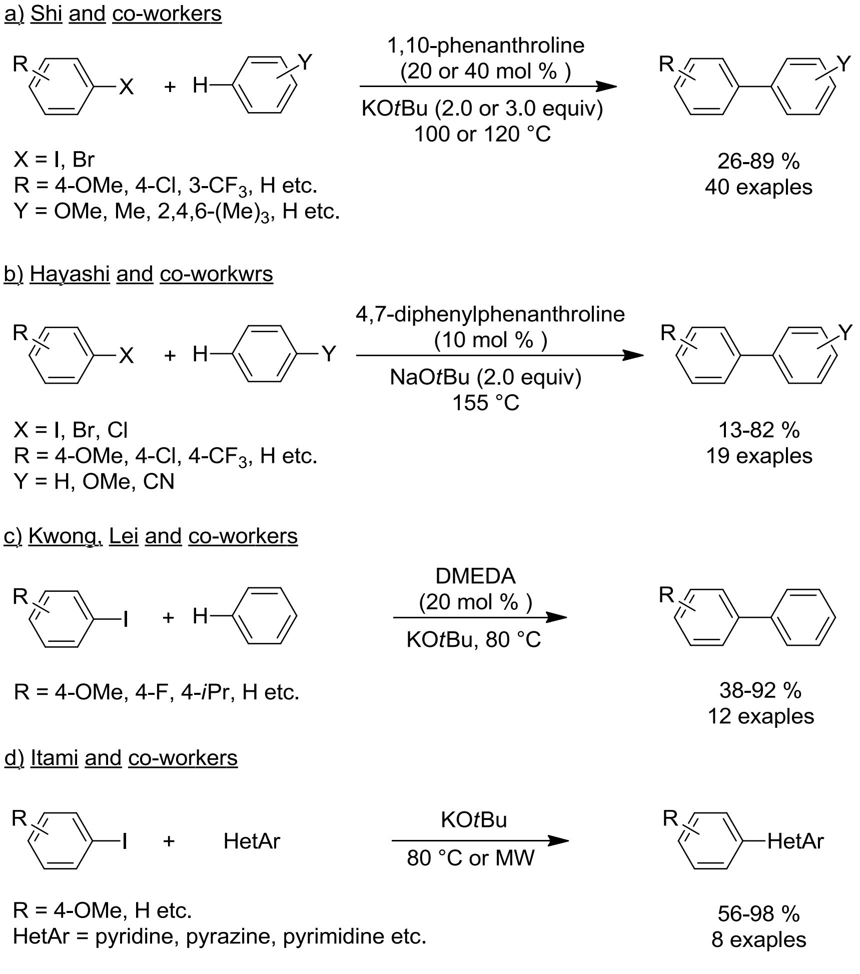
Scheme 36 Proposed carbanion cross-coupling mechanism of heterocycles

The Pd-catalyzed reactions can be performed either in the presence or in the absence of Cu^I salts. The Cu-free reactions were proved to proceed by a concerted metalation-deprotonation (CMD) mechanism,[94] which consists of the oxidative addition of the aryl halide to the Pd catalyst and attack of the resulting complex at the arene C-H bond with the assistance of a base to simultaneously cleave the C-H bond and form a C-Pd bond. Following reductive elimination furnishes the biaryl product. The CMD mechanism is involved in palladium catalyzed direct arylation of electron-deficient arenes[78d, 92f, 95] and heteroarenes (i.e. N-oxide derivatives[96]) and could be operable also for the broad spectrum of electron-rich, π-nucleophilic heteroarenes,[94b] which have been previously proposed to proceed via electrophilic aromatic substitution mechanism. Since CMD pathway corresponds to the lowest energy pathway, the regioselectivity of the direct arylation of arenes, regardless to their electronic properties, is well predictable. On the other hand, in several Cu-mediated reactions, direct metalation of the arene C–H bond by a base and copper salt was observed,[97, 80e] which generated an aryl cuprate that then underwent cross-coupling with an aryl halide (either Pd-catalyzed or noncatalyzed Ullmann type coupling). Pd-catalyzed arylations in the presence of copper(I) salts[98] follow the carbanion cross-coupling mechanism, and most probably involve the *in situ* generation of aryl cuprates which then undergo transmetalation to palladium catalyst, and final reductive elimination led to desired biaryl compounds. Since the metalation (cupration) of the heteroarenes proceeds in the position of the most acidic hydrogen, the control of regioselectivity in this type of direct arylations is also well predictable. Apart from Cu-mediated Pd-catalyzed reactions, Pd-free arylations were also reported[100a, 99] in the presence of excess of Cu salts, but usually such reactions are less efficient (Ullmann type coupling).

While electron-rich heterocycles are usually excellent substrates for C-H arylation, electron-poor heterocycles (i. e. pyridines or pyrimidines) have lower reactivity and there were only scarce examples of C-H arylations of electron-poor pyrimidines[100], therefore their corresponding N-oxides are usually used instead for the C-H arylations.[101]

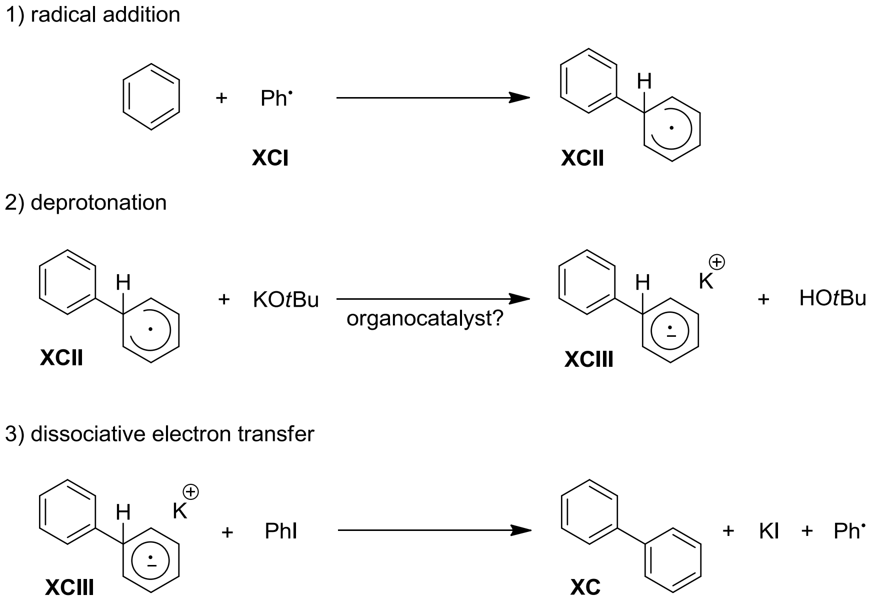
1.3.2. Non-transition metal catalyzed direct arylations

Recently, non-transition metal catalyzed direct arylations are also used for construction of biaryls using organocatalysis. Few research groups have recently reported independently the discovery of this type of reaction. The group of Shi and Hayashi described similar bimolecular reaction using phenantroline organocatalysts in the presence of potassium or sodium *tert*-butoxide as a base (Scheme 37a,[102] 37b[103]). Kwong, Lei and co-workers carried out the reaction between aryl iodides and benzene with the *N,N*-dimethylethane-1,2-diamine (DMEDA) as a catalyst using the same base (Scheme 37c).[104] Itami and co-workers described the arylation of electron-deficient nitrogen heterocycles with aryl iodides and bromides promoted even by *t*BuOK itself (Scheme 37d).[105]



Scheme 37 Recent examples of „metal-free“ direct C-H arylations

It is assumed that non-transition metal catalyzed direct arylations could follow the mechanism called base-promoted homolytic aromatic substitution (HAS).[106] The example in the Scheme 38 depicts a reaction between benzene and iodobenzene to provide biphenyl **XC**. Addition of the phenyl radical **XCI** to benzene gives the phenylcyclohexadienyl radical (**XCII**) (step 1), which is in turn deprotonated by the base (step 2). The resulting biphenyl radical anion (**XCIII**) is highly conjugated and must be a powerful reducing agent. This radical anion (**XCIII**) transfers an electron to starting iodide to provide biphenyl **XC**, potassium iodide, and a new phenyl radical which is introduced in next cycle (step 3). These types of electron-transfer reactions are thought to occur by dissociative (outer-sphere) electron transfer.[107] In other words, a long-lived aryl halide radical anion intermediate is not produced. The role of the organocatalyst is still not fully understood at this point.[106]



Scheme 38 Proposed mechanism for base-promoted organocatalytic biaryl synthesis

As a representative example of radical chemismy aproach is worth to mention biaryl synthesis of unactivated arenes in the presence of stoichiometric amount of radical source, such as tributyltin hydride and tris(trimethylsilyl)silicon hydride,[108] or irradiation.[109]

1.4. Trifluoromethylations of (hetero)arenes

1.4.1. Comercially available substances containing CF_3 group

Fluorinated compounds in general, and trifluoromethyl derivatives of arenes and heterocycles in particular, are of great current interest.[110] The trifluoromethyl group is important structural moiety present in diverse classes of pharmaceuticals, agrochemicals, liquid crystals, dyes, and polymers. The introduction of fluorine containing groups into molecules plays an important role in organic chemistry, because of the changes of molecular properties. The trifluoromethyl group has become an essential structural motif because of its unique size, electronic properties, and it often brings significant improvements in binding selectivity, lipophilicity, and metabolic stability,[110c,e,g] as evidenced by a large number of trifluoromethylated pharmaceuticals and drug candidates, such as antidepressant Fluoxetine (trade name Prozac, and Sarafem),[111] antiemetic Aprepitant (trade name Emend),[112] fungicide Trifloxystrobin (trade name Flint),[113] herbicide fluazifop-*p*-butyl (trade name Fusilade),[114] and many others (Figure 8).

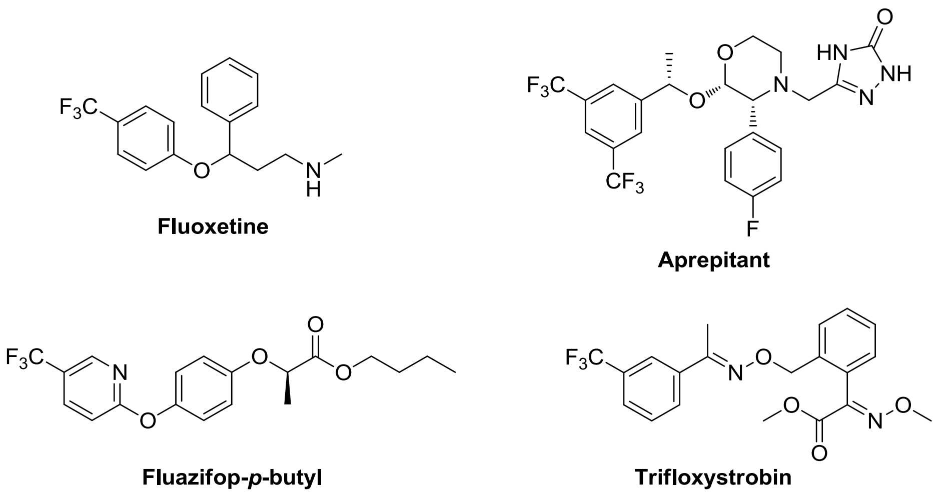


Figure 8 Commercially available substances containing CF_3 group

As an example of the trifluoromethylated uracil derivatives the trifluridine (trade name Viroptic) can be mentioned.[115] It is an anti-herpesvirus antiviral drug, used primarily for a treatment of eye infections. It is a nucleoside analogue, a modified form of deoxythymidine, similar enough to be incorporated into viral DNA, but the CF_3 group blocks base pairing. Trifluridine is also a component of the investigational drug TAS-102, candidate for treatment of metastatic colorectal cancer. In Japan, it is approved in 2014 for the treatment of unresectable advanced or recurrent colorectal cancer (trade name Lonsurf). TAS-102 or Lonsurf is a combination of two active pharmaceutical ingredients, trifluridine (the nucleoside analog) and tipiracil hydrochloride (a thymidine phosphorylase inhibitor). Tipiracil hydrochloride prevents from rapid metabolism of trifluiridine, increasing the bioavailability of trifluiridine. Another example of the trifluoromethylated uracil derivative is saflufenacil (trade name Kixor),[116] which is herbicide used to control annual broadleaf weeds in soy beans and corn (Figure 9).

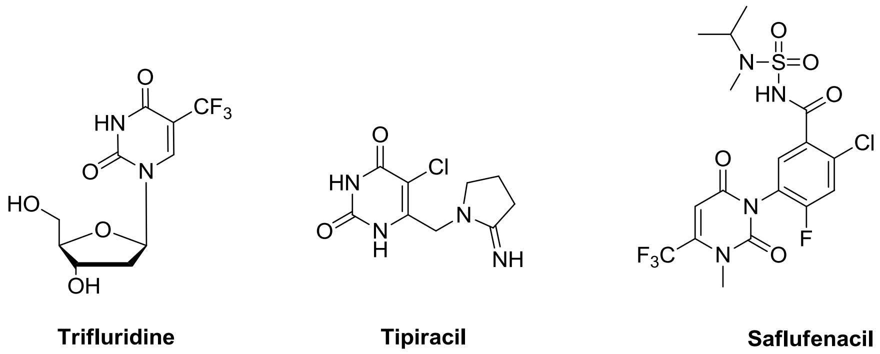
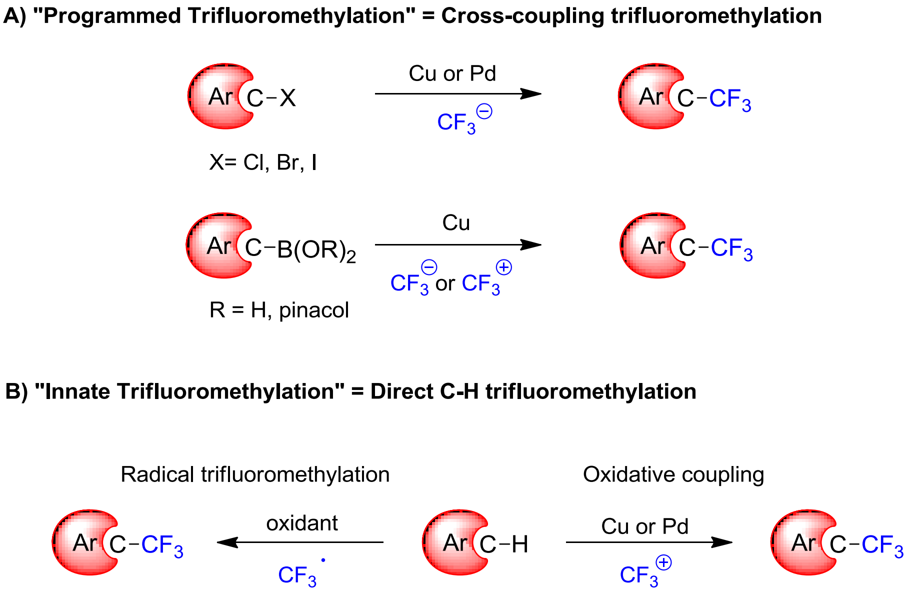

Trifluridine **Tipiracil** **Saflufenacil**

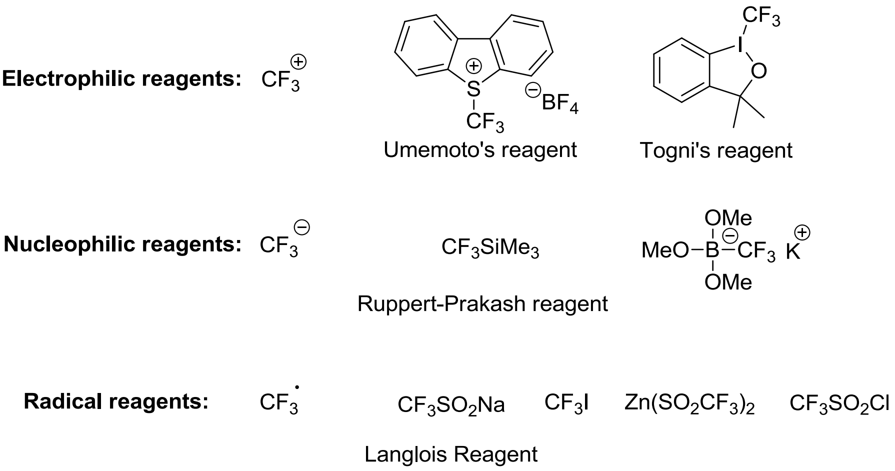
Figure 9 Commercially available trifluoromethylated uracil derivatives

1.4.2. Transition metal mediated/catalyzed methods for introduction of CF_3 group into organic molecules

Classical methods for preparation of CF_3-substituted aromatic compounds have relied on a transformation of a functional group using a reactive fluorinating reagent such as SbF_3 or SF_4 (Swarts-type reactions),[117] or on the C-C bond formation using [$CuCF_3$] reagent.[118] However, both of these methods have shortcomings, which include harsh reaction conditions, stoichiometric amounts of organometallic reagents, and occur only with limited substrate scope. In recent years, diverse methodologies of trifluoromethylations have been developed, either based on improved Cu or Pd-catalyzed cross-coupling reactions of (hetero)aryl halides or boronates,[119] or based on direct C-H activations (Scheme 39) using various trifluoromethylating reagents. The most widely used trifluoromethylating reagents are shown in Scheme 40. It should be noted, however, that depending on the reaction conditions, these reagents can be converted in situ into different reactive trifluoromethyl species.[120]



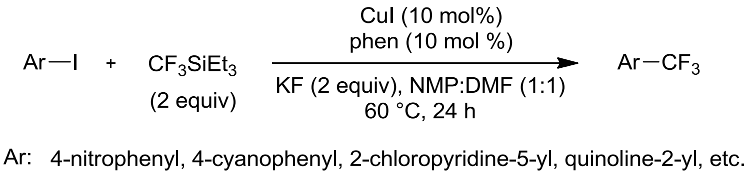
Scheme 39 Diverse methodologies for preparation of trifluoromethyl (hetero)arenes



Scheme 40 Exaples of the most widely used trifluoromethylating reagents

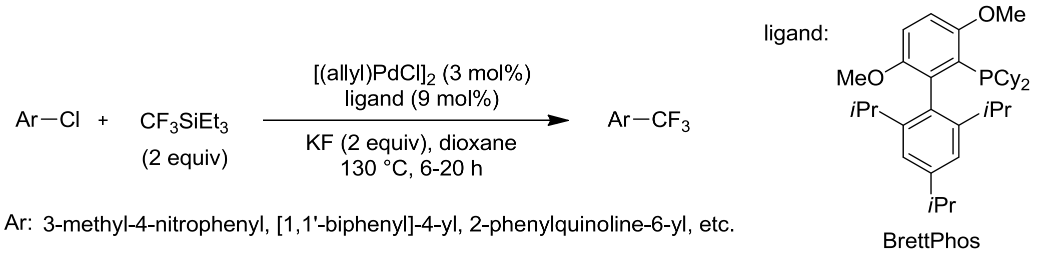
1.4.2.1. Trifluoromethylation by means of cross-coupling reactions

Several metal catalyzed trifluoromethylations of aryl halides or aryl boronic acids have been reported recently. For example, Amii and co-workers reported the first copper catalyzed trifluoromethylation of electron-poor aryl iodides with the CF_3SiEt_3 reagent, in the presence of CuI/1,10-phenanthroline (Scheme 41).[119c] Since then considerable advancement has been made in the development of catalytic procedures.



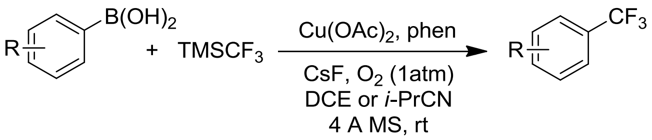
Scheme 41 Cu-catalyzed trifluoromethylation of aryl iodides

Thereafter Buchwald and co-workers reported a palladium catalyzed trifluoromethylation of aryl chlorides using sterically hindered electron-rich ligands (Scheme 42).[119d]



Scheme 42 Pd-catalyzed trifluoromethylation of aryl chlorides

Qing and Chu,[119e,f] and Buchwald and co-workers[119g] (Scheme 43) independently reported copper catalyzed trifluoromethylation of aryl boronic acids under oxidative conditions.

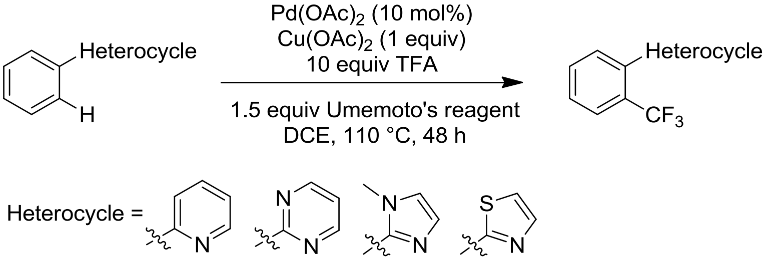


Scheme 43 Cu-catalyzed trifluoromethylation of aryl boronic acids

While these methods overcome the shortcomings of the classic Swarts reaction[117] or the [$CuCF_3$] strategy,[118] the trifluoromethyl group introduced by these catalytic methods was typically placed at the position of the C-X (X = halides or boron) bond of the prefunctionalized arenes. It is advantageous because of regiospecific trifluoromethylation, but such a prefunctionalization of substrates usually involves extra synthetic operations and also limits the application of these methodologies for the late-stage modification of drug candidates for structure-activity relationship (SAR) studies.

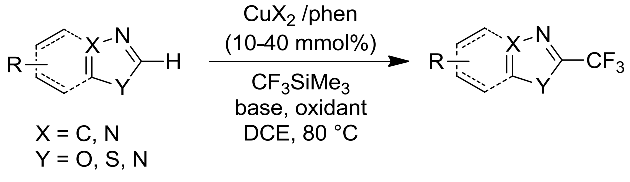
1.4.2.2. Direct C-H trifluoromethylation

Direct C-H trifluoromethylation proceeds to the inherently most reactive position of the substrate under specified conditions and converts the C-H bond of (hetero)arenes into C-CF_3 bonds directly. The great advantage of this strategy is that it bypasses the prefunctionalization of the substrate, therefore it is a highly desirable method. The direct C-H trifluoromethylations can proceed either as metal catalyzed (the most often Cu or Pd) reactions with either electrophilic[121] or nucleophilic[122] "CF_3" species or as radical reactions with $CF_3^{\cdot}$ generated either by photoredox catalysis,[123] Fenton oxidation[124] or by reaction with peroxides.[125] A two-step procedure based on Ir-catalyzed C-H borylation followed by electrophilic trifluoromethylation has also been reported.[126] For example, Yu and co-workers reported a straightforward protocol for direct *ortho*- trifluoromethylation of arenes using Umemoto's reagent in the presence of $Pd(OAc)_2$ (Scheme 44).[121a]



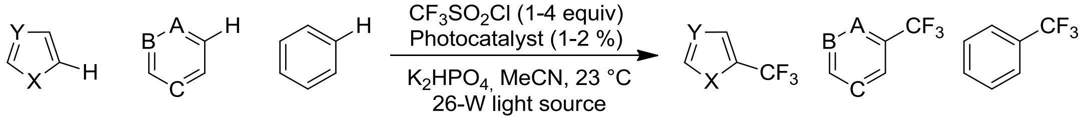
Scheme 44 Direct trifluoromethylation of arenes

Liu and co-workers[122a] and Chu and Qing[122c] respectively, reported the Pd- and Cu-catalyzed oxidative trifluoromethylation of indoles at the C2 position and heteroarenes containing an acidic C-H bond by direct C-H activation (Scheme 45).[122c]



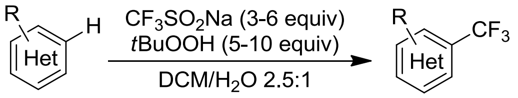
Scheme 45 Cu-catalyzed direct oxidative trifluoromethylation

A most of the CF_3 sources are expensive and not favorable for industrial applications. The groups of MacMillan and Baran tackled this drawback and investigated the possibility of trifluoromethylations with practical and cheap trifluoromethyl radical sources. They developed a very promising alternative, which consists of the direct functionalization of the inherently reactive positions of the substrates. Nagib and MacMillan described a mild, visible-light-induced C-H trifluoromethylation of nonfunctionalized (hetero)arenes using CF_3SO_2Cl, a practical, accessible, and cheap source of CF_3 radicals in the presence of a Ru- or Ir-based photocatalyst (Scheme 46).[123a] The electron-deficient CF_3 radical that is generated from the photoredox catalytic cycle selectively reacts at the most electron-rich position of the (hetero)arene. A myriad of 5- and 6-membered heterocycles as well as arenes that contain a wide range of ring substituents have been regioselectively functionalized at 23°C.[127]



Scheme 46 Direct radical trifluoromethylation of nonfunctionalized (hetero)arenes

Another remarkable advance was made by Baran and coworkers by means of CF_3 radicals that are generated from CF_3SO_2Na (Langlois reagent), a benchtop stable and inexpensive solid, in the presence of peroxides as radical initiators without the use of a metal (Scheme 47).[125] Different classes of heteroarenes have been used in the reaction and the method is tolerant of many functional groups.[127]



Scheme 47 Direct radical trifluoromethylation of heteroarenes

2. Specific aims of the thesis

1. Development of a practical synthesis of 5- and 6-aryluracil nucleobases using regioselective direct C-H arylations.
2. Exploration of scope of direct C-H arylations of uridine or protected uridines.
3. Development of a regioselective synthesis of 2,4-diarylpyrimidines using cross-coupling reactions.
4. Regioselective synthesis of 1,3-dimethyl-5- and 6-(trifluoromethyl)uracil using direct trifluoromethylation and its optional combination with direct C-H arylations.

2.1. Rationale of the specific aims

The major goal of this PhD thesis was development and/or exploration of straightforward and modern approaches such as C-H activations and cross-coupling reactions or combination thereof, being suitable in preparation for substituted uracils and pyrimidines.

The 5- or 6-aryluracils are most often prepared by heterocyclizations[3b] or by cross-coupling reactions,[62] however, some aryluracil derivatives are still difficult to prepare. In addition, cross-couplings, N-alkylation/arylation, and other reactions would be desirable to be combined in regioselective cascades in order to prepare libraries of substituted heterocycles. Therefore, developments of alternative methodologies are of interest. My first task was development of the regioselective direct C-H arylation of uracil or diverse protected uracils, in order to prepare free 5- and 6-aryluracil nucleobases. Since direct arylation on free uracil seems to be challenging, 1,3-dimethyluracil was selected as a model compound of pyrimidine nucleobases and nucleosides for development of the regioselective C-H arylation to the position 5 or 6. Consecutive application of this methodology on diverse protected uracils was examined, with the aim find out suitable N1 and N3 protection that should be compatible with the harsh conditions of the C-H arylations but, on the other hand, should be cleavable at the end of synthesis without decomposition of the aryluracils. Synthesized 5- and 6-aryluracil nucleobases were subjected to biological activity testing.

My second task was to explore the scope of this methodology to uridine or protected uridines. This task was even more challenging since harsh conditions are generly utilized in this type of reactions and nucleosides are notably sensitive compounds.

Next aim was a development of the regioselective synthesis of 2,4-diarylpyrimidines using cross-coupling reactions and preparation of series of 2,4-diarylpyrimidines bearing different aryl groups. A variety of synthetic methods have been reported for the synthesis of 2,4-diarylpyrimidines but, in many cases, the regioselectivities were not satisfactory and/or yields were only moderate. Therefore, alternative methods for the synthesis of diarylpyrimidines with sufficient regioselectivity are desirable, in particular in synthesis of combinatorial libraries of different derivatives for biological activity screening. I decided to use thiouracil as a starting compound which could be subjected to the phosphonium-mediated Suzuki cross coupling in combination with Liebeskind–Srogl reaction as a powerful alternative to cross-couplings of dihaloheterocycles with problematic regioselectivities.[51a,b, 80a, 128] Possibility of further direct arylation of 2,4-diarylated pyrimidines to position 5 or 6 was also explored, in order to acess multisubstituted uracils.

Due to importance of trifluoromethyl derivatives in medicinal chemistry,[110] diverse methodologies of trifluoromethylations of (hetero)arenes have been developed, either based on improved Cu or Pd-catalyzed cross-coupling reactions of (hetero)aryl halides or boronates,[129] or based on direct C-H activations.[121-125] Therefore, I was also interested in preparation of 1,3-dimethyl-5- and 6-(trifluoromethyl)uracil using direct regioselective trifluoromethylations. The continuation of this project was to attempt the synthesis of uracil derivatives bearing one trifluoromethyl and one aryl group at positions 5 and 6 by two consecutive C-H activations.

3. Results and discussion

3.1. Direct regioselective C-H arylations of uracils

3.1.1. Direct C-H arylation of 1,3-dimethyluracil: Reaction development and scope

Pd-Catalyzed C-H arylations of purine bases and nucleosides to position 8 in the presence of CuI and Cs_2CO_3[79] and Ir-catalyzed C-H borylations of 7-deazapurines have been developed in our group.[130] In order to extend the use of C-H arylations to pyrimidine bases, I have tried to apply the Pd-catalyzed C-H arylations[79] on unprotected uracil. However, this chemistry did not work and I observed formation of N-arylated products, but no products of C-H arylation were formed. As it is known, uracil and its N-unsubstituted derivatives generally form 1,3-dialkyl products under a variety of conditions. Large alkyl groups display a preference for the less hindered N-1 nitrogen. For N-1-substituted uracils, there is a competition in the further alkylation between N-3 nitrogen and the 4-oxo oxygen. N-Alkylation is favored, but hindered alkyl halides and diazomethane give a high proportion of O-alkyl products.[3b] Therefore, I have tried to develop the C-H arylation of 1,3-dimethyluracil (**1**) as a model compound for pyrimidine nucleobases and nucleosides. So far, only one example of an intramolecular C–H arylation of related compounds that leads to fused heterocycles has been reported[100a] during the course of our study.

1,3-Dimethyluracil (**1**) contains two C-H bonds capable of arylation in positions 5 and 6. Position 5 is known to be the preferred site for electrophilic substitution,[3b] while C-H in position 6 is more acidic and undergoes metalation[62] (Figure 1).

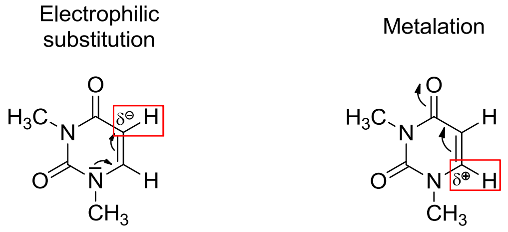
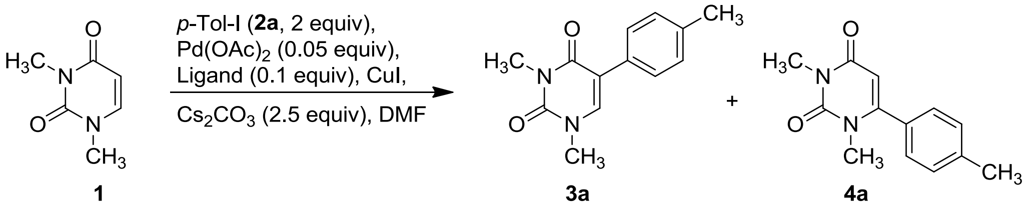


Figure 1 Regioselectivity of electrophilic substitution and metalation of 1,3-dimethyluracil (**1**)

Conditions for the direct C-H arylation of **1** were optimized using the reaction with *p*-tolyl iodide (**2a**) using $Pd(OAc)_2$ in combination with diverse ligands and with varying amounts of CuI in the presence of Cs_2CO_3 (Scheme 1, Table 1).



Scheme 1 C–H arylation of 1,3-dimethyluracil (**1**) with *p*-Tol-I (**2a**)

Table 1 Optimization of conditions of C–H arylation of 1,3-dimethyluracil (**1**)

Entry	*Ligand*	*CuI (equiv)*	*Temperature (°C)*	*Yield*[d] *(%)*	*Ratio*[e] ***3a:4a***
1	-	3	160	53	20:80
2	PPh_3	3	140	31	5:95
3	$(t\text{Bu})_2PMe.HBF_4$[a]	-	130	99	55:45
4	$(t\text{Bu})_2PMe.HBF_4$[a]	1	130	56	31:69
5	$(t\text{Bu})_2PMe.HBF_4$[a]	3	160	66	6:94
6	$(t\text{Bu})_2PMe.HBF_4$	3	160	62	19:81
7	$P(t\text{Bu})_3.HBF_4$[a]	-	130	57	62:38
8	$P(t\text{Bu})_3.HBF_4$[a]	3	130	72	14:86
9	PhDavePhos	3	140	40	20:80
10	$P(o\text{-Tol})_3$	3	140	50	22:78
11	$P(o\text{-Tol})_3$	3	160	68	22:78
12	$P(p\text{-FPh})_3$	3	160	53	9:91
13	$P(o\text{-MeOPh})_3$	3	160	14	30:70
14	$P(C_6F_5)_3$	-	160	62	86:14
15	$P(C_6F_5)_3$	0.1	160	62	86:14
16	$P(C_6F_5)_3$	1	160	50	24:76
17	$P(C_6F_5)_3$	3	160	78	6:94
18	-[b]	3	160	35	0:100
19	Phenanthroline[b,c]	0.2	140	22	4:96

[a] $Pd(OAc)_2$ (0.1 equiv), ligand (0.2 equiv); [b] In the absence of $Pd(OAc)_2$; [c] K_3PO_4, DMF/*m*-xylene (1:1); [d] The isolated yield of a mixture of **3a** and **4a**; [e] The ratio of **3a** and **4a** from ^1H NMR spectra of a isolated mixture

When I applied the ligand-free conditions at 160 °C (in analogy to the arylation of purines[79]) for reaction with 1,3-dimethyluracil (**1**), I observed moderate conversion to a mixture of 5-*p*-tolyl (**3a**) and 6-*p*-tolyl (**4a**) derivatives in a 1:4 ratio (entry 1). The regioisomers were separable only by repeated chromatography and were assigned by HMBC NMR spectroscopy (Figure 2, 3).

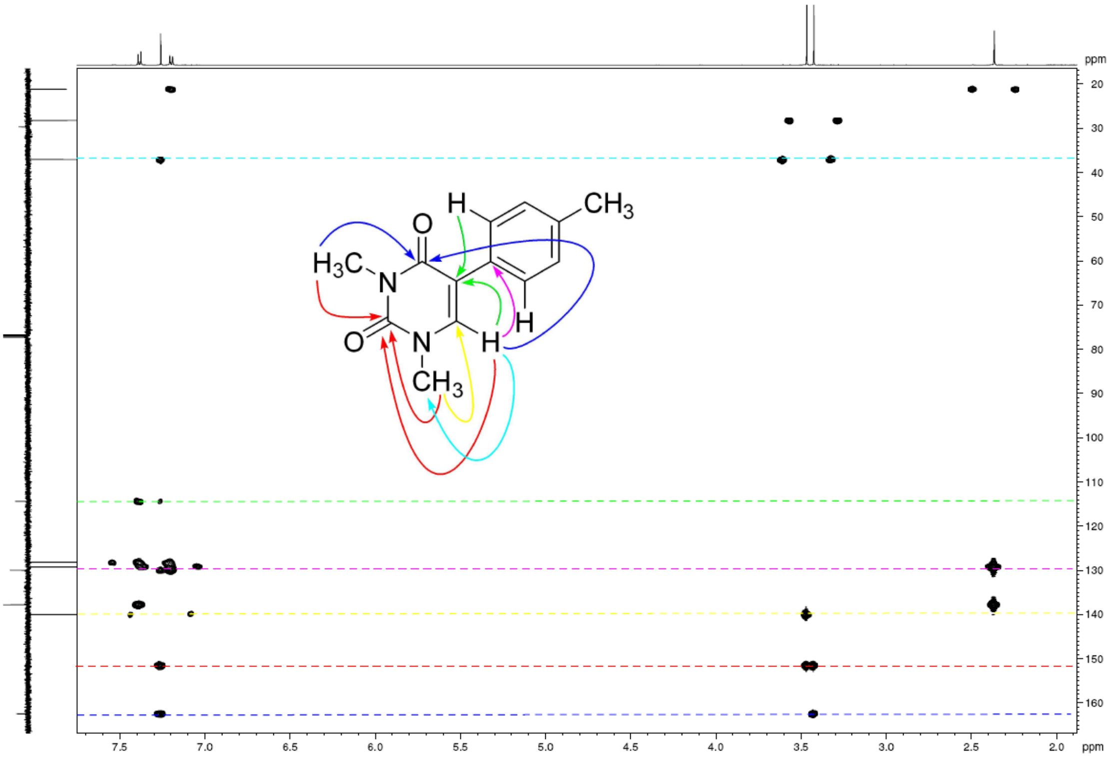


Figure 2 HMBC of **3a** in $CDCl_3$

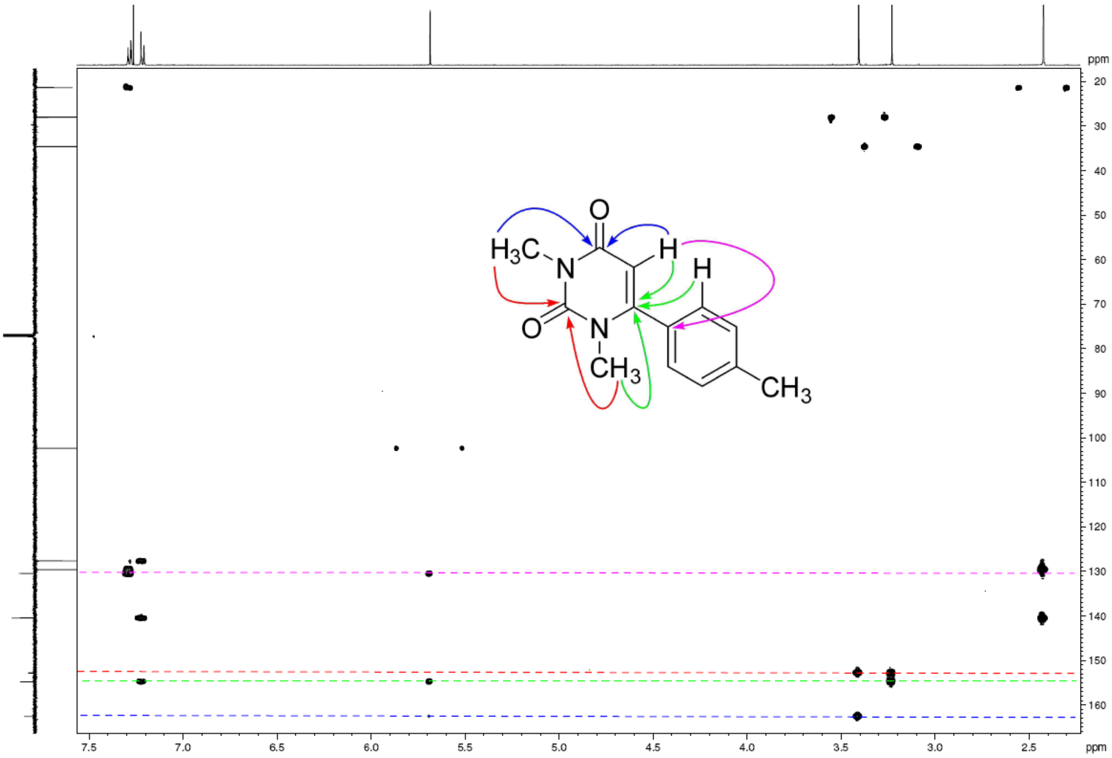


Figure 3 HMBC of **4a** in $CDCl_3$

Therefore, I tried to optimize the conditions for regioselective C-H arylation of 1,3-dimethyluracil (**1**), in order to achieve better regioselectivity and conversion of the reaction. When the PPh_3 ligand was used at 140 °C, the yield was lower and the ratio **3a**/**4a** was 1:19 (entry 2). The use of 10 mol % of $Pd(OAc)_2$ and 20 mol % of $(t\mathrm{Bu})_2PMe$[80c] in the absence of CuI at 130 °C gave quantitative conversion to an almost equimolar mixture **3a**/**4a** (entry 3). Interestingly, addition of 1 equiv of CuI dramatically lowered the yield (to 56 %), but on the other hand increased the selectivity of **4a** (entry 4). When 3 equiv of CuI were used at 160 °C, the yield was slightly better (66 %), in comparison with entry 3 and the selectivity towards **4a** significantly increased, the **3a**/**4a** ratio was 1:16 (entry 5). The use of smaller amount of $Pd(OAc)_2$ (5 mol %) and $(t\mathrm{Bu})_2PMe$ (10 mol %) at 160 °C reduced the conversion to 62 % (entry 6). The use of $P(t\mathrm{Bu})_3$ at 130 °C in the absence of CuI gave 57 % conversion to a ca. 2:1 mixture of **3a**/**4a**, while in the presence of 3 eqiuv of CuI, the ratio was switched to ca. 1:6 and the yield was 72 % (entries 7 and 8). A similar selectivity, but lowered conversion was achieved using PhDavePhos or $P(o\text{-Tol})_3$ in the presence of CuI (ratio 1:4, entries 9 and 10). The increased temperature to 160 °C resulted in an higher yield (68 %) with the same regioselectivity of the products (entry 11). A similar result was obtained using $P(p\text{-FPh})_3$[131] in the presence of 3 equiv of CuI (ratio 1:10, entry 12). The change of the ligand to $P(o\text{-MeOPh})_3$ proved to be disadvantageous due to low conversion (entry 13). $P(C_6F_5)_3$ was then used as a ligand in a series of experiments with varying amounts of CuI at 160 °C (entries 14-17). Reactions in the absence or with 0.1 equiv of CuI gave a decent (62 %) conversion to a ca. 6:1 mixture of **3a**/**4a** (entries 14 and 15), while in the presence of 1 equiv of CuI, the reaction afforded **4a** as the major product (ratios 1:3) in 50 % of yield (entry 16). The best conversion (78 %) and regioselectivity in favor of **4a** was achieved using 3 equiv of CuI (entry 17). When the reaction was performed in the presence of 3 equiv of CuI and in the absence of any Pd catalyst and ligand (entry 18), the conversion was lower but the reaction was fully regioselective to give only the product of C6-arylation (**4a**). The last optimization experiment involved the use of CuI in the presence of phenanthroline as ligand (in analogy to recent Cu-mediated C-H arylation of caffeine[99b]), but these conditions gave a low conversion (entry 19).

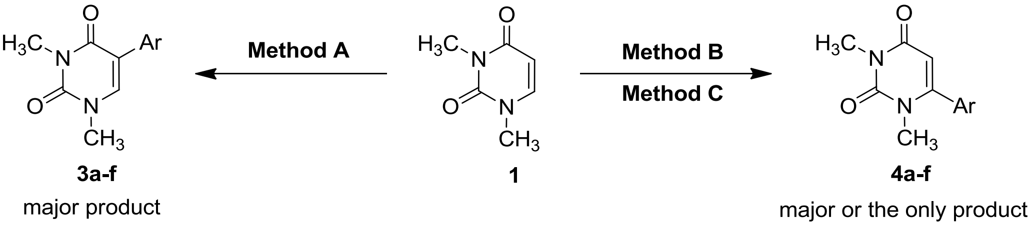
As it is evident from optimization experiments, three different sets of conditions were developed for regioselective C-H arylation of 1,3-dimethyluracil (**1**) to the position 5 or 6: (Method A) $Pd(OAc)_2$ in combination with $P(C_6F_5)_3$ in the presence of

Cs_2CO_3, (Method B) the same catalyst in combination with 3 equiv of CuI, and (Method C) CuI and Cs_2CO_3 in the absence of $Pd(OAc)_2$ and ligand.

The reaction in the absence of CuI (Method A) gave the 1,3-dimethyl-5-(*p*-tolyl)uracil (**3a**) as major product (entry 14), whereas the reactions in the presence of 3 equiv CuI (Methods B or C, entries 17 and 18) gave mainly or exclusively 1,3-dimethyl-6-(*p*-tolyl)uracil (**4a**).

3.1.1.1. Synthesis of 5- and 6-aryl-1,3-dimethyluracils

Three previously mentioned procedures were further utilized in preparative experiments with diverse aryl halides (Scheme 2, Table 2).

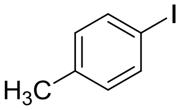
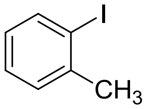
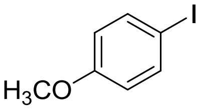
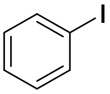
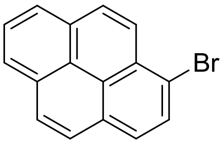
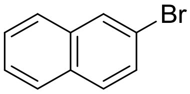


Method A: Ar-X (**2a-f**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), $P(C_6F_5)_3$ (0.1 equiv), Cs_2CO_3 (2.5 equiv), DMF, 160 °C, 50 h; **Method B**: Ar-X (**2a-f**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), $P(C_6F_5)_3$ (0.1 equiv), CuI (3 equiv), Cs_2CO_3 (2.5 equiv), DMF, 160 °C, 50 h; **Method C**: Ar-X (**2a-f**, 2 equiv), CuI (3 equiv), Cs_2CO_3 (2.5 equiv), DMF, 160 °C, 50 h.

Scheme 2 Preparative C–H arylations of 1,3-dimethyluracil (**1**)

The reactions with *p*-tolyl iodide (**2a**), 2-iodotoluene (**2b**), 4-iodoanisole (**2c**) and iodobenzene (**2d**) under conditions A gave 5-aryluracils **3a-d** as the major products in 54 - 80 % isolated yields (Table 2, entries 1, 4, 7, and 10). Under conditions B, the selectivity was reversed to afford 6-aryl derivatives **4a-d** as the major products in 54 - 72 % isolated yields (Table 2, entries 2, 5, 8, and 11). In all cases, minor amounts of the other regioisomers were isolated. Conditions C generally gave lower conversions but a high regioselectivity to give 6-substituted uracils **4a-d** as the only products (35 - 59 % yields) (Table 2, entries 3, 6, 9, and 12). Two aryl bromides (**2e, f**) were also successfully used for the C-H arylation of **1** under the same conditions (Table 2, entries 13-18) to show similar conversions and selectivity (with the exception of the reaction of **2e** under conditions B, which gave **4e** as the only product).

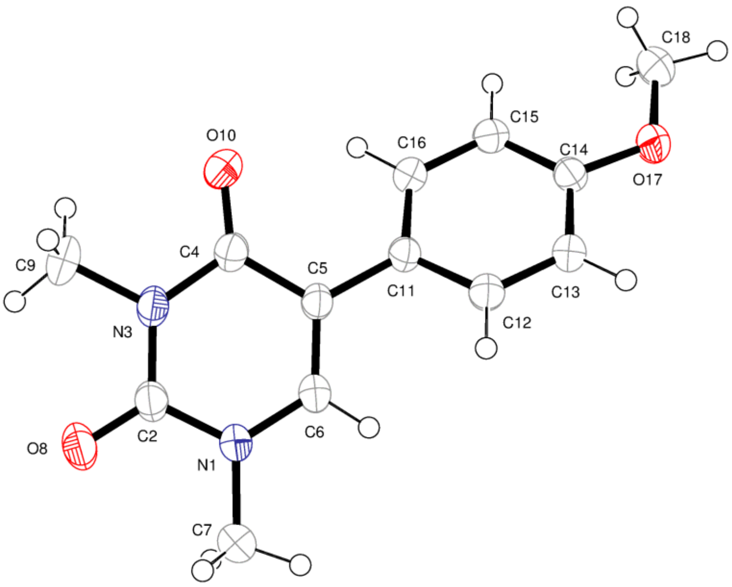
Table 2 C–H arylations of 1,3-dimethyluracil (**1**) with diverse aryl halides.

Entry	*Ar-X*		*Method*	*Yield*[a] *(%)*	*Ratio*[b] ***3**:**4*** *(%)*	*Yield (%)*	
						3	***4***
1		**2a**	A	62	86:14	54	7
2			B	78	6:94	5	72
3			C	35	0:100	0	35
4		**2b**	A	96	82:18	80	15
5			B	60	7:93	5	54
6			C	48	0:100	0	48
7		**2c**	A	68	81:19	56	12
8			B	68	9:91	6	62
9			C	59	0:100	0	59
10		**2d**	A	76	88:12	68	8
11			B	68	12:88	8	60
12			C	37	0:100	0	37
13		**2e**	A	88	77:23	68	20
14			B	68	0:100	0	68
15			C	36	0:100	0	36
16		**2f**	A	53	79:21	42	10
17			B	89	10:90	9	80
18			C	24	0:100	0	24

[a] The isolated yield of a mixture of **3** and **4**; [b] The ratio of **3** and **4** from ^{1}H NMR spectra of a isolated mixture

The structure of 5-(4-methoxyphenyl)-1,3-dimethyluracil (**3c**) (Figure 4) and the 1,3-dimethyl-6-(*p*-tolyl)uracil (**4a**) and 1,3-dimethyl-6-(pyren-1-yl)uracil (**4e**) were determined by X-ray diffraction (Figure 4).

a)



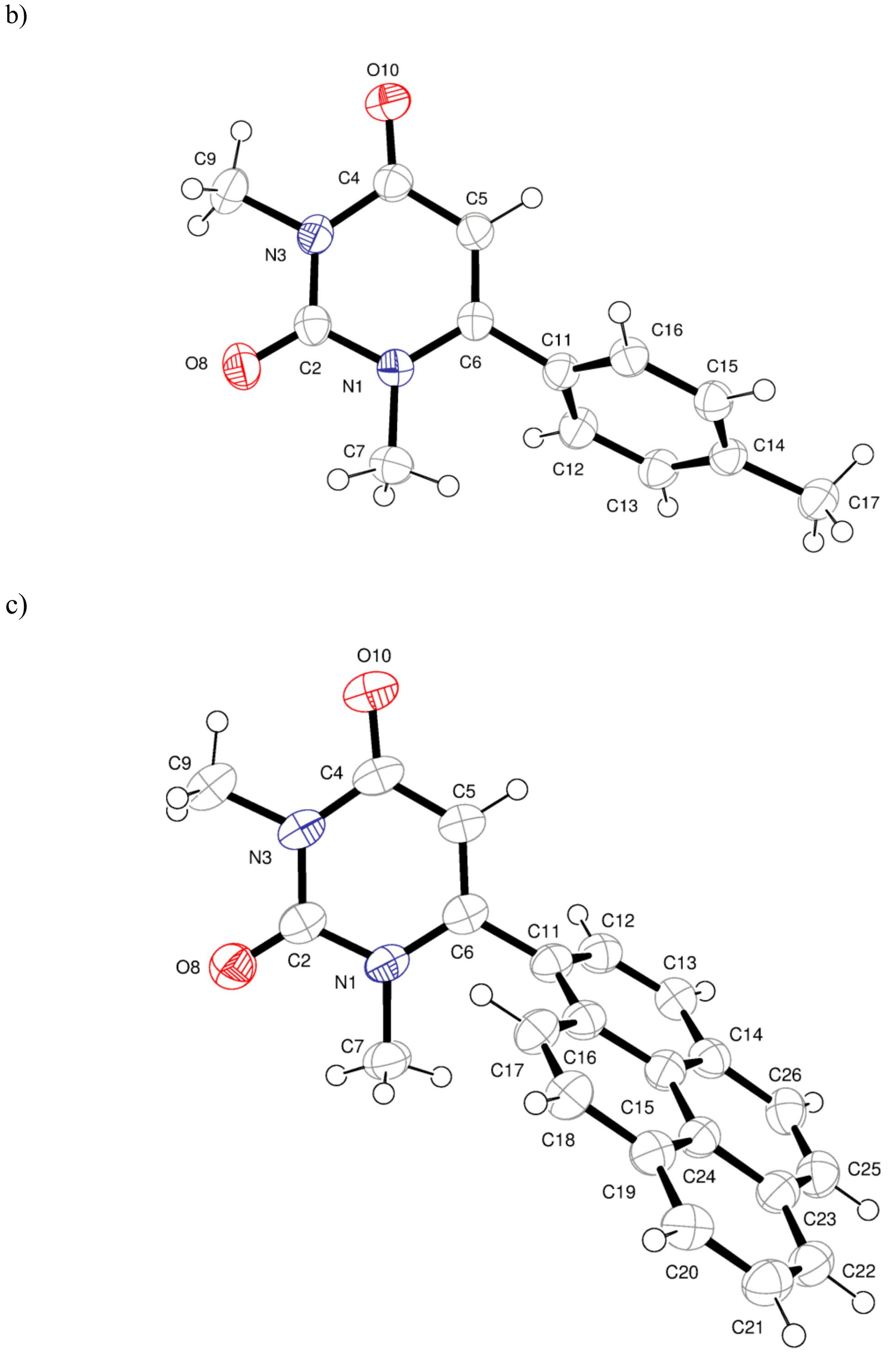


Figure 4 ORTEP drawing of **3c** (a), **4a** (b) and **4e** (c) with the atom numbering scheme. Thermal ellipsoids are drawn at the 50 % probability level.

Electron-poor aryl iodides (1-iodo-4-nitrobenzene, 4-iodobenzonitrile, 3-iodopyridine, 5-iodouracil, 5-iodo-1,3-dimethyluracil) were also tried in these reactions under conditions A-C, but in all cases, no reactions (or very low conversions < 10 %) were observed. Apparently this methodology is only applicable to electron-rich and neutral aryl halides. No product of 5,6-diarylation was observed in any of those reactions, and also additional experiments of further arylation of 5-aryluracil **3a** under conditions B and arylation of 6-aryluracil **4a** under conditions A with another aryl iodide (**2c**) did not proceed. The second C-H arylation probably does not proceed because of steric reasons.

The dichotomy of the reaction regioselectivity clearly indicates different reaction mechanisms in each case. While the reactions in the absence of CuI presumably proceed through the concerted metalation-deprotonation (CMD) mechanism[94] and thus follow the regioselectivity of electrophilic substitution (position 5) (Figure 5), the reactions in the presence of CuI most likely proceed through cupration[97, 80e] of the heterocycle in the position of the more acidic hydrogen (position 6) (Figure 6).

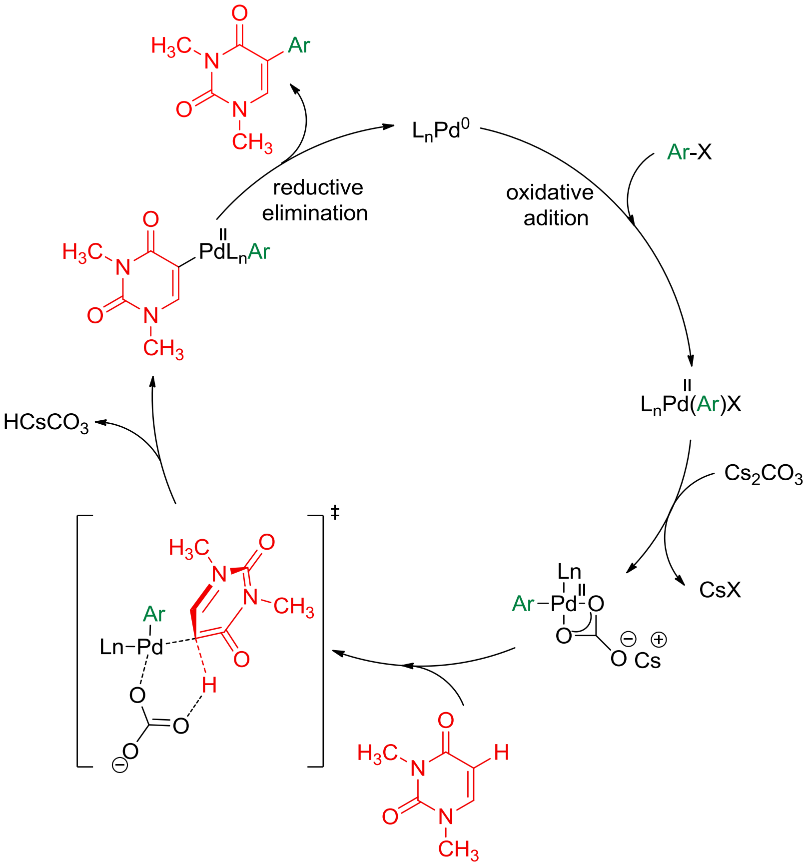


Figure 5 Proposed mechanism for the Pd-catalyzed direct arylation of 1,3-dimethyluracil (**1**) through the CMD mechanism to the position 5 (conditions A)

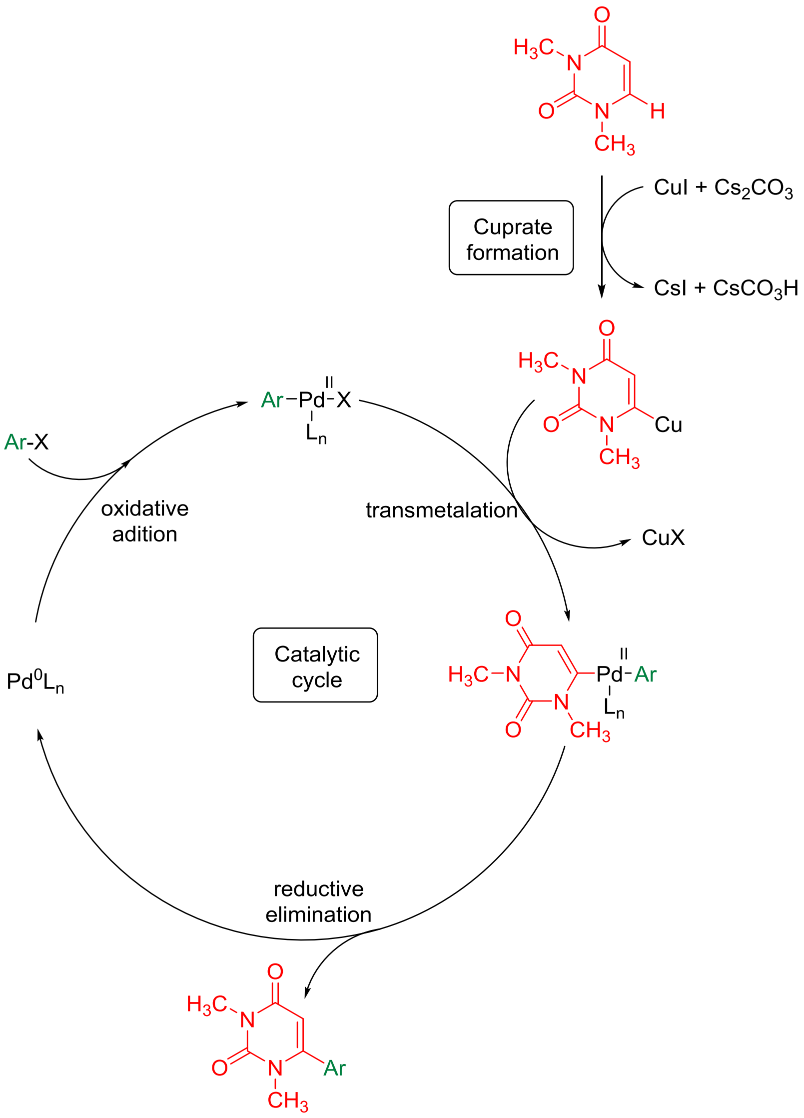


Figure 6 Proposed mechanism for the Pd-catalyzed and Cu-mediated direct arylation of 1,3-dimethyluracil (**1**) to the position 6 (conditions B) through cupration

The reaction in the absence of a Pd catalyst, which proceeds through an Ullmann coupling, is less efficient (but more selective) than reactions in the presence of $Pd(OAc)_2$ and a ligand (Figure 7). This shows that Pd catalysis does occur even in the presence of CuI and increases the efficiency of those reactions.

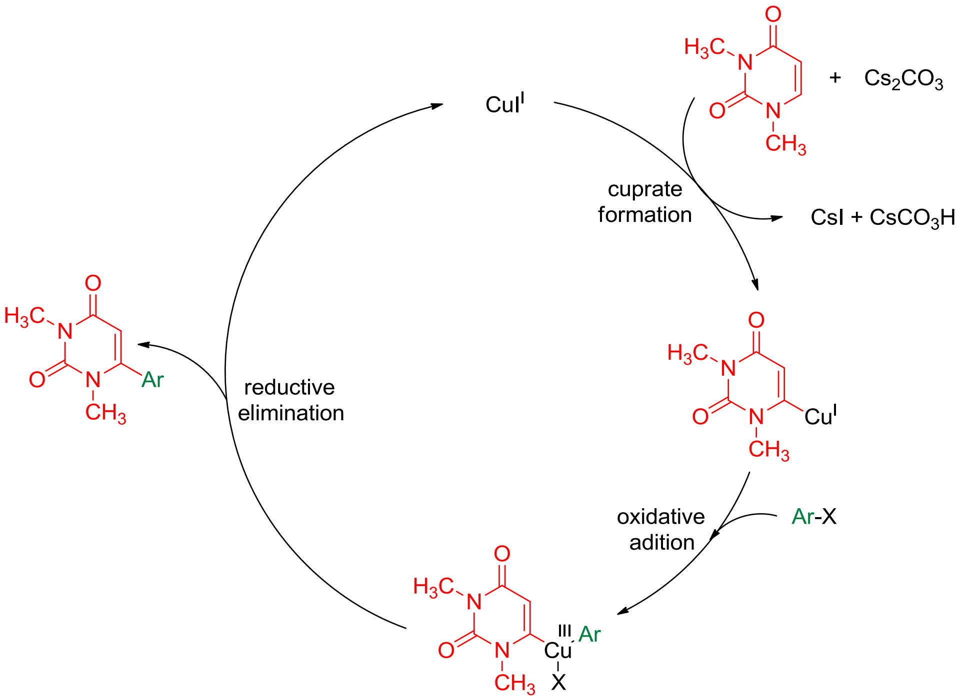


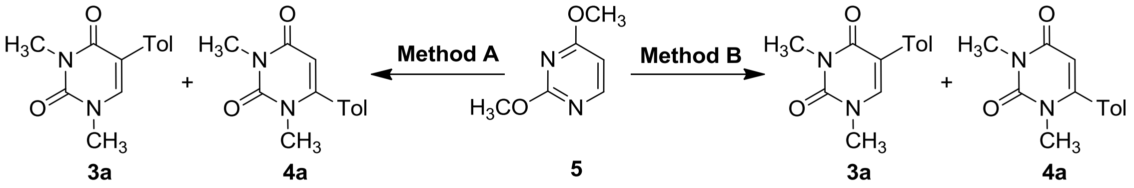
Figure 7 Proposed mechanism for the Cu-mediated direct arylation of 1,3-dimethyluracil (**1**) to the position 6 (conditions C) through an Ullmann type coupling

3.1.2. Direct C-H arylation of protected uracils and consecutive deprotection: Reaction development and scope

As I mentioned in the previous chapter, the methods for regioselective Pd-catalyzed and/or Cu-mediated direct C-H arylations were developed for 1,3-dimethyluracil (**1**).[132] I found that reactions in the absence of CuI provided 5-aryl-1,3-dimethyluracils **3** as major products, whereas the reactions in the presence of CuI gave preferentially 6-aryl-1,3-dimethyluracils **4**. The explanation of the dichotomy is probably the switch of the mechanism from concerted metalation-deprotonation (CMD)[94] to the cupration/Ullmann coupling[97, 80e]. However, this chemistry did not work on unprotected uracil and the methyl groups at N1 and N3 are not easily cleavable. Therefore, in order to access free aryluracil bases, there was a need for development of a suitable protection at N1 and N3 that should be compatible with the harsh conditions of the C-H arylations but should be cleavable at the end without decomposition of the aryluracils. As a result, I focused on the C-H arylations of diverse protected uracils and development of a practical synthesis of free arylated uracil bases.

Firstly, I have tried to apply previously developed conditions for regioselective C-H arylation in the experiments with commercially available 2,4-dimethoxypyrimidine

(**5**) as a representant of an *O*-protected uracil. The reaction was performed either in the absence (Method A) or in the presence of CuI (Method B) using Cs_2CO_3 as a base at 160 °C. (Scheme 3). After 48 hours under condition A formation of a mixture of 1,3-dimethyl-5-(*p*-tolyl)uracil (**3a**) and 1,3-dimethyl-6-(*p*-tolyl)uracil (**4a**) in 40 % yield in the ratio of 82:18 was observed, 58 % of 1,3-dimethyluracil (**1**) was isolated from the reaction mixture due to migration of the methyl groups to nitrogens. The condition B gave 45 % of the mixture of 5-*p*-tolyl (**3a**) and 6-*p*-tolyl (**4a**) derivatives in the 13:87 ratio and 55 % of 1,3-dimethyluracil (**1**) (Scheme 3).



Yield	Ratio **3a:4a**
40 %	82:18

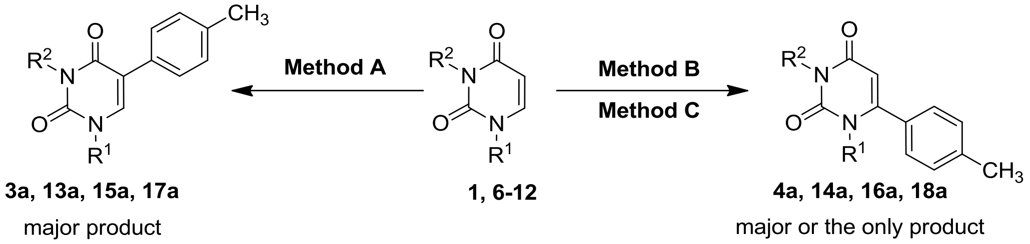
Yield	Ratio **3a:4a**
45 %	13:87

Method A: *p*-Tol-I (**2a**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), $P(C_6F_5)_3$ (0.1 equiv), Cs_2CO_3 (2.5 equiv), DMF, 160 °C, 48 h; **Method B**: *p*-Tol-I (**2a**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), $P(C_6F_5)_3$ (0.1 equiv), CuI (3 equiv), Cs_2CO_3 (2.5 equiv), DMF, 160 °C, 48 h.

Scheme 3 C–H arylation of 2,4-dimethoxypyrimidine (**5**) with *p*-Tol-I (**2a**)

This result was obtained most probably due to the lactim ether rearrangements to their isomeric and more stable lactam configurations. These transformations are not reversible and they are caused by the application of heat or through the influence of special catalytic agents, and have been observed in the acyclic (imid/amid) and cyclic (lactim/lactam) series of organic compounds. The substituted pyrimidines represented by the 2,4-dialkoxypyrimidines easily undergo rearrangement upon heating to form the 1,3-dialkyluracils.[133] The 1,3-dialkyluracil (**1**) is the most stable isomer compared to 2,4-dimethoxypyrimidine (**5**). This was confirmed by the magnitude of the energy difference between **1** and **5**, gas-phase enthalpy $\Delta H_g°$ is -38 ± 4,7 kcal/mol at 147 °C[133c].

Therefore, I decided to prepare (according to the published literature procedures) a set of N-protected uracils **6-12** bearing diverse protecting groups: silyl (TMS,[134d] TBDMS[134c]), benzyloxymethyl (BOM),[134a] benzoyl (Bz),[134b] methoxyethoxymethyl (MEM),[134a] *p*-methoxybenzyl (PMB),[134e] and benzyl (Bn).[134e] All of them were tested in C-H arylation reactions with *p*-tolyl iodide (**2a**) in order to test the stability of the protecting groups under the harsh C-H arylation conditions either in the absence (Method A) or in the presence of CuI (Method B) in the presence of Cs_2CO_3 at 160 °C (Scheme 4, Table 3). The Cu-catalyzed reaction in the absence of Pd gave exclusively 6-substituted derivatives but in lower conversions (Method C).



Method A: *p*-Tol-I (**2a**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), $P(C_6F_5)_3$ (0.1 equiv), Cs_2CO_3 (2.5 equiv), DMF, 160 °C, 48 h; **Method B**: *p*-Tol-I (**2a**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), $P(C_6F_5)_3$ (0.1 equiv), CuI (3 equiv), Cs_2CO_3 (2.5 equiv), DMF, 160 °C, 48 h; **Method C:** *p*-Tol-I (**2a**, 2 equiv), CuI (3 equiv), Cs_2CO_3 (2.5 equiv), DMF, 160 °C, 48 h.

Scheme 4 C-H arylation of diverse protected uracils with *p*-Tol-I (**2a**)

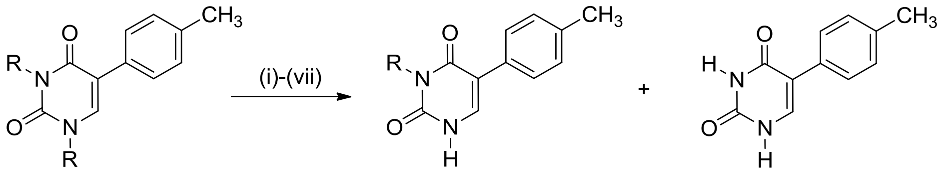
Table 3 C-H Arylation of diverse protected uracils with *p*-Tol-I (**2a**)

Entry	*Comp.*	*Protecting group*		*Method*	*Products*				*Ratio*[b]
		R^1	**R**^{2}		5-isomer	Yield (%)	6-isomer	Yield (%)	
1[a]	**1**	$-CH_3$	$-CH_3$	A	**3a**	54	**4a**	7	86:14
2[a]				B		5		72	6:94
3[a]				C		0		35	0:100
4	**6**	TMS	TMS		unstable				
5	**7**	TBDMS	TBDMS		unstable				
6	**8**	BOM	BOM	A	complex mixture				
7				B	complex mixture				
8	**9**	H	Bz	A	complex mixture				
9				B	complex mixture				
10	**10**	MEM	MEM	A	**13a**	24	**14a**	0	100:0
11				B		-		-	25:75[c]
12	**11**	PMB	PMB	A	**15a**	47	**16a**	6	88:12
13				B		8		46	14:86
14				C		4		34	10:90
15	**12**	Bn	Bn	A	**17a**	45	**18a**	7	86:14
16				B		10		66	14:86
17				C		4		42	9:91

[a] Taken from the previous chapter for comparison; [b] The ratio of 5- and 6-isomer from ^{1}H NMR spectra of a isolated mixture; [c] The isolated yield of mixture **13a** and **14a** was 25 %

Silylated uracils **6** and **7** (entries 4, 5) were unstable under the reaction conditions and quickly decomposed. The use of BOM-protected uracil **8** and 3-benzoyluracil (**9**) gave inseparable complex mixtures (entries 6-9). The MEM-protected uracil **10** was stable but gave only moderate conversions to 5-tolyl (**13a**) (the only product under conditions A, entry 10) and 6-tolyl (**14a**) (major product under conditions B, entry 11) derivatives. The most stable and efficient protective groups were the benzyl-type substituents: PMB or Bn. The corresponding benzylated uracils **11** and **12** reacted in almost the same manner and efficiency as the parent 1,3-dimethyluracil (**1**). The reactions in the absence of CuI (conditions A, entries 12 and 15) gave the 5-tolyluracils **15a** or **17a** as major products (ca 7:1) in acceptable yields (47 % and 45 %, respectively). The Pd-catalyzed reactions in the presence of CuI (conditions B, entries 13, 16) provided the 6-tolyluracils **16a** or **18a** as major products (ca 6:1) in reasonable yields (46 % and 66 %, respectively). The Cu-mediated reactions in the absence of Pd gave lower conversions (entries 14, 17).

The next task was to develop an efficient deprotection protocol for the benzylated aryluracils. The methods were tested on PMB- and Bn-protected 5-tolyluracils **15a** and **17a** (Scheme 5, Table 4). The deprotection of bis-PMB-uracil **15a** was attempted by treatment with neat refluxing TFA,[135] $Ce(NH_4)_2(NO_3)_6$[134e] and DDQ[136] (entries 1-3), but all these reactions were unsuccessful (either no reaction or complex mixtures). Catalytic transfer hydrogenolysis[137] with ammonium formate over 10 % Pd/C (1.1 equiv) gave only selective cleavage of one PMB group at N1 to afford monoprotected 3-PMB-derivative **19a** in 82 % yield (entry 4). Only the treatment of **15a** with BBr_3,[138] in the pressure tube at 140 °C led to complete cleavage of both PMB groups to give the desired 5-tolyluracil (**21a**) in moderate yield of 62 % (entry 5). Deprotection of benzyl protected uracil **17a** was performed using catalytic transfer hydrogenation with ammonium formate over 10 % Pd/C.[137] The use of 1.1 equiv of Pd/C provided a complete and efficient deprotection to give uracil **21a** in almost quantitative yield (entry 7). Decrease of the loading of Pd/C to 0.54 equiv led to incomplete deprotection giving the 3-benzyluracil **20a** as the major product in 80 % yield accompanied by only minor amount of **21a** (15 %). The use of BBr_3[138] in refluxing xylene converted protected uracil **17a** to uracil **21a** in 15 % yield.



15a, 17a **19a, 20a** **21a**

Scheme 5 Deprotection of **15a**, **17a**

Table 4 Deprotection of **15a**, **17a**

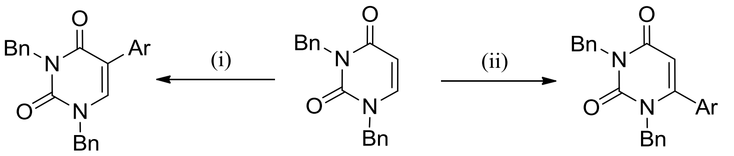
Entry	*Comp.*	***R***	*Reagents*	*Yield of* ***19a/20a*** *(%)*	*Yield of* ***21a*** *(%)*
1	**15a**	PMB	TFA [i]	0	0
2			$Ce(NH_4)_2(NO_3)_6$ [ii]	complex mixture	complex mixture
3			DDQ [iii]	0	0
4			NH_4HCO_2, 10 % Pd/C (1.1 equiv) [iv]	82 (**19a**)	0
5			BBr_3 [v]	0	62
6	**17a**	Bn	NH_4HCO_2, 10 % Pd/C (0.54 equiv) [vi]	80 (**20a**)	15
7			NH_4HCO_2, 10 % Pd/C (1.1 equiv) [iv]	0	98
8			BBr_3 [vii]	0	15

[i] TFA; reflux; 65 °C; [ii] $Ce(NH_4)_2(NO_3)_6$ 4 equiv, CH_3CN/H_2O 3:1, r.t.; 3 h; [iii] DDQ, DCM/H_2O 5:1, r.t., 3.5 days; [iv] 10 % Pd/C (1.1 equiv), NH_4HCO_2, MeOH, 72 °C, 17 h; [v] BBr_3, *m*-xylene, pressure tube 140 °C, 5 h; [vi] 10 % Pd/C (0.54 equiv), NH_4HCO_2, MeOH, 72 °C, 17 h; [vii] BBr_3, *m*-xylene, reflux, 140 °C, 19 h.

3.1.3. Synthesis of 5- and 6-arylated free uracils

3.1.3.1. Synthesis of 5- and 6-aryl-1,3-dibenzyluracils

On the basis of the above mentioned results, I selected Bn-protected uracil for the preparation of arylated uracil bases. 1,3-Dibenzyluracil (**12**) was used as a starting compound in a series of direct C-H arylations with diverse aryl halides **2a-2g** under the above mentioned conditions (A) $Pd(OAc)_2$, $P(C_6F_5)_3$ in the presence of Cs_2CO_3 and (B) the same catalyst and base in the presence of 3 equiv of CuI (Scheme 6, Table 5).



17a-g
major product

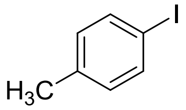
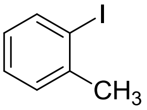
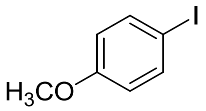
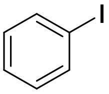
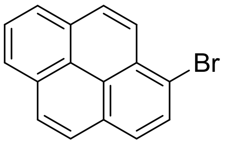
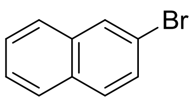
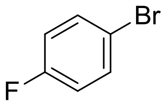
12

18a-g
major or the only product

(i) **Method A**: Ar-X (**2a-g**, 2 equiv), Pd(OAc)$_2$ (0.05 equiv), P(C$_6$F$_5$)$_3$ (0.1 equiv), Cs$_2$CO$_3$ (2.5 equiv), DMF, 160 °C, 48 h; (ii) **Method B**: Ar-X (**2a-g**, 2 equiv), Pd(OAc)$_2$ (0.05 equiv), P(C$_6$F$_5$)$_3$ (0.1 equiv), CuI (3 equiv), Cs$_2$CO$_3$ (2.5 equiv), DMF, 160 °C, 48 h.

Scheme 6 Preparative C-H arylations of 1,3-dibenzyluracil (**12**)

Table 5 C-H arylations of 1,3-dibenzyluracil (**12**) with diverse aryl halides

Entry	*Ar-X*		*Method*	*Yield of **17a-g***	*Yield of **18a-g***	*Ratio*[a] ***17:18***
1		**2a**	A	45 %	7 %	87:13
2			B	10 %	66 %	13:87
3		**2b**	A	70 %	18 %	80:20
4			B	0 %	28 %	0:100
5		**2c**	A	45 %	9 %	83:17
6			B	12 %	38 %	24:76
7		**2d**	A	47 %	8 %	85:15
8			B	7 %	42 %	14:86
13		**2e**	A	25 %	3 %	89:11
14			B	8 %	50 %	14:86
11		**2f**	A	19 %	4 %	83:17
12			B	8 %	33 %	20:80
9		**2g**	A	49 %	7 %	88:12
10			B	8 %	24 %	25:75

[a] The ratio of a isolated compounds **17** and **18**

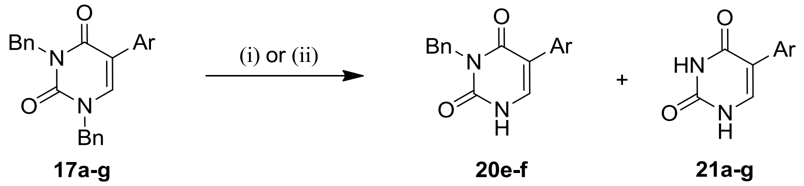
The reactions in the absence of CuI (Method A) gave 5-aryl-1,3-dibenzyluracils **17a-g** as major products (selectivities from 4:1 to 9:1) in 19 - 70 % yields (entries 1, 3, 5, 7, 9, 11, 13). In all cases minor amounts of the other regioisomer (6-aryluracils **18a-g**) were also isolated. More bulky and less reactive aryl bromides **2e** and **2f** gave generally lower yields. The reactions in the presence of CuI (Method B) gave predominantly (selectivities from 3:1 to 7:1) or even exclusively (for **2b**) 6-aryl-1,3-dibenzyluracils **18a-g** in 24 - 66 % yields (entries 2, 4, 6, 8, 10, 12, 14). The regioisomers were separable by column chromatography on silica (1 % of ethyl acetate in toluene) and were assigned by HMBC NMR spectroscopy. Both electron-rich (2-bromothiophene, 2-bromofuran) and electron-poor (3-iodopyridine, 9-benzyl-6-iodopurine) hetaryl halides were also examined in these reactions under conditions A and B, but in all cases the reactions did not proceed. Apparently this methodology is only applicable to carbocyclic aryl halides.

3.1.3.2. Deprotection of 5- and 6-aryl-1,3-dibenzyluracils

Two different cleavage procedures D (10 % Pd/C, ammonium formate, CH_3OH, refux, 17 h) and E (BBr_3, *m*-xylene, 140 °C, pressure tube, 5h) were further used in deprotection of 5- and 6-aryl-1,3-dibenzyluracils **17**, **18**.

The 5-aryl isomers **17a-d** and 6-aryl isomers **18a-d** bearing small electron-rich aryl groups were readily deprotected by transfer hydrogenolysis by ammonium formate over Pd/C (Method D) to give the desired free 5-aryl-uracil bases **21a-d** (Scheme 7, Table 6, entries 1-4) and 6-aryluracil bases **23a-d** (Scheme 8, Table 7, entries 1-4) in quantitative yields. In the case of compounds bearing bulky aromatic substituents (pyrenyl or naphtyl) at position 5- and 6- (**17e**, **17f**, **18e,** and **18f**), I observed only partial deprotection under conditions D giving 3-benzyluracils **20e**, **20f** (Scheme 7, Table 6, entries 5, 6) and **22e, 22f** (Scheme 8, Table 7, entries 5, 6) as major products and the rest was in all cases the starting material. The catalytic hydrogenolysis over Pd/C was not improved even by the increase of the amount of Pd/C or by the use of H_2 or 1,4-cyclohexadiene instead of ammonium formate. The transfer hydrogenation of the 4-fluorophenyl derivatives **17g** and **18g** gave inseparable mixtures mainly with the products of dehalogenation. Therefore, I used the 5-hours treatment with BBr_3 in overheated xylene in the pressure tube (Method E) which afforded quantitatively the fully deprotected 6-aryluracil **23g** (Scheme 8, Table 7, entry 7). The corresponding

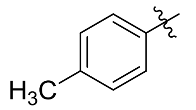
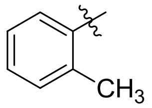
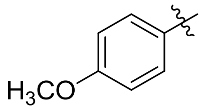
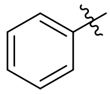
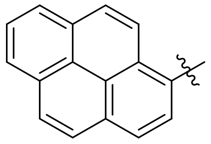
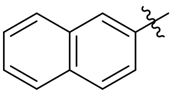
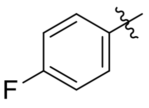
5-(4-fluorophenyl)uracil **21g** was unstable under these conditions and decomposed. Decrease of the temperature to 100 °C or r.t. did not lead to the desired product **21g** too. Under conditions E using BBr_3, the deprotection of **17e, 17f** and **18e, 18f** proceeded readily to afford the desired uracil bases **21e, 21f** (Scheme 7, Table 6, entries 5, 6) and **23f** (Scheme 8, Table 7, entry 6) in almost quantitative yields, apart from **23e,** obtained in moderate 38 % yield (Scheme 8, Table 7, entry 5).

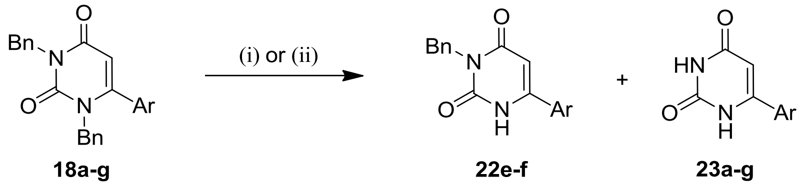


(i) **Method D**: 10 % Pd/C, NH_4HCO_2 , CH_3OH, refux, 17 h; (ii) **Method E**: BBr_3, *m*-xylene, 140 °C, pressure tube, 5 h.

Scheme 7 Deprotection of 5-regioisomers **17a-g**

Table 6 Deprotection of 5-regioisomers **17a-g**

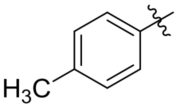
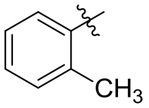
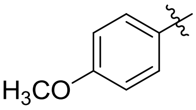
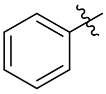
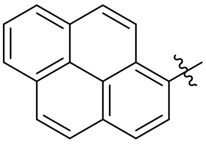
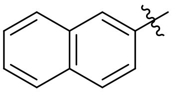
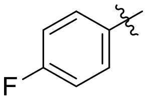
Entry	*Compounds*	*Ar*	*Deprotection method*	*Yield of* ***21a-g***
1	**17a**	 H3C	D	98 %
2	**17b**	 CH3	D	97 %
3	**17c**	 H3CO	D	95 %
4	**17d**		D	97 %
5	**17e**		D	0 % (67 % **20e**)
			E	98 %
6	**17f**		D	0 % (42 % **20f)**
			E	63 %
7	**17g**	 F	D	complex mixture
			E	decomposition



(i) **Method D**: 10 % Pd/C, NH_4HCO_2 , CH_3OH, refux, 17 h; (ii) **Method E**: BBr_3, *m*-xylene, 140 °C, pressure tube, 5 h.

Scheme 8 Deprotection of 6-regioisomers **18a-g**

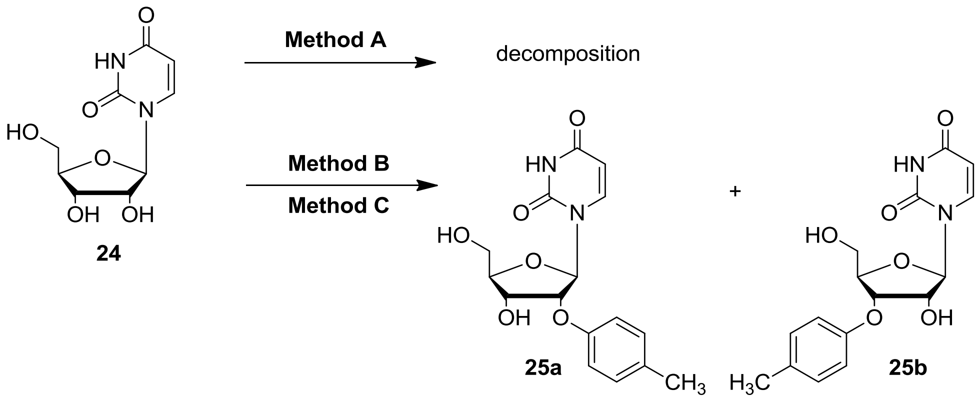
Table 7 Deprotection of 6-regioisomers **18a-g**

Entry	*Compounds*	*Ar*	*Deprotection method*	*Yield of* ***23a-g***
1	**18a**		D	97 %
2	**18b**		D	94 %
3	**18c**		D	92 %
4	**18d**		D	94 %
5	**18e**		D E	0 % (83% **22e**) 38 %
6	**18f**		D E	0 % (98% **22f**) 70 %
7	**18g**		D E	complex mixture 98 %

All the title compounds **17a-f** and **18a-g** were tested *in vitro* for their cytostatic activity against human cancer cell lines (HL-60, HeLa S3, CCRF-CEM and HepG2), but no significant effect was found.

3.1.4. Direct C-H arylation of nucleosides

In order to extend the use of C-H arylations to nucleosides, I have tried to apply the above mentioned procedures A, B, C in reaction with unprotected uridine (**24**). Our previously reported protocols for direct C–H arylation used rather harsh conditions (160 °C) and long reaction times (48 h) to achieve efficient conversions. Such conditions are not compatible with rather labile nucleosides and therefore, for such applications, the procedures where adapted by lowering the reaction temperature to 130 °C and/or shortening the reaction time to 17h. In a model reaction with *p*-tolyl iodide (**2a**), in the absence of CuI (condition A), I observed only complex mixture of products, most probably due to the decomposition of uridine (**24**). The Pd-catalyzed reaction in the presence of 3 equiv of CuI (conditions B) led surprisingly to mixture of 2'-*O*- (**25a)** and 3'-*O*-(*p*-tolyl)-uridine (**25b)** (ratio ca 3:7), products of *O*-arylation in 23 % yield. Under reaction condition in the absence of a Pd catalyst and a ligand and in the presence of 3 equiv of CuI (condition C) again only formation of products of *O*-arylation, in ratio 4:6 (**25a**:**25b)** was observed. In all cases no products of 5- or 6-arylation were observed (Scheme 9).

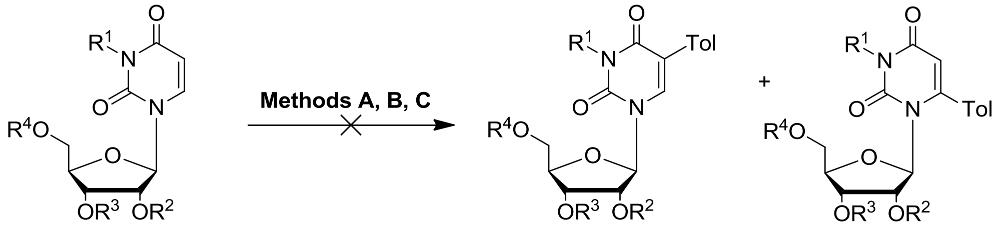


Method	Yield of mixture	Ratio of **25a:25b**
B	23 %	3 : 7
C	49 %	4 : 6

Method A: *p*-Tol-I (**2a**, 2 equiv), Pd(OAc)$_2$ (0.05 equiv), P(C$_6$F$_5$)$_3$ (0.1 equiv), Cs$_2$CO$_3$ (2.5 equiv), DMF, 130 °C; **Method B**: *p*-Tol-I (**2a**, 2 equiv), Pd(OAc)$_2$ (0.05 equiv), P(C$_6$F$_5$)$_3$ (0.1 equiv), CuI (3 equiv), Cs$_2$CO$_3$ (2.5 equiv), DMF, 130 °C; **Method C:** *p*-Tol-I (**2a**, 2 equiv), CuI (3 equiv), Cs$_2$CO$_3$ (2.5 equiv), DMF, 130 °C.

Scheme 9 Arylation of uridine (**24)** with *p*-tolyl iodide (**2a**)

With these results in hand, I was considering using the suitable protected uridine for direct arylation with *p*-tolyl iodide (**2a**). Therefore, I have prepared several protected uridines **26-28**: 2',3',5'-Tri-*O*-benzoyluridine[139] (**26**), 3-*N*-benzoyl-2',3',5'-tri-*O*-benzoyluridine[139] (**27**), and 2',3'-*O*-isopropylideneuridine[140] (**28**). However, the experiments under conditions A, B, C (temperatures 80 °C, 100 °C or 130 °C) provided the partial *N*-deprotection of benzoyl in case of 3-*N*-benzoyl-2',3',5'-tri-*O*-benzoyluridine (**27**) or no reaction in cases 2',3',5'-tri-*O* –benzoyluridine (**26**) and 2',3'-*O*-isopropylideneuridine (**28**). The formation of desired 5- or 6- arylated products was not observed (Scheme 10).



26, R^1 = H, R^2, R^3, R^4 = Bz
27, R^1, R^2, R^3, R^4 = Bz
28, R^1, R^4 = H, R^2, R^3 = isopropylidene

Method A: *p*-Tol-I (**2a**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), $P(C_6F_5)_3$ (0.1 equiv), Cs_2CO_3 (2.5 equiv), DMF, 130 °C; **Method B**: *p*-Tol-I (**2a**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), $P(C_6F_5)_3$ (0.1 equiv), CuI (3 equiv), Cs_2CO_3 (2.5 equiv), DMF, 130 °C; **Method C:** *p*-Tol-I (**2a**, 2 equiv), CuI (3 equiv), Cs_2CO_3 (2.5 equiv), DMF, 130 °C.

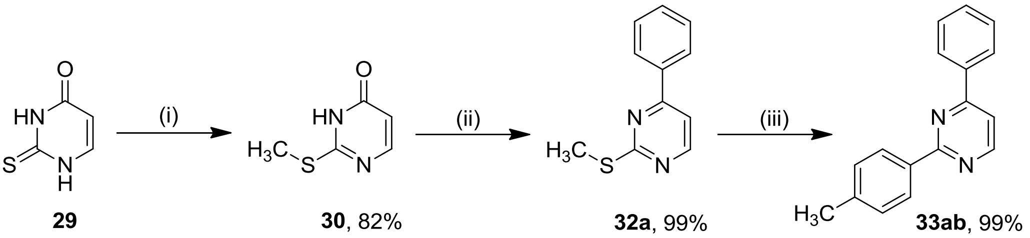
Scheme 10 Arylation of protected uridine **26, 27, 28** with *p*-tolyl iodide (**2a**)

3.2. Synthesis of 2,4-diarylpyrimidines: Reaction development and scope

A variety of synthetic methods has been reported for preparation of arylated pyrimidines mostly based on heterocyclic condensation reactions.[40, 141] Another important approach for the synthesis of this class of compounds (and generally other diarylheterocycles) is the regioselective double cross-coupling. Synthesis of some 2,4-diarylpyrimidines by consecutive double Suzuki reactions of 2,4-dihalopyrimidines was reported[50, 54, 55, 56, 59, 142] but, in many cases, the regioselectivities were not complete and/or yields were moderate. To overcome these problems, a longer sequence based on the coupling of 2-chloro-4-methoxypyrimidine followed by demethylation, chlorination and another coupling was also developed.[59] Recently, the Liebeskind-Srogl cross-couplings of 2,4-bis(methylsulfanyl)-pyrimidine with arylstannanes or boronic acids were reported with reasonable (but still not complete) regioselectivities.[143] Therefore, alternative improved methods for the synthesis of diarylpyrimidines with complete regioselectivity are warranted, in particular for synthesis of combinatorial libraries of derivatives.

Our synthesis starting from cheap 2-thiouracil (**29**) was envisaged based on two different orthogonal (and thus inherently chemoselective) reactions. The first one was phosphonium-mediated Suzuki coupling which is generally feasible with pyridones and related tautomerizable oxo-nitrogen heterocycles.[144] The second reaction of choice was the Liebeskind-Srogl cross-coupling[145] that generally proceeds with methylsulfanyl derivatives of arenes and heterocycles. The combination of these two reactions should result in a fully regioselective way for the synthesis of the title 2,4-disubstituted pyrimidines. Although, the regioselectivity of the Liebeskind-Srogl reaction[62a, 146] and phosphonium coupling[147] over the classical Suzuki or Stille coupling has been reported, the combination of these two reactions in one sequence for double arylation is unknown.

Thiouracil (**29**) itself underwent neither phosphonium-mediated Suzuki coupling nor the Liebeskind-Srogl reaction under standard or microwave[148] conditions. Therefore, it was necessary to make some structural changes to the skeleton of the molecule of thiouracil (**29**) and examine the phosphonium-mediated Suzuki coupling and/or the Liebeskind-Srogl reaction. Thus, I tried to perform either the C-H arylation,[132] or the N-arylation[149, 79c] of thiouracil (**29**), but after all examined reactions I observed products of the S-arylations. When thiouracil (**29**) was subjected to the reaction for protection of nitrogen[134e] with benzyl bromide, products of benzylation on sulfur atom were observed too. Therefore, I desided to advisedly convert thiouracil (**29**) by known methylation procedure[150] to 2-(methylsulfanyl)-4-oxo(3*H*)pyrimidine (**30**) which served as the starting compound for examination of further cross-couplings. Since this compound **30** did not undergo the Liebeskind-Srogl reaction neither under microwave irradiation nor conventional reflux conditions[62a, 148, 151] and I tried also the C-H arylation[132] and the N-arylation,[149, 79c] but these reactions did not work on 2-(methylsulfanyl)-4-oxo(3*H*)pyrimidine (**30**) too. Therefore, I decided to start with the phosphonium-mediated pyridone coupling. After some optimization, I came up with an efficient procedure for the Suzuki coupling of **30** based on the treatment with PyBroP in presence of Et_3N in dioxane, followed by addition of phenylboronic acid (**31a**), $PdCl_2(PPh_3)_2$ and Na_2CO_3 in water and heating at 100 °C for 4 h. The desired 2-(methylsulfanyl)-4-phenylpyrimidine (**32a**) was isolated in quantitative yield. No arylation at the position 2 was observed. Then, the Liebeskind-Srogl reaction of **32a** with *p*-tolylboronic acid (**31b**) in presence of Pd-catalyst and CuTC was attempted and the optimal conditions involved MW heating in THF at 100 °C for 1 h. This procedure gave the desired 4-phenyl-2-(*p*-tolyl)pyrimidine (**33ab**) quantitatively (Scheme 11). The correct regioselectivity of the reaction sequence was verified by X-ray crystal structure of **33ab** (Figure 8).



(i) MeI, NaOH, H_2O–EtOH, 60 °C, 20 min; (ii) PyBroP (1.2 equiv), Et_3N (3 equiv), 1,4-dioxane, r.t., 2 h; then $PhB(OH)_2$ (**31a**, 2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), Na_2CO_3 (5 equiv), H_2O, 100 °C, 4 h; (iii) *p*-$TolB(OH)_2$ (**31b**, 1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), CuTC (3 equiv), THF, 100 °C, MW, 1 h.

Scheme 11 The synthesis of 2,4-disubstituted pyrimidine **33ab** from 2-thiouracil (**29**)

This two-step sequence starting from compound **30** apparently has the potential for the synthesis of a series of pyrimidines bearing two different aryl groups at positions 2 and 4. To verify this claim and to prepare some derivatives relevant for biological activity screening, I designed 2,4-disubstituted pyrimidines bearing different combinations of methoxy- or methylenedioxyphenyl groups as heterocyclic analogues of some tubulin-binding natural products known as potent cytostatics (i.e. combretastatins).[152] Some other types of diarylheterocycle analogues of combrestatin exhibited high cytostatic activities.[153]

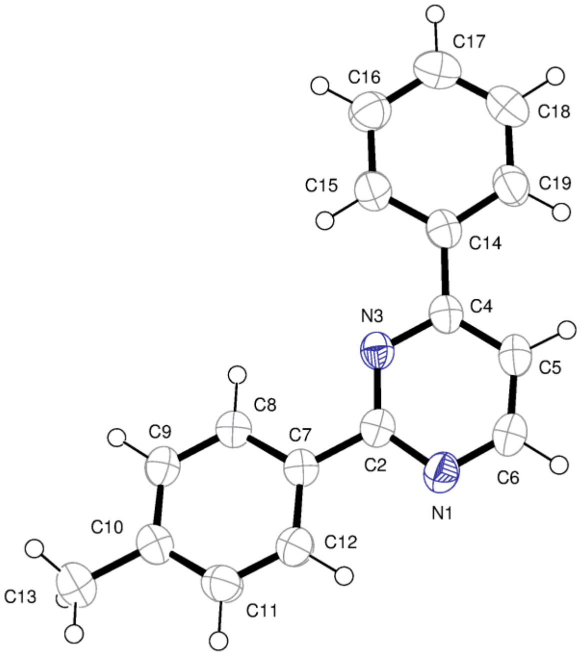
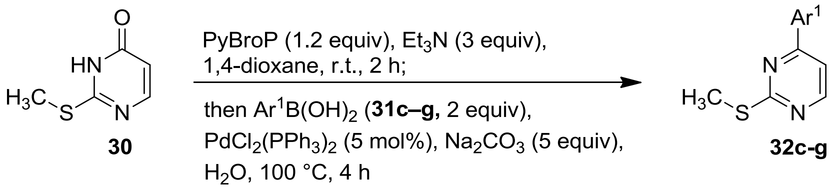


Figure 8 ORTEP drawing of **33ab** with the atom numbering scheme. Thermal ellipsoids are drawn at the 50 % probability level.

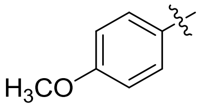
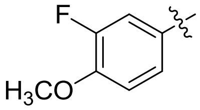
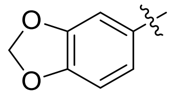
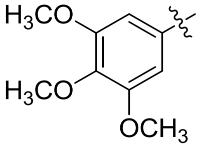
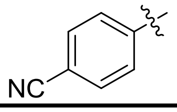
3.2.1. Synthesis of 4-aryl-2-(methylsulfanyl)pyrimidines

To access the target series of 2,4-diarylpyrimidine derivatives, the starting 2-(methylsulfanyl)-4-oxo(3*H*)pyrimidine (**30**) was first subjected to the PyBroP-mediated cross couplings with a series of four substituted (4-methoxy-, 3-fluoro-4-methoxy-, 3,4-methylenedioxy- and 3,4,5-trimethoxy-) phenylboronic acids **31c-f** (Scheme 12). All these reactions proceeded smoothly under the previously optimized conditions to give chemoselectively the series of 4-aryl-2-(methylsulfanyl)pyrimidines **32c-f** in good to excellent yields (70 - 96 %) (Table 8, entries 1-4). 4-Cyanophenylboronic acid (**31g**) was also tried, in order to verify electron-poor arylboronic acid in this reaction and this boronic acid reacted in the same manner as the electron-rich and neutral arylboronic acids (Scheme 12, Table 8, entry 5).



Scheme 12 Preparation of 4-aryl-2-(methylsulfanyl)pyrimidines **32c-g**

Table 8 Preparation of 4-aryl-2-(methylsulfanyl)pyrimidines **32c-g**

Entry	*Product*	*Ar^1*	*Yield of* ***32***
1	**32c**		75 %
2	**32d**		70 %
3	**32e**		77 %
4	**32f**		96 %
5	**32g**		80 %

The mechanistic studies of the phosphonium-mediated cross couplings have been thoroughly discussed.[154] Phosphonium mediated Suzuki-cross coupling reactions of 2-(methylsulfanyl)-4-oxo(3*H*)pyrimidine (**30**) presumably proceed through the mechanism shown in Figure 9.

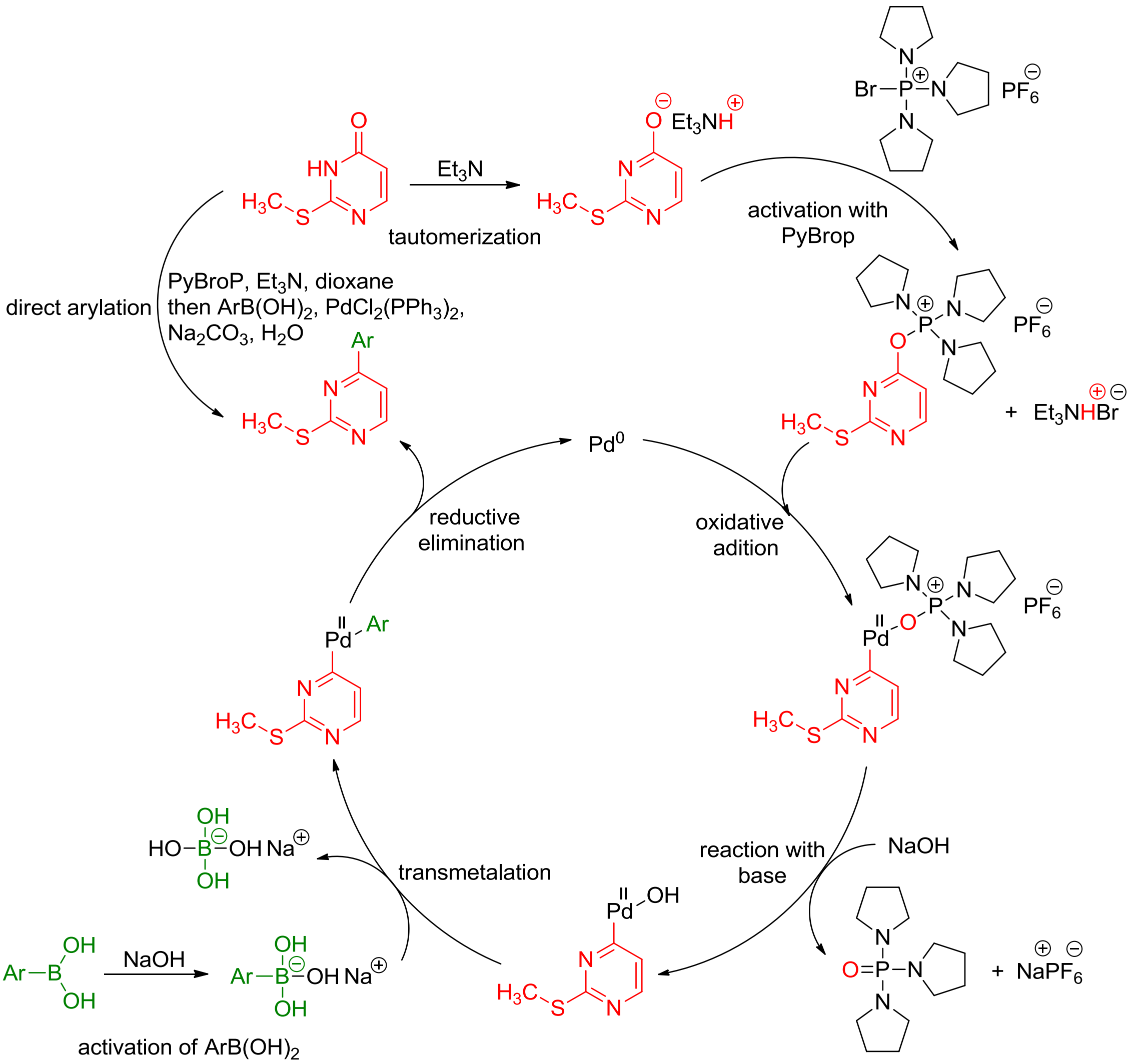
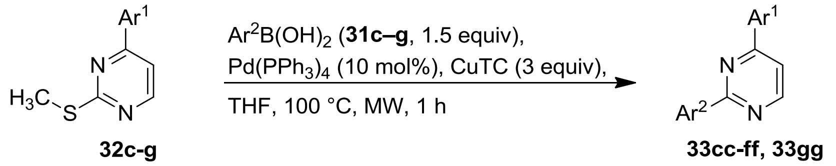


Figure 9 Proposed mechanism for the phosphonium-mediated Suzuki coupling of 2-(methylsulfanyl)-4-oxo(3*H*)pyrimidine (**30**)

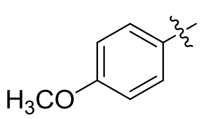
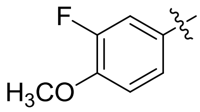
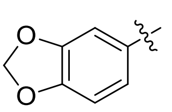
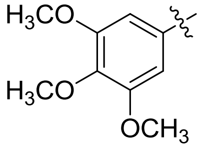
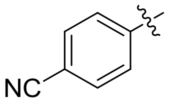
3.2.2. Synthesis of 2,4-diarylpyrimidines

Subsequently, I continued with the synthesis of 2,4-diarylpyrimidines and each of the thioethers **32c-f** underwent the Liebeskind-Srogl reactions with the same series of four arylboronic acids **31c-f** under the same conditions as for the synthesis of **33ab** (Scheme 13). Most of the reactions proceeded uneventfully to give the series of sixteen desired 2,4-diarylpyrimidines **33cc-ff** in good to quantitative yields (Table 9, entries 1-16). Only the reactions of the most electron-rich 2-(methylsulfanyl)-4-(3,4,5-trimethoxyphenyl)pyrimidine **32f** did not proceed with quantitative conversions giving the final products **33fc-ff** in good yields (51 - 80 %) along with part of the starting compound (Table 9, entries 13-16). Using 3,4,5-trimethoxyphenylboronic acid (**31c**) as a coupling partner I observed lower yields because 3,3',4,4',5,5'-hexamethoxy-1,1'-biphenyl was formed as a byproduct (Table 9, entries 4, 8, 16). No formation of biaryls was observed in any of the other cases. Electron-poor 4-cyanophenylboronic acid (**31g**) was also examined in this reaction with 4-(2-(methylsulfanyl)pyrimidin-4-yl)benzonitrile (**32g**) and the reaction proceeded quantitatively (Scheme 13, Table 9, entry 17). Thus, this facile two-step sequence gave the target 2,4-diarylpyrimidines in good overall yields of 49 - 79 % with exclusive chemoselectivity.



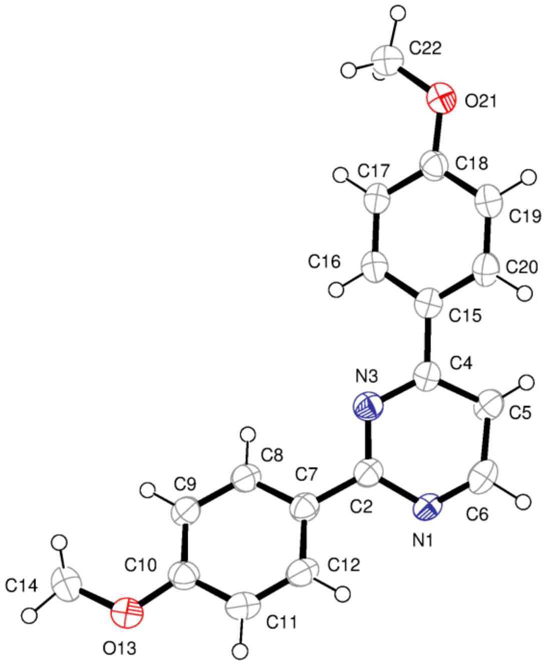
Scheme 13 Preparation of 2,4-diarylpyrimidines **33cc-33ff, 33gg**

Table 9 Preparation of 2,4-diarylpyrimidines **33cc-33ff, 33gg**

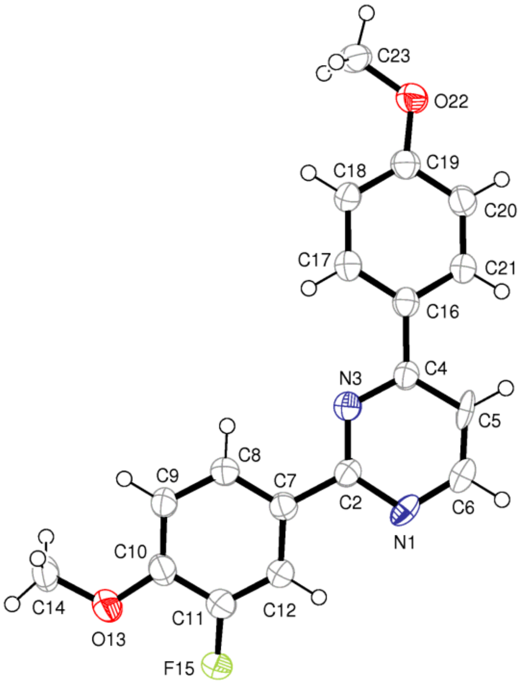
Entry	*Product*	*Ar¹*	*Ar²*	*Yield of **33***
1	**33cc**		4-(MeO)C_6H_4	75 %
2	**33cd**		3-F-4-(MeO)C_6H_3	89 %
3	**33ce**		3,4-(OCH_2O)C_6H_3	72 %
4	**33cf**		3,4,5-$(MeO)_3C_6H_2$	66 %
5	**33dc**		4-(MeO)C_6H_4	99 %
6	**33dd**		3-F-4-(MeO)C_6H_3	99 %
7	**33de**		3,4-(OCH_2O)C_6H_3	98 %
8	**33df**		3,4,5-$(MeO)_3C_6H_2$	86 %
9	**33ec**		4-(MeO)C_6H_4	98 %
10	**33ed**		3-F-4-(MeO)C_6H_3	98 %
11	**33ee**		3,4-(OCH_2O)C_6H_3	96 %
12	**33ef**		3,4,5-$(MeO)_3C_6H_2$	96 %
13	**33fc**		4-(MeO)C_6H_4	54 %
14	**33fd**		3-F-4-(MeO)C_6H_3	80 %
15	**33fe**		3,4-(OCH_2O)C_6H_3	52 %
16	**33ff**		3,4,5-$(MeO)_3C_6H_2$	51 %
17	**33gg**		4-CNC_6H_4	99 %

Structures of the final products were in some cases determined by X-ray diffraction (Figure 10) and the title compounds **33cc-ff** were tested *in vitro* for their cytostatic activity against human cancer cell lines (HL-60, HeLa S3, CCRF-CEM and HepG2), but no significant effect was found.

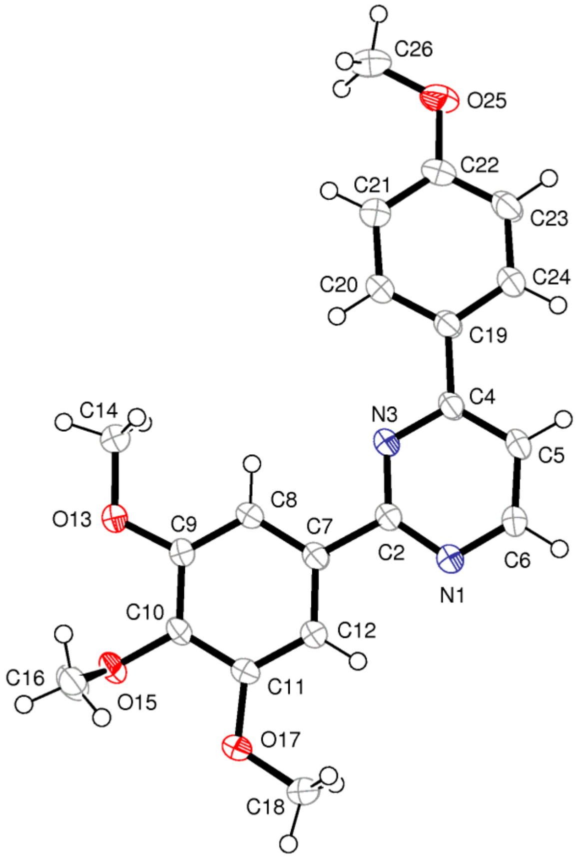
a)



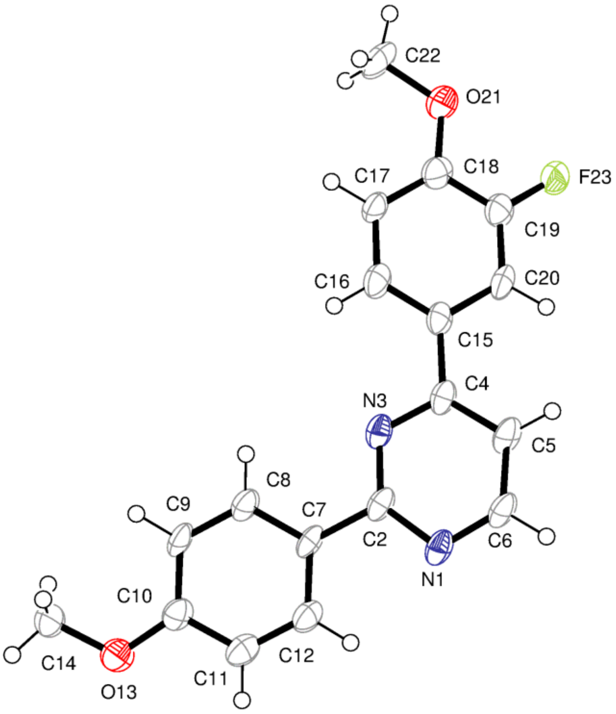
b)



c)


C26
O25
C22
C21
C23
C24
C20
C19
C4
N3
C5
C14
O13
C9
C8
C7
C2
C6
N1
C10
C12
C16
O15
C11
O17
C18

d)


C22
O21
F23
C18
C17
C19
C16
C20
C15
C4
N3
C5
C8
C9
C7
C2
C6
N1
C10
C14
O13
C11
C12

e)

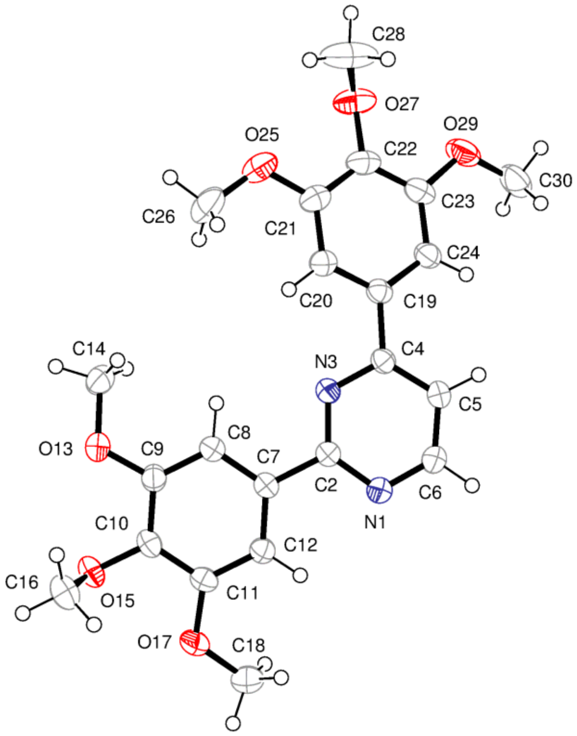


Figure 10 ORTEP drawings of **33cc** (a), **33cd** (b), **33cf** (c), **33dc** (d) and **33ff** (e) with the atom numbering scheme. Thermal ellipsoids are drawn at the 50 % probability level.

The reaction mechanism for the Cu^I-mediated Pd^0-catalyzed coupling has been intensively investigated.[145b, 155] Proposed mechanism for the Liebeskind-Srogl cross coupling reaction of 4-aryl-2-(methylsulfanyl)pyrimidines (**32**) is shown in Figure 11.

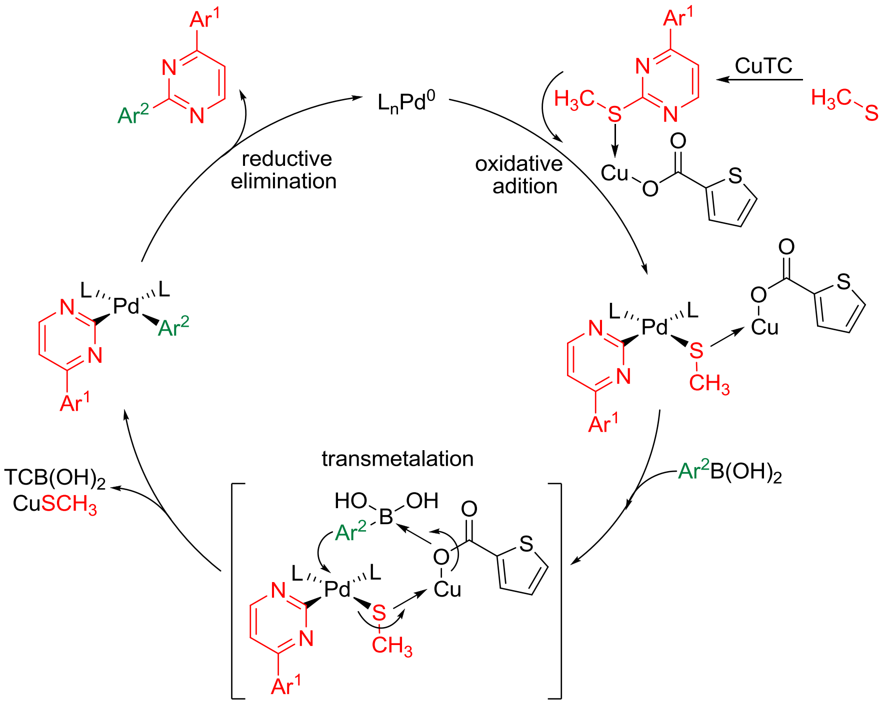


Figure 11 Proposed mechanism for the Liebeskind-Srogl cross coupling reaction of 4-aryl-2-(methylsulfanyl)pyrimidines (**32**)

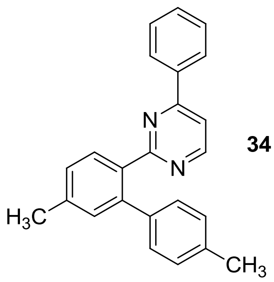
3.2.3. Attempted direct C-H arylations of 2,4-diarylpyrimidines

In order to apply direct C-H arylation on 2,4-diarylpyrimidines which would lead to multisubstituted pyrimidines, I examined several conditions for direct C-H arylation of 4-phenyl-2-(*p*-tolyl)pyrimidine (**33ab**) with *p*-tolyl iodide (**2a**) as an aryl reagent (Table 10). The study started by screening of my previously reported conditions[132, 156] using $Pd(OAc)_2$ catalyst in combination with $P(C_6F_5)_3$ either in the absence or in the presence of CuI or using the Cu-catalyzed reaction in the absence of Pd-catalyst (Table 10, entries 1-3), but no desired arylated compounds were observed under any of these conditions. Consecutive screening of various catalytical systems under conventional heating or microwave irradiation also did not lead to any desired products (Table 10, entries 4-15). In nearly all cases mainly the starting material or some traces of undefined products were observed in reaction mixtures. In only one case, when using [RhCl(CO)$_2$]$_2$ as a catalyst[157] (Table 10, entry 9) I obtained reasonable amount of the byproduct of *ortho*-arylation on tolyl moiety of 4-phenyl-2-(*p*-tolyl)pyrimidine (**33ab**). Resulting 2-(4',5-dimethyl-[1,1'-biphenyl]-2-yl)-4-phenylpyrimidine (**34**) was isolated in 10 % yield.

Table 10 C-H arylation of 4-phenyl-2-(*p*-tolyl)pyrimidine (**33ab**) with *p*-tolyl iodide (**2a**)

Entry	*Catalytical system*	*Additive*	*Base*	*Solvent*	*Temper. (°C)*	*Time*
1	Pd(OAc)$_2$[132] P(C$_6$F$_5$)$_3$	-	Cs$_2$CO$_3$	DMF	160	48 h
2	Pd(OAc)$_2$[132] P(C$_6$F$_5$)$_3$	CuI	Cs$_2$CO$_3$	DMF	160	48 h
3	CuI[132]	-	Cs$_2$CO$_3$	DMF	160	48 h
4	CuI	-	Cs$_2$CO$_3$	DMF	100 (MW)	2 h
5	CuI[100b] phenantroline	-	*t*BuOLi	DMF	125	18 h
6	CuI phenantroline	-	*t*BuOLi	DMF	100 (MW)	2 h
7	Na$_2$PdCl$_4$ cataCXium F sulf	- -	K$_2$CO$_3$	H$_2$O	95	23 h
8	-[105a]	-	*t*BuOK	DMF	80 (MW)	0.5 h
9[a]	[RhCl(CO)$_2$]$_2$[157]	-	-	dioxane	175	20 h
10	[RhCl(CO)$_2$]$_2$	-	-	DMF	160 (MW)	1 h
11	Cy$_3$PAuCl[158]	-	*t*BuOK	DMF	100	22 h
12	Cy$_3$PAuCl	PivOH/ Ag$_2$O	K$_2$CO$_3$	DMF	50	19 h
13	Cy$_3$PAuCl	PivOH/ Ag$_2$O	K$_2$CO$_3$	DMF	160	12 h
14	Pd(OAc)$_2$[159]	*o*-NO$_2$-C$_6$H$_4$-COOH	Ag$_2$O	DMF	25	15 h
15	Pd(OAc)$_2$	*o*-NO$_2$-C$_6$H$_4$-COOH	Ag$_2$O	DMF	160	24 h

[a] 10 % of 2-(4',5-dimethyl-[1,1'-biphenyl]-2-yl)-4-phenylpyrimidine (**34**)



34

Due to unsuccessful attempts when *p*-tolyl iodide (**2a**) was used as a coupling partner, I tried to change the aryl reagent to *p*-tolylboronic acid (**31b**). It was subjected in reactions with 4-phenyl-2-(*p*-tolyl)pyrimidine (**33ab**) using AgNO$_3$ or Mn(OAc)$_3$

catalyst (Table 11, entries 1-4), but these couplings did not meet with the success. Palladium/silver catalyzed decarboxylative direct arylation of **33ab** with 2-nitrobenzoic acid was also examined, but did not work (Table 11, entry 5).

Table 11 C-H arylation of 4-phenyl-2-(*p*-tolyl)pyrimidine (**33ab**) with *p*-tolylboronic acid[a] (**31b**) or 2-nitrobenzoic acid[b]

Entry	*Catalytical system*	*Additive*	*Solvent*	*Temperature*	*Time*
1	$AgNO_3/(NH_4)_2S_2O_8$[a160]	TFA	DCM/H_2O 1:1	r.t. (air)	19 h
2	$AgNO_3/(NH_4)_2S_2O_8$[a]	TFA	DCM/H_2O 1:1	r.t. (argon)	12 h
3	$AgNO_3/(NH_4)_2S_2O_8$[a]	TFA	DCM/H_2O 1:1	reflux	19 h
4	$Mn(OAc)_3.2H_2O$[a161]	-	EtOH	170 °C (MW)	15 min
5	$Pd(MeCN)_2Cl_2/Ag_2CO_3$[b162]	-	DMF/DMSO	110 °C	41 h

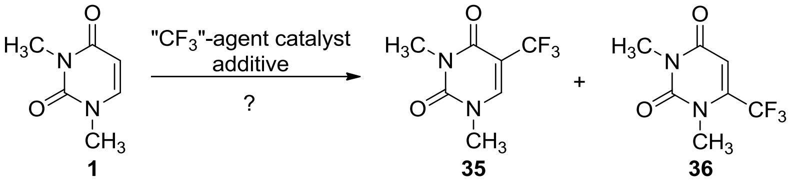
Unfortunately none of above mentioned conditions led to desired 5 or 6 arylated 4-phenyl-2-(*p*-tolyl)pyrimidine (**33ab**). Since only one case the product of *ortho*-arylation was observed, leaving this idea as a non-applicable most probably due to deactivation of desired 5 or 6 positions from the C-H direct arylation perspective, influenced by the presence of aryl substituents on pyrimidine scaffold (**33ab**). The C-H activation at pyrimidine scaffold is probably indeed possible because *ortho*-position of the tolyl substituent is more reactive and probably would be still preferred over an arylation of pyrimidine scaffold.

3.3. Direct trifluoromethylation of 1,3-dimethyluracil and consecutive C-H arylation

3.3.1. Direct trifluoromethylation of 1,3-dimethyluracil: Reaction development and scope

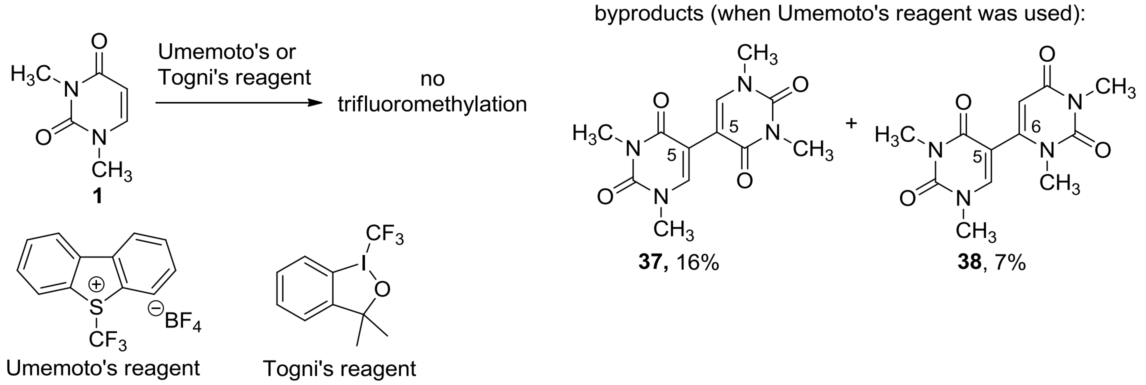
The 5-(trifluoromethyl)uracil and -uridine they were prepared either by heterocyclization[163] or by cross-coupling of 5-halogenouracil derivatives with diverse CF_3-M species in the past.[164] The continuation of my project was to attempt the synthesis of uracil derivatives bearing one trifluoromethyl and one aryl group at positions 5 and 6 by two consecutive C-H activations.

C-H trifluoromethylations of 1,3-dimethyluracil (**1**)[123a,124a] or uracil[125] have been previously reported by radical reactions to proceed at position 5 in good yields. Only trace amounts (< 1 %) of 6-trifluoromethyl-uracil were detected using Fenton oxidation. Therefore, I started my study by systematic screening of diverse trifluoromethylating agents and conditions in analogy to literature (usually C-H trifluoromethylations of other heterocycles)[121,122] in the presence or in the absence of Cu(I) salts in order to see whether the trifluoromethylation of 1,3-dimethyluracil (**1**) proceeds and what is the regioselectivity of formation of either 1,3-dimethyl-5- (**35**) or 6-(trifluoromethyl)uracil (**36**) (Scheme 14).



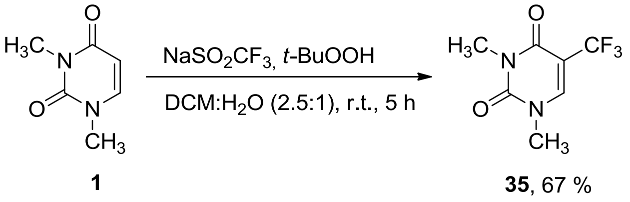
Scheme 14 Screening of diverse trifluoromethylating reagents on 1,3-dimethyluracil (**1**)

The study started by screening of electrophilic trifluoromethylating reagents. The Umemoto's reagent (*S*-(trifluoromethyl)dibenzothiophenium trifluoroborate)[121a] was used in combination with $Pd(OAc)_2$ and/or CuI or $Cu(OAc)_2$ in the presence or absence of $P(C_6F_5)_3$ ligand and/or Cs_2CO_3 or CsF as a base in DMF or DCE at 160 °C. No trifluoromethylation reaction was observed under any of these conditions. Only in the reaction with $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$ and TFA,[121a] formation of unexpected 5,5- (**37**) and 5,6-dimers (**38**) of 1,3-dimethyluracil (**1**) was observed (Scheme 15). This confirms that the C-H activation at positions 5 and 6 is indeed possible but the oxidative dimerization of the heterocycle is preferred over trifluoromethylation. The Togni's reagent (3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole)[121c] was also tried in the presence of CuOAc,[121c] CuTC,[126] $Pd(OAc)_2$ or AuCl with $P(C_6F_5)_3$ or phenanthroline and Cs_2CO_3 or $LiOH.H_2O$ but no trifluromethylation was observed either.



Scheme 15

Next, I tested selected nucleophilic trifluoromethylating agents themselves or after generation of radicals. Rupert's reagent (CF_3SiMe_3)[122a,c] was used in a series of experiments in reaction with **1** in the presence of $Pd(OAc)_2$, $PhI(OAc)_2$, TEMPO and CsF[122a] or in the presence of $Cu(OAc)_2$, phenanthroline, (*t*BuO)$_2$, NaO*t*Bu and NaOAc[122c] but no trifluoromethylation was observed. Only the reaction of **1** with CF_3SiMe_3 in the presence of $Cu(OAc)_2$, phenanthroline, Ag_2CO_3 and KF in DCE[122c] at 80 °C after 12 hours gave the desired 1,3-dimethyl-5-(trifluoromethyl)uracil (**35**) in moderate yield of 27 %. The reaction of **1** with CF_3SO_2Na in the presence of CuI and Cs_2CO_3 did not work. However, the same reagent under radical conditions in the presence of *t*BuOOH at r.t. (analogy to ref.[125]) after 5 hours gave the 5-trifluoromethylated uracil **35** in good yield of 67 % (Scheme 16, X-ray structure of **35** in Figure 12). No formation of 6-(trifluoromethyl)uracil (**36**) was observed in any of the direct C-H activations.



Scheme 16 Preparation of 5-trifluoromethylated uracil **35**

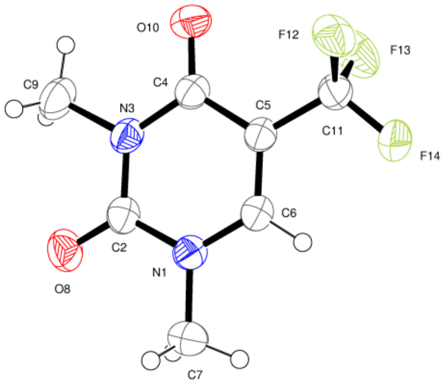
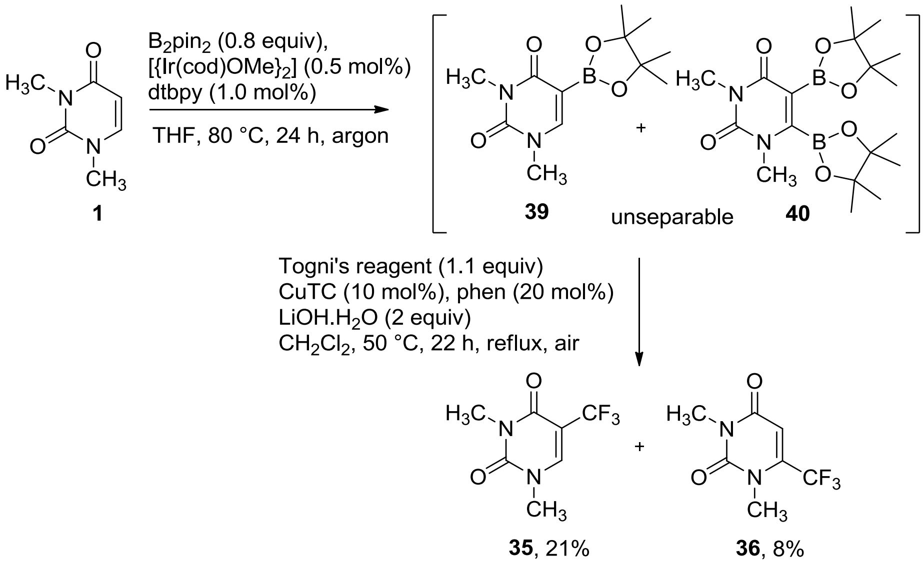


Figure 12 Crystal structure of compound **35** (a, CCDC 945178) with the atom numbering scheme. Thermal ellipsoids are drawn at the 50 % probability level.

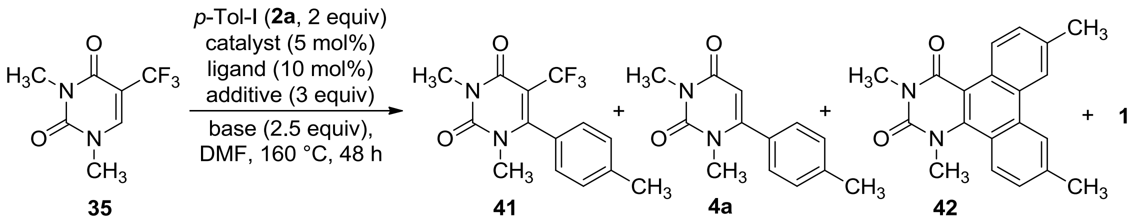
Another possible way to trifluoromethylated heterocycles is based on Ir-catalyzed C-H borylation followed by electrophilic trifluoromethylation.[126] Therefore, I have tried to perform the C-H borylation of **1** with bis(pinacolato)diboron under [{Ir(cod)OMe}$_2$] + di-*tert*-butylbipyridine (dtbpy) catalysis in THF. This reaction led to an unseparable mixture of starting compound **1**, 5-pinacolatoboryl- **39** and 5,6-bis(pinacolatoboryl)uracil **40** in ca. 2:5:3 ratio. Therefore, the whole reaction mixture was only evaporated and directly used in the second step in the reaction with the Togni's reagent, in the presence of CuTC, phenanthroline and LiOH·H$_2$O in air. The two-step sequence then gave 1,3-dimethyl-5-(trifluoromethyl)uracil (**35**) in 21 % and 1,3-dimethyl-6-(trifluoromethyl)uracil (**36**) in 8 % (Scheme 17). Any attempted optimization did not improve the yields of the final trifluoromethylated uracils. Since no 6-(pinacolatoboryl)uracil was observed in the reaction mixture after the borylation, the formation of **36** apparently must have resulted from trifluoromethylation (at position 6) and proto-deborylation (at position 5) of diborylated uracil **40**. Although, no method examined in this thesis gave higher yield than the previously reported MacMillan radical trifluoromethylation,[123a] the synthesis of 1,3-dimethyl-5-(trifluoromethyl)uracil (**35**) by the Baran protocol is also very efficient and it was used for larger scale synthesis of this compound. On the other hand, the borylation/trifluoromethylation sequence gave for the first time a trifluoromethylation at position 6 (though in low yield).



Scheme 17 Ir-catalyzed C-H borylation of **1** followed by trifluoromethylation

3.3.2. Direct C-H arylation of 1,3-dimethyl-5-(trifluoromethyl)uracil

Having sufficient amount of 1,3-dimethyl-5-(trifluoromethyl)uracil (**35**) in hand, I set up a series of Pd-catalyzed reactions with *p*-tolyl iodide (**2a**) to explore the possibility of further C-H arylation at position 6 (Scheme 18, Table 12).



Scheme 18 C-H arylations of 1,3-dimethyl-5-(trifluoromethyl)uracil (**35**)

At first, the conditions from my previously reported C-H arylations of **1**[132, 156] were attempted. The reaction in the presence of Pd(OAc)$_2$, P(C$_6$F$_5$)$_3$, CuI and Cs$_2$CO$_3$ did not give even a trace amounts of the desired product **41**. Surprisingly, it gave only a mixture of 1,3-dimethyl-6-(*p*-tolyl)uracil (**4a**) and 1,3-dimethyluracil (**1**) where both products lost the trifluoromethyl group at position 5 (entry 1). The same reaction in the absence of CuI gave the same products in lower yields accompanied by unexpected phenanthrene-fused uracil **42**, as a result of double arylation at positions 5 and 6 followed by oxidative C-H coupling (entry 2). Also the reaction in presence of pivalic acid and K$_2$CO$_3$ (analogy to ref.[165]) led to formation of de-trifluoromethylated products

4a and **1** (entry 3). However, when CsF was used as a base in the presence of $P(C_6F_5)_3$ and CuI, the formation of the desired 5-(trifluoromethyl)-6-tolyluracil **(41)** (for X-ray structure see Figure 13) was observed in 9 % of yield and no CF_3 group cleavage was observed (entry 4). The same reaction with the addition of piperidine gave lower yield of desired product **41** (entry 5). The absence of CuI gave the fused product **42** in low yield (entry 6), whereas the presence of PivOH led to low yield of the desired **41** (entry 7). The reaction in the presence of Hünig's base or piperidine as a base did not proceed (entry 8, 9), while the use of DBU gave low yield of **41** again (entry 10). The use of 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride as ligand gave product **41** in 10 % (entry 11). Some improvement of the yield was achieved by the use of $(t\mathrm{Bu})_2\mathrm{PMe}\cdot\mathrm{HBF}_4$ as a ligand precursor to give product **41** in 15 % (entry 12). The same reaction in the absence of CuI gave the phenanthrene-fused uracil **42** in very low yield (entry 13). The best conversion was achieved in the reaction in the presence of CuI and CsF in the absence of any ligand. Under these conditions, desired product **41** was isolated in 25 % yield (entry 14). Changing the base to KF led to formation of desired product **41** in lower yield (entry 15). The use of copper thiophene-2-carboxylate (CuTC) in combination with CsF as a base did not lead to improvement of the yield (entry 16), whereas the absence of any Cu(I) salt led to formation of **42** (entry 17). Changing the $Pd(OAc)_2$ catalyst to $PdCl_2$ or $Pd(dba)_2$ led to formation of **41** in 7 % of yield (entry 18, 19). The reaction in the presence of 3 equiv of CuI as a catalyst did not proceed (entry 20).

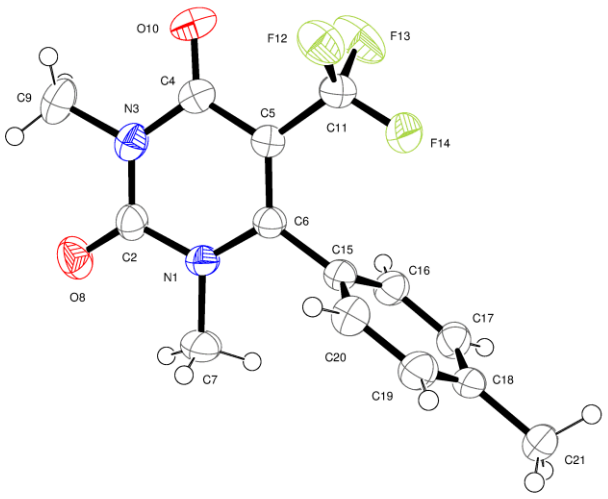


Figure 13 Crystal structure of compound **41** (b, CCDC 945179) with the atom numbering scheme. Thermal ellipsoids are drawn at the 50 % probability level.

Table 12 C-H arylations of 1,3-dimethyl-5-(trifluoromethyl)uracil (**35**)

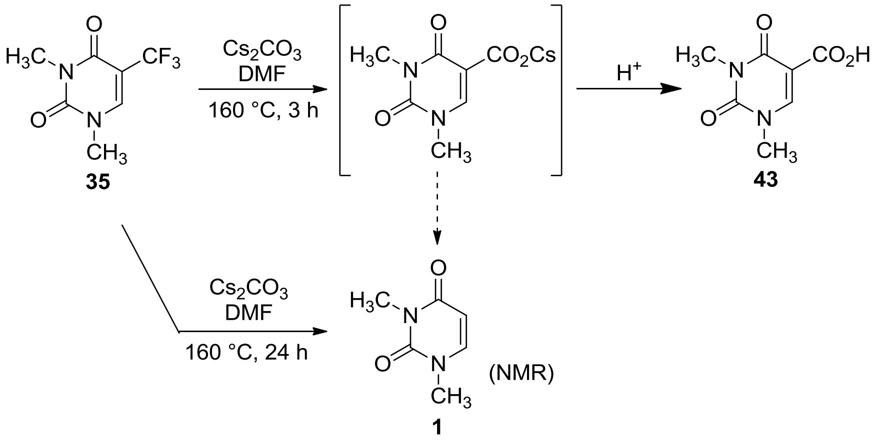
Entry	*Catalyst*	*Ligand*	*Additives*	*Base*	*Yield (%)*			
					41	**4a**	**42**	**1**
1	$Pd(OAc)_2$	$P(C_6F_5)_3$	CuI	Cs_2CO_3	0	43	0	57
2	$Pd(OAc)_2$	$P(C_6F_5)_3$	-	Cs_2CO_3	0	25	11	30
3[a]	$Pd(OAc)_2$	-	PivOH (2.5 equiv)	K_2CO_3 (1.25 equiv)	0	18	0	37
4	$Pd(OAc)_2$	$P(C_6F_5)_3$	CuI	CsF	9	0	0	0
5	$Pd(OAc)_2$	$P(C_6F_5)_3$	CuI piperidine (1 equiv)	CsF	3	0	0	0
6	$Pd(OAc)_2$	$P(C_6F_5)_3$	-	CsF	0	0	3	0
7	$Pd(OAc)_2$	$P(C_6F_5)_3$	PivOH (1 equiv)	CsF	5	0	0	0
8	$Pd(OAc)_2$	$P(C_6F_5)_3$	CuI	Hünig's base	0	0	0	0
9	$Pd(OAc)_2$	$P(C_6F_5)_3$	CuI	piperidine (5 equiv)	0	0	0	0
10	$Pd(OAc)_2$	$P(C_6F_5)_3$	CuI	DBU	9	0	0	0
11	$Pd(OAc)_2$	imidazolium[b] chloride	CuI	CsF	10	0	0	0
12	$Pd(OAc)_2$	$(t\text{Bu})_2PMe.HBF_4$	CuI	CsF	15	0	0	0
13	$Pd(OAc)_2$	$(t\text{Bu})_2PMe.HBF_4$	-	CsF	0	0	3	0
14	$Pd(OAc)_2$	-	CuI	CsF	25	0	0	0
15	$Pd(OAc)_2$	-	CuI	KF	11	0	0	0
16	$Pd(OAc)_2$	-	CuTC	CsF	20	0	0	0
17	$Pd(OAc)_2$	-	-	CsF	0	0	3	0
18	$PdCl_2$	-	CuI	CsF	7	0	0	0
19	$Pd(dba)_2$	-	CuI	CsF	7	0	0	0
20	CuI[c]	-	-	CsF	0	0	0	0

[a] 3 mol % $Pd(OAc)_2$, DMA, 110 °C, 24 h; [b] 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride; [c] CuI (3 equiv)

Prolongation of reaction time, use of microwave irradiation, various temperatures, increasing the amount of catalysts or change of solvent (DMA) did not lead to any improvement of the reactivity. Conditions for C-H arylation with $[RhCl(CO)_2]_2$ in dioxane (analogy to ref.[157]) and conditions with $Pd(OAc)_2$ and Ag_2O as a base in the presence of *o*-NO_2-C_6H_4-COOH in DMF (analogy to ref.[159]) did not lead to any improvement of the reactivity too.

Since the C-H arylation reactions in presence of Cs_2CO_3 led to loss of the CF_3 group, it was interesting to look into possible mechanism of this C-C bond cleavage. Therefore a model reaction in the absence of aryl halide and catalyst was performed. Thus, 1,3-dimethyl-5-(trifluoromethyl)uracil (**35**) was treated with Cs_2CO_3 in DMF at

160 °C. When the reaction was stopped after 3 h using acidic work up, formation of 1,3-dimethyluracil-5-carboxylic acid **43** was observed, whereas, after prolonged reaction time, dimethyluracil **1** was observed as the major product (by NMR of the crude mixture) (Scheme 19). To verify whether the transformation of CF_3 to CO_2H is a substitution (due to cleavage of C-C bond) or a "hydrolysis", the same reaction was performed with $K_2{}^{13}CO_3$ which showed no ^{13}C enrichment of product **43** confirming the CF_3 "hydrolysis" hypothesis, probably caused by nucleofilic substitution of fluoride anion to carboxylate anion and consecutive decarboxylation due to the influence of temperature. Other bases (K_2CO_3, *t*BuONa, NaOH) were also tried in this reaction and 1,3-dimethyluracil (**1**) was observed as the major product too, therefore these bases are not suitable for arylation of 1,3-dimethyl-5-(trifluoromethyl)uracil (**35**) too. Because of the above mentioned problems it is important to use non-nucleophilic bases (Hünig's base, DBU) or bases with low nucleophilicity (piperidine, KF, CsF) for C-H arylation of 1,3-dimethyl-5-(trifluoromethyl)uracil (**35**).



Scheme 19 1,3-Dimethyl-5-(trifluoromethyl)uracil (**35**) subjected to reaction with base

Attempted applications of the best conditions (from entry 14) to the analogous reactions of **35** with iodobenzene, 4-iodoanisole, 5-iodo-1,2,3-trimethoxybenzene, 5-iodo-1,3-benzodioxole or bromobenzene did not lead to any detectable amounts of 6-arylated products. Apparently, the reaction is not general and C-H arylations with other aryl halides would require complete re-optimization of the conditions. Also attempted C-H trifluoromethylation (with CF_3SO_2Na in the presence of *t*BuOOH) or C-H borylation (with bis(pinacolato)diboron under [{Ir(cod)OMe}$_2$] + di-*tert*-butylbipyridine) of 1,3-dimethyl-6-(*p*-tolyl)uracil (**4a**) or isomeric 1,3-dimethyl-5-(*p*-tolyl)uracil (**3a**) did not lead to any 5,6-disubstituted uracil products.

4. Conclusion

A general and regioselective methodology of Pd-catalyzed and/or Cu-mediated direct C-H arylations to position 5 or 6 of 1,3-dimethyluracil was developed and also regiospecific direct C-H arylation to position 6 of 1,3-dimethyluracil was successfully achieved. Pd-catalyzed reactions in the absence of CuI provide 5-aryluracils as the major products, while Pd-catalyzed reactions in the presence of 3 equiv of CuI give preferentially 6-aryluracils. Regiospecific substitution in position 6 could be achieved using copper mediated arylation in the absence of Pd-catalyst. The scope of developed conditions was examined on different aryl halides. It was found that diverse electron-rich and neutral aryl iodides and bromides afforded the desired arylated products in high to moderate yields. Electron-poor aryl iodides failed, no reaction or very low conversions (< 10 %) were observed. Interestingly, no 5,6-diarylated byproduct was observed using developed methods. This fact was proved also by arylation of monoarylated uracils which did not proceed.

Synthesis of free 5-aryluracil and 6-aryluracil bases was succesfully accomplished by applying direct arylation methodologies. Since the direct arylation of unprotected uracil did not meet with the success, there was a need for the development of a suitable protection at N1 and N3 that should be compatible with the harsh conditions of the C-H arylations but on the other hand to be easily cleavable at the end of synthesis without decomposition of the aryluracils. Several protecting groups were examinated and benzyl group was found as a best candidate. Above mentioned methodologies for regioselective arylation were efficiently applied in direct C-H arylation of 1,3-dibenzyluracil resulting in the desired 5-arylbenzyluracils and 6-arylbenzyluracils in the same regioselectivity fashion. For the final deprotection two different protocols needs to be applied. For the debenzylation of arylbenzyluracils bearing bulky aromatic substituents BBr_3 was used, while deprotection of uracils bearing simple arenes was achieved smoothly by transfer hydrogenolysis with ammonium formate over Pd/C.

The attempt to apply the above mentioned methods of direct arylation in nucleosides (performed at lower temperature and/or shorter reaction time due to thermal instability of N-glycosidic bond) was not successful. Neither free uridine nor protected uridines were suitable, and found to be too complex substrates and the reactions never led to desired arylated products.

A general, facile, and efficient two-step synthesis of 2,4-diarylpyrimidines bearing two different aryl groups was developed. The synthesis was based on combination of two different reactions, the first one was phosphonium-mediated Suzuki coupling and the second reaction of choice was the Liebeskind-Srogl cross-coupling. Since tiouracil itself underwent neither phosphonium-mediated Suzuki coupling nor the Liebeskind-Srogl reaction under standard or microwave conditions, 2-(methylsulfanyl)-4-oxo(3*H*)pyrimidine was proved as suitable starting compound. The proper order of these two reactions resulted in a fully regioselective way for the synthesis of the title 2,4-disubstituted pyrimidines. Unlike the previous published approaches to these compounds, this methodology is fully chemoselective. It certainly has the potential for automation and for high-throughput synthesis of combinatorial libraries of derivatives. The orthogonality of the phosphonium-mediated Suzuki coupling and Liebeskind-Srogl reaction makes their combination a powerful alternative to cross-couplings of dihaloheterocycles with problematic regioselectivities.

The idea of subsequent C-H arylation of 2,4-diarylpyrimidines which would lead to multisubstituted pyrimidines was not favourable. Various published conditions of C-H arylation were performed on 4-phenyl-2-(*p*-tolyl)pyrimidine in a reaction with *p*-tolyl iodide or with *p*-tolylboronic acid as a coupling partner, but desired product of arylation was never observed.

Direct C-H trifluoromethylations of 1,3-dimethyluracil with diverse trifluoromethylating agents were systematically studied. While attempted electrophilic trifluoromethylations led to uracil dimers and nucleophilic trifluoromethylations did not work or gave low conversions, radical trifluoromethylation with CF_3SO_2Na in the presence of *t*BuOOH gave 1,3-dimethyl-5-(trifluoromethyl)uracil in good yield. Ir-catalyzed C-H borylation of 1,3-dimethyluracil gave an unseparable mixture of mono- and diborylated products which upon reaction with the Togni's reagent gave separable mixture of 1,3-dimethyl-5-(trifluoromethyl)uracil and 1,3-dimethyl-6-(trifluoromethyl)uracil. The borylation/trifluoromethylation sequence gave for the first time a trifluoromethylation at position 6 (though in low yield). Attempted C-H arylation of 1,3-dimethyl-5-(trifluoromethyl)uracil in presence of Cs_2CO_3 was difficult due to electron withdrawing effect of the CF_3 group on the pyrimidine ring and was also accompanied by cleavage of the CF_3 group due to "hydrolysis" hypothesis. C-H arylations of 1,3-dimethyl-5-(trifluoromethyl)uracil with *p*-tolyl iodide in the presence of a Cu(I) salt and CsF gave the desired 1,3-dimethyl-6-(*p*-tolyl)-5-(trifluoromethyl)uracil in moderate yield only and the reaction did not work for other aryl halides. This study shows possible severe limitations of further derivatizations and reactivity of trifluoromethyl-derivatives of heterocycles which can undergo number of side-reactions resulting from reactivity and instability of the CF_3 group.

5. Experimental section

5.1. General remarks

1,3-dimethyluracil (**1**), 2,4-dimethoxypyrimidine (**5**), all starting aryl halides **2a-g**, 2-thiouracil (**29**), all aryl boronic acids **31a-g**, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $[Ir(cod)(OMe)]_2$, CuI, CuTC, $Cu(OAc)_2$, PyBroP, B_2Pin_2, trifluoromethylating reagents, all ligands and other catalysts and reagents were purchased from commercial suppliers and used without any further treatment. Protected uracils bearing benzyloxymethyl (BOM) (**8**),[134a] benzoyl (Bz) (**9**),[134b] methoxyethoxymethyl (MEM) (**10**),[134a] *p*-methoxybenzyl (PMB) (**11**),[134e] benzyl (Bn) (**12**)[134e] protegting groups, protected uridines 2',3',5'-tri-*O*-benzoyluridine (**26**)[139], 3-*N*-benzoyl-2',3',5'-tri-*O*-benzoyluridine (**27**)[139], 2',3'-*O*-isopropylideneuridine (**28**)[140] and 2-(methylsulfanyl)pyrimidin-4(3*H*)-one (**30**)[150] were prepared according to the published literature procedures. All solvents were used as received from supplier. Cs_2CO_3 and CsF are extremely hygroscopic and must be kept away from moisture, therefore they were dried at 500 °C under *vacuum* for 10 minutes prior to each use. All compounds were fully characterized by NMR spectroscopy and spectra were recorded on the Bruker Avance 600 MHz (^1H at 600.1 MHz, ^{13}C at 150.9 MHz) or on the Bruker Avance 500 MHz (499.8 or 500.0 MHz for ^1H, 125.7 MHz for ^{13}C and 470.3 MHz for ^{19}F) spectrometers. The samples were mostly measured in $CDCl_3$ and chemical shifts (in ppm, δ-scale) were referenced toTMS as internal standard or solvent signal for ^1H and ^{13}C ($\delta(^1H) = 7.26$ ppm, $\delta(^{13}C) = 77.0$ ppm) and to external standard C_6F_6 (-163 ppm) for ^{19}F (1H decoupling). The chemical shifts (in ppm, δ-scale) were referenced to1,4-dioxane as internal standard ($\delta(^1H) = 3.75$ ppm, $\delta(^{13}C) = 69.3$ ppm) for the samples measured in D_2O solutions or to the residual solvent signal (^1H NMR δ 2.50 ppm, ^{13}C NMR 39.7 ppm) for the samples measured in DMSO-d_6. Coupling constants (*J*) are given in Hz. ^1H and ^{13}C resonances were assigned using H,C-HSQC and H,C-HMBC spectra. For monoprotected derivatives, H,C-HMBC measurements showed characteristic cross-peaks between CH_2-Ph and C-2,6 (1-benzyl derivative); and CH_2-Ph and C-2,4 (3-benzyl derivative). Protected uracils and free uracils were assigned also by ^{13}C-APT analysis. IR spectra (wavenumbers in cm^{-1}) were recorded using KBr technique (Bruker IFS 88 spectrometer) or using ATR technique (Bruker

Alpha FT-IR spectrometer). Melting points were determined on a Kofler block and are uncorrected. High resolution mass spectra were measured on a LTQ Orbitrap XL (Thermo Fisher Scientific) spectrometer using EI or ESI ionization technique. Elemental analyses were measured on PE 2400 Series II CHNS/O (Perkin Elmer, USA, 1999). X-ray diffraction experiment of single crystals was carried out on an Xcalibur X-ray diffractometr with $Cu_{K\alpha}$ (λ=1.54180 Å) at 190 K.

5.2. 5- and 6-Aryl-1,3-dimethyluracils

Method A

General procedure for C-H arylation of 1,3-dimethyluracil (1) with aryl halides 2a-f at the C-5 position

DMF (3 mL) was added through a septum to an argon purged vial containing a 1,3-dimethyluracil (**1**, 70 mg, 0.5 mmol), aryl halide (**2a-f**, 1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol %), $P(C_6F_5)_3$ (27 mg, 0.05 mmol, 10 mol %) and Cs_2CO_3 (407 mg, 1.25 mmol). Reaction mixture was stirred at 160 °C for 50 h. After cooling to r.t., the mixture was diluted with chloroform (20 ml) and solvents were evaporated under reduced pressure. The mixture of C-5 and C-6 substituted products was isolated by column chromatography (hexanes / ethyl acetate 8:2). Second flash column chromatography (hexanes / THF 8:2) was used to separate the 5- and 6-arylated isomers.

Method B

General procedure for C-H arylation of 1,3-dimethyluracil (1) with aryl halides 2a-f at the C-6 position

DMF (3 mL) was added through a septum to an argon purged vial containing a 1,3-dimethyluracil (**1**, 70 mg, 0.5 mmol), aryl halide (**2a-f**, 1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol %), $P(C_6F_5)_3$ (27 mg, 0.05 mmol, 10 mol %), CuI (286 mg, 1.5 mmol) and Cs_2CO_3 (407 mg, 1.25 mmol). Reaction mixture was stirred at 160 °C for 50 h. After cooling to r.t., the mixture was diluted with chloroform (20 ml) and solvents were evaporated under reduced pressure. The mixture of C-5 and C-6 substituted products was isolated by column chromatography (hexanes / ethyl acetate 8:2). Second flash column chromatography (hexanes / THF 8:2) was used to separate the 5- and 6-arylated isomers.

Method C

General procedure for C-H arylation of 1,3-dimethyluracil (1) with aryl halides 2a-f at the C-6 position

DMF (3 mL) was added through a septum to an argon purged vial containing a 1,3-dimethyluracil (**1**, 70 mg, 0.5 mmol), aryl halide (**2a-f**, 1 mmol), CuI (286 mg, 1.5 mmol) and Cs_2CO_3 (407 mg, 1.25 mmol). Reaction mixture was stirred at 160 °C for 50 h. After cooling to r.t., the mixture was diluted with chloroform (20 ml) and solvents were evaporated under reduced pressure. The C-6 substituted product was isolated by column chromatography (hexanes / ethyl acetate 8:2) as the only product.

Assignment of 5- and 6-arylated 1,3-dimethyluracils

5- And 6-aryluracil regioisomers were distinguished based on NMR analysis. ^1H and ^{13}C NMR provided typical values of chemical shift for uracil derivatives (Table 13, 14). Moreover, position of aryl substituent was unambiguously proved by inspection of H,C-HMBC spectra. In case of 5-aryluracils, cross-peaks between proton H-6 and carbons C-2, C-4, C-*i*-aryl and CH_3-1 corresponding to strong vicinal coupling and weak cross-peak between H-6 and C-5 could be observed, while H,C-HMBC of 6-substituted derivatives provides only two strong cross-peaks between proton H-5 and carbons C-6 and C-*i*-aryl. The same NMR experiment was able to distinguish between 1- and 3-methyl groups of uracil. Protons of CH_3-1 are coupled with C-2 and C-6, while protons of CH_3-3 correlate with C-2 and C-4.

Table 13 ^{1}H chemical shifts of uracil (in ppm):

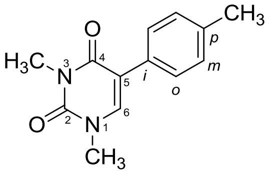
Compound	CH_3-1	CH_3-3	H-5	H-6
3a	3.47	3.42	-	7.26
4a	3.23	3.41	5.69	-
3b	3.45	3.42	-	7.13
4b	3.08	3.42	5.66	-
3c	3.46	3.42	-	7.24
4c	3.25	3.40	5.69	-
3d	3.48	3.43	-	7.29
4d	3.22	3.41	5.70	-
3e	3.54	3.52	-	7.40
4e	3.07	3.53	5.95	-
3f	3.51	3.47	-	7.41
4f	3.27	3.44	5.81	-

Table 14 ^{13}C chemical shifts of uracil (in ppm):

Compound	C-2	C-4	C-5	C-6	CH_3-1	CH_3-3
3a	151.48	162.41	114.41	139.93	37.06	28.23
4a	152.76	162.51	102.36	154.76	34.57	28.00
3b	151.79	162.05	115.12	141.16	36.99	28.23
4b	152.55	162.59	102.13	154.10	33.21	28.02
3c	151.47	162.53	114.11	139.56	37.02	28.22
4c	152.80	162.53	102.33	154.55	34.63	27.99
3d	151.48	162.32	114.44	140.36	37.11	28.26
4d	152.69	162.44	102.49	154.56	34.56	28.02
3e	151.85	162.81	114.02	142.61	37.18	28.45
4e	152.67	162.53	103.94	153.78	33.89	28.20
3f	151.47	162.45	114.34	140.66	37.19	28.30
4f	152.72	162.48	102.75	154.64	34.72	28.07

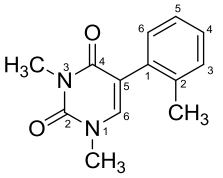
5.2.1. 5-Aryl-1,3-dimethyluracils

1,3-Dimethyl-5-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione 3a



Compound **3a** was prepared from **1** according to general procedure (Method A) in 54 % yield, as white crystals from $CHCl_3$/n-heptane, mp 162 - 163 °C, ^{1}H NMR (499.8 MHz, $CDCl_3$): 2.36 (s, 3H, CH_3-*p*); 3.42 (s, 3H, CH_3-3); 3.47 (s, 3H, CH_3-1); 7.20 (m, 2H, H-*m*-$C_6H_4CH_3$); 7.26 (s, 1H, H-6); 7.39 (m, 2H, H-*o*-$C_6H_4CH_3$). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.17 (CH_3-*p*); 28.23 (CH_3-3); 37.06 (CH_3-1); 114.41 (C-5); 128.12 (CH-*o*-$C_6H_4CH_3$); 129.14 (CH-*m*-$C_6H_4CH_3$); 129.90 (C-*i*-$C_6H_4CH_3$); 137.73 (C-*p*-$C_6H_4CH_3$); 139.93 (CH-6); 151.48 (C-2); 162.41 (C-4). IR: 2921, 2853, 1688, 1643, 1515, 1448, 1431, 1408, 1350, 1208, 1125. MS (EI^+), *m/z* (% relative intensity): 77 (14), 104 (36), 116 (38), 132 (57), 145 (19), 158 (17), 172 (56), 230 (M^+, 100). HR MS (M^+): 230.1053 (calcd for $C_{13}H_{14}N_2O_2$ 230.1055). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.71; H, 6.15; N, 12.05.

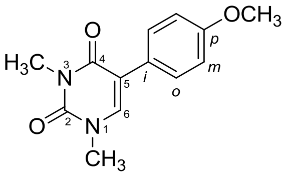
1,3-Dimethyl-5-(*o*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione 3b



Compound **3b** was prepared from **1** according to general procedure (Method A) in 80 % yield, as a beige powder, mp 86 - 88 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$): 2.24 (s, 3H, CH_3); 3.42 (s, 3H, CH_3-3); 3.45 (s, 3H, CH_3-1); 7.11 (dd, 1H, $J_{6,5}$ = 7.6, $J_{6,4}$ = 1.5, H-6-C_6H_4Me); 7.13 (s, 1H, H-6); 7.20 (dddq, 1H, $J_{5,6}$ = 7.6, $J_{5,4}$ = 7.0, $J_{5,3}$ = 1.8, $J_{5,CH3}$ =0.6, H-5-C_6H_4Me); 7.24 (dddq, 1H, $J_{3,4}$ = 7.6, $J_{3,5}$ = 1.8, $J_{3,6}$ = 1.2, $J_{3,CH3}$ =0.6, H-3-C_6H_4Me); 7.28 (ddd, 1H, $J_{4,3}$ = 7.6, $J_{4,5}$ = 7.0, $J_{4,6}$ = 1.5, H-4-C_6H_4Me). ^{13}C NMR (125.7 MHz, $CDCl_3$): 20.02 (CH_3); 28.23 (CH_3-3); 36.99 (CH_3-1); 115.12 (C-5); 125.81 (CH-5-C_6H_4Me); 128.55 (CH-4-C_6H_4Me); 130.25 (CH-3-C_6H_4Me); 130.41 (CH-6-C_6H_4Me); 132.41 (C-1-C_6H_4Me); 137.87 (C-2-C_6H_4Me); 141.16 (CH-6); 151.79 (C-2); 162.05 (C-4). IR: 2953, 2924, 1702, 1633, 1487, 1455, 1425, 1348, 1006. MS (EI^+), *m/z* (%

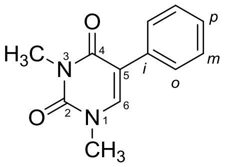
relative intensity): 77 (4), 103 (10), 116 (42), 130 (4), 144 (26), 158 (7), 173 (20), 213 (91), 230 (M^+, 100). HR MS (M^+): 230.1051 (calcd for $C_{13}H_{14}N_2O_2$ 230.1055).

5-(4-Metoxyphenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione 3c



Compound **3c** was prepared from **1** according to general procedure (Method A) in 56 % yield, as white crystals from $CHCl_3$/n-heptane, mp 101 - 103 °C, ^1H NMR (499.8 MHz, $CDCl_3$): 3.42 (s, 3H, CH_3-3); 3.46 (s, 3H, CH_3-1); 3.82 (s, 3H, CH_3O); 6.92 (m, 2H, H-*m*-$C_6H_4OCH_3$); 7.24 (s, 1H, H-6); 7.42 (m, 2H, H-*o*-$C_6H_4OCH_3$). ^{13}C NMR (125.7 MHz, $CDCl_3$): 28.22 (CH_3-3); 37.02 (CH_3-1); 55.30 (CH_3O); 113.88 (CH-*m*-$C_6H_4OCH_3$); 114.11 (C-5); 125.18 (C-*i*-$C_6H_4OCH_3$); 129.45 (CH-*o*-$C_6H_4OCH_3$); 139.56 (CH-6); 151.47 (C-2); 159.32 (C-*p*-$C_6H_4OCH_3$); 162.53 (C-4). IR: 2921, 2851, 1693, 1645, 1630, 1607, 1512, 1454, 1345, 1246, 1178, 1117, 1031. MS (EI^+), *m/z* (% relative intensity): 89 (3), 120 (11), 132 (16), 148 (23), 161 (5), 174 (9), 189 (21), 231 (6), 246 (M^+, 100). HR MS (M^+): 246.1006 (calcd for $C_{13}H_{14}N_2O_3$ 246.1004). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.10; H, 5.79; N, 11.17.

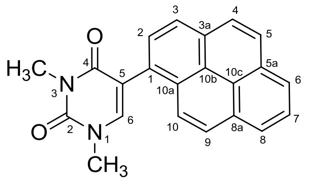
1,3-Dimethyl-5-phenylpyrimidine-2,4(1*H*,3*H*)-dione 3d



Compound **3d** was prepared from **1** according to general procedure (Method A) in 68 % yield, as white crystals from $CHCl_3$/n-heptane, mp 145 - 147 °C, ^1H NMR (499.8 MHz, $CDCl_3$): 3.43 (s, 3H, CH_3-3); 3.48 (s, 3H, CH_3-1); 7.29 (s, 1H, H-6); 7.33 (m, 1H, H-*p*-Ph); 7.39 (m, 2H, H-*m*-Ph); 7.50 (m, 2H, H-*o*-Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$): 28.26 (CH_3-3); 37.11 (CH_3-1); 114.44 (C-5); 127.87 (CH-*p*-Ph); 128.28 (CH-*o*-Ph); 128.45 (CH-*m*-Ph); 132.86 (C-*i*-Ph); 140.36 (CH-6); 151.48 (C-2); 162.32 (C-4). IR: 2941, 1688, 1646, 1636, 1599, 1495, 1480, 1444, 1424, 1349, 1202, 1124, 1007. MS (EI^+), *m/z* (% relative intensity): 63 (2), 71 (5), 90 (10), 102 (10), 118 (21), 130 (10), 158 (57), 216 (M^+, 100). HR MS (M^+): 216.0898 (calcd for $C_{12}H_{12}N_2O_2$ 216.0899).

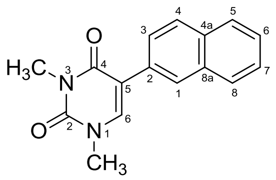
Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.30; H, 5.50; N, 12.89.

1,3-Dimethyl-5-(pyren-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione 3e



Compound **3e** was prepared from **1** according to general procedure (Method A) in 68 % yield, as a yellowish powder, mp 105 - 107 °C, ^{1}H NMR (500.0 MHz, $CDCl_3$): 3.52 (s, 3H, CH_3-3); 3.54 (s, 3H, CH_3-1); 7.40 (s, 1H, H-6); 7.88 (d, 1H, $J_{2,3}$ = 7.8, H-2-pyrenyl); 7.97 (d, 1H, $J_{10,9}$ = 9.2, H-10-pyrenyl); 8.02 (t, 1H, $J_{7,6}$ = $J_{7,8}$ = 7.6, H-7-pyrenyl); 8.07 (d, 1H, $J_{4,5}$ = 9.0, H-4-pyrenyl); 8.08 (d, 1H, $J_{9,10}$ = 9.2, H-9-pyrenyl); 8.11 (d, 1H, $J_{5,4}$ = 9.0, H-5-pyrenyl); 8.20 (m, 3H, H-3,6,8-pyrenyl). ^{13}C NMR (125.7 MHz, $CDCl_3$): 28.45 (CH_3-3); 37.18 (CH_3-1); 114.02 (C-5); 124.54 (CH-10-pyrenyl); 124.64 (CH-3-pyrenyl); 124.67 (C-10c-pyrenyl); 124.92 (CH-10b-pyrenyl); 125.27 (CH-8-pyrenyl); 125.43 (CH-6-pyrenyl); 126.08 (CH-7-pyrenyl); 127.26 (CH-4-pyrenyl); 127.57 (C-1-pyrenyl); 127.87 and 127.88 (CH-5,9-pyrenyl); 128.29 (CH-2-pyrenyl); 130.00 (C-10a-pyrenyl); 130.83 (C-8a-pyrenyl); 131.24 (C-5a-pyrenyl); 131.50 (C-3a-pyrenyl); 142.61 (CH-6); 151.85 (C-2); 162.81 (C-4). IR: 3041, 2923, 2853, 1700, 1644, 1450, 1345. MS (EI$^+$), *m/z* (% relative intensity): 170 (3), 201 (7), 213 (20), 242 (16), 255 (11), 273 (4), 283 (4), 316 (8), 340 (M$^+$, 100). HR MS (M$^+$): 340.1214 (calcd for $C_{22}H_{16}N_2O_2$ 340.1212).

1,3-Dimethyl-5-(naphthalen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione 3f

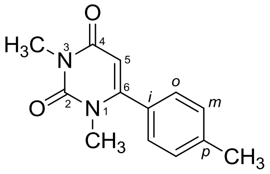


Compound **3f** was prepared from **1** according to general procedure (Method A) in 42 % yield, as white crystals from $CHCl_3$/n-heptane, mp 186 - 188 °C, ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.47 (s, 3H, CH_3-3); 3.51 (s, 3H, CH_3-1); 7.41 (s, 1H, H-6); 7.48 (m, 1H, H-6-naphth); 7.49 (m, 1H, H-7-naphth); 7.62 (dd, 1H, $J_{3,4}$ = 8.5, $J_{3,1}$ = 1.8, H-3-naphth); 7.82-7.86 (m, 2H, H-5,8-naphth); 7.86 (m, 1H, H-4-naphth); 8.00 (m, 1H, H-1-naphth).

^{13}C NMR (125.7 MHz, $CDCl_3$): 28.30 (CH_3-3); 37.19 (CH_3-1); 114.34 (C-5); 126.13 (CH-3-naphth); 126.21 and 126.24 (CH-6,7-naphth); 127.16 (CH-1-naphth); 127.58 (CH-5-naphth); 127.98 (CH-4-naphth); 128.07 (CH-8-naphth); 130.36 (C-2-naphth); 132.79 (C-4a-naphth); 133.30 (C-8a-naphth); 140.66 (CH-6); 151.47 (C-2); 162.45 (C-4). IR: 3058, 2942, 1693, 1646, 1597, 1505, 1475, 1450, 1423, 1371, 1350, 1207, 1109. MS (ESI$^+$), *m/z* (% relative intensity): 267 (M^++H, 7), 289 (M^++Na, 46), 555 ($2M^+$+Na, 100). HR MS (M^++H): 267.1129 (calcd for $C_{16}H_{15}N_2O_2$ 267.1128). Anal. Calcd for $C_{16}H_{14}N_2O_2 \cdot 0.20H_2O$: C, 71.2; H, 5.38; N, 10.38. Found: C, 71.34; H, 5.48; N, 10.29.

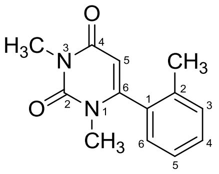
5.2.2. 6-Aryl-1,3-dimethyluracils

1,3-Dimethyl-6-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione 4a



Compound **4a** was prepared from **1** according to general procedure (Method B) in 72 % yield, as white crystals from $CHCl_3$/n-heptane, mp 105 - 107 °C, ^{1}H NMR (499.8 MHz, $CDCl_3$): 2.42 (s, 3H, CH_3-*p*); 3.23 (s, 3H, CH_3-1); 3.41 (s, 3H, CH_3-3); 5.69 (s, 1H, H-5); 7.22 (m, 2H, H-*o*-$C_6H_4CH_3$); 7.29 (m, 2H, H-*m*-$C_6H_4CH_3$). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.35 (CH_3-*p*); 28.00 (CH_3-3); 34.57 (CH_3-1); 102.36 (CH-5); 127.67 (CH-*o*-$C_6H_4CH_3$); 129.59 (CH-*m*-$C_6H_4CH_3$); 130.48 (C-*i*-$C_6H_4CH_3$); 140.46 (C-*p*-$C_6H_4CH_3$); 152.76 (C-2); 154.76 (C-6); 162.51 (C-4). IR: 2923, 2854, 1702, 1651, 1618, 1514, 1456, 1430, 1390, 1368, 1185, 1007. MS (EI$^+$), *m/z* (% relative intensity): 65 (14), 77 (11), 82 (25), 91 (30), 101 (10), 105 (19), 116 (30), 132 (93), 144 (30), 158 (6), 172 (60), 202 (7), 230 (M^+, 100). HR MS (M^+): 230.1053 (calcd for $C_{13}H_{14}N_2O_2$ 230.1055).

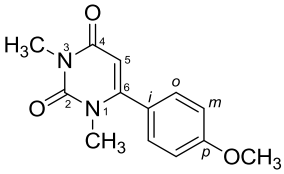
1,3-Dimethyl-6-(*o*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione 4b



Compound **4b** was prepared from **1** according to general procedure (Method B) in 54 % yield, as white crystals from $CHCl_3$/n-heptane, mp 123 - 125 °C, ^{1}H NMR (499.8 MHz, $CDCl_3$): 2.24 (s, 3H, CH_3); 3.08 (s, 3H, CH_3-1); 3.42 (s, 3H, CH_3-3); 5.66 (s, 1H, H-5);

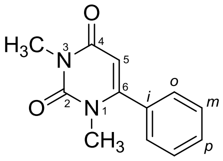
7.16 (m, 1H, H-6-C_6H_4Me); 7.30 (m, 1H, H-5-C_6H_4Me); 7.31 (m, 1H, H-3-C_6H_4Me); 7.40 (ddd, 1H, $J_{4,3}$ = 8.15, $J_{4,5}$ = 7.0, $J_{4,6}$ = 1.4, H-4-C_6H_4Me). ^{13}C NMR (125.7 MHz, $CDCl_3$): 19.26 (CH_3); 28.02 (CH_3-3); 33.21 (CH_3-1); 102.13 (CH-5); 126.49 (CH-5-C_6H_4Me); 127.93 (CH-6-C_6H_4Me); 130.11 (CH-4-C_6H_4Me); 130.63 (CH-3-C_6H_4Me); 132.97 (C-1-C_6H_4Me); 135.23 (C-2-C_6H_4Me); 152.55 (C-2); 154.10 (C-6); 162.59 (C-4). IR: 2955, 2922, 2853, 1705, 1691, 1644, 1613, 1597, 1425, 1387, 1361, 1202, 1005. MS (EI$^+$), *m/z* (% relative intensity): 63 (8), 65 (13), 77 (9), 82 (22), 89 (16), 103 (16), 115 (50), 131 (30), 144 (100), 158 (52), 172 (31), 201 (4), 215 (76), 230 (M$^+$, 100). HR MS (M$^+$): 230.1051 (calcd for $C_{13}H_{14}N_2O_2$ 230.1055).

6-(4-Metoxyphenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione 4c



Compound **4c** was prepared from **1** according to general procedure (Method B) in 62 % yield, as white crystals from $CHCl_3$/n-heptane, mp 74 - 76 °C, ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.25 (s, 3H, CH_3-1); 3.40 (s, 3H, CH_3-3); 3.87 (s, 3H, CH_3O); 5.69 (s, 1H, H-5); 6.99 (m, 2H, H-*m*-$C_6H_4OCH_3$); 7.27 (m, 2H, H-*o*-$C_6H_4OCH_3$). ^{13}C NMR (125.7 MHz, $CDCl_3$): 27.99 (CH_3-3); 34.63 (CH_3-1); 55.42 (CH_3O); 102.33 (CH-5); 114.31 (CH-*m*-$C_6H_4OCH_3$); 125.52 (C-*i*-$C_6H_4OCH_3$); 129.28 (CH-*o*-$C_6H_4OCH_3$); 152.80 (C-2); 154.55 (C-6); 160.94 (C-*p*-$C_6H_4OCH_3$);162.53 (C-4). IR: 2955, 1698, 1650, 1610, 1514, 1433, 1249, 1177, 1029. MS (EI$^+$), *m/z* (% relative intensity): 63 (8), 77 (8), 82 (17), 89 (14), 105 (11), 121 (11), 133 (26), 148 (80), 160 (16), 174 (4), 188 (41), 203 (4), 218 (4), 246 (M$^+$, 100). HR MS (M$^+$): 246.0997 (calcd for $C_{13}H_{14}N_2O_3$ 246.1004).

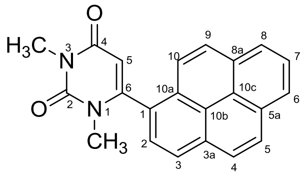
1,3-Dimethyl-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione 4d



Compound **4d** was prepared from **1** according to general procedure (Method B) in 60 % yield, as a white powder, mp 86 - 88 °C, ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.22 (s, 3H, CH_3-1); 3.41 (s, 3H, CH_3-3); 5.70 (s, 1H, H-5); 7.33 (m, 2H, H-*o*-Ph); 7.42-7.53 (m, 3H, H-*m,p*-Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$): 28.02 (CH_3-3); 34.56 (CH_3-1); 102.49

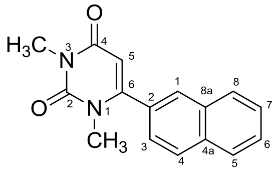
(CH-5); 127.74 (CH-*o*-Ph); 128.97 (CH-*m*-Ph); 130.17 (CH-*p*-Ph); 133.36 (C-*i*-Ph); 152.69 (C-2); 154.56 (C-6); 162.44 (C-4). IR: 2923, 2853, 1689, 1637, 1602, 1486, 1447, 1429, 1395, 1366, 1206, 1010. MS (EI$^+$), *m/z* (% relative intensity): 63 (6), 77 (41), 82 (32), 91 (15), 102 (28), 118 (100), 130 (26), 158 (56), 188 (5), 216 (M$^+$, 90). HR MS (M$^+$): 216.0897 (calcd for $C_{12}H_{12}N_2O_2$ 216.0899).

1,3-Dimethyl-6-(pyren-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione 4e



Compound **4e** was prepared from **1** according to general procedure (Method B) in 68 % yield, as brown crystals from ethyl acetete / hexanes, mp 185 - 187 °C, ^{1}H NMR (500.0 MHz, CDCl$_3$): 3.07 (s, 3H, CH$_3$-1); 3.53 (s, 3H, CH$_3$-3); 5.95 (s, 1H, H-5); 7.89 (d, 1H, $J_{2,3}$ = 7.6, H-2-pyrenyl); 7.90 (d, 1H, $J_{10,9}$ = 9.2, H-10-pyrenyl); 8.10 (t, 1H, $J_{7,6}$ = $J_{7,8}$ = 7.6, H-7-pyrenyl); 8.13 (d, 1H, $J_{4,5}$ = 9.0, H-4-pyrenyl); 8.19 (d, 1H, $J_{9,10}$ = 9.2, H-9-pyrenyl); 8.20 (d, 1H, $J_{5,4}$ = 9.0, H-5-pyrenyl); 8.26 (d, 1H, $J_{3,2}$ = 7.6, H-3-pyrenyl); 8.28 (dd, 1H, $J_{8,7}$ = 7.6, $J_{8,6}$ = 1.3, H-8-pyrenyl); 8.30 (dd, 1H, $J_{6,7}$ = 7.6, $J_{6,8}$ = 1.3, H-6-pyrenyl). ^{13}C NMR (125.7 MHz, CDCl$_3$): 28.20 (CH$_3$-3); 33.89 (CH$_3$-1); 103.94 (CH-5); 123.07 (CH-10-pyrenyl); 124.28 (C-10c-pyrenyl); 124.49 (CH-10b-pyrenyl); 124.77 (CH-3-pyrenyl); 125.63 (CH-2-pyrenyl); 126.18 (CH-8-pyrenyl); 126.41 (CH-6-pyrenyl); 126.74 (CH-7-pyrenyl); 127.04 (C-1-pyrenyl and CH-4-pyrenyl);128.27 (C-10a-pyrenyl); 129.00 (CH-5-pyrenyl); 129.61 (CH-9-pyrenyl); 130.60 (C-8a-pyrenyl); 131.14 (C-5a-pyrenyl); 132.51 (C-3a-pyrenyl); 152.67 (C-2); 153.78 (C-6); 162.53 (C-4). IR: 2957, 2923, 2853, 1702, 1641, 1425, 1365, 1259, 1080, 1006. MS (EI$^+$), *m/z* (% relative intensity): 170 (3), 201 (3), 213 (19), 242 (16), 255 (12), 283 (5), 340 (M$^+$, 100). HR MS (M$^+$): 340.1216 (calcd for $C_{22}H_{16}N_2O_2$ 340.1212). Anal. Calcd for $C_{22}H_{16}N_2O_2 \cdot 0.30H_2O$: C, 76.42; H, 4.84; N, 8.1. Found: C, 76.65; H, 4.80; N, 7.79.

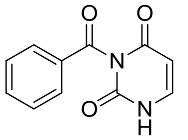
1,3-Dimethyl-6-(naphthalen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione 4f



Compound **4f** was prepared from **1** according to general procedure (Method B) in 80 % yield, as white crystals from $CHCl_3$/n-heptane, mp 105 - 107 °C, ^{1}H NMR (600.1 MHz, $CDCl_3$): 3.27 (s, 3H, CH_3-1); 3.44 (s, 3H, CH_3-3); 5.81 (s, 1H, H-5); 7.39 (dd, 1H, $J_{3,4}$ = 8.4, $J_{3,1}$ = 1.8, H-3-naphth); 7.60 (m, 1H, H-7-naphth); 7.62 (m, 1H, H-6-naphth); 7.85 (m, 1H, H-1-naphth); 7.91 (m, 1H, H-8-naphth); 7.92 (m, 1H, H-5-naphth); 7.96 (m, 1H, H-4-naphth). ^{13}C NMR (150.9 MHz, $CDCl_3$): 28.07 (CH_3-3); 34.72 (CH_3-1); 102.75 (CH-5); 124.42 (CH-3-naphth); 127.32 (CH-7-naphth); 127.72 (CH-1,6-naphth); 127.88 (CH-5-naphth); 128.36 (CH-8-naphth); 128.82 (CH-4-naphth); 130.64 (C-2-naphth); 132.76 (C-8a-naphth); 133.56 (C-4a-naphth); 152.72 (C-2); 154.64 (C-6); 162.48 (C-4). IR: 3036, 2945, 1670, 1641, 1609, 1598, 1486, 1430, 1398, 1367, 1274, 1192, 1128, 1017. MS (ESI$^+$), *m/z* (% relative intensity): 267 (M^++H, 33), 289 (M^++Na, 77), 555 ($2M^+$+Na, 100). HR MS (M^++H): 267.1129 (calcd for $C_{16}H_{15}N_2O_2$ 267.1128). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.04; H, 5.27; N, 10.32.

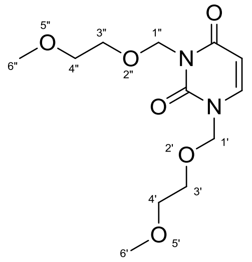
5.3. Protected uracils and uridines

3-Benzoylpyrimidine-2,4(1*H*,3*H*)-dione (9)



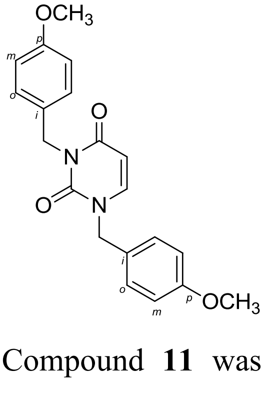
Compound **9** was prepared from uracil **1** according to published procedure[134b] in 61 % yield, as white crystals from $CHCl_3$/MeOH, mp 203 - 204 °C (lit[166] mp 200 - 202 °C). ^{1}H NMR (500.0 MHz, DMSO-d_6): 5.74 (d, 1H, $J_{5,6}$ = 7.7, H-5); 7.60 (m, 2H, H-*m*-Ph); 7.66 (d, 1H, $J_{6,5}$ = 7.7, H-6); 7.77 (m, 1H, H-*p*-Ph); 7.96 (m, 2H, H-*o*-Ph); 11.61 (bs, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 100.3 (CH-5); 129.7 (CH-*m*-Ph); 130.4 (CH-*o*-Ph); 131.5 (C-*i*-Ph); 135.6 (CH-*p*-Ph); 143.5 (CH-6); 150.3 (C-2); 163.1 (C-4); 170.2 (CO). IR (KBr): 1765, 1748, 1706, 1656, 1597, 1416, 1390, 1231, 1181. MS (ESI$^+$), *m/z* (% relative intensity): 239 (M^++Na, 100). HR MS (M^++H): 239.0426 (calcd for $C_{11}H_8N_2NaO_3$ 239.0427).

1,3-Bis[(2-methoxyethoxy)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (10)



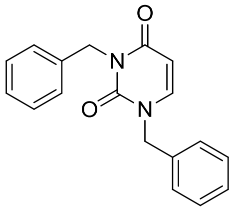
To a mixture of uracil **1** (336 mg, 3 mmol) and anhydrous K_2CO_3 (2.07 g, 15 mmol) in dry DMF (5 mL) $ClCH_2OC_2H_5$ (1.12 g, 9 mmol) was added dropwise at a temperature below 0 °C. The mixture was allowed to warm to room temperature and was stirred overnight. Inorganic salts were removed by filtration, and the filtrate was concentrated under reduced pressure. The protected compound **10** was isolated by column chromatography on 60 g of silica gel in a gradient of chloroform to 1 % methanol in chloroform in 35 % yield, as a colourless oil. ^{1}H NMR (500.0 MHz, $CDCl_3$): 3.36, 3.37 (2 × s, 2 × 3H, H-6',6"); 3.53 (m, 2H, H-4"); 3.54 (m, 2H, H-4'); 3.75 (m, 2H, H-3'); 3.80 (m, 2H, H-3"); 5.23 (s, 2H, H-1'); 5.47 (s, 2H, H-1"); 5.80 (d, 1H, $J_{5,6}$ = 8.0, H-5); 7.33 (d, 1H, $J_{6,5}$ = 8.0, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 59.0, 59.0 (CH_3-6',6"); 69.0 (CH_2-3'); 69.8 (CH_2-3"); 71.0 (CH_2-1"); 71.5 (CH_2-4"); 71.6 (CH_2-4'); 77.9 (CH_2-1'); 102.6 (CH-5); 141.8 (CH-6); 151.9 (C-2); 162.8 (C-4). IR (KBr): 2821, 1719, 1671, 1638, 1452, 1103, 1089. MS (ESI$^+$), *m/z* (% relative intensity): 289 (M^++H, 6), 311 (M^++Na, 100), 599 ($2M^+$+Na, 25). HR MS (M^++Na): 311.1213 (calcd for $C_{12}H_{20}N_2NaO_6$ 311.1214).

1,3-Bis(4-methoxybenzyl)pyrimidine-2,4(1*H*,3*H*)-dione (11)



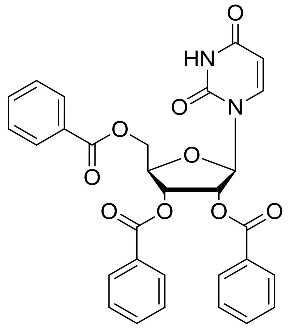
Compound **11** was prepared from uracil **1** according to published procedure and experimental data are in accordance to literature.[134e] Yield 99 %, a white powder, mp 96 - 97 °C. ^{1}H NMR (600.1 MHz, $CDCl_3$): 3.78 (s, 3H, CH_3O-3); 3.80 (s, 3H, CH_3O-1); 4.83 (s, 2H, CH_2N-1); 5.07 (s, 2H, CH_2N-3); 5.71 (d, 1H, $J_{5,6}$ = 7.9, H-5); 6.83 (m, 2H, H-*m*-C_6H_4OMe-3); 6.88 (m, 2H, H-*m*-C_6H_4OMe-1); 7.07 (d, 1H, $J_{6,5}$ = 7.9, H-6); 7.21 (m, 2H, H-*o*-C_6H_4OMe-1); 7.46 (m, 2H, H-*o*-C_6H_4OMe-3). ^{13}C NMR (150.9 MHz, $CDCl_3$): 43.8 (CH_2N-3); 51.8 (CH_2N-1); 55.2 (CH_3O-3); 55.3 (CH_3O-1); 102.1 (CH-5); 113.7 (CH-*m*-C_6H_4OMe-3); 114.4 (CH-*m*-C_6H_4OMe-1); 127.1 (C-*i*-C_6H_4OMe-1); 129.1 (C-*i*-C_6H_4OMe-3); 129.7 (CH-*o*-C_6H_4OMe-1); 130.7 (CH-*o*-C_6H_4OMe-3); 141.5 (CH-6); 151.7 (C-2); 159.0 (C-*p*-C_6H_4OMe-3); 159.7 (C-*p*-C_6H_4OMe-1); 162.9 (C-4). IR (KBr): 2837, 1711, 1667, 1611, 1585, 1514, 1454, 1388, 1256, 1026. MS (ESI$^+$), *m/z* (% relative intensity): 353 (M^++H, 14), 375 (M^++Na, 100), 391 (M^++K, 30). HR MS (M^++H): 353.1496 (calcd for $C_{20}H_{21}N_2O_4$ 353.1496).

1,3-Dibenzylpyrimidine-2,4(1*H*,3*H*)-dione (12)

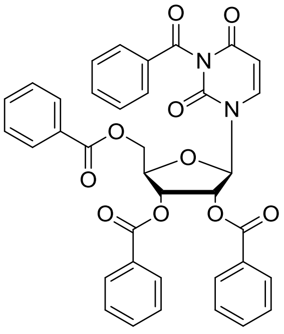


Anhydrous DMF (35 mL) was added through a septum to an argon purged flask containing uracil (**1**, 930 mg, 8.29 mmol) and K_2CO_3 (2.75 g, 19.89 mmol) and the mixture was stirred for 18 h at r.t., resulting in a thick gel. Benzyl bromide (2.99 ml [4.3 g], 24.87 mmol) was added and the reaction was stirred for another 3 days. The reaction mixture was concentrated and redissolved in water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on a 150 g of silica gel (1:4 EtOAc/hexanes) afforded the product **12** in 89 % yield, as white crystals from hexane/ethylacetate, mp 67 - 69 °C (lit[167] mp 67 - 68 °C). ^{1}H NMR (499.8 MHz, $CDCl_3$): 4.91 (s, 2H, CH_2-1); 5.15 (s, 2H, CH_2-3); 5.74 (d, 1H, $J_{5,6}$ = 7.9, H-5); 7.11 (d, 1H, $J_{6,5}$ = 7.9, H-6); 7.26 (m, 1H, H-*p*-3Bn); 7.27 (m, 2H, H-*o*-1Bn); 7.31 (m, 2H, H-*m*-3Bn); 7.36 (m, 1H, H-*p*-1Bn); 7.37 (m, 2H, H-*m*-1Bn); 7.48 (m, 2H, H-*o*-3Bn). ^{13}C NMR (125.7 MHz, $CDCl_3$): 44.41 (CH_2-3); 52.24 (CH_2-1); 102.16 (CH-5); 127.58 (CH-*p*-3Bn); 128.01 (CH-*o*-1Bn); 128.38 (CH-*m*-3Bn); 128.49 (CH-*p*-1Bn); 128.97 (CH-*o*-3Bn); 129.11 (CH-*m*-1Bn); 135.20 (C-*i*-1Bn); 136.77 (C-*i*-3Bn); 141.70 (CH-6); 151.74 (C-2); 162.81 (C-4). IR (KBr): 1700, 1663, 1605, 1585, 1495, 1452, 1393, 1218. MS (ESI$^+$), *m/z* (% relative intensity): 315 (M^++Na, 100). HR MS (M^++H): 293.1285 (calcd for $C_{18}H_{17}N_2O_2$ 293.1285).

2’,3’,5’-Tri-*O*-benzoyluridine (26) and 3-*N*-benzoyl-2’,3’,5’-tri-*O*-benzoyluridine (27)



26

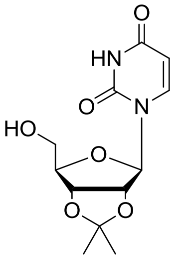


27

Compound **26** and **27** were prepared from uridine (**24**) according to published procedure.[139] The compound **26**: yield 22 %, white crystals from hexane/ethyl acetate, mp 140 - 142 °C (lit[139] mp 142 - 143 °C). ^{1}H NMR (500.0 MHz, CDCl$_3$): 4.67 (dd, 1H, J_{gem} = 12.3, $J_{5'\text{b},4'}$ = 3.8, H-5'b); 4.73 (ddd, 1H, $J_{4',3'}$ = 4.6, $J_{4',5'}$ = 3.8, 2.8, H-4'); 4.85 (dd, 1H, J_{gem} = 12.3, $J_{5'\text{a},4'}$ = 2.8, H-5'a); 5.61 (dd, 1H, $J_{5,6}$ = 8.1, $J_{5,\text{NH}}$ = 2.4, H-5); 5.75 (dd, 1H, $J_{2',3'}$ = 6.0, $J_{2',1'}$ = 5.6, H-2'); 5.89 (dd, 1H, $J_{3',2'}$ = 6.0, $J_{3',4'}$ = 4.6, H-3'); 6.32 (d, 1H, $J_{1',2'}$ = 5.6, H-1'); 7.37 (m, 2H, H-*m*-Bz-2'); 7.41 (d, 1H, $J_{6,5}$ = 8.1, H-6); 7.41 (m, 2H, H-*m*-Bz-3'); 7.50 (m, 2H, H-*m*-Bz-5'); 7.56 (m, 1H, H-*p*-Bz-2'); 7.59 (m, 1H, H-*p*-Bz-3'); 7.62 (m, 1H, H-*p*-Bz-5'); 7.95 (m, 2H, H-*o*-Bz-2'); 7.98 (m, 2H, H-*o*-Bz-3'); 8.11 (m, 2H, H-*o*-Bz-5'). ^{13}C NMR (125.7 MHz, CDCl$_3$): 63.68 (CH$_2$-5'); 71.10 (CH$_2$-3'); 73.68 (CH-2'); 80.51 (CH-4'); 87.97 (CH-1'); 103.39 (CH-5); 128.26 (C-*i*-Bz-2'); 128.50 (C-*i*-Bz-3'); 128.55, 128.56 (CH-*m*-Bz-2',3'); 128.79 (CH-*m*-Bz-5'); 129.12 (C-*i*-Bz-5'); 129.61 (CH-*o*-Bz-5'); 129.82 (CH-*o*-Bz-3'); 129.90 (CH-*o*-Bz-2'); 133.71, 133.80 and 133.86 (CH-*p*-BzO-2',3',5'); 139.50 (CH-6); 149.85 (C-2); 162.31 (C-4); 165.27 (COO-2'); 165.33 (COO-3'); 166.03 (COO-5'). (ESI$^+$), *m/z* (% relative intensity): 579 (M$^+$+Na, 100). HR MS (M$^+$+H): 557.1552 (calcd for $C_{30}H_{25}N_2O_9$ 557.1557). The compound **27**: yield 71 %, white crystals from hexane/ethyl acetate, mp 145 - 147 °C (lit[139] mp 147 - 148 °C). ^{1}H NMR (500.0 MHz, CDCl$_3$): 4.69 (dd, 1H, J_{gem} = 12.2, $J_{5'\text{b},4'}$ = 3.6, H-5'b); 4.74 (ddd, 1H, $J_{4',3'}$ = 4.2, $J_{4',5'}$ = 3.6, 2.8, H-4'); 4.84 (dd, 1H, J_{gem} = 12.2, $J_{5'\text{a},4'}$ = 2.8, H-5'a); 5.75 (d, 1H, $J_{5,6}$ = 8.3, H-5); 5.75 (dd, 1H, $J_{2',3'}$ = 6.0, $J_{2',1'}$ = 5.8, H-2'); 5.90 (dd, 1H, $J_{3',2'}$ = 6.0, $J_{3',4'}$ = 4.2, H-3'); 6.33 (d, 1H, $J_{1',2'}$ = 5.8, H-1'); 7.33 (m, 2H, H-*m*-BzO-2'); 7.40 (m, 2H, H-*m*-BzO-3'); 7.43 (bm, 2H, H-*m*-BzN); 7.50 (m, 2H, H-*m*-BzO-5'); 7.53 (d, 1H, $J_{6,5}$ = 8.3, H-6); 7.54 (m, 1H, H-*p*-BzO-2'); 7.58 (m, 1H, H-*p*-BzO-3'); 7.61 (m, 1H, H-*p*-BzN); 7.63 (m, 1H, H-*p*-BzO-5'); 7.89 (m, 2H, H-*o*-BzO-2'); 7.93 (m, 2H, H-*o*-BzN); 7.99 (m, 2H, H-*o*-BzO-3'); 8.11 (m, 2H, H-*o*-BzO-5'). ^{13}C NMR (125.7 MHz, CDCl$_3$): 63.61 (CH$_2$-5'); 71.17 (CH$_2$-3'); 73.86 (CH-2'); 80.65 (CH-4'); 88.17

(CH-1'); 103.39 (CH-5); 128.17 (C-*i*-BzO-2'); 128.48 (C-*i*-BzO-3'); 128.53 (CH-*m*-BzO-2'); 128.59 (CH-*m*-BzO-3'); 128.82 (CH-*m*-BzO-5'); 129.04 (C-*i*-BzO-5'); 129.14 (CH-*m*-BzN); 129.62 (CH-*o*-BzO-5'); 129.80 (CH-*o*-BzO-3'); 129.87 (CH-*o*-BzO-2'); 130.50 (CH-*o*-BzN); 131.14 (C-*i*-BzN); 133.87, 133.84 and 133.76 (CH-*p*-BzO-2',3',5'); 135.13 (CH-*p*-BzN); 139.21 (CH-6); 149.22 (C-2); 161.57 (C-4); 165.29 (COO-3'); 165.45 (COO-2'); 166.05 (COO-5'); 168.10 (CON). (ESI$^+$), *m/z* (% relative intensity): 683 (M$^+$+Na, 80), 1343 (2M$^+$+Na, 100). HR MS (M$^+$+Na): 683.1639 (calcd for $C_{37}H_{28}N_2NaO_{10}$ 683.1636).

2',3'-*O*-isopropylideneuridine (28)



Compound **28** was prepared from uridine (**24**) according to published procedure.[140] Yield 97 %, white crystals from MeOH/$CHCl_3$, mp 162 - 164 °C (lit[168] mp 160 - 161 °C). ^{1}H NMR (499.8 MHz, DMSO-d_6): 1.28, 1.48 (2 × q, 2 × 3H, $^4J = 0.6$, $(CH_3)_2C$); 3.53-3.61 (m, 2H, H-5'); 4.06 (td, 1H, $J_{4',5'} = 4.6$, $J_{4',3'} = 3.6$, H-4'); 4.74 (dd, 1H, $J_{3',2'} = 6.4$, $J_{3',4'} = 3.6$, H-3'); 4.89 (dd, 1H, $J_{2',3'} = 6.4$, $J_{2',1'} = 2.7$, H-2'); 5.09 (t, 1H, $J_{OH,5'} = 5.3$, OH-5'); 5.63 (d, 1H, $J_{5,6} = 8.0$, H-5); 5.83 (d, 1H, $J_{1',2'} = 2.7$, H-1'); 7.79 (d, 1H, $J_{6,5} = 8.0$, H-6); 11.37 (bs, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 25.39, 27.26 ($(\mathbf{C}H_3)_2C$); 61.47 (CH_2-5'); 80.68 (CH-3'); 83.89 (CH-2'); 86.73 (CH-4'); 91.33 (CH-1'); 101.94 (CH-5); 113.18 ($(CH_3)_2\mathbf{C}$); 142.16 (CH-6); 150.54 (C-2); 163.40 (C-4). Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.50; H, 5.59; N, 9.70.

5.4. 5- and 6-Arylated protected uracils

Method A

General procedure for C-H arylation of 1,3-dibenzyluracil (12) with aryl halides 2a-g at the C-5 position

DMF (6 mL) was added through a septum to an argon purged vial containing a 1,3-dibenzyluracil (**12**, 292 mg, 1 mmol), aryl halide (**2a-g**, 2 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol %), $P(C_6F_5)_3$ (53 mg, 0.1 mmol, 10 mol %) and Cs_2CO_3 (814 mg, 2.5 mmol). Reaction mixture was stirred at 160 °C for 48 h. After cooling to r.t., the mixture was diluted with chloroform (20 ml) and solvents were evaporated under reduced pressure. The crude mixture was separated by column chromatography on 120 g of silica gel in a gradient of toluene to 1 % ethyl acetate in toluene to give regioisomer substituted in C-5 position (**17a-g**) as a major product and regioisomer at C-6 position (**18a-g**) as a minor product.

Method B

General procedure for C-H arylation of 1,3-dibenzyluracil (12) with aryl halides 2a-g at the C-6 position

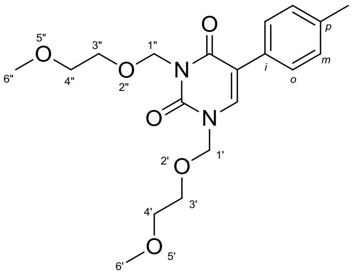
DMF (6 mL) was added through a septum to an argon purged vial containing a 1,3-dibenzyuracil (**12**, 292 mg, 1 mmol), aryl halide (**2a-g**, 2 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol %), $P(C_6F_5)_3$ (53 mg, 0.1 mmol, 10 mol %), CuI (571 mg, 3 mmol) and Cs_2CO_3 (814 mg, 2.5 mmol). Reaction mixture was stirred at 160 °C for 48 h. After cooling to r.t., the mixture was diluted with chloroform (20 ml) and solvents were evaporated under reduced pressure. The crude mixture was separated by column chromatography on 120 g of silica gel in a gradient of toluene to 1 % ethyl acetate in toluene to give regioisomer substituted in C-6 position (**18a-g**) as a major product and regioisomer at C-5 position (**17a-g**) as a minor product.

Method C

General procedure for C-H arylation of protected uracils 11, 12 with *p*-tolyl iodide 2a at the C-6 position in the absence of Pd catalyst and ligand

DMF (3 mL) was added through a septum to an argon purged vial containing protected uracils (**11**, 160 mg, 0.5 mmol or **12**, 146 mg, 0.5 mmol), *p*-tolyl iodide (**2a**, 218 mg, 1 mmol), CuI (286 mg, 1.5 mmol) and Cs_2CO_3 (407 mg, 1.25 mmol). Reaction mixture was stirred at 160 °C for 48 h. After cooling to r.t., the mixture was diluted with chloroform (20 ml) and solvents were evaporated under reduced pressure. The crude mixture was separated by column chromatography on 60 g of silica gel in a gradient of toluene to 1 % ethyl acetate in toluene to give regioisomer substituted in C-6 position (**16a, 18a**) as a major product and regioisomer at C-5 position (**15a, 17a**) as a minor product.

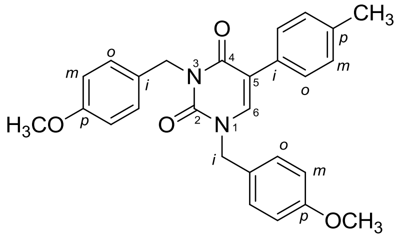
1,3-Bis[(2-methoxyethoxy)methyl]-5-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (13a)



DMF (2 mL) was added through a septum to an argon purged vial containing compound **10** (86.5 mg, 0.3 mmol), *p*-tolyl iodide (**2a**, 131 mg, 0.6 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol %), $P(C_6F_5)_3$ (16 mg, 0.03 mmol, 10 mol %) and Cs_2CO_3 (244 mg, 0.75 mmol). Reaction mixture was stirred at 160 °C for 48 h. After cooling to r.t., the mixture was diluted with chloroform (20 ml) and solvents were evaporated under reduced pressure. The crude mixture was separated by column chromatography on 40 g of silica gel in a gradient of chloroform to 1% metanol in chloroform to give regioisomer **13a** substituted in C-5 position as a major product in 24 % yield, as a yellow oil. ^{1}H NMR (500.0 MHz, $CDCl_3$): 2.37 (s, 3H, CH_3); 3.36, 3.37 (2 × s, 2 × 3H, H-6',6"); 3.54 (m, 2H, H-4"); 3.55 (m, 2H, H-4'); 3.79 (m, 2H, H-3'); 3.84 (m, 2H, H-3"); 5.30 (s, 2H, H-1'); 5.56 (s, 2H, H-1"); 7.20 (m, 2H, H-*m*-Ph); 7.40 (m, 2H, H-*o*-Ph); 7.47 (s, 1H, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.2 (CH_3); 59.0, 59.0 (CH_3-6',6"); 69.1 (CH_2-3'); 69.9 (CH_2-3"); 71.5 (CH_2-4"); 71.5 (CH_2-1"); 71.7 (CH_2-4'); 78.0

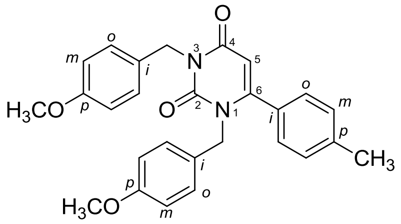
(CH_2-1'); 115. 5 (C-5); 128.1 (CH-*o*-Ph); 129.1 (CH-*m*-Ph); 129.4 (C-*i*-Ph); 138.0 (C-*i*-Ph); 138.7 (CH-6); 151.5 (C-2); 162.1 (C-4). IR (KBr): 2820, 1715, 1666, 1516, 1453, 1353, 1279, 1103. MS (ESI^+), *m/z* (% relative intensity): 379 (M^++H, 26), 401 (M^++Na, 100). HR MS (M^++Na): 401.1685 (calcd for $C_{19}H_{26}N_2NaO_6$ 401.1683).

1,3-Bis(4-methoxybenzyl)-5-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (15a)



DMF (3 mL) was added through a septum to an argon purged vial containing a 1,3-dimethoxybenzyluracil (**11**, 176 mg, 0.5 mmol), *p*-tolyl iodide (**2a**, 218 mg, 1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol %), $P(C_6F_5)_3$ (27 mg, 0.05 mmol, 10 mol %) and Cs_2CO_3 (407 mg, 1.25 mmol). Reaction mixture was stirred at 160 °C for 48 h. After cooling to r.t., the mixture was diluted with chloroform (20 ml) and solvents were evaporated under reduced pressure. The crude mixture was separated by column chromatography on 50 g of silica gel in a gradient of hexane to 20 % ethyl acetate in hexane to give regioisomer **15a** substituted in C-5 position as a major product in 47 % yield, as a yellow oil. ^{1}H NMR (500.0 MHz, $CDCl_3$): 2.27 (s, 3H, CH_3); 3.70 (s, 3H, CH_3O-PMB-3); 3.73 (s, 3H, CH_3O-PMB-1); 4.84 (s, 2H, CH_2-1); 5.08 (s, 2H, CH_2-3); 6.76 (m, 2H, H-*m*-PMB-3); 6.81 (m, 2H, H-*m*-PMB-1); 7.09 (m, 2H, H-*m*-C_6H_4Me); 7.18 (m, 2H, H-*o*-PMB-1); 7.19 (s, 1H, H-6); 7.24 (m, 2H, H-*o*-C_6H_4Me); 7.45 (m, 2H, H-*o*-PMB-3). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.2 (CH_3); 44.3 (CH_2-3); 51.9 (CH_2-1); 55.2, 55.3 (CH_3O-PMB-1,3); 113.7 (CH-*m*-PMB-3); 114.5 (CH-*m*-PMB-1); 115.0 (C-5); 127.3 (C-*i*-PMB-1); 128.2 (CH-*o*-C_6H_4Me); 129.1 (CH-*m*-C_6H_4Me); 129.2 (C-*i*-PMB-3); 129.7 (CH-*o*-PMB-1); 130.0 (C-*i*-C_6H_4Me); 131.0 (CH-*o*-PMB-3); 137.8 (C-*p*-C_6H_4Me); 138.7 (CH-6); 151.4 (C-2); 159.1 (C-*p*-PMB-3); 159.7 (C-*p*-PMB-1); 162.0 (C-4). IR (KBr): 2835, 1701, 1652, 1612, 1513, 1453, 1249, 1033. MS (ESI^+), *m/z* (% relative intensity): 443 (M^++H, 10), 465 (M^++Na, 100). HR MS (M^++H): 443.1964 (calcd for $C_{27}H_{27}N_2O_4$ 443.1965).

1,3-Bis(4-methoxybenzyl)-6-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (16a)

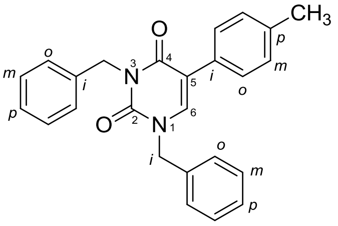


DMF (3 mL) was added through a septum to an argon purged vial containing a 1,3-dimethoxybenzyluracil (**11**, 176 mg, 0.5 mmol), *p*-tolyl iodide (**2a**, 218 mg, 1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol %), $P(C_6F_5)_3$ (27 mg, 0.05 mmol, 10 mol %), CuI (286 mg, 1.5 mmol) and Cs_2CO_3 (407 mg, 1.25 mmol). Reaction mixture was stirred at 160 °C for 48 h. After cooling to r.t., the mixture was diluted with chloroform (20 ml) and solvents were evaporated under reduced pressure. The crude mixture was separated by column chromatography on 50 g of silica gel in a gradient of hexane to 20 % ethyl acetate in hexane to give regioisomer **16a** substituted in C-6 position as a major product in 46 % yield, as a yellow oil. ^{1}H NMR (500.0 MHz, $CDCl_3$): 2.32 (s, 3H, CH_3); 3.69 (s, 3H, CH_3O-PMB-3); 3.72 (s, 3H, CH_3O-PMB-1); 4.80 (bs, 2H, CH_2-1); 5.06 (s, 2H, CH_2-3); 5.59 (s, 1H, H-5); 6.67 (m, 2H, H-*m*-PMB-1); 6.74 (m, 2H, H-*o*-PMB-1); 6.78 (m, 2H, H-*m*-PMB-3); 6.98 (m, 2H, H-*o*-C_6H_4Me); 7.11 (m, 2H, H-*m*-C_6H_4Me); 7.43 (m, 2H, H-*o*-PMB-3). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.3 (CH_3); 44.0 (CH_2-3); 48.8 (CH_2-1); 55.2 (CH_3O-PMB-1,3); 103.4 (CH-5); 113.7 (CH-*m*-PMB-3); 113.9 (CH-*m*-PMB-1); 127.9 (CH-*o*-C_6H_4Me); 128.3 (CH-*o*-PMB-1); 128.6 (C-*i*-PMB-1); 129.3 (C-*i*-PMB-3); 129.3 (CH-*m*-C_6H_4Me); 130.4 (C-*i*-C_6H_4Me); 130.8 (CH-*o*-PMB-3); 140.3 (C-*p*-C_6H_4Me); 152.5 (C-2); 154.9 (C-6); 158.9 (C-*p*-PMB-3); 159.1 (C-*p*-PMB-1); 162.1 (C-4). IR (KBr): 2836, 1703, 1660, 1613, 1513, 1441, 1248, 1034. MS (ESI$^+$), *m/z* (% relative intensity): 465 (M^++Na, 100). HR MS (M^++Na): 465.1783 (calcd for $C_{27}H_{26}N_2NaO_4$ 465.1785).

5.4.1. 5- and 6-Aryl-1,3-dibenzyluracils

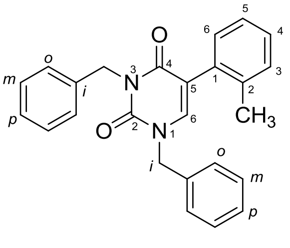
5.4.1.1. 5-Aryl-1,3-dibenzyluracils

1,3-Dibenzyl-5-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (17a)



Compound **17a** was prepared from **12** according to general procedure (Method A) in 45 % yield, as a yellowish oil. ^{1}H NMR (600.1 MHz, CDCl$_3$): 2.34 (s, 3H, CH$_3$); 4.99 (s, 2H, CH$_2$-1); 5.23 (s, 2H, CH$_2$-3); 7.17 (m, 2H, H-*m*-C$_6$H$_4$Me); 7.25 (s, 1H, H-6); 7.26 (m, 1H, H-*p*-3Bn); 7.31 (m, 4H, H-*o*-1Bn, H-*m*-3Bn); 7.33 (m, 2H, H-*o*-C$_6$H$_4$Me); 7.36 (m, 1H, H-*p*-1Bn); 7.37 (m, 2H, H-*m*-1Bn); 7.55 (m, 2H, H-*o*-3Bn). ^{13}C NMR (150.9 MHz, CDCl$_3$): 21.2 (CH$_3$); 44.9 (CH$_2$-3); 52.4 (CH$_2$-1); 115.1 (C-5); 127.6 (CH-*p*-3Bn); 128.0 (CH-*o*-1Bn); 128.2 (CH-*o*-C$_6$H$_4$Me); 128.4 (CH-*m*-3Bn); 128.5 (CH-*p*-1Bn); 129.1 (CH-*m*-C$_6$H$_4$Me); 129.1 (CH-*m*-1Bn); 129.4 (CH-*o*-3Bn); 129.8 (C-*i*-C$_6$H$_4$Me); 135.3 (C-*i*-1Bn); 136.9 (C-*i*-3Bn); 137.8 (C-*p*-C$_6$H$_4$Me); 138.9 (CH-6); 151.4 (C-2); 162.0 (C-4). IR (KBr): 1704, 1652, 1584, 1515, 1495, 1451, 1379, 1284, 1219, 1083. MS (ESI$^+$), *m/z* (% relative intensity): 383 (M$^+$+H, 10), 405 (M$^+$+Na, 100), 421 (M$^+$+K, 12). HR MS (M$^+$+H): 383.1754 (calcd for C$_{25}$H$_{23}$N$_2$O$_2$ 383.1754).

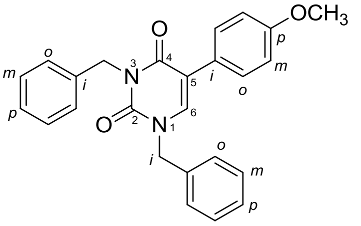
1,3-Dibenzyl-5-(*o*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (17b)



Compound **17b** was prepared from **12** according to general procedure (Method A) in 70 % yield, as a white powder, mp 115 - 116 °C. ^{1}H NMR (499.8 MHz, CDCl$_3$):2.17 (s, 3H, CH$_3$); 4.97 (s, 2H, CH$_2$-1); 5.22 (s, 2H, CH$_2$-3); 7.06 (dd, 1H, $J_{6,5}$ = 7.6, $J_{6,4}$ = 1.4, H-6-C$_6$H$_4$Me); 7.12 (s, 1H, H-6); 7.16 (m, 1H, H-5-C$_6$H$_4$Me); 7.21 (m, 1H, H-3-C$_6$H$_4$Me); 7.25 (ddd, 1H, $J_{4,3}$ = 7.6, $J_{4,5}$ = 7.0, $J_{4,6}$ = 1.4, H-4-C$_6$H$_4$Me); 7.26-7.40 (m, 8H, H-*o,m,p*-1Bn, H-*m,p*-3Bn); 7.54 (m, 2H, H-*o*-3Bn). ^{13}C NMR (125.7 MHz, CDCl$_3$):

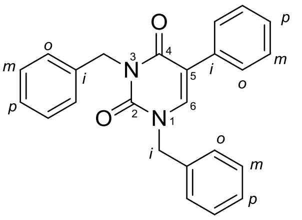
20.1 (CH_3); 44.9 (CH_2-3); 52.3 (CH_2-1); 115.6 (C-5); 125.8 (CH-5-C_6H_4Me); 127.6 (CH-*p*-3Bn); 128.1 (CH-*o*-1Bn); 128.4 (CH-*m*-3Bn); 128.5, 128.5 (CH-4-C_6H_4Me, CH-*p*-1Bn); 129.2 (CH-*m*-1Bn); 129.4 (CH-*o*-3Bn); 130.1 (CH-3-C_6H_4Me); 130.5 (CH-6-C_6H_4Me); 132.3 (C-1-C_6H_4Me); 135.3 (C-*i*-1Bn); 137.0 (C-*i*-3Bn); 137.7 (C-2-C_6H_4Me); 140.2 (CH-6); 151.6 (C-2); 161.7 (C-4). IR (KBr): 1703, 1649, 1634, 1586, 1495, 1446, 1379, 1294, 1217. MS (ESI^+), *m/z* (% relative intensity): 383 (M^++H, 93), 405 (M^++Na, 100), 421 (M^++K, 30). HR MS (M^++H): 383.1753 (calcd for $C_{25}H_{23}N_2O_2$ 383.1754).

1,3-Dibenzyl-5-(4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (17c)



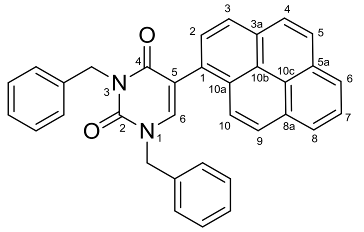
Compound **17c** was prepared from **12** according to general procedure (Method A) in 45 % yield, as a yellowish oil. ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.80 (s, 3H, OCH_3); 4.99 (s, 2H, CH_2-1); 5.23 (s, 2H, CH_2-3); 6.89 (m, 2H, H-*m*-C_6H_4OMe); 7.22 (s, 1H, H-6); 7.26 (m, 1H, H-*p*-3Bn); 7.31 (m, 4H, H-*o*-1Bn, H-*m*-3Bn); 7.36 (m, 1H, H-*p*-1Bn); 7.37 (m, 4H, H-*m*-1Bn, H-*o*-C_6H_4OMe); 7.55 (m, 2H, H-*o*-3Bn). ^{13}C NMR (150.9 MHz, $CDCl_3$): 45.0 (CH_2-3); 52.4 (CH_2-1); 55.3 (CH_3); 113.9 (CH-*m*-C_6H_4OMe); 114.8 (C-5); 125.1 (C-*i*-C_6H_4OMe); 127.6 (CH-*p*-3Bn); 128.0 (CH-*o*-1Bn); 128.4 (CH-*m*-3Bn); 128.5 (CH-*p*-1Bn); 129.1 (CH-*m*-1Bn); 129.3 (CH-*o*-3Bn); 129.5 (CH-*o*-C_6H_4OMe); 135.4 (C-*i*-1Bn); 136.9 (C-*i*-3Bn); 138.5 (CH-6); 151.4 (C-2); 159.4 (C-*p*-C_6H_4OMe); 162.1 (C-4). IR (KBr): 1702, 1651, 1609, 1515, 1495, 1451, 1380, 1249, 1179, 1049. MS (ESI^+), *m/z* (% relative intensity): 399 (M^++H, 100), 421 (M^++Na, 88), 819 ($2M^+$+Na, 37). HR MS (M^++H): 399.1704 (calcd for $C_{25}H_{23}N_2O_3$ 399.1703).

1,3-Dibenzyl-5-phenylpyrimidine-2,4(1*H*,3*H*)-dione (17d)



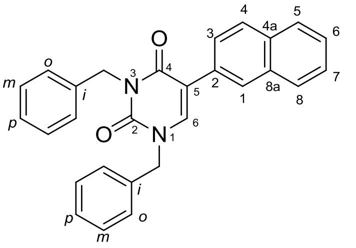
Compound **17d** was prepared from **12** according to general procedure (Method A) in 47 % yield, as a white powder, mp 125 - 126 °C. ^{1}H NMR (500.0 MHz, CDCl$_3$): 5.00 (s, 2H, CH$_2$-1); 5.24 (s, 2H, CH$_2$-3); 7.28 (s, 1H, H-6); 7.28-7.40 (m, 11H, H-*o,m,p*-1Bn, H-*m,p*-3Bn, H-*m,p*-Ph); 7.44 (m, 2H, H-*o*-Ph); 7.56 (m, 2H, H-*o*-3Bn). ^{13}C NMR (125.7 MHz, CDCl$_3$): 45.0 (CH$_2$-3); 52.4 (CH$_2$-1); 115.1 (C-5); 127.7 (CH-*p*-3Bn); 127.9 (CH-*p*-Ph); 128.0 (CH-*o*-1Bn); 128.3 (CH-*o*-Ph); 128.4 (CH-*m*-3Bn); 128.4 (CH-*m*-Ph); 128.5 (CH-*p*-1Bn); 129.2 (CH-*m*-1Bn); 129.4 (CH-*o*-3Bn); 132.8 (C-*i*-Ph); 135.3 (C-*i*-1Bn); 136.9 (C-*i*-3Bn); 139.3 (CH-6); 151.4 (C-2); 161.9 (C-4). IR (KBr): 1698, 1648, 1602, 1581, 1495, 1455, 1439, 1378, 1337, 1280, 1206, 1181, 1078. MS (ESI$^+$), *m/z* (% relative intensity): 369 (M$^+$+H, 11), 391 (M$^+$+Na, 100). HR MS (M$^+$+H): 369.1597 (calcd for $C_{24}H_{21}N_2O_2$ 369.1598).

1,3-Dibenzyl-5-(pyren-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (17e)



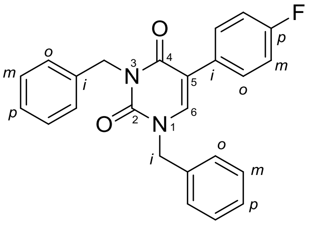
Compound **17e** was prepared from **12** according to general procedure (Method A) in 25 % yield, as a yellow powder, mp 82 - 84 °C. ^{1}H NMR (499.8 MHz, CDCl$_3$): 5.05 (bs, 2H, CH$_2$-1); 5.31 (s, 2H, CH$_2$-3); 7.30 (m, 1H, H-*p*-3Bn); 7.35 (m, 2H, H-*m*-3Bn); 7.37 (m, 3H, H-*o,p*-1Bn); 7.40 (m, 2H, H-*m*-1Bn); 7.41 (s, 1H, H-6); 7.62 (m, 2H, H-*o*-3Bn); 7.86 (d, 1H, $J_{2,3}$ = 7.8, H-2-pyrenyl); 7.87 (d, 1H, $J_{10,9}$ = 9.2, H-10-pyrenyl); 8.00 (t, 1H, $J_{7,6}$ = $J_{7,8}$ = 7.6, H-7-pyrenyl); 8.01 (d, 1H, $J_{9,10}$ = 9.2, H-9-pyrenyl); 8.04 (d, 1H, $J_{4,5}$ = 8.9, H-4-pyrenyl); 8.08 (d, 1H, $J_{5,4}$ = 8.9, H-5-pyrenyl); 8.15 (d, 1H, $J_{3,2}$ = 7.8, H-3-pyrenyl); 8.16 (dd, 1H, $J_{8,7}$ = 7.6, $J_{8,6}$ = 1.1, H-8-pyrenyl); 8.19 (dd, 1H, $J_{6,7}$ = 7.6, $J_{6,8}$ = 1.1, H-6-pyrenyl). ^{13}C NMR (125.7 MHz, CDCl$_3$): 45.1 (CH$_2$-3); 52.5 (CH$_2$-1); 114.4 (C-5); 124.4 (CH-10-pyrenyl); 124.6 (CH-3-pyrenyl); 124.6 (C-10c-pyrenyl); 124.9 (CH-10b-pyrenyl); 125.2 (CH-8-pyrenyl); 125.4 (CH-6-pyrenyl); 126.1 (CH-7-pyrenyl); 127.2 (CH-4-pyrenyl); 127.4 (C-1-pyrenyl); 127.7 (CH-*p*-3Bn); 127.8 (CH-9-pyrenyl); 127.9 (CH-5-pyrenyl); 128.2 (CH-*o*-1Bn); 128.3 (CH-2-pyrenyl); 128.5 (CH-*m*-3Bn); 128.6 (CH-*p*-1Bn); 129.2 (CH-*m*-1Bn); 129.6 (CH-*o*-3Bn); 129.8 (C-10a-pyrenyl); 130.8 (C-8a-pyrenyl); 131.2 (C-5a-pyrenyl); 131.4 (C-3a-pyrenyl); 135.3 (C-*i*-1Bn); 136.9 (C-*i*-3Bn); 141.7 (CH-6); 151.6 (C-2); 162.4 (C-4). IR: 1700, 1649, 1602, 1584, 1495, 1432, 1389, 1341, 1179, 1070. MS (ESI$^+$), *m/z* (% relative intensity): 493 (M$^+$+H, 15), 515 (M$^+$+Na, 100). HR MS (M$^+$+H): 493.1909 (calcd for $C_{34}H_{25}N_2O_2$ 493.1911).

1,3-Dibenzyl-5-(naphthalen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (17f)



Compound **17f** was prepared from **12** according to general procedure (Method A) in 19 % yield, as a yellowish powder, mp 62 - 64 °C. ^{1}H NMR (499.8 MHz, CDCl$_3$): 5.04 (bs, 2H, CH$_2$-1); 5.27 (s, 2H, CH$_2$-3); 7.28 (m, 1H, H-*p*-3Bn); 7.33 (m, 2H, H-*m* -3Bn); 7.35 (m, 2H, H-*o*-1Bn); 7.37 (m, 1H, H-*p*-1Bn); 7.40 (m, 2H, H-*m*-1Bn); 7.41 (s, 1H, H-6); 7.46 (m, 1H, H-6-naphth); 7.48 (m, 1H, H-7-naphth); 7.56 (dd, 1H, $J_{3,4}$ = 8.5, $J_{3,1}$ = 1.9, H-3-naphth); 7.58 (m, 2H, H-*o*-3Bn); 7.81 (m, 1H, H-8-naphth); 7.82 (m, 2H, H-4,5-naphth); 7.94 (m, 1H, H-1-naphth). ^{13}C NMR (150.9 MHz, CDCl$_3$): 45.0 (CH$_2$-3); 52.5 (CH$_2$-1); 115.1 (C-5); 126.1 (CH-3-naphth); 126.2 (CH-6,7-naphth); 127.2 (CH-1-naphth); 127.6 (CH-8-naphth); 127.7 (CH-*p*-3Bn); 128.0 (CH-4 or 5-naphth); 128.0 (CH-*o*-1Bn); 128.1 (CH-4 or 5-naphth); 128.4 (CH-*m*-3Bn); 128.6 (CH-*p*-1Bn); 129.2 (CH-*m*-1Bn); 129.3 (CH-*o*-3Bn); 130.3 (C-2-naphth); 132.8 (C-4a-naphth); 133.2 (C-8a-naphth); 135.3 (C-*i*-1Bn); 136.8 (C-*i*-3Bn); 139.6 (CH-6); 151.4 (C-2); 162.0 (C-4). IR (KBr): 1703, 1652, 1600, 1586, 1495, 1449, 1380, 1280, 1219, 1081, 1050. MS (ESI$^+$), *m/z* (% relative intensity): 419 (M$^+$+H, 84), 441 (M$^+$+Na, 100), 457 (M$^+$+K, 9), 859 (2M$^+$+Na, 28). HR MS (M$^+$+H): 419.1758 (calcd for $C_{28}H_{23}N_2O_2$ 419.1754).

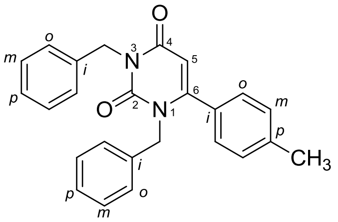
1,3-Dibenzyl-5-(4-fluorophenyl)pyrimidine-2,4(1*H*,3*H*)-dione (17g)



Compound **17g** was prepared from **12** according to general procedure (Method A) in 49 % yield, as a yellow powder, mp 45 - 47 °C. ^{1}H NMR (499.8 MHz, CDCl$_3$): 5.00 (s, 2H, CH_2-1); 5.23 (s, 2H, CH_2-3); 7.04 (m, 2H, H-*m*-C_6H_4F); 7.25 (s, 1H, H-6); 7.26-7.34 (m, 5H, H-*o*-1Bn, H-*m,p*-3Bn); 7.34-7.43 (m, 5H, H-*m,p*-1Bn, H-*o*-C_6H_4F); 7.54 (m, 2H, H-*o*-3Bn). ^{13}C NMR (125.7 MHz, $CDCl_3$): 45.0 (CH_2-3); 52.5 (CH_2-1); 114.2 (C-5); 115.4 (d, $J_{C,F}$ = 21.6, CH-*m*-C_6H_4F); 127.7 (CH-*p*-3Bn); 128.0 (CH-*o*-1Bn); 128.4 (CH-*m*-3Bn); 128.6 (CH-*p*-1Bn); 128.7 (d, $J_{C,F}$ = 3.3, C-*i*-C_6H_4F); 129.2 (CH-*m*-1Bn); 129.3 (CH-*o*-3Bn); 130.1 (d, $J_{C,F}$ = 8.1, CH-*o*-C_6H_4F); 135.2 (C-*i*-1Bn); 136.8 (C-*i*-3Bn); 139.1 (CH-6); 151.3 (C-2); 161.9 (C-4); 162.5 (d, $J_{C,F}$ = 247.7, C-*p*-C_6H_4F). $^{19}F\{^1H\}$ NMR (470.3 MHz, $CDCl_3$): -109.95. IR: 1701, 1646, 1602, 1510, 1495, 1448, 1408, 1378, 1222, 1159, 1080. MS (ESI^+), *m/z* (% relative intensity): 387 (M^++H, 54), 409 (M^++Na, 100), 425 (M^++K, 35), 795 ($2M^+$+Na, 8). HR MS (M^++H): 387.1503 (calcd for $C_{24}H_{20}FN_2O_2$ 387.1503).

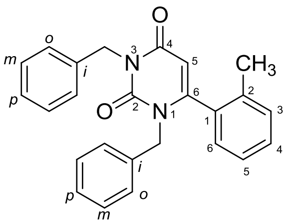
5.4.1.2. 6-Aryl-1,3-dibenzyluracils

1,3-Dibenzyl-6-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (18a)



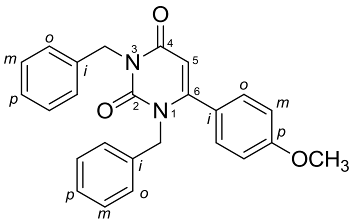
Compound **18a** was prepared from **12** according to general procedure (Method B) in 66 % yield, as a yellowish oil. ^1H NMR (499.8 MHz, $CDCl_3$): 2.38 (s, 3H, CH_3); 4.94 (bs, 2H, CH_2-1); 5.20 (s, 2H, CH_2-3); 5.70 (s, 1H, H-5); 6.90 (m, 2H, H-*o*-1Bn); 7.05 (m, 2H, H-*o*-C_6H_4Me); 7.16 (m, 2H, H-*m*-C_6H_4Me); 7.22 (m, 3H, H-*m,p*-1Bn); 7.29 (m, 1H, H-*p*-3Bn); 7.33 (m, 2H, H-*m*-3Bn); 7.53 (m, 2H, H-*o*-3Bn). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.3 (CH_3); 44.5 (CH_2-3); 49.4 (CH_2-1); 103.4 (CH-5); 126.7 (CH-*o*-1Bn); 127.5 (CH-*p*-1Bn); 127.6 (CH-*p*-3Bn); 127.8 (CH-*o*-C_6H_4Me); 128.4 (CH-*m*-3Bn); 128.5 (CH-*m*-1Bn); 129.1 (CH-*o*-3Bn); 129.3 (CH-*m*-C_6H_4Me); 130.2 (C-*i*-C_6H_4Me); 136.6 (C-*i*-1Bn); 136.9 (C-*i*-3Bn); 140.3 (C-*p*-C_6H_4Me); 152.5 (C-2); 155.0 (C-6); 162.1 (C-4). IR: 1703, 1658, 1580, 1549, 1513, 1492, 1451, 1383, 1279, 1243, 1181, 1083. MS (ESI^+), *m/z* (% relative intensity): 383 (M^++H, 4), 405 (M^++Na, 100), 421 (M^++K, 16). HR MS (M^++H): 383.1754 (calcd for $C_{25}H_{23}N_2O_2$ 383.1754).

1,3-Dibenzyl-6-(*o*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (18b)



Compound **18b** was prepared from **12** according to general procedure (Method B) in 28 % yield, as white crystals from hexane/ethylacetate, mp 131 - 132 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$): 1.97 (s, 3H, CH_3); 4.69 and 4.91 (2 × bd, 2 × 1H, J_{gem} = 14.9, CH_2-1); 5.22 and 5.26 (2 × d, 2 × 1H, J_{gem} = 13.7, CH_2-3); 5.65 (s, 1H, H-5); 6.78 (m, 2H, H-*o*-1Bn); 6.98 (dd, 1H, $J_{6,5}$ = 7.6, $J_{6,4}$ = 1.4, H-6-C_6H_4Me); 7.16 (m, 1H, H-5-C_6H_4Me); 7.18 (m, 2H, H-*m*-1Bn); 7.19 (m, 2H, H-*p*-1Bn); 7.20 (m, 1H, H-3-C_6H_4Me); 7.29 (m, 1H, H-*p*-3Bn); 7.35 (m, 3H, H-4-C_6H_4Me and H-*m*-3Bn); 7.55 (m, 2H, H-*o*-3Bn). ^{13}C NMR (125.7 MHz, $CDCl_3$): 19.2 (CH_3); 44.7 (CH_2-3); 49.0 (CH_2-1); 103.2 (CH-5); 125.9 (CH-5-C_6H_4Me); 127.4 (CH-*o*-1Bn); 127.6 (CH-*p*-3Bn); 127.7 (CH-*p*-1Bn); 128.4, 128.4 (CH-*m*-1Bn and CH-*m*-3Bn); 128.5 (CH-6-C_6H_4Me); 129.1 (CH-*o*-3Bn); 130.1 (CH-4-C_6H_4Me); 130.5 (CH-3-C_6H_4Me); 132.4 (C-1-C_6H_4Me); 135.8 (C-2-C_6H_4Me); 136.2 (C-*i*-1Bn); 136.9 (C-*i*-3Bn); 152.7 (C-2); 154.0 (C-6); 162.2 (C-4). IR (KBr): 1698, 1660, 1621, 1585, 1495, 1438, 1395, 1344, 1216. MS (EI$^+$), *m/z* (% relative intensity): 65 (19), 77 (13), 91 (100), 103 (7), 115 (15), 132 (21), 149 (5), 186 (32), 220 (3), 248 (7), 289 (10), 367 (46), 382 (M$^+$, 33). HR MS (M$^+$): 382.1674 (calcd for $C_{25}H_{22}N_2O_2$ 382.1681).

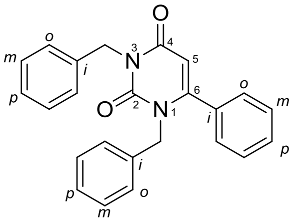
1,3-Dibenzyl-6-(4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (18c)



Compound **18c** was prepared from **12** according to general procedure (Method B) in 38 % yield, as a yellowish oil. ^{1}H NMR (600.1 MHz, $CDCl_3$): 3.82 (s, 3H, OCH_3); 4.95 (bs, 2H, CH_2-1); 5.20 (s, 2H, CH_2-3); 5.70 (s, 1H, H-5); 6.86 (m, 2H, H-*m*-C_6H_4OMe); 6.91 (m, 2H, H-*o*-1Bn); 7.09 (m, 2H, H-*o*-C_6H_4OMe); 7.22 (m, 3H, H-*m,p*-1Bn); 7.28 (m, 1H, H-*p*-3Bn); 7.33 (m, 2H, H-*m*-3Bn); 7.53 (m, 2H, H-*o*-3Bn). ^{13}C NMR (150.9 MHz, $CDCl_3$): 44.6 (CH_2-3); 49.4 (CH_2-1); 55.4 (CH_3O); 103.5 (CH-5); 114.0 (CH-*m*-

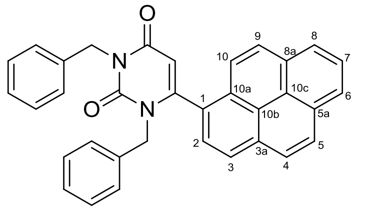
C_6H_4OMe); 125.3 (C-*i*-C_6H_4OMe); 126.6 (CH-*o*-1Bn); 127.5 (CH-*p*-1Bn); 127.6 (CH-*p*-3Bn); 128.4 (CH-*m*-3Bn); 128.6 (CH-*m*-1Bn); 129.1 (CH-*o*-3Bn); 129.4 (CH-*o*-C_6H_4OMe); 136.6 (C-*i*-1Bn); 136.9 (C-*i*-3Bn); 152.6 (C-2); 154.8 (C-6); 160.8 (C-*p*-C_6H_4OMe); 162.1 (C-4). IR (KBr): 1702, 1651, 1514, 1495, 1449, 1378, 1248, 1178, 1070. MS (ESI^+), *m/z* (% relative intensity): 399 (M^++H, 35), 421 (M^++Na, 100), 437 (M^++K, 30), 819 ($2M^+$+Na, 10). HR MS (M^++H): 399.1703 (calcd for $C_{25}H_{23}N_2O_3$ 399.1703).

1,3-Dibenzyl-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione (18d)



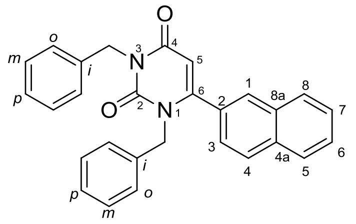
Compound **18d** was prepared from **12** according to general procedure (Method B) in 42 % yield, as a white powder, mp 76 - 78 °C. The experimental data are in accordance to literature.[169] ^1H NMR (600.1 MHz, $CDCl_3$): 4.93 (bs, 2H, CH_2-1); 5.21 (s, 2H, CH_2-3); 5.71 (s, 1H, H-5); 6.86 (m, 2H, H-*o*-1Bn); 7.14 (m, 2H, H-*o*-Ph); 7.21 (m, 3H, H-*m,p*-1Bn); 7.29 (m, 1H, H-*p*-3Bn); 7.33 (m, 2H, H-*m*-3Bn); 7.35 (m, 2H, H-*m*-Ph); 7.44 (m, 1H, H-*p*-Ph); 7.54 (m, 2H, H-*o*-3Bn). ^{13}C NMR (150.9 MHz, $CDCl_3$): 44.6 (CH_2-3); 49.4 (CH_2-1); 103.5 (CH-5); 126.7 (CH-*o*-1Bn); 127.5 (CH-*p*-1Bn); 127.6 (CH-*p*-3Bn); 127.9 (CH-*o*-Ph); 128.4 (CH-*m*-3Bn); 128.5 (CH-*m*-1Bn); 128.6 (CH-*m*-Ph); 129.2 (CH-*o*-3Bn); 130.1 (CH-*p*-Ph); 133.0 (C-*i*-Ph); 136.55 (C-*i*-1Bn); 136.9 (C-*i*-3Bn); 152.5 (C-2); 154.8 (C-6); 162.0 (C-4). IR (KBr): 1705, 1659, 1604, 1574, 1496, 1450, 1437, 1389, 1349, 1242, 1205, 1192, 1075. MS (ESI^+), *m/z* (% relative intensity): 369 (M^++H, 7), 391 (M^++Na, 100). HR MS (M^++H): 369.1597 (calcd for $C_{24}H_{21}N_2O_2$ 369.1598).

1,3-Dibenzyl-6-(pyren-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (18e)



Compound **18e** was prepared from **12** according to general procedure (Method B) in 50 % yield, as a yellow powder, mp 78 - 80 °C. ^{1}H NMR (600.1 MHz, CDCl$_3$): 4.49, 5.12 (2 × d, 2 × 1H, J_{gem} = 15.5, CH$_2$-1); 5.30, 5.37 (2 × d, 2 × 1H, J_{gem} = 13.3, CH$_2$-3); 5.94 (s, 1H, H-5); 6.58 (m, 2H, H-*o*-1Bn); 6.99 (m, 2H, H-*m*-1Bn); 7.08 (m, 2H, H-*m*-1Bn); 7.34 (m, 1H, H-*p*-3Bn); 7.40 (m, 2H, H-*m*-3Bn); 7.63 (d, 1H, $J_{2,3}$ = 7.9, H-2-pyrenyl); 7.64 (m, 2H, H-*o*-3Bn); 7.82 (d, 1H, $J_{10,9}$ = 9.1, H-10-pyrenyl); 8.08 (m, 3H, H-3,4,5-pyrenyl); 8.09 (t, 1H, $J_{7,6}$ = $J_{7,8}$ = 7.7, H-7-pyrenyl); 8.18 (d, 1H, $J_{9,10}$ = 9.1, H-9-pyrenyl); 8.25 (dd, 1H, $J_{8,7}$ = 7.7, $J_{8,6}$ = 1.2, H-8-pyrenyl); 8.29 (dd, 1H, $J_{6,7}$ = 7.7, $J_{6,8}$ = 1.2, H-6-pyrenyl). ^{13}C NMR (150.9 MHz, CDCl$_3$): 44.8 (CH$_2$-3); 49.5 (CH$_2$-1); 105.0 (C-5); 123.1 (CH-10-pyrenyl); 124.2 (C-10c-pyrenyl); 124.3 (CH-10b-pyrenyl, CH-3-pyrenyl); 126.2 (CH-8-pyrenyl); 126.3 (CH-7-pyrenyl); 126.3 (CH-6-pyrenyl); 126.6 (CH-1-pyrenyl); 126.7 (CH-4-pyrenyl); 127.0 (CH-*o*-1Bn); 127.1 (CH-5-pyrenyl); 127.5 (CH-*p*-1Bn); 127.7 (CH-*p*-3Bn); 128.3 (CH-*m*-1Bn); 128.4 (C-10a-pyrenyl); 128.5 (CH-*m*-3Bn); 129.0 (CH-9-pyrenyl); 129.3 (CH-*o*-3Bn); 129.4 (CH-2-pyrenyl); 130.6 (C-8a-pyrenyl); 131.1 (C-5a-pyrenyl); 132.4 (C-3a-pyrenyl); 136.3 (C-*i*-1Bn); 136.9 (C-*i*-3Bn); 152.7 (C-2); 153.8 (C-6); 162.1 (C-4). IR: 1700, 1652, 1601, 1584, 1494, 1430, 1389, 1340, 1179, 1070. MS (ESI$^+$), *m/z* (% relative intensity): 493 (M$^+$+H, 16), 515 (M$^+$+Na, 100), 531 (M$^+$+K, 30), 1007 (2M$^+$+Na, 13). HR MS (M$^+$+H): 493.1910 (calcd for C$_{34}$H$_{25}$N$_2$O$_2$ 493.1911).

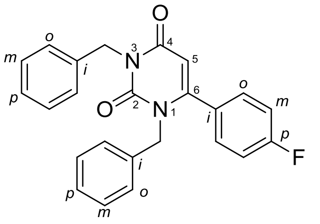
1,3-Dibenzyl-6-(naphthalen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (18f)



Compound **18f** was prepared from **12** according to general procedure (Method B) in 33 % yield, as a yellowish powder, mp 55 - 58 °C. ^{1}H NMR (499.8 MHz, CDCl$_3$): 4.97 (bs, 2H, CH$_2$-1); 5.24 (s, 2H, CH$_2$-3); 5.81 (s, 1H, H-5); 6.86 (m, 2H, H-*o*-1Bn); 7.19

(m, 3H, H-*m,p*-1Bn); 7.23 (dd, 1H, $J_{3,4}$ = 8.5, $J_{3,1}$ = 1.9, H-3-naphth); 7.30 (m, 1H, H-*p*-3Bn); 7.35 (m, 2H, H-*m*-3Bn); 7.54 (ddd, 1H, $J_{7,8}$ = 8.2, $J_{7,6}$ = 6.9, $J_{7,5}$ = 1.4, H-7-naphth); 7.55 (m, 2H, H-*o*-3Bn); 7.58 (ddd, 1H, $J_{6,5}$ = 8.2, $J_{6,7}$ = 6.9, $J_{6,8}$ = 1.4, H-6-naphth); 7.63 (d, 1H, $J_{1,3}$ = 1.9, H-1-naphth); 7.74 (m, 1H, H-8-naphth); 7.83 (d, 1H, $J_{4,3}$ = 8.5, H-4-naphth); 7.87(m, 1H, H-5-naphth). ^{13}C NMR (125.7 MHz, $CDCl_3$): 44.63 (CH_2-3); 49.70 (CH_2-1); 103.76 (CH-5); 124.58 (CH-3-naphth); 126.72 (CH-*o*-1Bn); 127.18 (CH-7-naphth); 127.56 (CH-*p*-1Bn); 127.63 (CH-6-naphth); 127.65 (CH-*p*-3Bn); 127.80 (CH-5-naphth); 128.10 (CH-1-naphth); 128.35 (CH-8-naphth); 128.42 (CH-*m*-3Bn); 128.53 (CH-4-naphth); 128.55 (CH-*m*-1Bn); 129.16 (CH-*o*-3Bn); 130.31 (C-2-naphth); 132.46 (C-8a-naphth); 133.47 (C-4a-naphth); 136.54 (C-*i*-1Bn); 136.90 (C-*i*-3Bn); 152.56 (C-2); 154.93 (C-6); 162.05 (C-4). IR (KBr): 1705, 1662, 1617, 1495, 1472, 1440, 1392, 1340, 1273, 1187, 1070. MS (ESI$^+$), *m/z* (% relative intensity): 419 (M$^+$+H, 59), 441 (M$^+$+Na, 100), 457 (M$^+$+K, 10), 859 (2M$^+$+Na, 22). HR MS (M$^+$+H): 419.1756 (calcd for $C_{28}H_{23}N_2O_2$ 419.1754).

1,3-Dibenzyl-6-(4-fluorophenyl)pyrimidine-2,4(1*H*,3*H*)-dione (18g)

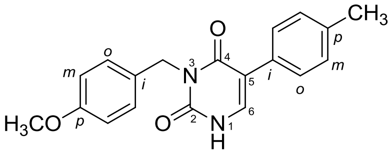


Compound **18g** was prepared from **12** according to general procedure (Method B) in 24 % yield, as a yellowish oil. ^{1}H NMR (499.8 MHz, $CDCl_3$): 4.92 (bs, 2H, CH_2-1); 5.22 (s, 2H, CH_2-3); 5.69 (s, 1H, H-5); 6.86 (m, 2H, H-*o*-1Bn); 7.04 (m, 2H, H-*m*-C_6H_4F); 7.11 (m, 2H, H-*o*-C_6H_4F); 7.22 (m, 3H, H-*m,p*-1Bn); 7.30 (m, 1H, H-*p*-3Bn); 7.33 (m, 2H, H-*m*-3Bn); 7.54 (m, 2H, H-*o*-3Bn). ^{13}C NMR (125.7 MHz, $CDCl_3$): 44.7 (CH_2-3); 49.4 (CH_2-1); 103.9 (CH-5); 115.9 (d, $J_{C,F}$ = 22.0, CH-*m*-C_6H_4F); 126.5 (CH-*o*-1Bn); 127.7 (CH-*p*-1Bn); 127.7 (CH-*p*-3Bn); 128.4 (CH-*m*-3Bn); 128.7 (CH-*m*-1Bn); 129.1 (d, $J_{C,F}$ = 3.6, C-*i*-C_6H_4F); 129.2 (CH-*o*-3Bn); 130.0 (d, $J_{C,F}$ = 8.5, CH-*o*-C_6H_4F); 136.3 (C-*i*-1Bn); 136.8 (C-*i*-3Bn); 152.5 (C-2); 153.8 (C-6); 161.9 (C-4); 163.5 (d, $J_{C,F}$ = 251.5, C-*p*-C_6H_4F). ^{19}F NMR (470.3 MHz, $CDCl_3$): -105.64. IR (KBr): 1705, 1665, 1621, 1600, 1511, 1496, 1441, 1392, 1345, 1226, 1160, 1071. MS (ESI$^+$), *m/z* (% relative intensity): 387 (M$^+$+H, 42), 409 (M$^+$+Na, 100), 425 (M$^+$+K, 25), 795 (2M$^+$+Na, 8). HR MS (M$^+$+H): 387.1504 (calcd for $C_{24}H_{20}FN_2O_2$ 387.1503).

5.5. Deprotected 5- and 6-aryluracils

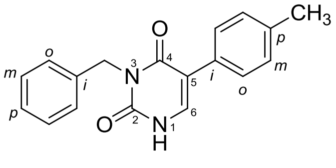
5.5.1. Monodeprotected 5- and 6-aryuracils

3-(4-Methoxybenzyl)-5-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (19a)



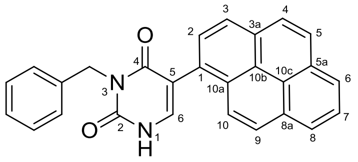
A mixture of compound **15a** (50 mg, 0.113 mmol), ammonium formate (2.8 ml of a 0.4 N solution in dry MeOH) and 10 % palladium-charcoal (132 mg 10% Pd/C, 0.124 mmol of Pd, 1.1 equiv of Pd) was refluxed for 17 h. The mixture was filtered through celite and the solid residue was extensively washed with MeOH and $CHCl_3$ (cca 120 ml). Removal of solvents under reduced pressure and following column chromatography on 40 g of silica gel in a gradient of chloroform to 1 % methanol in chloroform gave the pure monodeprotected product **19a** in 82 % yield, as a white powder, mp 175 - 177 °C. ^{1}H NMR (500.0 MHz, $CDCl_3$): 2.36 (s, 3H, CH_3); 3.77 (s, 3H, CH_3O); 5.13 (s, 2H, CH_2Ph); 6.83 (m, 2H, H-*m*-C_6H_4OMe); 7.20 (m, 2H, H-*m*-C_6H_4Me); 7.26 (d, 1H, $J_{6,NH}$ = 5.9, H-6); 7.38 (m, 2H, H-*o*-C_6H_4Me); 7.49 (m, 2H, H-*o*-C_6H_4OMe); 9.62 (bs, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.18 (CH_3); 43.63 (CH_2); 55.22 CH_3O); 113.70 (CH-*m*-C_6H_4OMe); 115.09 (C-5); 128.18 (CH-*o*-C_6H_4Me); 128.90 (C-*i*-C_6H_4OMe); 129.15 (CH-*m*-C_6H_4Me); 129.75 (C-*i*-C_6H_4Me); 130.81 (CH-*o*-C_6H_4OMe); 135.25 (CH-6); 137.87 (C-*p*-C_6H_4Me); 152.53 (C-2); 159.13 (C-*p*-C_6H_4OMe); 162.31 (C-4). IR: 2920, 1713, 1628, 1611, 1512, 1440, 1292, 1245, 1150, 1038. MS (ESI$^+$), *m/z* (% relative intensity): 323 (M$^+$+H, 30), 345 (M$^+$+Na, 100), 667 (2M$^+$+Na, 15). HR MS (M$^+$+H): 323.1390 (calcd for $C_{19}H_{19}N_2O_3$ 323.1390).

3-Benzyl-5-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (20a)



A mixture of compound **17a** (50 mg, 0.131 mmol), ammonium formate (3.3 ml of a 0.4 N solution in dry MeOH) and 10 % palladium-charcoal (77 mg 10 % Pd/C, 0.072 mmol of Pd, 0.55 equiv of Pd) was refluxed for 17 h. The mixture was filtered through celite and the solid residue was extensively washed with MeOH and $CHCl_3$ (cca 120 ml). Removal of solvents under reduced pressure and following column chromatography on 40 g of silica gel in a gradient of chloroform to 1 % methanol in chloroform gave the pure monodeprotected product **20a** in 80 % yield, as a white powder, mp 205 - 208 °C. ^{1}H NMR (500.0 MHz, $CDCl_3$): 2.28 (s, 3H, CH_3); 5.11 (s, 2H, CH_2Ph); 7.12 (m, 2H, H-*m*-C_6H_4Me); 7.19 (m, 2H, H-6, H-*p*-Bn); 7.22 (m, 2H, H-*m*-Bn); 7.30 (m, 2H, H-*o*-C_6H_4Me); 7.44 (m, 2H, H-*o*-Bn), 9.97 (bs, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.18 (CH_3); 44.19 (CH_2Ph); 115.02 (C-5); 127.68 (CH-*p*-Bn); 128.17 (CH-*o*-C_6H_4Me); 128.40 (CH-*m*-Bn); 129.11, 129.15 (CH-*m*-C_6H_4Me, CH-*o*-Bn); 129.70 (C-*i*-C_6H_4Me); 135.34 (CH-6); 136.61 (C-*i*-Bn); 137.89 (C-*p*-C_6H_4Me); 152.59 (C-2); 162.30 (C-4). IR : 3179, 1703, 1628, 1515, 1494, 1434, 1289, 1210, 1152. MS (ESI$^+$), *m/z* (% relative intensity): 315 (M^++Na, 100). HR MS (M^++H): 315.1104 (calcd for $C_{18}H_{16}N_2NaO_2$ 315.1104).

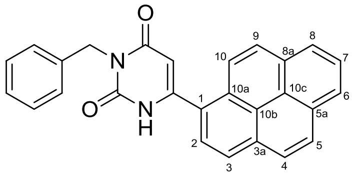
3-Benzyl-5-(pyren-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (20e)



A mixture of compound **17e** (50 mg, 0.102 mmol), ammonium formate (2.6 ml of a 0.4 N solution in dry MeOH) and 10 % palladium-charcoal (120 mg 10 % Pd/C, 0.113 mmol of Pd, 1.1 equiv of Pd) was refluxed for 17 h. The mixture was filtered through celite and the solid residue was extensively washed with MeOH and $CHCl_3$ (cca 120 ml). Removal of solvents under reduced pressure and following column chromatography on 40 g of silica gel in a gradient of 10 % ethylacetate in hexane to 50 % ethylacetate in hexane gave the pure monodebenzylated product **20e** in 67 % yield, as a yellow powder, mp > 300 °C. ^{1}H NMR (499.8 MHz, DMSO-d_6): 5.11 (bs, 2H, CH_2-3); 7.28 (m, 1H, H-*p*-Bn); 7.36 (m, 2H, H-*m*-Bn); 7.38 (m, 2H, H-*o*-Bn); 7.78 (d, 1H, $J_{6,NH}$ = 5.5, H-6); 7.96 (d, 1H, $J_{2,3}$ = 7.8, H-2-pyrenyl); 8.01 (d, 1H, $J_{10,9}$ = 9.2, H-10-pyrenyl); 8.08 (t, 1H, $J_{7,6}$ = $J_{7,8}$ = 7.6, H-7-pyrenyl); 8.15 (d, 1H, $J_{9,10}$ = 9.2, H-9-pyrenyl); 8.21 (s, 2H, H-4,5-pyrenyl); 8.30 (d, 1H, $J_{3,2}$ = 7.8, H-3-pyrenyl); 8.31 (m, 2H, H-6,8-pyrenyl); 11.65 (bd, 1H, $J_{NH,6}$ = 5.5, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 43.5 (CH_2Ph); 112.0 (C-5); 124.0 (C-10c-pyrenyl); 124.1 (CH-10b-pyrenyl); 124.8 (CH-3-pyrenyl); 125.4 (CH-10-pyrenyl); 125.5, 125.6 (CH-6,8-pyrenyl); 126.5 (CH-7-

pyrenyl); 127.4 (CH-*p*-Bn); 127.4 (CH-9-pyrenyl); 127.5 (CH-4-pyrenyl); 127.7 (CH-5-pyrenyl); 127.9 (CH-*o*-Bn); 128.6 (CH-*m*-Bn); 129.2 (CH-2-pyrenyl); 129.3 (C-1-pyrenyl); 129.7 (C-10a-pyrenyl); 130.6 (C-8a-pyrenyl); 130.7 (C-3a-pyrenyl); 131.0 (C-5a-pyrenyl); 137.6 (C-*i*-Bn); 140.7 (CH-6); 151.6 (C-2); 162.9 (C-4). IR (KBr): 3169, 1711, 1635, 1583, 1495, 1440, 1417, 1329, 1281, 1212, 1150, 1068. MS (ESI$^-$), *m/z* (% relative intensity): 401 (M$^-$-H, 100), 803 (2M$^-$-H, 17), 825 (2[M$^-$-H]+Na, 19). HR MS (M$^-$-H): 401.1296 (calcd for $C_{27}H_{17}N_2O_2$ 401.1296).

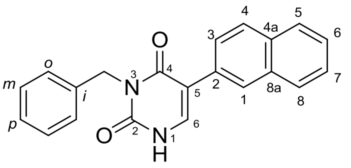
3-Benzyl-6-(pyren-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (22e)



A mixture of compound **18e** (50 mg, 0.102 mmol), ammonium formate (2.6 ml of a 0.4 N solution in dry MeOH) and 10 % palladium-charcoal (120 mg 10 % Pd/C, 0.113 mmol of Pd, 1.1 equiv of Pd) was refluxed for 17 h. The mixture was filtered through celite and the solid residue was extensively washed with MeOH and $CHCl_3$ (cca 120 ml). Removal of solvents under reduced pressure and following column chromatography on 40 g of silica gel in a gradient of 10 % ethylacetate in hexane to 50 % ethylacetate in hexane gave the pure monodebenzylated product **22e** in 83 % yield, as a yellow powder, mp 291 - 293 °C. ^{1}H NMR (500.0 MHz, DMSO-d_6): 5.10 (s, 2H, CH_2Ph); 5.92 (s, 1H, H-5); 7.30 (m, 1H, H-*p*-Bn); 7.38 (m, 2H, H-*m*-Bn); 7.43 (m, 2H, H-*o*-Bn); 8.15 (t, 1H, $J_{7,6} = J_{7,8} = 7.7$, H-7-pyrenyl); 8.16 (d, 1H, $J_{2,3} = 7.9$, H-2-pyrenyl); 8.26 (d, 1H, $J_{9,10} = 9.1$, H-9-pyrenyl); 8.31 (m, 3H, H-4,5,10-pyrenyl); 8.39 (m, 3H, H-3,6,8-pyrenyl); 11.81 (bs, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 43.0 (CH_2Ph); 101.9 (C-5); 123.7 (C-10c-pyrenyl); 123.9 (CH-10b-pyrenyl); 124.2 (CH-10-pyrenyl); 124.8 (CH-3-pyrenyl); 126.1, 126.3 (CH-6,8-pyrenyl); 126.8 (CH-9-pyrenyl); 127.0 (CH-7-pyrenyl); 127.35, 127.38 (CH-2-pyrenyl, CH-*p*-Bn); 127.6 (C-1-pyrenyl); 128.0 (CH-*o*-Bn); 128.1 (C-10a-pyrenyl); 128.6 (CH-*m*-Bn); 128.9 (CH-4,5-pyrenyl); 130.4, 130.9 (C-5a,8a-pyrenyl); 132.2 (C-3a-pyrenyl); 137.6 (C-*i*-Bn); 151.7 (C-2); 151.8 (C-6); 162.9 (C-4). IR (KBr): 3154, 1711, 1636, 1584, 1488, 1437, 1422, 1357, 1236, 1179, 1089, 1050. MS (ESI$^-$), *m/z* (% relative intensity): 401 (M$^-$-H, 100), 803 (2M$^-$-H, 22), 825 (2[M$^-$-H]+Na, 66). HR MS (M$^-$-H): 401.1293 (calcd for

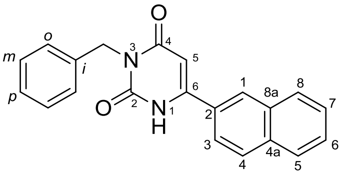
$C_{27}H_{17}N_2O_2$ 401.1296). Anal. Calcd for $C_{27}H_{18}N_2O_2{\cdot}0.75H_2O$: C, 77.96; H, 4.73; N, 6.73. Found: C, 78.21; H, 4.72; N, 6.35.

3-Benzyl-5-(naphthalen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (20f)



A mixture of compound **17f** (60 mg, 0.143 mmol), ammonium formate (4 ml of a 0.4 N solution in dry MeOH) and 10 % palladium-charcoal (168 mg 10 % Pd/C, 0.158 mmol of Pd, 1.1 equiv of Pd) was refluxed for 17 h. The mixture was filtered through celite and the solid residue was extensively washed with MeOH and $CHCl_3$ (cca 120 ml). Removal of solvents under reduced pressure and following column chromatography on 40 g of silica gel in a gradient of hexane to 20 % ethylacetate in hexane gave the pure monodebenzylated product **20f** in 42 % yield, as a white powder, mp 200 - 202 °C. ^1H NMR (500.0 MHz, DMSO-d_6): 5.08 (bs, 2H, CH_2Ph); 7.26 (m, 1H, H-*p*-Bn); 7.32 (m, 2H, H-*m*-Bn); 7.33 (m, 2H, H-*o*-Bn); 7.49 (m, 1H, H-6-naphth); 7.51 (m, 1H, H-7-naphth); 7.70 (dd, 1H, $J_{3,4}$ = 8.6, $J_{3,1}$ = 1.9, H-3-naphth); 7.86 (s, 1H, H-6); 7.90 (m, 3H, H-4,5,8-naphth); 8.14 (d, 1H, $J_{1,3}$ = 1.9, H-1-naphth). ^{13}C NMR (125.7 MHz, DMSO-d_6): 43.4 (CH_2Ph); 111.8 (C-5); 126.2 (CH-6-naphth); 126.3 (CH-7-naphth); 126.7 (CH-3-naphth); 126.8 (CH-1-naphth); 127.3 (CH-*p*-Bn); 127.4 (CH-8-naphth); 127.6 (CH-4 or 5-naphth); 127.9 (CH-*o*-Bn); 128.1 (CH-4 or 5-naphth); 128.6 (CH-*m*-Bn); 131.3 (C-2-naphth); 132.2 (C-4a-naphth); 133.0 (C-8a-naphth); 137.5 (C-*i*-Bn); 139.2 (CH-6); 151.1 (C-2); 162.4 (C-4). IR (KBr): 3173, 1724, 1711, 1688, 1627, 1597, 1496, 1439, 1364, 1213, 1189, 1081. MS (ESI$^+$), *m/z* (% relative intensity): 329 (M^++H, 48), 351 (M^++Na, 100). HR MS (M^++H): 329.1285 (calcd for $C_{21}H_{17}N_2O_2$ 329.1285).

3-Benzyl-6-(naphthalen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (22f)



A mixture of compound **18f** (110 mg, 0.263 mmol), ammonium formate (6.6 ml of a 0.4 N solution in dry MeOH) and 10 % palladium-charcoal (308 mg 10 % Pd/C, 0.289 mmol of Pd, 1.1 equiv of Pd) was refluxed for 17 h. The mixture was filtered through celite and the solid residue was extensively washed with MeOH and $CHCl_3$ (cca 200 ml). Removal of solvents under reduced pressure and following column chromatography on 70 g of silica gel in a gradient of hexane to 20 % ethylacetate in hexane gave the pure monodebenzylated product **22f** in 98 % yield, as a white powder, mp 183 - 185 °C. ^{1}H NMR (500.0 MHz, DMSO-d_6): 5.03 (bs, 2H, CH_2Ph); 6.18 (s, 1H, H-5); 7.26 (m, 1H, H-*p*-Bn); 7.33 (m, 4H, H-*o,m*-Bn); 7.61 (m, 1H, H-7-naphth); 7.64 (m, 1H, H-6-naphth); 7.84 (dd, 1H, $J_{3,4}$ = 8.6, $J_{3,1}$ = 2.0, H-3-naphth); 7.99 (m, 1H, H-5-naphth); 8.01 (m, 1H, H-8-naphth); 8.04 (m, 1H, H-4-naphth); 8.43 (d, 1H, $J_{1,3}$ = 2.0, H-1-naphth). ^{13}C NMR (125.7 MHz, DMSO-d_6): 42.9 (CH_2Ph); 98.1 (CH-5); 124.0 (CH-3-naphth); 127.2 (CH-7-naphth); 127.3 (CH-*p*-Bn); 127.5 (CH-1-naphth); 127.7 (CH-*o*-Bn); 127.8 (CH-5-naphth); 128.1 (CH-6-naphth); 128.5 (CH-*m*-Bn); 128.7 (CH-4-naphth); 128.7 (C-2-naphth); 129.0 (CH-8-naphth); 132.5 (C-8a-naphth); 134.1 (C-4a-naphth); 137.5 (C-*i*-Bn); 151.2 (C-6); 152.0 (C-2); 163.0 (C-4). IR: 3165, 1722, 1711, 1698, 1625, 1483, 1466, 1439, 1377, 1244, 1213, 1150, 1128, 1081. MS (ESI$^+$), *m/z* (% relative intensity): 329 (M^++H, 70), 351 (M^++Na, 100). HR MS (M^++H): 329.1283 (calcd for $C_{21}H_{17}N_2O_2$ 329.1285).

5.5.2. 5- and 6-Arylated free uracils

Method D

General procedure for the removal of the benzyl protecting groups using transfer hydrogenation

A mixture of dibenzyluracil derivative **17a-d, 18a-d** (0.3 mmol), ammonium formate (7.5 ml of a 0.4 N solution in dry MeOH) and 10 % palladium-charcoal (0.33 mmol of Pd) was refluxed for 17 h. The mixture was filtered through celite and the solid residue was extensively washed with MeOH and $CHCl_3$ (cca 250 ml). Removal of solvents under reduced pressure and following column chromatography on 40 g of silica gel in a gradient of chloroform to 2 % methanol in chloroform gave the pure debenzylated products (**21a-d, 23a-d)**.

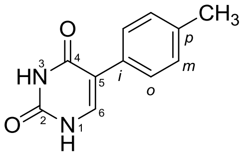
Method E

General procedure for the removal of the benzyl protecting groups with boron tribromide

Boron tribromide 1M in DCM (1.5 mmol) was added to dibenzyluracil derivate **17e-g, 18e-g** (0.3 mmol) in *m*-xylene (6 ml). The mixture was heated in pressure tube at 140 °C for 5 h, cooled to r.t. and MeOH (1.5 ml) was added. The mixture was stirred at room temperature for 30 min. Solvents were evaporated under reduced pressure and products **21f, g** and **23e-g** were isolated by column chromatography on 60 g of silica gel in a gradient of chloroform to 5 % methanol in chloroform.

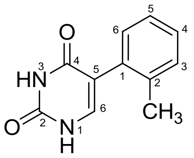
5.5.2.1. 5-Arylated free uracils

5-(*p*-Tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (21a)



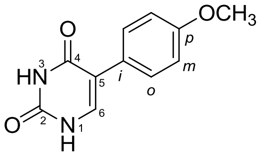
Compound **21a** was prepared from **17a** (100 mg, 0.261 mmol) according to general procedure (Method D), in 98 % yield, as a white powder, mp 228 - 230 °C. ^{1}H NMR (600.1 MHz, DMSO-d_6): 2.29 (s, 3H, CH_3); 7.15 (m, 2H, H-*m*-C_6H_4Me); 7.42 (m, 2H, H-*o*-C_6H_4Me); 7.56 (s, 1H, H-6); 11.21 (bs, 2H, NH-1,3). ^{13}C NMR (150.9 MHz, DMSO-d_6): 20.95 (CH_3); 112.3 (C-5); 128.0 (CH-*o*-C_6H_4Me); 128.8 (CH-*m*-C_6H_4Me); 130.6 (C-*i*-C_6H_4Me); 136.4 (C-*p*-C_6H_4Me); 139.4 (CH-6); 151.2 (C-2); 163.4 (C-4). IR: 3079, 1747, 1718, 1665, 1618, 1515, 1444, 1423, 1230, 1109. MS (ESI$^+$), *m/z* (% relative intensity): 203 (M$^+$+H, 16), 225 (M$^+$+Na, 100), 427 (2M$^+$+Na, 37). HR MS (M$^+$+H): 203.0815 (calcd for $C_{11}H_{11}N_2O_2$ 203.0815). Anal. Calcd for $C_{11}H_{10}N_2O_2 \cdot 1H_2O$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.14; H, 5.12; N, 12.63.

5-(*o*-Tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (21b)



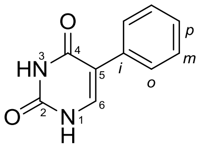
Compound **21b** was prepared from **17b** (100 mg, 0.261 mmol) according to general procedure (Method D), in 97 % yield, as a white powder, mp 265 - 268 °C. The experimental data are in accordance to literature.[170] ^{1}H NMR (499.8 MHz, DMSO-d_6): 2.15 (s, 3H, CH_3); 7.10 (dd, 1H, $J_{6,5}$ = 7.4, $J_{6,4}$ = 1.6, H-6-C_6H_4Me); 7.17 (m, 1H, H-5-C_6H_4Me); 7.21 (m, 2H, H-3-C_6H_4Me); 7.24 (ddd, 1H, $J_{4,3}$ = 7.5, $J_{4,5}$ = 6.7, $J_{4,6}$ = 1.6, H-4-C_6H_4Me); 7.36 (s, 1H, H-6); 11.00, 11.19 (2 × bs, 2 × 1H, NH-1,3). ^{13}C NMR (125.7 MHz, DMSO-d_6): 19.9 (CH_3); 113.5 (C-5); 125.7 (CH-5-C_6H_4Me); 127.9 (CH-4-C_6H_4Me); 129.8 (CH-3-C_6H_4Me); 130.8 (CH-6-C_6H_4Me); 133.5 (C-1-C_6H_4Me); 137.6 (C-2-C_6H_4Me); 140.4 (CH-6); 151.5 (C-2); 163.1 (C-4). IR (KBr): 3100, 1748, 1699, 1662, 1603, 1574, 1490, 1385, 1233. MS (ESI$^+$), *m/z* (% relative intensity): 203 (M$^+$+H, 6), 225 (M$^+$+Na, 100), 427 (2M$^+$+Na, 77). HR MS (M$^+$+H): 203.0814 (calcd for $C_{11}H_{11}N_2O_2$ 203.0815).

5-(4-Methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (21c)



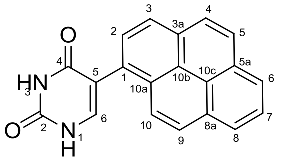
Compound **21c** was prepared from **17c** (128 mg, 0.321 mmol) according to general procedure (Method D), in 95 % yield, as a white powder, mp > 300 °C. The experimental data are in accordance to literature.[171] ^{1}H NMR (499.8 MHz, DMSO-d_6): 3.75 (s, 3H, OCH_3); 6.91 (m, 2H, H-*m*-C_6H_4OMe); 7.46 (m, 2H, H-*o*-C_6H_4OMe); 7.52 (s, 1H, H-6); 11.14 (bs, 2H, NH-1,3). ^{13}C NMR (125.7 MHz, DMSO-d_6): 55.3 (OCH_3); 112.2 (C-5); 113.7 (CH-*m*-C_6H_4OMe); 125.8 (C-*i*-C_6H_4OMe); 129.4 (CH-*o*-C_6H_4OMe); 138.9 (CH-6); 151.2 (C-2); 158.6 (C-*p*-C_6H_4Me); 163.6 (C-4). IR (KBr): 3080, 1762, 1711, 1672, 1616, 1579, 1518, 1492, 1450, 1301, 1255, 1183, 1078. MS (ESI$^+$), *m/z* (% relative intensity): 219 (M$^+$+H, 98), 241 (M$^+$+Na, 100), 257 (M$^+$+K, 32), 459 (2M$^+$+Na, 35). HR MS (M$^+$+H): 219.0764 (calcd for $C_{11}H_{11}N_2O_3$ 219.0764).

5-Phenylpyrimidine-2,4(1*H*,3*H*)-dione (21d)



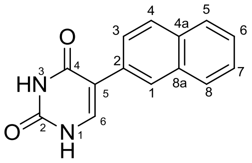
Compound **21d** was prepared from **17d** (100 mg, 0.271 mmol) according to general procedure (Method D), in 97 % yield, as a white powder, mp > 300 °C (lit[172] mp > 350 °C). ^{1}H NMR (600.1 MHz, DMSO-d_6): 7.26 (m, 1H, H-*p*-Ph); 7.35 (m, 2H, H-*m*-Ph); 7.53 (m, 2H, H-*o*-Ph); 7.61 (s, 1H, H-6); 11.15, 11.25 (2 × bs, 2 × 1H, NH-1,3). ^{13}C NMR (150.9 MHz, DMSO-d_6): 112.3 (C-5); 127.2 (CH-*p*-Ph); 128.2 (CH-*o*-Ph); 128.2 (CH-*m*-Ph); 133.5 (C-*i*-Ph); 139.9 (CH-6); 151.2 (C-2); 163.4 (C-4). IR (KBr): 3062, 1749, 1688, 1676, 1631, 1605, 1498, 1448, 1353, 1236, 1078. MS (ESI$^+$), *m/z* (% relative intensity): 189 (M$^+$+H, 35), 211 (M$^+$+Na, 100). HR MS (M$^+$+H): 189.0657 (calcd for $C_{10}H_9N_2O_2$ 189.0659).

5-(Pyren-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (21e)



Compound **21e** was prepared from **17e** (95 mg, 0.193 mmol) according to general procedure (Method E), in 98 % yield, as a white powder, mp > 300 °C. ^{1}H NMR (499.8 MHz, DMSO-d_6): 7.67 (d, 1H, $J_{6,\mathrm{NH}}$ = 5.8, H-6); 7.93 (d, 1H, $J_{2,3}$ = 7.8, H-2-pyrenyl); 8.02 (d, 1H, $J_{10,9}$ = 9.2, H-10-pyrenyl); 8.08 (t, 1H, $J_{7,6}$ = $J_{7,8}$ = 7.6, H-7-pyrenyl); 8.16 (d, 1H, $J_{9,10}$ = 9.2, H-9-pyrenyl); 8.20 (s, 2H, H-4,5-pyrenyl); 8.28-8.32 (m, 3H, H-3,6,8-pyrenyl); 11.23 (bdd, 1H, $J_{\mathrm{NH},6}$ = 5.5, $J_{\mathrm{NH,NH}}$ = 2.0, NH-1); 11.39 (bd, 1H, $J_{\mathrm{NH,NH}}$ = 2.0, NH-3). ^{13}C NMR (125.7 MHz, DMSO-d_6): 112.5 (C-5); 124.0 (C-10c-pyrenyl); 124.1 (CH-10b-pyrenyl); 124.7 (CH-3-pyrenyl); 125.3, 125.5 (CH-6,8-pyrenyl); 125.6 (CH-10-pyrenyl); 126.5 (CH-7-pyrenyl); 127.3 (CH-9-pyrenyl); 127.5, 127.6 (CH-4,5-pyrenyl); 129.1 (CH-2-pyrenyl); 129.2 (C-1-pyrenyl); 129.7 (C-10a-pyrenyl); 130.6, 130.7 (C-3a,8a-pyrenyl); 131.0 (C-5a-pyrenyl); 141.9 (CH-6); 151.7 (C-2); 163.9 (C-4). IR: 3140, 1721, 1698, 1636, 1555, 1480, 1437, 1363, 1344, 1236, 1179, 1089. MS (ESI$^+$), *m/z* (% relative intensity): 313 (M$^+$+H, 30), 335 (M$^+$+Na, 100). HR MS (M$^+$+H): 313.0972 (calcd for $C_{20}H_{13}N_2O_2$ 313.0972).

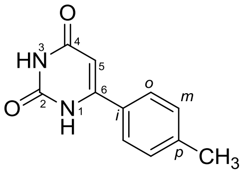
5-(Naphthalen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (21f)



Compound **21f** was prepared from **17f** (100 mg, 0.239 mmol) according to general procedure (Method E), in 63 % yield, as a yellowish powder, mp > 300 °C. ^{1}H NMR (499.8 MHz, DMSO-d_6): 7.49 (ddd, 1H, $J_{6,5}$ = 8.8, $J_{6,7}$ = 6.8, $J_{6,8}$ = 1.7, H-6-naphth); 7.70 (ddd, 1H, $J_{7,8}$ = 8.8, $J_{7,6}$ = 6.8, $J_{7,5}$ = 1.7, H-7-naphth); 7.70 (dd, 1H, $J_{3,4}$ = 8.5, $J_{3,1}$ = 1.8, H-3-naphth); 7.77 (bd, 1H, $J_{6,\mathrm{NH}}$ = 5.6, H-6); 7.87-7.91 (m, 3H, H-4,5,8-naphth); 8.12 (m, 1H, H-1-naphth); 11.23 (bd, 1H, $J_{\mathrm{NH},6}$ = 5.6, NH-1); 11.31 (bs, 1H, NH-3). ^{13}C NMR (125.7 MHz, DMSO-d_6): 112.2 (C-5); 126.1 (CH-6-naphth); 126.3 (CH-7-naphth); 126.5 (CH-1-naphth); 126.6 (CH-3-naphth); 127.4 (CH-4-naphth); 127.6 (CH-5-naphth); 128.1 (CH-8-naphth); 131.2 (C-2-naphth); 132.1 (C-4a-naphth); 133.0 (C-8a-naphth); 140.4 (C-6); 151.2 (C-2); 163.5 (C-4). IR: 3135, 1748, 1664, 1597, 1509, 1445, 1330, 1228, 1127, 1075. MS (ESI$^+$), *m/z* (% relative intensity): 239 (M$^+$+H, 30), 261 (M$^+$+Na, 100). HR MS (M$^+$+H): 239.0814 (calcd for $C_{14}H_{11}N_2O_2$ 239.0815).

5.5.2.2. 6-Arylate free uracils

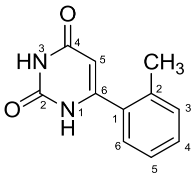
6-(*p*-Tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (23a)



Compound **23a** was prepared from **18a** (100 mg, 0.261 mmol) according to general procedure (Method D), in 97 % yield, as a white powder, mp > 300 °C (lit[173] mp 315 - 318 °C). ^{1}H NMR (600.1 MHz, DMSO-d_6): 2.35 (s, 3H, CH_3); 5.78 (d, 1H, J = 1.7, H-5); 7.30 (m, 2H, H-*m*-C_6H_4Me); 7.62 (m, 2H, H-*o*-C_6H_4Me); 11.08, 11.12 (2 × bs, 2 × 1H, NH-1,3). ^{13}C NMR (150.9 MHz, DMSO-d_6): 21.1 (CH_3); 97.6 (CH-5); 127.0 (CH-*o*-C_6H_4Me); 128.9 (C-*i*-C_6H_4Me); 129.6 (CH-*m*-C_6H_4Me); 141.3 (C-*p*-C_6H_4Me); 152.1 (C-2); 152.6 (C-6); 164.3 (C-4). IR (KBr): 3132, 1698, 1667, 1618, 1517, 1493, 1406, 1385, 1238, 1191. MS (ESI$^+$), *m/z* (% relative intensity): 203 (M$^+$+H, 28), 225 (M$^+$+Na, 81), 427 (2M$^+$+Na, 100). HR MS (M$^+$+H): 203.0815 (calcd for

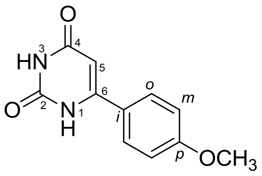
$C_{11}H_{11}N_2O_2$ 203.0815). Anal. Calcd for $C_{11}H_{10}N_2O_2 \cdot 1H_2O$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.65; H, 5.09; N, 12.57.

6-(*o*-Tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (23b)



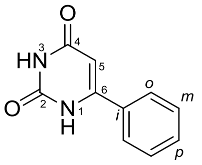
Compound **23b** was prepared from **18b** (80 mg, 0.209 mmol) according to general procedure (Method D), in 94 % yield, as a white powder, mp 185 - 187 °C. ^{1}H NMR (600.1 MHz, DMSO-d_6): 2.30 (s, 3H, CH_3); 5.40 (s, 1H, H-5); 7.28 (m, 1H, H-5-C_6H_4Me); 7.31 (m, 2H, H-3,6-C_6H_4Me); 7.39 (td, 1H, $J_{4,3} = J_{4,5} = 7.4$, $J_{4,6} = 1.8$, H-4-C_6H_4Me), 11.03, 11.14 (2 × bs, 2 × 1H, NH-1,3). ^{13}C NMR (150.9 MHz, DMSO-d_6): 19.6 (CH_3); 100.6 (CH-5); 126.2 (CH-5-C_6H_4Me); 128.7 (CH-6-C_6H_4Me); 130.1 (CH-4-C_6H_4Me); 130.7 (CH-3-C_6H_4Me); 133.2 (C-1-C_6H_4Me); 135.7 (C-2-C_6H_4Me); 151.7 (C-2); 153.9 (C-6); 164.3 (C-4). IR: 3158, 1731, 1656, 1600, 1577, 1485, 1385, 1292. MS (ESI$^+$), *m/z* (% relative intensity): 203 (M^++H, 23), 225 (M^++Na, 100), 427 (2M^++Na, 65). HR MS (M^++H): 203.0815 (calcd for $C_{11}H_{11}N_2O_2$ 203.0815).

6-(4-Methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (23c)



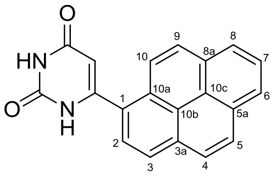
Compound **23c** was prepared from **18c** (100 mg, 0.251 mmol) according to general procedure (Method D), in 92 % yield, as a yellowish powder, mp 286 - 288 °C (lit[174] mp 288 °C). ^{1}H NMR (500.0 MHz, DMSO-d_6): 3.81 (s, 3H, OCH_3); 5.76 (s, 1H, H-5); 7.03 (m, 2H, H-*m*-C_6H_4OMe); 7.71 (m, 2H, H-*o*-C_6H_4OMe); 11.01, 11.06 (2 × bs, 2 × 1H, NH-1,3). ^{13}C NMR (125.7 MHz, DMSO-d_6): 55.7 (OCH_3); 996.8 (CH-5); 114.4 (CH-*o*-C_6H_4OMe); 123.7 (C-*i*-C_6H_4OMe); 128.8 (CH-*m*-C_6H_4OMe); 152.1, 152.2 (C-2,6); 161.7 (C-*p*-C_6H_4OMe); 164.3 (C-4). IR (KBr): 3140, 1714, 1677, 1653, 1609, 1572, 1521, 1491, 1446, 1297, 1263, 1183, 1082. MS (ESI$^+$), *m/z* (% relative intensity): 219 (M^++H, 100), 241 (M^++Na, 75), 257 (M^++K, 27), 459 (2M^++Na, 80). HR MS (M^++H): 219.0764 (calcd for $C_{11}H_{11}N_2O_3$ 219.0764).

6-Phenylpyrimidine-2,4(1*H*,3*H*)-dione (23d)



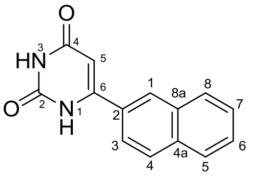
Compound **23d** was prepared from **18d** (100 mg, 0.271 mmol) according to general procedure (Method D), in 94 % yield, as a white powder, mp 268 - 271 °C (lit^{175} mp 270 °C). ^{1}H NMR (600.1 MHz, DMSO-d_6): 5.81 (s, 1H, H-5); 7.49 (m, 2H, H-*m*-Ph); 7.54 (m, 1H, H-*p*-Ph); 7.72 (m, 2H, H-*o*-Ph); 11.14, 11.16 (2 × bs, 2 × 1H, NH-1,3). ^{13}C NMR (150.9 MHz, DMSO-d_6): 98.3 (CH-5); 127.2 (CH-*o*-Ph); 129.0 (CH-*m*-Ph); 131.3 (CH-*p*-Ph); 131.8 (C-*i*-Ph); 152.1 (C-2); 152.1 (C-6); 164.3 (C-4). IR (KBr): 3098, 1721, 1652, 1600, 1578, 1489, 1446, 1354, 1239, 1079. MS (ESI$^+$), *m/z* (% relative intensity): 189 (M$^+$+H, 34), 211 (M$^+$+Na, 100), 399 (2M$^+$+Na, 100). HR MS (M$^+$+H): 189.0658 (calcd for $C_{10}H_9N_2O_2$ 189.0659).

6-(Pyren-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (23e)



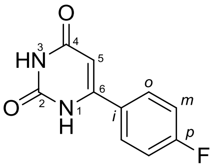
Compound **23e** was prepared from **18e** (100 mg, 0.203 mmol) according to general procedure (Method E), in 38 % yield, as a yellow powder, mp > 300 °C. ^{1}H NMR (499.8 MHz, DMSO-d_6): 71 (d, 1H, $J_{5,\mathrm{NH}}$ = 1.8, H-5); 8.12 (d, 1H, $J_{2,3}$ = 7.9, H-2-pyrenyl); 8.15 (t, 1H, $J_{7,6}$ = $J_{7,8}$ = 7.6, H-7-pyrenyl); 8.26 (d, 1H, $J_{4,5}$ = 9.1, H-4-pyrenyl); 8.27 (d, 1H, $J_{9,10}$ = 9.3, H-9-pyrenyl); 8.308 (d, 1H, $J_{5,4}$ = 9.1, H-5-pyrenyl); 8.314 (d, 1H, $J_{10,9}$ = 9.3, H-10-pyrenyl); 8.38 (d, 1H, $J_{3,2}$ = 7.9, H-3-pyrenyl); 8.39 (d, 2H, $J_{6\&8,7}$ = 7.6, H-6,8-pyrenyl); 11.29, 11.41 (2 × bs, 2 × 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 102.40 (C-5); 123.75 (C-10c-pyrenyl); 123.84 (CH-10b-pyrenyl); 124.17 (CH-10-pyrenyl); 124.82 (CH-3-pyrenyl); 126.06, 126.28 (CH-6,8-pyrenyl); 126.60 (CH-2-pyrenyl); 126.96 (CH-7-pyrenyl); 127.37 (CH-4-pyrenyl); 127.97 (C-1-pyrenyl); 128.09 (C-10a-pyrenyl); 128.82, 128.84 (CH-5,9-pyrenyl); 130.41 (C-8a-pyrenyl); 130.89 (C-5a-pyrenyl); 132.07 (C-3a-pyrenyl); 151.81 (C-2); 153.06 (C-6); 164.16 (C-4). IR: 3138, 1721, 1699, 1636, 1580, 1488, 1436, 1422, 1357, 1344, 1236, 1170, 1081. MS (ESI$^+$), *m/z* (% relative intensity): 313 (M$^+$+H, 33), 335 (M$^+$+Na, 100). HR MS (M$^+$+H): 313.09714 (calcd for $C_{20}H_{13}N_2O_2$ 313.09715).

6-(Naphthalen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (23f)



Compound **23f** was prepared from **18f** (100 mg, 0.261 mmol) according to general procedure (Method E), in 70 % yield, as a yellowish powder, mp > 300 °C. ^{1}H NMR (500.0 MHz, DMSO-d_6): 5.98 (d, 1H, J = 1.9, H-5); 7.61 (ddd, 1H, $J_{6,5}$ = 8.7, $J_{6,7}$ = 6.9, $J_{6,8}$ = 1.9, H-6-naphth); 7.63 (ddd, 1H, $J_{7,8}$ = 8.7, $J_{7,6}$ = 6.9, $J_{7,5}$ = 1.9, H-7-naphth); 7.81 (dd, 1H, $J_{3,4}$ = 8.7, $J_{3,1}$ = 2.0, H-3-naphth); 7.99 (m, 1H, H-5-naphth); 8.01 (m, 1H, H-8-naphth); 8.02 (m, 1H, H-4-naphth); 8.39 (m, 1H, H-1-naphth); 11.19, 11.23 (2 × bs, 2 × 1H, NH-1,3). ^{13}C NMR (125.7 MHz, DMSO-d_6): 98.63 (CH-5); 124.00 (CH-3-naphth); 127.16 (CH-6-naphth); 127.28 (CH-1-naphth); 127.80 (CH-5-naphth); 127.96 (CH-7-naphth); 128.62 (CH-4-naphth); 128.96 (CH-8-naphth); 129.00 (C-2-naphth); 132.47 (C-8a-naphth); 134.02 (C-4a-naphth); 152.06 (C-2); 152.47 (C-6); 164.27 (C-4). IR (KBr): 3132, 1722, 1650, 1613, 1594, 1517, 1494, 1447, 1424, 1337, 1217, 1082. MS (ESI$^+$), *m/z* (% relative intensity): 239 (M^++H, 10), 261 (M^++Na, 28), 399 ($2M^+$+Na, 100). HR MS (M^++H): 239.0814 (calcd for $C_{14}H_{11}N_2O_2$ 239.0815).

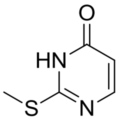
6-(4-Fluorophenyl)pyrimidine-2,4(1*H*,3*H*)-dione (23g)



Compound **23g** was prepared from **18g** (120 mg, 0.311 mmol) according to general procedure (Method E), in 98 % yield, as a white powder, mp > 300 °C (lit[173] mp 311 - 313 °C). ^{1}H NMR (600.1 MHz, DMSO-d_6): 5.81 (s, 1H, H-5); 7.34 (m, 2H, H-*m*-C_6H_4F); 7.79 (m, 2H, H-*o*-C_6H_4F); 11.15, 11.16 (2 × bs, 2 × 1H, NH). ^{13}C NMR (150.9 MHz, DMSO-d_6): 98.3 (CH-5); 116.0 (d, $J_{C,F}$ = 21.9, CH-*m*-C_6H_4F); 128.3 (d, $J_{C,F}$ = 3.1, C-*i*-C_6H_4F); 129.8 (d, $J_{C,F}$ = 8.9, CH-*o*-C_6H_4F); 151.7 (C-6); 152.0 (C-2); 163.8 (d, $J_{C,F}$ = 249.0, C-*p*-C_6H_4F); 164.2 (C-4). ^{19}F{^{1}H} NMR (376.5 MHz, DMSO-d_6): -109.94. IR: 3115, 1699, 1652, 1647, 1601, 1488, 1452, 1422, 1356, 1231, 1166, 1081. MS (ESI$^+$), *m/z* (% relative intensity): 229 (M^++Na, 100), 435 ($2M^+$+Na, 20). HR MS (M^++Na): 229.0383 (calcd for $C_{10}H_7FN_2NaO_2$ 229.0384).

5.5. 2,4-Diarylpyrimidines

2-(Methylsulfanyl)pyrimidin-4(3*H*)-one (30)



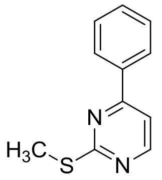
Compound **30** was prepared from 2-thiouracil (**29**) according to published procedure, in 82 % yield, as white crystals from ethanol, mp 198 - 199 °C (lit[150] mp 198 °C). ^{1}H NMR (499.8 MHz, $CDCl_3$): 2.59 (s, 3H, CH_3); 6.25 (d, 1H, $J_{5,6}$ = 6.6, H-5); 7.89 (d, 1H, $J_{6,5}$ = 6.6, H-6); 12.94 (bs, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.29 (CH_3); 110.91 (CH-5); 154.90 (CH-6); 162.55 (C-2); 164.58 (C-4). IR: 2929, 1665, 1623, 1565, 1535, 1467, 1451, 1400, 1269, 1229, 1181, 1078. MS (EI$^+$), *m/z* (% relative intensity): 67 (8), 74 (5), 95 (35), 114 (9), 142 (M$^+$, 100). HR MS (M$^+$): 142.0205 (calcd for $C_5H_6N_2OS$ 142.0201). Anal. Calcd for $C_5H_6N_2OS$: C, 42.24; H, 4.25; N, 19.70; S, 22.55. Found: C, 42.29; H, 4.27; N, 19.40; S, 22.28.

5.5.1. 4-Aryl-2-(methylsulfanyl)pyrimidines

General procedure for phosphonium mediated Suzuki cross-coupling reaction of 2-(methylsulfanyl)pyrimidin-4(3*H*)-one (30) with aryl boronic acids 31a, 31c-g

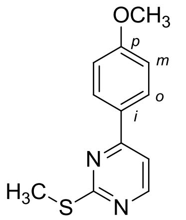
1,4-Dioxane (4 mL) and Et_3N (0.21 mL, 1.5 mmol) were added through a septum to an argon purged vial containing 2-(methylsulfanyl)pyrimidin-4(3*H*)-one (**30**, 71 mg, 0.5 mmol), PyBroP (280 mg, 0.6 mmol) and the mixture was stirred in a sealed tube at r.t. for 2 h. Then, the aryl boronic acid (**31a, 31c-g**, 1 mmol), $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol, 5 mol %), Na_2CO_3 (265 mg, 2.5 mmol) and water (1 mL) were added, and the mixture was stirred at 100 °C in the sealed tube for 4 h. After cooling to r.t., the mixture was diluted with EtOAc, washed with water and brine, and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Compounds **32a, 32c-e, 32g** were purified by column chromatography on 70 g of silica gel in a eluent of 3 % ethyl acetate in hexane and the compound **32f** in a gradient of 3 % ethyl acetate to 10 % ethyl acetate in hexane.

2-(Methylsulfanyl)-4-phenylpyrimidine (32a)



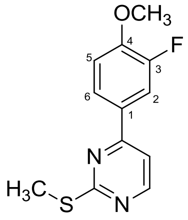
Compound **32a** was prepared from **30** according to general procedure, in 99 % yield, as a white powder, mp 76 - 78 °C (lit[176] mp 76 - 77 °C). ^1H NMR (499.8 MHz, $CDCl_3$): 2.61 (s, 3H, CH_3S); 7.35 (d, 1H, $J_{5,6}$ = 5.1, H-5); 7.42-7.49 (m, 3H, H-*m,p*-Ph); 8.04 (m, 2H, H-*o*-Ph); 8.495 (d, 1H, $J_{6,5}$ = 5.1, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.21 (CH_3S); 111.80 (CH-5); 127.35 (CH-*o*-Ph); 128.98 (CH-*m*-Ph); 131.53 (CH-*p*-Ph); 136.00 (C-*i*-Ph); 156.64 (CH-6); 164.47 (C-4); 172.23 (C-2). IR: 3064, 2923, 1603, 1556, 1541, 1494, 1413, 1349, 1309, 1200, 1180, 1075. MS (EI^+), *m/z* (% relative intensity): 77 (6), 102 (11), 129 (22), 156 (43), 202 (M^+, 100). HR MS (M^+): 202.0570 (calcd for $C_{11}H_{10}N_2S$ 202.0565).

4-(4-Methoxyphenyl)-2-(methylsulfanyl)pyrimidine (32c)



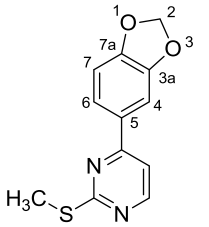
Compound **32c** was prepared from **30** according to general procedure, in 75 % yield, as a yellowish powder, mp 78 - 80 °C. (lit[177] mp 80 °C). ^1H NMR (600.1 MHz, $CDCl_3$): 2.59 (s, 3H, CH_3S); 3.81 (s, 3H, CH_3O); 6.93 (m, 2H, H-*m*-C_6H_4OMe); 7.25 (d, 1H, $J_{5,6}$ = 5.4, H-5); 8.02 (m, 2H, C_6H_4OMe); 8.42 (d, 1H, $J_{6,5}$ = 5.4, H-6). ^{13}C NMR (150.9 MHz, $CDCl_3$): 14.17 (CH_3S); 55.45 (CH_3O); 110.91 (CH-5); 114.33 (CH-*m*-C_6H_4OMe); 128.49 (C-*i*-C_6H_4OMe); 128.96 (CH-*o*-C_6H_4OMe); 156.49 (CH-6); 162.46 (C-*p*-C_6H_4OMe); 163.75 (C-4); 172.07 (C-2). IR: 3058, 2924, 1605, 1556, 1539, 1509, 1454, 1427, 1400, 1346, 1312, 1248, 1203, 1175, 1074, 1029. MS (EI^+), *m/z* (% relative intensity): 63 (5), 77 (4), 89 (7), 121 (8), 143 (4), 155 (7), 171 (31), 186 (33), 201 (36), 214 (21), 232 (M^+, 100). HR MS (M^+): 232.0674 (calcd for $C_{12}H_{12}N_2OS$ 232.0670).

4-(3-Fluoro-4-methoxyphenyl)-2-(methylsulfanyl)pyrimidine (32d)



Compound **32d** was prepared from **30** according to general procedure, in 70 % yield, as a beige powder, mp 104 - 106 °C. ^{1}H NMR (600.1 MHz, CDCl$_3$): 2.57 (s, 3H, CH$_3$S); 3.89 (s, 3H, CH$_3$O); 6.98 (t, 1H, $J_{H,F}$ = $J_{5,6}$ = 8.6, H-5-C$_6$H$_3$FOMe); 7.20 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.78 (ddd, 1H, $J_{6,5}$ = 8.6, $J_{6,2}$ = 2.2, $J_{H,F}$ = 1.20, H-6-C$_6$H$_3$FOMe); 7.83 (dd, 1H, $J_{H,F}$ = 12.4, $J_{2,6}$ = 2.2, H-2-C$_6$H$_3$FOMe); 8.44 (d, 1H, $J_{6,5}$ = 5.4, H-6). ^{13}C NMR (150.9 MHz, CDCl$_3$): 14.19 (CH$_3$S); 56.30 (CH$_3$O); 111.02 (CH-5); 113.11 (d, $J_{C,F}$ = 2.0, CH-5-C$_6$H$_3$FOMe); 114.83 (d, $J_{C,F}$ = 19.9, CH-2-C$_6$H$_3$FOMe); 123.45 (d, $J_{C,F}$ = 3.4, CH-6-C$_6$H$_3$FOMe); 129.37 (d, $J_{C,F}$ = 6.3, C-1-C$_6$H$_3$FOMe); 150.26 (d, $J_{C,F}$ = 10.9, C-4-C$_6$H$_3$FOMe); 152.52 (d, $J_{C,F}$ = 246.4, C-3-C$_6$H$_3$FOMe); 157.58 (CH-6); 162.25 (d, $J_{C,F}$ = 2.4, C-4); 172.79 (C-2). ^{19}F{^{1}H} NMR (470.3 MHZ, CDCl$_3$): -130.41. IR: 3063, 2926, 1608, 1562, 1544, 1514, 1447, 1400, 1348, 1327, 1274, 1206, 1180, 1127, 1074, 1026. MS (EI$^+$), *m/z* (% relative intensity): 107 (7), 127 (4), 142 (3), 161 (4), 173 (9), 189 (23), 204 (28), 250 (M$^+$, 100). HR MS (M$^+$): 250.0573 (calcd for C$_{12}$H$_{11}$FN$_2$OS 250.0576).

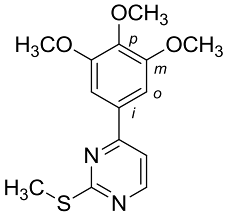
4-(Benzo[*d*][1,3]dioxol-5-yl)-2-(methylsulfanyl)pyrimidine (32e)



Compound **32e** was prepared from **30** according to general procedure, in 77 % yield, as a white powder, mp 112 - 113 °C. ^{1}H NMR (499.8 MHz, CDCl$_3$): 2.64 (s, 3H, CH$_3$S); 6.05 (s, 2H, OCH$_2$O); 6.91 (d, 1H, $J_{7,6}$ = 8.6, H-7-C$_6$H$_3$(OCH$_2$O)); 7.26 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.63 (d, 1H, $J_{4,6}$ = 1.8, H-4-C$_6$H$_3$(OCH$_2$O)); 7.64 (dd, 1H, $J_{6,7}$ = 8.6, $J_{6,4}$ = 1.8, H-6-C$_6$H$_3$(OCH$_2$O)); 8.49 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (125.7 MHz, CDCl$_3$): 14.19 (CH$_3$S); 101.66 (OCH$_2$O); 107.26 (CH-4-C$_6$H$_3$(OCH$_2$O)); 108.53 (CH-7-C$_6$H$_3$(OCH$_2$O)); 111.15 (CH-5); 121.99 (CH-6-C$_6$H$_3$(OCH$_2$O)); 130.61 (C-5-C$_6$H$_3$(OCH$_2$O)); 148.43 (C-3a-C$_6$H$_3$(OCH$_2$O)); 150.30 (C-7a-C$_6$H$_3$(OCH$_2$O)); 157.36

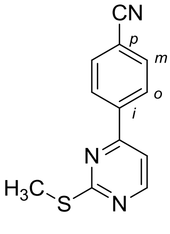
(CH-6); 163.13 (C-4); 172.52 (C-2). IR: 3073, 2929, 1562, 1541, 1498, 1453, 1409, 1364, 1302, 1263, 1243, 1204, 1180, 1099, 1031. MS (EI^+), *m/z* (% relative intensity): 63 (6), 89 (5), 114 (4), 142 (13), 170 (12), 200 (39), 246 (M^+, 100). HR MS (M^+): 246.0458 (calcd for $C_{12}H_{10}N_2O_2S$ 246.0463).

2-(Methylsulfanyl)-4-(3,4,5-trimethoxyphenyl)pyrimidine (32f)



Compound **32f** was prepared from **30** according to general procedure, in 96 % yield, as a white powder, mp 73 - 75 °C. ^1H NMR (499.8 MHz, $CDCl_3$): 2.64 (s, 3H, CH_3S); 3.92 (s, 3H, CH_3O-*p*-$C_6H_2(OMe)_3$); 3.96 (s, 6H, CH_3O-*m*-$C_6H_2(OMe)_3$); 7.31 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.34 (s, 2H, (s, 3H, H-*o*-$C_6H_2(OMe)_3$); 8.53 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.18 (CH_3S); 56.26 (CH_3O-*m*-$C_6H_2(OMe)_3$); 60.98 (CH_3O-*p*-$C_6H_2(OMe)_3$); 104.44 (CH-*o*-$C_6H_2(OMe)_3$); 111.63 (CH-5); 131.70 (C-*i*-$C_6H_2(OMe)_3$); 140.86 (C-*p*-$C_6H_2(OMe)_3$); 153.53 (C-*m*-$C_6H_2(OMe)_3$); 157.53 (CH-6); 163.42 (C-4); 172.66 (C-2). IR: 2994, 2919, 1590, 1556, 1539, 1501, 1465, 1448, 1420, 1401, 1359, 1335, 1262, 1226, 1203, 1175, 1121, 1004. MS (EI^+), *m/z* (% relative intensity): 66 (7), 84 (5), 97 (3), 149 (3), 215 (6), 234 (4), 246 (9), 261 (6), 277 (14), 292 (M^+, 100). HR MS (M^+): 292.0888 (calcd for $C_{14}H_{16}N_2O_3S$ 292.0882).

4-(2-(Methylsulfanyl)pyrimidin-4-yl)benzonitrile (32g)



Compound **32g** was prepared from **30** according to general procedure, in 80 % yield, as a white powder, mp 168 - 170 °C. The experimental data are in accordance to literature.[178] ^1H NMR (499.8 MHz, $CDCl_3$): 2.65 (s, 3H, CH_3S); 7.39 (d, 1H, $J_{5,6}$ = 5.2, H-5); 7.80 (m, 2H, H-*m*-C_6H_4CN); 8.20 (m, 2H, H-*o*-C_6H_4CN); 8.63 (d, 1H, $J_{6,5}$ = 5.2, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.25 (CH_3S); 112.15 (CH-5); 114.48 (C-*p*-C_6H_4CN); 118.32 (CN); 127.71 (CH-*o*-C_6H_4CN); 132.67 (CH-*m*-C_6H_4CN); 140.49 (C-

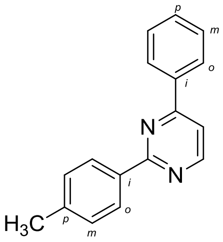
i-C_6H_4CN); 158.24 (CH-6); 161.73 (C-4); 173.50 (C-2). IR: 3037, 2934, 2235, 1562, 1545, 1502, 1471, 1426, 1402, 1349, 1324, 1281, 1208, 1187, 1103, 1048, 1019. MS (EI^+), *m/z* (% relative intensity): 127 (4), 154 (7), 181 (24), 227 (M^+, 100). HR MS (M^+): 227.0516 (calcd for $C_{12}H_9N_3S$ 227.0517).

5.5.2. 2,4-Diarylpyrimidines

General procedure for Liebeskind-Srogl cross-coupling of 2-(methylsulfanyl)-4-arylpyrimidines 32a, 32c-f with aryl boronic acids 31b-f

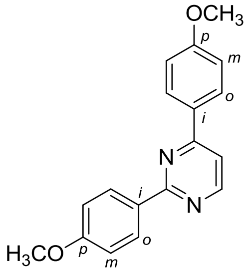
A microwave vial sealed with septum was charged with 2-(methylsulfanyl)-4-arylpyrimidines (**32a, 32c-g,** 0.5 mmol), the corresponding aryl boronic acid (**31b-g**, 0.75 mmol), CuTC (286 mg, 1.5 mmol), and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 10 mol %). The reaction vessel was sealed and flushed with argon. Through the septum anhydrous THF (4 mL) was added. The mixture was heated in a microwave reactor at 100 °C for 1 h. After cooling to r.t., the solvent was evaporated. The crude reaction mixture was purified by column chromatography on silica gel to provide the desired 2,4-diarylpyrimidine **33**.

4-Phenyl-2-(*p*-tolyl)pyrimidine (33ab)



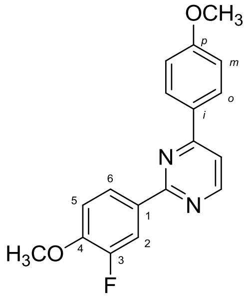
Compound **33ab** was prepared from **32a** (101 mg, 0.5 mmol) according to general procedure, in 99 % yield, as white crystals from hexane/ethyl acetate, mp 86 - 87 °C (lit[40a] mp 86 - 87 °C). ^1H NMR (500.0 MHz, $CDCl_3$): 2.45 (s, 3H, CH_3); 7.34 (m, 2H, H-*m*-Tol); 7.55 (m, 3H, H-*m,p*-Ph); 7.62 (d, 1H, $J_{5,6}$ = 5.4, H-5); 8.24 (m, 2H, H-*o*-Ph); 8.50 (m, 2H, H-*o*-Tol); 8.84 (d, 1H, $J_{6,5}$ = 5.4, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.54 (CH_3); 114.20 (CH-5); 127.36 (CH-*o*-Ph); 128.40 (CH-*o*-Tol); 128.99 (CH-*m*-Ph); 129.41 (CH-*m*-Tol); 131.25 (CH-*p*-Ph); 134.30 (C-*i*-Tol); 136.73 (C-*i*-Ph); 141.49 (C-*p*-Tol); 156.84 (CH-6); 163.07 (C-2); 164.51 (C-4). IR: 3058, 2921, 1582, 1545, 1492, 1424, 1405, 1381, 1322, 1276, 1175, 1104, 1020. MS (EI^+), *m/z* (% relative intensity): 77 (4), 102 (17), 117 (10), 129 (6), 169 (4), 232 (8), 246 (M^+, 100). HR MS (M^+): 246.1155 (calcd for $C_{17}H_{14}N_2$ 246.1157). Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.60; H, 5.56; N, 11.17.

2,4-Bis(4-methoxyphenyl)pyrimidine (33cc)



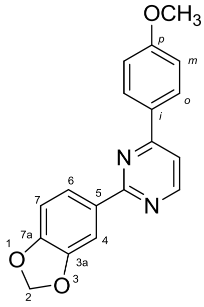
Compound **33cc** was prepared from **32c** (116 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in a gradient of hexane to 5 % ethyl acetate in hexane, in 75 % yield, as white crystals from hexane/ethyl acetate, mp 151 - 152 °C. ^{1}H NMR (500.0 MHz, $CDCl_3$): 3.896, 3.898 (2 × s, 2 × 3H, CH_3O); 7.02 (m, 2H, H-*m*-C_6H_4OMe-2); 7.04 (m, 2H, H-*m*-C_6H_4OMe-4); 7.47 (d, 1H, $J_{5,6}$ = 5.3, H-5); 8.20 (m, 2H, H-*o*-C_6H_4OMe-4); 8.53 (m, 2H, H-*o*-C_6H_4OMe-2); 8.73 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 55.37, 55.43 (CH_3O); 112.97 (CH-5); 113.81 (CH-*m*-C_6H_4OMe-2); 114.24 (CH-*m*-C_6H_4OMe-4); 128.70 (CH-*o*-C_6H_4OMe-4); 129.58 (C-*i*-C_6H_4OMe-4); 129.85 (CH-*o*-C_6H_4OMe-2); 130.76 (C-*i*-C_6H_4OMe-2); 157.46 (CH-6); 161.79 (C-*p*-C_6H_4OMe-2); 161.99 (C-*p*-C_6H_4OMe-4); 163.22 (C-4); 164.20 (C-2). IR: 3012, 2963, 1606, 1581, 1560, 1541, 1509, 1464, 1434, 1409, 1379, 1300, 1243, 1178, 1111, 1053, 1022. MS (EI^+), *m/z* (% relative intensity): 132 (12), 249 (3), 277 (17), 292 (M^+, 100). HR MS (M^+): 292.1210 (calcd for $C_{18}H_{16}N_2O_2$ 292.1212). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.61; H, 5.40; N, 9.36.

2-(3-Fluoro-4-methoxyphenyl)-4-(4-methoxyphenyl)pyrimidine (33cd)



Compound **33cd** was prepared from **32c** (116 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in a gradient of hexane to 5 % ethyl acetate in hexane, in 89 % yield, as a white powder, mp 143 - 145 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.90 (s, 3H, CH_3O-C_6H_4OMe); 3.98 (s, 3H, CH_3O-C_6H_3FOMe); 7.05 (m, 2H, H-*m*-C_6H_4OMe); 7.07 (t, 1H, $J_{5,6} = J_{H,F} = 8.5$, H-5-C_6H_3FOMe); 7.50 (d, 1H, $J_{5,6} = 5.3$, H-5); 8.19 (m, 2H, H-*o*-C_6H_4OMe); 8.32 (dd, 1H, $J_{H,F} = 12.9$, $J_{2,6} = 2.1$, H-2-C_6H_3FOMe); 8.33 (ddd, 1H, $J_{6,5} = 8.5$, $J_{6,2} = 2.1$, $J_{H,F} = 1.6$, H-6-C_6H_3FOMe); 8.73 (d, 1H, $J_{6,5} = 5.3$, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 55.44 (CH_3O-C_6H_4OMe); 56.23 (CH_3O-C_6H_3FOMe); 112.70 (CH-5-C_6H_3FOMe-2); 113.35 (CH-5); 114.28 (CH-*o*-C_6H_4OMe); 115.90 (d, $J_{C,F} = 20.0$, CH-2-C_6H_3FOMe); 124.50 (d, $J_{C,F} = 3.2$, CH-6-C_6H_3FOMe); 128.72 (CH-*o*-C_6H_4OMe); 129.22 (C-*i*-C_6H_4OMe); 131.30 (d, $J_{C,F} = 6.2$, C-1-C_6H_3FOMe); 149.81 (d, $J_{C,F} = 10.8$, C-4-C_6H_3FOMe); 152.35 (d, $J_{C,F} = 244.8$, C-3-C_6H_3FOMe); 157.44 (CH-6); 162.10 (C-*p*-C_6H_4OMe); 163.15 (d, $J_{C,F} = 3.2$, C-2); 163.35 (C-4). ^{19}F{^{1}H} NMR (470.3 MHZ, $CDCl_3$): -131.67. IR: 3069, 2922, 1607, 1581, 1561, 1542, 1510, 1427, 1414, 1365, 1272, 1248, 1198, 1170, 1121, 1050, 1019. MS (EI$^+$), *m/z* (% relative intensity): 89 (4), 117 (4), 132 (12), 151 (5), 224 (5), 252 (4), 267 (8), 295 (28), 310 (M^+, 100). HR MS (M^+): 310.1120 (calcd for $C_{18}H_{15}FN_2O_2$ 310.1118).

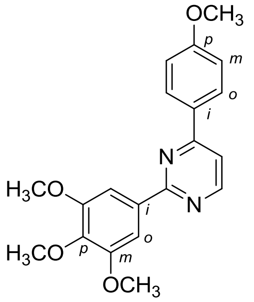
2-(Benzo[*d*][1,3]dioxol-5-yl)-4-(4-methoxyphenyl)pyrimidine (33ce)



Compound **33ce** was prepared from **32c** (116 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in a gradient of hexane to 5 % ethyl acetate in hexane, in 72 % yield, as a white powder, mp 135 - 136 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.90 (s, 3H, CH_3O); 6.05 (s, 2H, OCH_2O); 6.94 (dd, 1H, $J_{7,6} = 8.2$, $J_{7,4} = 0.4$, H-7-$C_6H_3(OCH_2O)$); 7.04 (m, 2H, H-*m*-C_6H_4OMe); 7.48 (d, 1H, $J_{5,6} = 5.3$, H-5); 8.06 (dd, 1H, $J_{4,6} = 1.7$, $J_{4,7} = 0.4$, H-4-$C_6H_3(OCH_2O)$); 8.18 (dd, 1H, $J_{6,7} = 8.2$, $J_{6,4} = 1.7$, H-6-$C_6H_3(OCH_2O)$); 8.19 (m, 2H, H-*o*-C_6H_4OMe); 8.72 (d, 1H, $J_{6,5} = 5.3$, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 55.43 (CH_3O); 101.39

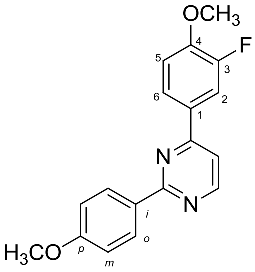
(OCH$_2$O); 108.21 (CH-7-C$_6$H$_3$(OCH$_2$O)); 108.46 (CH-4-C$_6$H$_3$(OCH$_2$O)); 113.16 (CH-5); 114.25 (CH-*m*-C$_6$H$_4$OMe); 123.05 (CH-6-C$_6$H$_3$(OCH$_2$O)); 128.69 (CH-*o*-C$_6$H$_4$OMe); 129.39 (C-i-C$_6$H$_4$OMe); 132.49 (C-5-C$_6$H$_3$(OCH$_2$O)); 148.03 (C-3a-C$_6$H$_3$(OCH$_2$O)); 149.80 (C-7a-C$_6$H$_3$(OCH$_2$O)); 157.43 (CH-6); 162.02 (C-*p*-C$_6$H$_4$OMe); 163.20 (C-4); 163.85 (C-2). IR: 3012, 2918, 1610, 1569, 1543, 1513, 1498, 1449, 1434, 1413, 1388, 1328, 1245, 1229, 1178, 1104, 1085, 1036. MS (EI$^+$), *m/z* (% relative intensity): 57 (11), 71 (6), 89 (7), 97 (5), 117 (7), 132 (11), 146 (5), 152 (5), 205 (3), 291 (3), 306 (M$^+$, 100). HR MS (M$^+$): 306.1005 (calcd for $C_{18}H_{14}N_2O_3$ 306.1004).

4-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)pyrimidine (33cf)



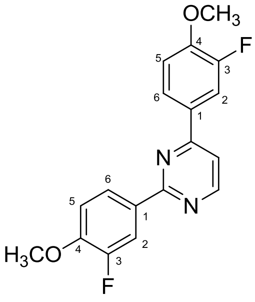
Compound **33cf** was prepared from **32c** (116 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in a gradient of 3 % ethyl acetate to 20 % ethyl acetate in hexane, in 66 % yield, as a beige powder, mp 139 - 141 °C. ^{1}H NMR (499.8 MHz, CDCl$_3$, t = 50 °C): 3.90 (s, 3H, CH$_3$O-C$_6$H$_4$OMe); 3.94 (s, 3H, CH$_3$O-*p*-C$_6$H$_2$(OMe)$_3$); 4.01 (s, 6H, CH$_3$O-*m*-C$_6$H$_2$(OMe)$_3$); 7.05 (m, 2H, H-*m*-C$_6$H$_4$OMe); 7.52 (d, 1H, $J_{5,6}$ = 5.4, H-5); 7.92 (s, 2H, H-*o*-C$_6$H$_2$(OMe)$_3$); 8.18 (m, 2H, H-*o*-C$_6$H$_4$OMe); 8.75 (d, 1H, $J_{6,5}$ = 5.4, H-6). ^{13}C NMR (125.7 MHz, CDCl$_3$, t = 50 °C): 55.50 (CH$_3$O-C$_6$H$_4$OMe); 56.49 (CH$_3$O-*m*-C$_6$H$_2$(OMe)$_3$); 60.93 (CH$_3$O-*p*-C$_6$H$_2$(OMe)$_3$); 106.19 (CH-*o*-C$_6$H$_2$(OMe)$_3$); 113.36 (CH-5); 114.55 (CH-*m*-C$_6$H$_4$OMe); 129.02 (CH-*o*-C$_6$H$_4$OMe); 129.17 (C-*i*-C$_6$H$_4$OMe); 132.42 (C-*i*-C$_6$H$_2$(OMe)$_3$); 141.39 (C-*p*-C$_6$H$_2$(OMe)$_3$); 153.50 (C-*m*-C$_6$H$_2$(OMe)$_3$); 156.26 (CH-6); 162.60 (C-*p*-C$_6$H$_4$OMe); 163.38 (C-2); 164.20 (C-4). IR: 3009, 2934, 1606, 1584, 1562, 1548, 1507, 1456, 1435, 1406, 1376, 1308, 1288, 1249, 1219, 1172, 1125, 1069, 1029. MS (EI$^+$), *m/z* (% relative intensity): 57 (10), 71 (6), 83 (5), 97 (5), 139 (7), 176 (5), 279 (25), 307 (20), 321 (5), 337 (47), 352 (M$^+$, 100). HR MS (M$^+$): 352.1420 (calcd for $C_{20}H_{20}N_2O_4$ 352.1423).

4-(3-Fluoro-4-methoxyphenyl)-2-(4-methoxyphenyl)pyrimidine (33dc)



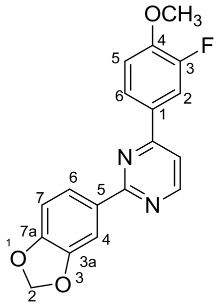
Compound **33dc** was prepared from **32d** (125 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in an eluent of 10 % ethyl acetate in hexane, in 99 % yield, as a white powder, mp 134 - 136 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.83 (s, 3H, CH_3O-C_6H_4OMe); 3.91 (s, 3H, CH_3O-C_6H_3FOMe); 6.96 (m, 2H, H-*m*-C_6H_4OMe); 7.01 (t, 1H, $J_{H,F} = J_{5,6} = 8.6$, H-5-C_6H_3FOMe); 7.37 (d, 1H, $J_{5,6} = 5.3$, H-5); 7.88 (ddd, 1H, $J_{6,5} = 8.6$, $J_{6,2} = 2.2$, $J_{H,F} = 1.2$, H-6-C_6H_3FOMe); 7.97 (dd, 1H, $J_{H,F} = 12.5$, $J_{2,6} = 2.2$, H-2-C_6H_3FOMe); 8.45 (m, 2H, H-*o*-C_6H_4OMe); 8.68 (d, 1H, $J_{6,5} = 5.3$, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 55.37 (CH_3O-C_6H_4OMe); 56.29 (CH_3O-C_6H_3FOMe); 112.98 (CH-5); 113.07 (d, $J_{C,F} = 1.7$, CH-5-C_6H_3FOMe); 113.84 (CH-*m*-C_6H_4OMe); 114.83 (d, $J_{C,F} = 19.8$, CH-2-C_6H_3FOMe); 123.31 (d, $J_{C,F} = 3.3$, CH-6-C_6H_3FOMe); 129.87 (CH-*o*-C_6H_4OMe); 130.14 (d, $J_{C,F} = 6.4$, C-1-C_6H_3FOMe); 130.43 (C-*i*-C_6H_4OMe); 150.00 (d, $J_{C,F} = 10.9$, C-4-C_6H_3FOMe); 152.59 (d, $J_{C,F} = 246.1$, C-3-C_6H_3FOMe); 157.71 (CH-6); 161.88 (C-*p*-C_6H_4OMe); 162.11 (d, $J_{C,F} = 2.3$, C-4); 164.28 (C-2). ^{19}F{^{1}H} NMR (470.3 MHZ, $CDCl_3$): -130.57. IR: 3060, 2939, 1607, 1546, 1512, 1448, 1414, 1372, 1283, 1246, 1161, 1122, 1053, 1019. MS (EI$^+$), *m/z* (% relative intensity): 77 (14), 107 (8), 133 (10), 150 (14), 183 (19), 199 (20), 201 (17), 252 (4), 267 (6), 277 (100), 295 (17), 310 (M$^+$, 98). HR MS (M$^+$): 310.1123 (calcd for $C_{18}H_{15}FN_2O_2$ 310.1118).

2,4-Bis(3-fluoro-4-methoxyphenyl)pyrimidine (33dd)



Compound **33dd** was prepared from **32d** (125 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in an eluent of 10 % ethyl acetate in hexane, in 99 % yield, as a white powder, mp 159 - 161°C. ^{1}H NMR (499.8 MHz, CDCl$_3$): 3.978, 3.981 (2 × s, 2 × 3H, CH$_3$O-C$_6$H$_3$FOMe-2,4); 7.07 (dd, 1H, $J_{5,6}$ = 8.6, $J_{H,F}$ = 7.6, H-5-C$_6$H$_3$FOMe-2); 7.09 (t, 1H, $J_{H,F}$ = $J_{5,6}$ = 8.5, H-5-C$_6$H$_3$FOMe-4); 7.47 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.95 (ddd, 1H, $J_{6,5}$ = 8.6, $J_{6,2}$ = 2.2, $J_{H,F}$ = 1.2, H-6-C$_6$H$_3$FOMe-4); 8.02 (dd, 1H, $J_{H,F}$ = 12.5, $J_{2,6}$ = 2.2, H-2-C$_6$H$_3$FOMe-4); 8.30 (dd, 1H, $J_{H,F}$ = 12.5, $J_{2,6}$ = 2.1, H-2-C$_6$H$_3$FOMe-2); 8.32 (ddd, 1H, $J_{6,5}$ = 8.5, $J_{6,2}$ = 2.1, $J_{H,F}$ = 1.1, H-6-C$_6$H$_3$FOMe-2); 8.74 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (125.7 MHz, CDCl$_3$): 56.22, 56.29 (CH$_3$O-C$_6$H$_3$FOMe-2,4); 112.69 (CH-5-C$_6$H$_3$FOMe-2); 113.08 (CH-5-C$_6$H$_3$FOMe-4); 113.37 (CH-5); 114.80 (d, $J_{C,F}$ = 19.8, CH-2-C$_6$H$_3$FOMe-4); 115.88 (d, $J_{C,F}$ = 20.0, CH-2-C$_6$H$_3$FOMe-2); 123.37 (d, $J_{C,F}$ = 3.3, CH-6-C$_6$H$_3$FOMe-4); 124.55 (d, $J_{C,F}$ = 3.3, CH-6-C$_6$H$_3$FOMe-2); 129.81 (d, $J_{C,F}$ = 6.4, C-1-C$_6$H$_3$FOMe-4); 131.02 (d, $J_{C,F}$ = 6.4, C-1-C$_6$H$_3$FOMe-2); 149.92 (d, $J_{C,F}$ = 10.9, C-4-C$_6$H$_3$FOMe-2); 150.12 (d, $J_{C,F}$ = 10.8, C-4-C$_6$H$_3$FOMe-4); 152.34 (d, $J_{C,F}$ = 244.7, C-3-C$_6$H$_3$FOMe-2); 152.57 (d, $J_{C,F}$ = 246.2, C-3-C$_6$H$_3$FOMe-4); 157.74 (CH-6); 162.22 (d, $J_{C,F}$ = 2.3, C-4); 163.28 (d, $J_{C,F}$ = 2.6, C-2). ^{19}F{^{1}H} NMR (470.3 MHZ, CDCl$_3$): -131.53, -130.42. IR: 3068, 2924, 1617, 1563, 1545, 1516, 1454, 1416, 1322, 1277, 1199, 1173, 1123, 1050, 1016. MS (EI$^+$), *m/z* (% relative intensity): 71 (30), 85 (20), 97 (18), 127 (16), 149 (10), 167 (14), 221 (9), 281 (8), 293 (18), 328 (M$^+$, 100). HR MS (M$^+$): 328.1027 (calcd for C$_{18}$H$_{14}$F$_2$N$_2$O$_2$ 328.1023).

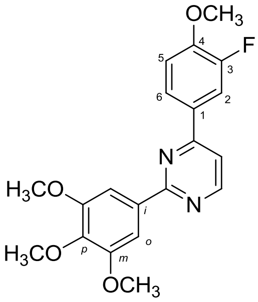
2-(Benzo[*d*][1,3]dioxol-5-yl)-4-(3-fluoro-4-methoxyphenyl)pyrimidine (33de)



Compound **33de** was prepared from **32d** (125 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in an eluent of 10 % ethyl acetate in hexane, in 98 % yield, as a white powder, mp 176 - 178 °C. ^{1}H NMR (499.8 MHz, CDCl$_3$): 3.91 (s, 3H, CH$_3$O-C$_6$H$_3$FOMe); 5.99 (s, 2H, OCH$_2$O); 6.87 (dd, 1H, $J_{7,6}$ = 8.2, $J_{7,4}$ = 0.4, H-7-C$_6$H$_3$(OCH$_2$O)); 7.01 (t, 1H, $J_{H,F}$ = $J_{5,6}$ = 8.6, H-5-C$_6$H$_3$FOMe); 7.38 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.88 (ddd, 1H, $J_{6,5}$ = 8.6, $J_{6,2}$ = 2.2, $J_{H,F}$ = 1.2, H-6-C$_6$H$_3$FOMe); 7.95 (dd, 1H, $J_{H,F}$ = 12.5, $J_{2,6}$ = 2.2, H-2-C$_6$H$_3$FOMe); 7.98 (dd, 1H,

$J_{4,6}$ = 1.7, $J_{4,7}$ = 0.4, H-4-$C_6H_3(OCH_2O)$); 8.10 (dd, 1H, $J_{6,7}$ = 8.2, $J_{6,4}$ = 1.7, H-6-$C_6H_3(OCH_2O)$); 8.67 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 56.29 (CH_3O-C_6H_3FOMe); 101.44 (OCH_2O); 108.25 (CH-7-$C_6H_3(OCH_2O)$); 108.43 (CH-4-$C_6H_3(OCH_2O)$); 113.08 (d, $J_{C,F}$ = 1.7, CH-5-C_6H_3FOMe); 113.17 (CH-5); 114.81 (d, $J_{C,F}$ = 19.8, CH-2-C_6H_3FOMe); 123.12 (CH-6-$C_6H_3(OCH_2O)$); 123.33 (d, $J_{C,F}$ = 3.4, CH-6-C_6H_3FOMe); 129.99 (d, $J_{C,F}$ = 6.3, C-1-C_6H_3FOMe); 132.20 (C-5-$C_6H_3(OCH_2O)$); 148.07 (C-3a-$C_6H_3(OCH_2O)$); 149.94 (C-7a-$C_6H_3(OCH_2O)$); 150.06 (d, $J_{C,F}$ = 10.9, C-4-C_6H_3FOMe); 152.58 (d, $J_{C,F}$ = 246.4, C-3-C_6H_3FOMe); 157.70 (CH-6); 162.11 (d, $J_{C,F}$ = 2.4, C-4); 163.96 (C-2). $^{19}F\{^1H\}$ NMR (470.3 MHZ, $CDCl_3$): -130.50. IR: 2919, 1620, 1569, 1546, 1503, 1445, 1384, 1332, 1276, 1255, 1175, 1130, 1111, 1078, 1024. MS (EI^+), m/z (% relative intensity): 107 (6), 117 (3), 135 (7), 150 (8), 162 (9), 223 (3), 309 (3), 324 (M^+, 100). HR MS (M^+): 324.0907 (calcd for $C_{18}H_{13}FN_2O_3$ 324.0910). Anal. Calcd for $C_{18}H_{13}FN_2O_3$: C, 66.66; H, 4.04; F, 5.86; N, 8.64. Found: C, 66.49; H, 3.72; F, 5.92; N, 8.35.

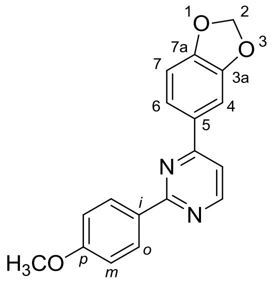
4-(3-Fluoro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)pyrimidine (33df)



Compound **33df** was prepared from **32d** (125 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in a gradient of 10 % ethyl acetate to 20 % ethyl acetate in hexane, in 86 % yield, as a beige powder, mp 133 - 135 °C. ^1H NMR (499.8 MHz, $CDCl_3$): 3.94 (s, 3H, CH_3O-*p*-$C_6H_2(OMe)_3$); 3.99 (s, 3H, CH_3O-C_6H_3FOMe); 4.02 (s, 6H, CH_3O-*m*-$C_6H_2(OMe)_3$); 7.11 (t, 1H, $J_{H,F}$ = $J_{5,6}$ = 8.5, H-5-C_6H_3FOMe); 7.49 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.86 (s, 2H, H-*o*-$C_6H_2(OMe)_3$); 7.95 (ddd, 1H, $J_{6,5}$ = 8.5, $J_{6,2}$ = 2.2, $J_{H,F}$ = 1.2, H-6-C_6H_3FOMe); 8.01 (dd, 1H, $J_{H,F}$ = 12.4, $J_{2,6}$ = 2.2, H-2-C_6H_3FOMe); 8.78 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 56.25 (CH_3O-*m*-$C_6H_2(OMe)_3$); 56.31 (CH_3O-C_6H_3FOMe); 60.96 (CH_3O-*p*-$C_6H_2(OMe)_3$); 105.36 (CH-*o*-$C_6H_2(OMe)_3$); 113.16 (d, $J_{C,F}$ = 2.0, CH-5-C_6H_3FOMe); 113.55 (CH-5); 114.82 (d, $J_{C,F}$ = 19.8, CH-2-C_6H_3FOMe); 123.37 (d, $J_{C,F}$ = 3.3, CH-6-C_6H_3FOMe); 129.93 (d, $J_{C,F}$ = 6.2, C-1-C_6H_3FOMe); 133.13 (C-*i*-

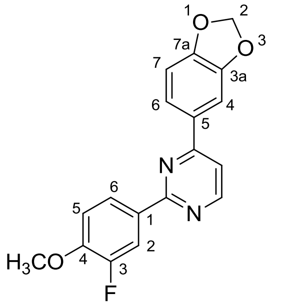
$C_6H_2(OMe)_3$); 140.56 (C-*p*-$C_6H_2(OMe)_3$); 150.13 (d, $J_{C,F}$ = 10.9, C-4-C_6H_3FOMe); 152.59 (d, $J_{C,F}$ = 246.3, C-3-C_6H_3FOMe); 153.31 (C-*m*-$C_6H_2(OMe)_3$); 157.67 (CH-6); 162.27 (d, $J_{C,F}$ = 2.3, C-4); 164.02 (C-2). $^{19}F\{^1H\}$ NMR (470.3 MHZ, $CDCl_3$): -130.37. IR: 2930, 1566, 1552, 1506, 1430, 1406, 1375, 1275, 1219, 1177, 1118, 1017. MS (EI^+), *m/z* (% relative intensity): 149 (6), 155 (8), 185 (6), 282 (6), 297 (16), 312 (8), 327 (14), 355 (36), 370 (M^+, 100). HR MS (M^+): 370.1330 (calcd for $C_{20}H_{19}FN_2O_4$ 370.1329).

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)pyrimidine (33ec)



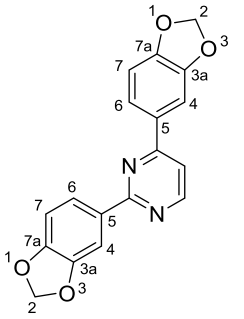
Compound **33ec** was prepared from **32e** (123 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in an eluent of 10 % ethyl acetate in hexane , in 98 % yield, as a white powder, mp 120 - 122 °C. ^1H NMR (499.8 MHz, $CDCl_3$): 3.90 (s, 3H, CH_3O); 6.07 (s, 2H, OCH_2O); 6.95 (dd, 1H, $J_{7,6}$ = 8.1, $J_{7,4}$ = 0.4, H-7-$C_6H_3(OCH_2O)$); 7.02 (m, 2H, H-*m*-C_6H_4OMe); 7.43 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.74 (dd, 1H, $J_{6,7}$ = 8.1, $J_{6,4}$ = 1.8, H-6-$C_6H_3(OCH_2O)$); 7.78 (dd, 1H, $J_{4,6}$ = 1.8, $J_{4,7}$ = 0.4, H-4-$C_6H_3(OCH_2O)$); 8.51 (m, 2H, H-*o*-C_6H_4OMe); 8.73 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 55.37 (CH_3O); 101.60 (OCH_2O); 107.33 (CH-4-$C_6H_3(OCH_2O)$); 108.53 (CH-7-$C_6H_3(OCH_2O)$); 113.13 (CH-5); 113.81 (CH-*m*-C_6H_4OMe); 121.80 (CH-6-$C_6H_3(OCH_2O)$); 129.85 (CH-*o*-C_6H_4OMe); 130.57 (C-*i*-C_6H_4OMe); 131.43 (C-5-$C_6H_3(OCH_2O)$); 148.45 (C-3a-$C_6H_3(OCH_2O)$); 150.04 (C-7a-$C_6H_3(OCH_2O)$); 157.56 (CH-6); 161.82 (C-*p*-C_6H_4OMe); 162.99 (C-4); 164.17 (C-2). IR: 3043, 2907, 1607, 1586, 1566, 1545, 1491, 1415, 1297, 1241, 1223, 1165, 1088, 1029. MS (EI^+), *m/z* (% relative intensity): 89 (3), 116 (3), 133 (8), 146 (18), 152 (6), 173 (3), 205 (4), 263 (5), 291 (11), 306 (M^+, 100). HR MS (M^+): 306.1010 (calcd for $C_{18}H_{14}N_2O_3$ 306.1004).

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-(3-fluoro-4-methoxyphenyl)pyrimidine (33ed)



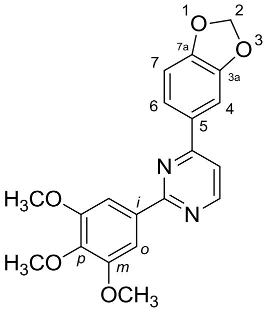
Compound **33ed** was prepared from **32e** (123 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in an eluent of 10 % ethyl acetate in hexane, in 98 % yield, as a white powder, mp 156 - 158 °C. ^{1}H NMR (600.1 MHz, $CDCl_3$): 3.98 (s, 3H, CH_3O-C_6H_3FOMe); 6.07 (s, 2H, OCH_2O); 6.95 (dd, 1H, $J_{7,6}$ = 8.2, $J_{7,4}$ = 0.4, H-7-$C_6H_3(OCH_2O)$); 7.07 (t, 1H, $J_{5,6}$ = $J_{H,F}$ = 8.5, H-5-C_6H_3FOMe); 7.45 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.74 (dd, 1H, $J_{6,7}$ = 8.2, $J_{6,4}$ = 1.8, H-6-$C_6H_3(OCH_2O)$); 7.76 (dd, 1H, $J_{4,6}$ = 1.8, $J_{4,7}$ = 0.4, H-4-$C_6H_3(OCH_2O)$); 8.30 (dd, 1H, $J_{H,F}$ = 12.9, $J_{2,6}$ = 2.1, H-2-C_6H_3FOMe); 8.32 (ddd, 1H, $J_{6,5}$ = 8.5, $J_{6,2}$ = 2.1, $J_{H,F}$ = 1.1, H-6-C_6H_3FOMe); 8.73 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (150.9 MHz, $CDCl_3$): 56.28 (CH_3O-C_6H_3FOMe); 101.66 (OCH_2O); 107.31 (CH-4-$C_6H_3(OCH_2O)$); 108.58 (CH-7-$C_6H_3(OCH_2O)$); 112.80 (d, $J_{C,F}$ = 1.8, CH-5-C_6H_3FOMe); 113.52 (CH-5); 115.94 (d, $J_{C,F}$ = 20.0, CH-2-C_6H_3FOMe); 121.88 (CH-6-$C_6H_3(OCH_2O)$); 124.54 (d, $J_{C,F}$ = 3.3, CH-6-C_6H_3FOMe); 131.20 (C-5-$C_6H_3(OCH_2O)$); 131.22 (d, $J_{C,F}$ = 5.6, C-1-C_6H_3FOMe); 148.54 (C-3a-$C_6H_3(OCH_2O)$); 149.90 (d, $J_{C,F}$ = 10.8, C-4-C_6H_3FOMe); 150.21 (C-7a-$C_6H_3(OCH_2O)$); 152.42 (d, $J_{C,F}$ = 244.8, C-3-C_6H_3FOMe); 157.60 (CH-6); 163.14 (C-4); 163.24 (d, $J_{C,F}$ = 3.1, C-2);. ^{19}F{^{1}H} NMR (470.3 MHZ, $CDCl_3$): -131.61. IR: 2917, 1608, 1562, 1547, 1495, 1428, 1379, 1262, 1223, 1196, 1174, 1128, 1080, 1020. MS (EI$^+$), *m/z* (% relative intensity): 88 (3), 108 (3), 140 (7), 146 (11), 161 (6), 223 (5), 251 (3), 281 (5), 309 (20), 324 (M$^+$, 100). HR MS (M$^+$): 324.0906 (calcd for $C_{18}H_{13}FN_2O_3$ 324.0910). Anal. Calcd for $C_{18}H_{13}FN_2O_3$: C, 66.66; H, 4.04; F, 5.86; N, 8.64. Found: C, 66.52; H, 3.93; F, 5.94; N, 8.33.

2,4-Di(benzo[*d*][1,3]dioxol-5-yl)pyrimidine (33ee)



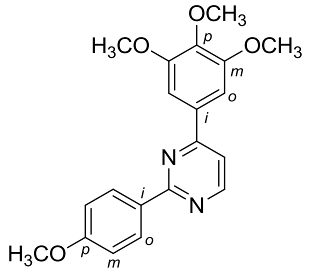
Compound **33ee** was prepared from **32e** (123 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in an eluent of 10 % ethyl acetate in hexane, in 96 % yield, as a white powder, mp 95 - 97 °C. ^{1}H NMR (600.1 MHz, CDCl$_3$): 6.05, 6.07 (2 × s, 2 × 2H, OCH$_2$O); 6.93 (dd, 1H, $J_{7,6}$ = 8.2, $J_{7,4}$ = 0.4, H-7-C$_6$H$_3$(OCH$_2$O)-2); 6.95 (dd, 1H, $J_{7,6}$ = 8.2, $J_{7,4}$ = 0.4, H-7-C$_6$H$_3$(OCH$_2$O)-4); 7.43 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.74 (dd, 1H, $J_{6,7}$ = 8.2, $J_{6,4}$ = 1.8, H-6-C$_6$H$_3$(OCH$_2$O)-4); 7.76 (dd, 1H, $J_{4,6}$ = 1.8, $J_{4,7}$ = 0.4, H-4-C$_6$H$_3$(OCH$_2$O)-4); 8.05 (dd, 1H, $J_{4,6}$ = 1.7, $J_{4,7}$ = 0.4, H-4-C$_6$H$_3$(OCH$_2$O)-2); 8.17 (dd, 1H, $J_{6,7}$ = 8.2, $J_{6,4}$ = 1.7, H-6-C$_6$H$_3$(OCH$_2$O)-2); 8.72 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (150.9 MHz, CDCl$_3$): 101.41, 101.63 (OCH$_2$O); 107.33 (CH-4-C$_6$H$_3$(OCH$_2$O)-4); 108.22 (CH-7-C$_6$H$_3$(OCH$_2$O)-2); 108.48 (CH-4-C$_6$H$_3$(OCH$_2$O)-2); 108.55 (CH-7-C$_6$H$_3$(OCH$_2$O)-4); 113.32 (CH-5); 121.84 (CH-6-C$_6$H$_3$(OCH$_2$O)-4); 123.11 (CH-6-C$_6$H$_3$(OCH$_2$O)-2); 131.34 (C-5-C$_6$H$_3$(OCH$_2$O)-4); 132.39 (C-5-C$_6$H$_3$(OCH$_2$O)-2); 148.07 (C-3a-C$_6$H$_3$(OCH$_2$O)-2); 148.50 (C-3a-C$_6$H$_3$(OCH$_2$O)-4); 149.89 (C-7a-C$_6$H$_3$(OCH$_2$O)-2); 150.13 (C-7a-C$_6$H$_3$(OCH$_2$O)-4); 157.54 (CH-6); 163.02 (C-4); 163.90. IR: 2918, 1565, 1546, 1498, 1439, 1421, 1376, 1354, 1249, 1223, 1097, 1034. MS (EI$^+$), *m/z* (% relative intensity): 89 (3), 117 (4), 146 (16), 159 (12), 203 (3), 263 (3), 320 (M$^+$, 100). HR MS (M$^+$): 320.0793 (calcd for C$_{18}$H$_{12}$N$_2$O$_4$ 320.0797).

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-(3,4,5-trimethoxyphenyl)pyrimidine (33ef)



Compound **33ef** was prepared from **32e** (123 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in a gradient of 10 % ethyl acetate to 20 % ethyl acetate in hexane, in 96 % yield, as a yellow powder, mp 172 - 174 °C. ^{1}H NMR (500.0 MHz, $CDCl_3$): 3.94 (s, 3H, CH_3O-*p*-$C_6H_2(OMe)_3$); 4.01 (s, 6H, CH_3O-*m*-$C_6H_2(OMe)_3$); 6.07 (s, 2H, OCH_2O); 6.96 (dd, 1H, $J_{7,6} = 8.1$, $J_{7,4} = 0.3$, H-7-$C_6H_3(OCH_2O)$); 7.47 (d, 1H, $J_{5,6} = 5.3$, H-5); 7.73 (dd, 1H, $J_{6,7} = 8.1$, $J_{6,4} = 1.8$, H-6-$C_6H_3(OCH_2O)$); 7.75 (dd, 1H, $J_{4,6} = 1.8$, $J_{4,7} = 0.3$, H-2-$C_6H_3(OCH_2O)$); 7.86 (s, 2H, H-*o*-$C_6H_2(OMe)_3$); 8.75 (d, 1H, $J_{6,5} = 5.3$, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 56.95 (CH_3O-*m*-$C_6H_2(OMe)_3$); 60.95 (CH_3O-*p*-$C_6H_2(OMe)_3$); 101.64 (OCH_2O); 105.42 (H-*o*-$C_6H_2(OMe)_3$); 107.30 (CH-4-$C_6H_3(OCH_2O)$); 108.61 (CH-7-$C_6H_3(OCH_2O)$); 113.69 (CH-5); 121.87 (CH-6-$C_6H_3(OCH_2O)$); 131.26 (C-5-$C_6H_3(OCH_2O)$); 133.28 (C-*i*-$C_6H_2(OMe)_3$); 140.55 (C-*p*-$C_6H_2(OMe)_3$); 148.50 (C-3a-$C_6H_3(OCH_2O)$); 150.17 (C-7a-$C_6H_3(OCH_2O)$); 153.30 (C-*m*-$C_6H_2(OMe)_3$); 157.51 (CH-6); 163.15 (C-4); 163.92 (C-2). IR: 2933, 1566, 1549, 1504, 1407, 1382, 1332, 1262, 1220, 1177, 1122, 1027. MS (EI^{+}), *m/z* (% relative intensity): 76 (5), 104 (9), 118 (10), 127 (5), 146 (18), 149 (50), 167 (5), 183 (10), 207 (5), 237 (9), 251 (6), 280 (4), 293 (38), 308 (11), 320 (12), 323 (23), 351 (51), 366 (M^{+}, 100). HR MS (M^{+}): 366.1215 (calcd for $C_{20}H_{18}N_2O_5$ 366.1216).

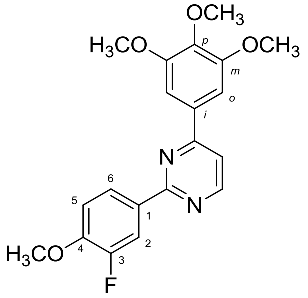
2-(4-Methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)pyrimidine (33fc)



Compound **33fc** was prepared from **32f** (146 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in an eluent of 10 % ethyl acetate in hexane, in 54 % yield, as a yellowish powder, mp 125 - 127 °C. ^{1}H NMR (600.1 MHz, $CDCl_3$): 3.90 (s, 3H, CH_3O-C_6H_4OMe); 3.94 (s, 3H, CH_3O-*p*-$C_6H_2(OMe)_3$); 4.00 (s, 6H, CH_3O-*m*-$C_6H_2(OMe)_3$); 7.03 (m, 2H, H-*m*-C_6H_4OMe); 7.46 (s, 2H, H-*o*-$C_6H_2(OMe)_3$); 7.48 (d, 1H, $J_{5,6} = 5.3$, H-5); 8.51 (m, 2H, H-*o*-C_6H_4OMe); 8.77 (d, 1H, $J_{6,5} = 5.3$, H-6). ^{13}C NMR (150.9 MHz, $CDCl_3$): 55.38 (CH_3O-C_6H_4OMe); 56.30 (CH_3O-*m*-$C_6H_2(OMe)_3$); 61.00 (CH_3O-*p*-$C_6H_2(OMe)_3$); 104.40 (CH-*o*-

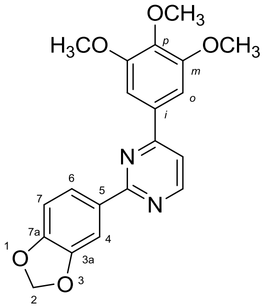
$C_6H_2(OMe)_3$); 113.63 (CH-5); 113.86 (CH-*m*-C_6H_4OMe); 129.84 (CH-*o*-C_6H_4OMe); 130.46 (C-*i*-C_6H_4OMe); 132.56 (C-*i*-$C_6H_2(OMe)_3$); 140.60 (C-*p*-$C_6H_2(OMe)_3$); 153.58 (C-*m*-$C_6H_2(OMe)_3$); 157.67 (CH-6); 161.87 (C-*p*-C_6H_4OMe); 163.35 (C-4); 164.22 (C-2). IR: 2922, 1603, 1584, 1561, 1545, 1506, 1449, 1429, 1410, 1378, 1340, 1315, 1243, 1168, 1122, 1020. MS (EI^+), *m/z* (% relative intensity): 215 (3), 246 (5), 261 (5), 277 (20), 292 (47), 306 (13), 319 (15), 334 (15), 337 (26), 352 (M^+, 100). HR MS (M^+): 352.1425 (calcd for $C_{20}H_{20}N_2O_4$ 352.1423).

2-(3-Fluoro-4-methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)pyrimidine (33fd)



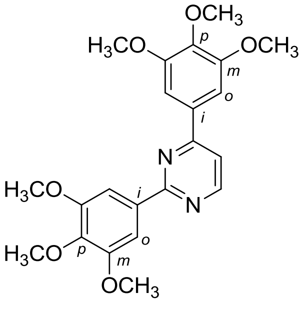
Compound **33fd** was prepared from **32f** (146 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in an eluent of 10 % ethyl acetate in hexane, in 80 % yield, as a beige powder, mp 135 - 137 °C. ^1H NMR (600.1 MHz, $CDCl_3$): 3.94 (s, 3H, CH_3O-*p*-$C_6H_2(OMe)_3$); 3.98 (s, 3H, CH_3O-C_6H_3FOMe); 4.01 (s, 6H, CH_3O-*m*-$C_6H_2(OMe)_3$); 7.09 (t, 1H, $J_{5,6} = J_{H,F} = 8.6$, H-5-C_6H_3FOMe); 7.44 (s, 2H, H-*o*-$C_6H_2(OMe)_3$); 7.51 (d, 1H, $J_{5,6} = 5.3$, H-5); 8.30 (dd, 1H, $J_{H,F} = 12.7$, $J_{2,6} = 2.1$, H-2-C_6H_3FOMe); 8.33 (ddd, 1H, $J_{6,5} = 8.6$, $J_{6,2} = 2.1$, $J_{H,F} = 1.2$, H-6-C_6H_3FOMe); 8.77 (d, 1H, $J_{6,5} = 5.3$, H-6). ^{13}C NMR (150.9 MHz, $CDCl_3$): 56.23 (CH_3O-C_6H_3FOMe); 56.32 (CH_3O-*m*-$C_6H_2(OMe)_3$); 61.01 (CH_3O-*p*-$C_6H_2(OMe)_3$); 104.41 (CH-*o*-$C_6H_2(OMe)_3$); 112.72 (d, $J_{C,F} = 1.6$, CH-5-C_6H_3FOMe-2); 114.05 (CH-5); 115.87 (d, $J_{C,F} = 20.0$, CH-2-C_6H_3FOMe); 124.54 (d, $J_{C,F} = 3.2$, CH-6-C_6H_3FOMe); 131.07 (d, $J_{C,F} = 6.6$, C-1-C_6H_3FOMe); 132.28 (C-*i*-$C_6H_2(OMe)_3$); 140.74 (C-*p*-$C_6H_2(OMe)_3$); 149.91 (d, $J_{C,F} = 10.9$, C-4-C_6H_3FOMe); 152.33 (d, $J_{C,F} = 244.7$, C-3-C_6H_3FOMe); 153.62 (C-*m*-$C_6H_2(OMe)_3$); 157.72 (CH-6); 163.26 (d, $J_{C,F} = 2.7$, C-2); 163.48 (C-4). $^{19}F\{^1H\}$ NMR (470.3 MHZ, $CDCl_3$): -131.49. IR: 2923, 1594, 1564, 1545, 1506, 1422, 1370, 1342, 1323, 1276, 1224, 1177, 1121, 1004. MS (EI^+), *m/z* (% relative intensity): 57 (30), 69 (20), 85 (15), 97 (15), 111 (13), 125 (5), 277 (17), 297 (16), 312 (5), 327 (11), 355 (29), 370 (M^+, 100). HR MS (M^+): 370.1325 (calcd for $C_{20}H_{19}N_2O_4F$ 370.1329).

2-(Benzo[*d*][1,3]dioxol-5-yl)-4-(3,4,5-trimethoxyphenyl)pyrimidine (33fe)



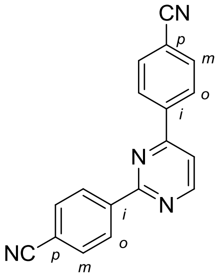
Compound **33fe** was prepared from **32f** (146 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in an eluent of 10 % ethyl acetate in hexane, in 52 % yield, as a beige powder, mp 145 - 147 °C. ^{1}H NMR (600.1 MHz, CDCl$_3$): 3.94 (s, 3H, CH$_3$O-*p*-C$_6$H$_2$(OMe)$_3$); 4.00 (s, 6H, CH$_3$O-*m*-C$_6$H$_2$(OMe)$_3$); 6.06 (s, 2H, OCH$_2$O); 6.95 (dd, 1H, $J_{7,6}$ = 8.2, $J_{7,4}$ = 0.4, H-7-C$_6$H$_3$(OCH$_2$O)); 7.44 (s, 2H, H-*o*-C$_6$H$_2$(OMe)$_3$); 7.49 (d, 1H, $J_{5,6}$ = 5.3, H-5); 8.04 (dd, 1H, $J_{4,6}$ = 1.7, $J_{4,7}$ = 0.4, H-4-C$_6$H$_3$(OCH$_2$O)); 8.17 (dd, 1H, $J_{6,7}$ = 8.2, $J_{6,4}$ = 1.7, H-6-C$_6$H$_3$(OCH$_2$O)); 8.76 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (150.9 MHz, CDCl$_3$): 56.32 (CH$_3$O-*m*-C$_6$H$_2$(OMe)$_3$); 61.00 (CH$_3$O-*p*-C$_6$H$_2$(OMe)$_3$); 101.43 (OCH$_2$O); 104.40 (CH-*o*-C$_6$H$_2$(OMe)$_3$); 108.27 (CH-7-C$_6$H$_3$(OCH$_2$O)); 108.41 (CH-4-C$_6$H$_3$(OCH$_2$O)); 113.85 (CH-5); 123.11 (CH-6-C$_6$H$_3$(OCH$_2$O)); 132.24 (C-5-C$_6$H$_3$(OCH$_2$O)); 132.42 (C-*i*-C$_6$H$_2$(OMe)$_3$); 140.66 (C-*p*-C$_6$H$_2$(OMe)$_3$); 148.04 (C-3a-C$_6$H$_3$(OCH$_2$O)); 149.92 (C-7a-C$_6$H$_3$(OCH$_2$O)); 153.59 (C-*m*-C$_6$H$_2$(OMe)$_3$); 157.64 (CH-6); 163.37 (C-4); 163.91 (C-2). IR: 2922, 1564, 1545, 1503, 1421, 1407, 1367, 1332, 1307, 1230, 1122, 1097, 1038, 1000. MS (EI$^+$), *m/z* (% relative intensity): 118 (4), 146 (6), 183 (5), 199 (6), 237 (5), 261 (3), 277 (27), 293 (25), 308 (13), 319 (50), 334 (40), 351 (33), 366 (M$^+$, 100). HR MS (M$^+$): 366.1213 (calcd for C$_{20}$H$_{18}$N$_2$O$_5$ 366.1216).

2,4-Bis(3,4,5-trimethoxyphenyl)pyrimidine (33ff)



Compound **33ff** was prepared from **32f** (146 mg, 0.5 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in a gradient of 10 % ethyl acetate to 50 % ethyl acetate in hexane, in 51 % yield, as a white powder, mp 156 - 158 °C. ^{1}H NMR (500.0 MHz, CDCl$_3$): 3.94 (s, 6H, CH$_3$O-*p*-C$_6$H$_2$(OMe)$_3$-2,4); 3.99 (s, 6H, CH$_3$O-*m*-C$_6$H$_2$(OMe)$_3$-4); 4.00 (s, 6H, CH$_3$O-*m*-C$_6$H$_2$(OMe)$_3$-2); 7.47 (s, 2H, H-*o*-C$_6$H$_2$(OMe)$_3$-4); 7.54 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.88 (s, 2H, H-*o*-C$_6$H$_2$(OMe)$_3$-2); 8.80 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (125.7 MHz, CDCl$_3$): 56.04, 56.13 (CH$_3$O-*m*-C$_6$H$_2$(OMe)$_3$-2,4); 60.98, 61.04 (CH$_3$O-*p*-C$_6$H$_2$(OMe)$_3$-2,4); 104.20 (CH-*o*-C$_6$H$_2$(OMe)$_3$-4); 105.08 (CH-*o*-C$_6$H$_2$(OMe)$_3$-2); 114.09 (CH-5); 132.27 (C-*i*-C$_6$H$_2$(OMe)$_3$-4); 133.10 (C-*i*-C$_6$H$_2$(OMe)$_3$-2); 140.29 (C-*p*-C$_6$H$_2$(OMe)$_3$-2); 140.53 (C-*p*-C$_6$H$_2$(OMe)$_3$-4); 153.22 (C-*m*-C$_6$H$_2$(OMe)$_3$-2); 153.53 (C-*m*-C$_6$H$_2$(OMe)$_3$-4); 157.69 (CH-6); 163.28 (C-4); 163.81 (C-2). IR: 2922, 1593, 1559, 1542, 1505, 1471, 1408, 1380, 1336, 1222, 1189, 1120. MS (EI$^+$), *m/z* (% relative intensity): 206 (4), 339 (5), 366 (5), 397 (22), 412 (M$^+$, 100). HR MS (M$^+$): 412.1621 (calcd for C$_{22}$H$_{24}$N$_2$O$_6$ 412.1634).

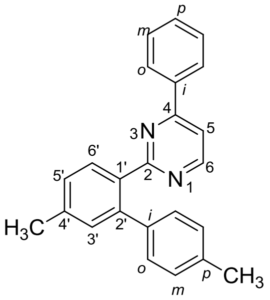
4,4'-(Pyrimidine-2,4-diyl)dibenzonitrile (33gg)



Compound **33gg** was prepared from **32g** (60 mg, 0.26 mmol) according to general procedure and was isolated by column chromatography on 70 g of silica gel in a gradient of 10 % ethyl acetate to 20 % ethyl acetate in hexane, in 99 % yield, as a white powder, mp 247 - 249 °C (lit[179] mp 239 - 241 °C). ^{1}H NMR (499.8 MHz, CDCl$_3$): 7.71 (d, 1H, $J_{5,6}$ = 5.2, H-5); 7.82 (m, 2H, H-*m*-C$_6$H$_4$CN-2); 7.86 (m, 2H, H-*m*-C$_6$H$_4$CN-4); 8.33 (m, 2H, H-*o*-C$_6$H$_4$CN-4); 8.70 (m, 2H, H-*o*-C$_6$H$_4$CN-2); 8.97 (d, 1H, $J_{6,5}$ = 5.2, H-6). ^{13}C NMR (125.7 MHz, CDCl$_3$): 114.37 (C-*p*-C$_6$H$_4$CN-2); 114.73 (C-*p*-C$_6$H$_4$CN-4); 115.84 (CH-5); 118.25 (CN-4); 118.69 (CN-2); 127.79 (CH-*o*-C$_6$H$_4$CN-4); 128.81 (CH-*o*-C$_6$H$_4$CN-2); 132.44 (CH-*m*-C$_6$H$_4$CN-2); 132.83 (CH-*m*-C$_6$H$_4$CN-4); 140.54 (C-*i*-C$_6$H$_4$CN-4); 141.32 (C-*i*-C$_6$H$_4$CN-2); 158.73 (CH-6); 162.18 (C-4); 163.15 (C-2). IR: 2932, 2239, 2225, 1584, 1561, 1549, 1506, 1443, 1412, 1383, 1329, 1305, 1280, 1191, 1111, 1047, 1018. MS (EI$^+$), *m/z* (% relative intensity): 43 (9), 55 (10), 73 (9), 101 (7), 128 (28), 154 (18), 282 (M^+, 100). HR MS (M^+): 282.0899 (calcd for $C_{18}H_{10}N_4$ 282.0905).

5.5.3. Attempted direct C-H arylations of 2,4-diarylpyrimidines

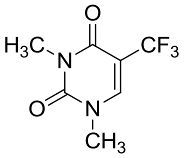
2-(4',5-Dimethyl-[1,1'-biphenyl]-2-yl)-4-phenylpyrimidine (34)



To a pressure tube was added 4-phenyl-2-(*p*-tolyl)pyrimidine (**33ab**, 123 mg, 0.5 mmol, 1 equiv), *p*-tolyl iodide (**2a**, 218 mg, 1.0 mmol, 2 equiv), $[RhCl(CO)_2]_2$ (10 mg, 0.025 mmol) and 3 mL of 1,4-dioxane. The reaction mixture was sealed heated at 175 °C for 20 hours and then cooled to room temperature. The solvent was evaporated and the crude reaction mixture was purified by column chromatography on 70 g of silica gel in a chloroform. The derivative **34** obtained in 10 % yield, as a white powder, mp 100 - 102 °C. ^{1}H NMR (500.0 MHZ, $CDCl_3$): 2.33 (s, 3H, CH_3-Tol); 2.46 (s, 3H, CH_3-4'); 7.10 (m, 2H, H-*m*-C_6H_4Me); 7.13 (m, 2H, H-*o*-C_6H_4Me); 7.29 (m, 1H, H-5'); 7.30 (m, 1H, H-3'); 7.34 (m, 2H, H-*m*-Ph); 7.41 (m, 1H, H-*p*-Ph); 7.44 (d, 1H, $J_{5,6}$ = 5.3, H-5); 7.51 (m, 2H, H-*o*-Ph); 7.91 (m, 1H, H-6'); 8.75 (d, 1H, $J_{6,5}$ = 5.3, H-6). ^{13}C NMR (125.7 MHZ, $CDCl_3$): 21.05 (CH_3-Tol); 21.36 (CH_3-4'); 113.63 (CH-5); 127.24 (CH-*o*-Ph); 127.99 (CH-5'); 128.54 (CH-*m*-C_6H_4Me); 128.69 (CH-*m*-Ph); 129.08 (CH-*o*-C_6H_4Me); 130.60 (CH-*p*-Ph); 130.87 (CH-6'); 131.75 (CH-3'); 135.22 (C-1'); 135.90 (C-*p*-C_6H_4Me); 136.82 (C-*i*-Ph); 139.47 (C-4'); 139.82 (C-*i*-C_6H_4Me); 141.87 (C-2'); 157.55 (CH-6); 163.23 (C-4); 167.44 (C-2). IR: 3025, 2956, 2851, 1726, 1609, 1545, 1515, 1491, 1408, 1373, 1277, 1260, 1148, 1106, 1020. MS (ESI$^+$), *m/z* (% relative intensity): 337 (M^++H, 100), 289 (M^++Na, 8). HR MS (M^++H): 337.1699 (calcd for $C_{24}H_{21}N_2$ 337.1699).

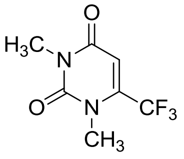
5.6. Trifluoromethylated 1,3-dimethyluracil and products or byproducts of consecutive direct C-H arylation

1,3-Dimethyl-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (35)



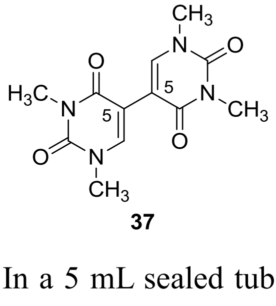
To a solution of 1,3-dimethyluracil (**1**) (70 mg, 0.5 mmol, 1.0 equiv) and sodium trifluoromethylsulfinate (234 mg, 1.5 mmol, 3.0 equiv) in CH_2Cl_2 (2.0 mL) and water (0.8 mL) at 0 ºC *tert*-butylhydroperoxide (70 % solution in water, 0.34 mL, 2.5 mmol, 5.0 equiv) was slowly added with vigorous stirring under an air atmosphere. The reaction was allowed to warm to room temperature and monitored by thin layer chromatography (hexanes / EtOAc 1:1) until completion. Upon consumption of the starting material (4 h), the reaction was partitioned between CH_2Cl_2 (4.0 mL) and saturated sodium bicarbonate (4.0 mL). The combined organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 4.0 mL). The organic layers were dried over magnesium sulfate, concentrated, and isolated by column chromatography on 50 g of silica gel in eluent hexanes / EtOAc 8:2, in 67 % yield, as white crystals from hexanes / EtOAc, mp 100 - 102 °C (lit[180] mp 101 - 102 °C). ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.37 (s, 3H, CH_3-3); 3.49 (s, 3H, CH_3-1); 7.67 (q, 1H, $J_{H,F}$ = 1.1, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 28.03 (CH_3-3); 37.77 (CH_3-1); 104.17 (q, $J_{C,F}$ = 33.3, C-5); 121.95 (q, $J_{C,F}$ = 269.8, CF_3); 143.45 (q, $J_{C,F}$ = 5.8, CH-6); 150.90 (C-2); 158.65 (C-4). $^{19}F\{^1H\}$ NMR (470.3 MHz, $CDCl_3$): -59.99. IR: 1727, 1665, 1648, 1501, 1462, 1391, 1360, 1329, 1215, 1119, 1074, 1021. MS (EI^+), *m/z* (% relative intensity): 42 (43), 56 (10), 60 (8), 75 (10), 91 (7), 103 (5), 123 (31), 132 (13), 150 (33), 160 (10), 179 (4), 188 (34), 208 (M^+, 100). HR MS (M^+): 208.0462 (calcd for $C_7H_7N_2O_2F_3$ 208.0460).

1,3-Dimethyl-6-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (36)

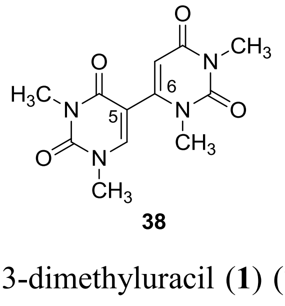


1.3-Dimethyluracil (**1**) (70 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (1.7 mg, 0.5 mol %), dtbpy (1.4 mg, 1.0 mol %), and B_2pin_2 (102 mg, 0.4 mmol) were placed into an oven-dried sealed vial. The vial was evacuated and refilled with argon three times. Under flow of argon, dry THF (1.0 mL) was added. The reaction mixture was stirred at 80 °C for 24 h. After cooling to r.t., the reaction mixture was diluted with $CHCl_3$ and the volatiles were removed under vacuum. To the residue CuTC (9.5 mg, 0.05 mmol), 1,10-phenanthroline (18 mg, 0.10 mmol), $LiOH{\cdot}H_2O$ (42 mg, 1.0 mmol), Togni's reagent (182 mg, 0.55 mmol) and 2.0 mL of CH_2Cl_2 were added. The reaction mixture was refluxed under air at 50 °C for 22 h. After cooling to r.t., the solvent was evaporated under reduced pressure and products were isolated by column chromatography on silica gel (70 g) in eluent hexanes / EtOAc 8:2. It gave compound **35** (22 mg, 21 %) and compound **36** (8 mg, 8 %). Compound **36**: white powder, mp 84 - 86 °C (lit[181] mp 85 - 87 °C). ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.37 (s, 3H, CH_3-3); 3.52 (q, 3H, $J_{H,F}$ = 1.3 CH_3-1); 6.25 (s, 1H, H-5). ^{13}C NMR (125.7 MHz, $CDCl_3$): 28.48 (CH_3-3); 32.48 (q, $J_{C,F}$ = 3.6, CH_3-1); 102.63 (q, $J_{C,F}$ = 5.6, CH-5); 119.45 (q, $J_{C,F}$ = 275.1, CF_3); 140.51 (q, $J_{C,F}$ = 34.3, C-6); 151.66 (C-2); 161.05 (C-4). $^{19}F\{^1H\}$ NMR (470.3 MHz, $CDCl_3$): -62.05. IR: 1721, 1684, 1661, 1637, 1498, 1444, 1411, 1377, 1274, 1219, 1178, 1163, 1128, 1077, 1024. MS (EI^+), *m/z* (% relative intensity): 44 (12), 82 (100), 115 (9), 141 (20), 151 (12), 208 (M^+, 51). HR MS (M^+): 208.0465 (calcd for $C_7H_7N_2O_2F_3$ 208.0460).

1,1',3,3'-Tetramethyl-[5,5'-bipyrimidine]-2,2',4,4'(1*H*,1'*H*,3*H*,3'*H*)-tetraone (37) and 1,1',3,3'- tetramethyl-[4,5'-bipyrimidine]-2,2',4',6(1*H*,1'*H*,3*H*,3'*H*)-tetraone (38)



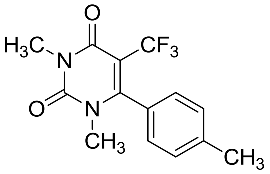
37



38

In a 5 mL sealed tube, 1,3-dimethyluracil (**1**) (70 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.1 equiv), $Cu(OAc)_2$ (91 mg, 0.5 mmol, 1.0 equiv) and 5-(trifluoromethyl)-dibenzothiophenium tetrafluoroborate (255 mg, 0.75 mmol, 1.5 equiv) were dissolved in 2.5 mL dry CH_2Cl_2 under air, and then trifluoroacetic acid (372 μL, 5.0 mmol, 10 equiv) was added. The tube was sealed with a cap and the reaction mixture was stirred at 100 °C for 48 h. After cooling to r.t., the volatiles were removed under vacuum and the residue was purified by column chromatography on 40 g of silica gel in a gradient of 10 % hexanes in EtOAc to 100 % EtOAc to afford compound **37** (23 mg, 16 %) and compound **38** (10 mg, 7 %). Compound **37**: yellowish powder, identical spectroscopic data to those previously described.[182] ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.40 (s, 6H, CH_3-3); 3.48 (s, 6H, CH_3-1); 8.41 (s, 2H, H-6). ^{13}C NMR (125.7 MHz, $CDCl_3$): 28.33 (CH_3-3); 37.58 (CH_3-1); 104.03 (C-5); 142.96 (CH-6); 150.68 (C-2); 162.58 (C-4). IR: 1696, 1647, 1442, 1380, 1344, 1314, 1220, 1192, 1130, 1112, 1006. MS (EI$^+$), *m/z* (% relative intensity): 43 (47), 55 (87), 69 (61), 83 (73), 97 (77), 111 (51), 125 (29), 139 (15), 149 (43), 167 (13), 180 (26), 193 (57), 221 (10), 252 (6), 278 (M$^+$, 100). HR MS (M$^+$): 278.1013 (calcd for $C_{12}H_{14}N_4O_4$ 278.1015). Compound **38**: yellowish powder, identical spectroscopic data to those previously described.[182] ^{1}H NMR (499.8 MHz, $CDCl_3$): 3.29 (s, 3H, CH_3-1B); 3.37 (s, 3H, CH_3-3B); 3.40 (s, 3H, CH_3-3A); 3.50 (s, 3H, CH_3-1A); 5.65 (s,1H, H-5B); 7.40 (s, 2H, H-6A). ^{13}C NMR (125.7 MHz, $CDCl_3$): 28.09 (CH_3-3B); 28.40 (CH_3-3A); 33.57 (CH_3-1B); 37.60 (CH_3-1A); 103.71 (CH-5B); 108.31 (C-5A); 143.08 (CH-6A); 147.56 (C-6B); 151.00 (C-2A); 152.14 (C-2B); 160.34 (C-4A); 162.33 (C-4B). IR: 1707, 1649, 1607, 1440, 1402, 1379, 1350, 1189, 1102, 1083, 1011. MS (ESI$^+$), *m/z* (% relative intensity): 279 (M$^+$+H, 100), 579 (2M$^+$+Na, 11). HR MS (M$^+$+H): 279.10882 (calcd for $C_{12}H_{15}O_4N_4$ 279.10878).

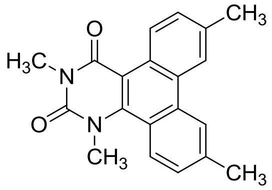
1,3-Dimethyl-6-(*p*-tolyl)-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (41)



Dry DMF (2 mL) was added through a septum to an argon purged vial containing 1,3-dimethyl-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**35**) (62 mg, 0.3 mmol), *p*-tolyl iodide (**2a**, 131 mg, 0.6 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol %), CuI (171 mg, 0.9 mmol) and CsF (114 mg, 0.75 mmol). Reaction mixture was stirred at 160 °C for 48 h. After cooling to r.t., the mixture was diluted with $CHCl_3$ (20 mL) and solvents were evaporated under reduced pressure. Products were isolated by column chromatography on 40 g of silica gel in eluent hexanes / EtOAc 8:2. Compound **41** (22 mg, 25 %) was obtained as white crystals by recrystallization from hexanes / EtOAc, mp 191 - 193 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$): 2.24 (s, 3H, C**H$_3$**-C_6H_4); 3.05 (s, 3H, CH_3-1); 3.44 (s, 3H, CH_3-3); 7.11 (m, 2H, H-*o*-C_6H_4Me); 7.32 (m, 2H, H-*m*-C_6H_4Me). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.43 (**C**H_3-C_6H_4); 28.39 (CH_3-3); 34.47

(CH_3-1); 103.94 (q, $J_{C,F}$ = 30.3, C-5); 122.42 (q, $J_{C,F}$ = 272.2, CF_3); 126.77 (q, $J_{C,F}$ = 1.3, CH-*o*-C_6H_4Me); 128.33 (C-*i*-C_6H_4Me); 129.78 (CH-*m*-C_6H_4Me); 140.58 (C-*p*-C_6H_4Me); 151.12 (C-2); 155.95 (C-6); 158.82 (C-4). $^{19}F\{^1H\}$ NMR (470.3 MHz, $CDCl_3$): -51.84. IR: 1721, 1663, 1623, 1609, 1520, 1455, 1433, 1405, 1370, 1334, 1152, 1114, 1058, 1017. MS (ESI$^+$), *m/z* (% relative intensity): 299 (M^++H, 10), 321 (M^++Na, 100). HR MS (M^++Na): 321.08211 (calcd for $C_{14}H_{13}O_2N_2F_3Na$ 321.08213).

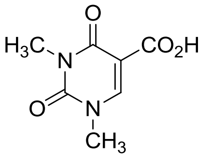
1,3,7,10-tetramethyldibenzo[*f*,*h*]quinazoline-2,4(1*H*,3*H*)-dione (42)



Dry DMF (2 mL) was added through a septum to an argon purged vial containing 1,3-dimethyl-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**35**) (62 mg, 0.3 mmol), *p*-tolyl iodide (**2a**, 131 mg, 0.6 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol %), $P(C_6F_5)_3$ (16 mg, 0.03 mmol, 10 mol %) and Cs_2CO_3 (244 mg, 0.75 mmol). Reaction mixture was stirred at 160 °C for 24 h. After cooling to r.t., the mixture was diluted with $CHCl_3$ (20 mL) and solvents were evaporated under reduced pressure. Products were isolated by column chromatography on 40 g of silica gel in a gradient of 10 % hexanes in EtOAc to 100 % EtOAc. It gave compound **1** (13 mg, 30 %), compound **4a** (17 mg, 25 %) and compound **42** (11 mg, 11 %). Compound **1**: white crystals from EtOAc, identical spectroscopic data to authentic commercial sample. Compound **4a**: white crystals from hexanes / EtOAc, identical spectroscopic data to those previously described.[132] Compound **42**: white powder, ^1H NMR (600.1 MHz, $CDCl_3$): 2.61 (s, 3H, CH_3-7); 2.64 (s, 3H, CH_3-10); 3.55 (s, 3H, CH_3-3); 3.80 (s, 3H, CH_3-1); 7.42 (ddq, 1H, $J_{11,12}$ = 8.5, $J_{11,9}$ = 1.7, $J_{11,CH3}$ = 0.5, H-11); 7.53 (ddq, 1H, $J_{6,5}$ = 8.5, $J_{6,8}$ = 1.7, $J_{6,CH3}$ = 0.5, H-6); 8.05 (d, 1H, $J_{12,11}$ = 8.5, H-12); 8.38 (dq, 1H, $J_{8,6}$ = 1.7, $J_{8,CH3}$ = 0.7, H-8); 8.45 (dq, 1H, $J_{9,11}$ = 1.7, $J_{9,CH3}$ = 0.7, H-9); 9.68 (d, 1H, $J_{5,6}$ = 8.5, H-5). ^{13}C NMR (150.9 MHz, $CDCl_3$): 21.74 (CH_3-7); 22.05 (CH_3-10); 28.48 (CH_3-3); 41.73 (CH_3-1); 108.76 (C-4a); 121.05 (C-12a); 122.10 (CH-8); 123.72 (CH-9); 126.38 (CH-5); 126.43 (CH-12); 126.46 (C-4b); 127.37 (CH-11); 127.94 (C-8a); 130.26 (CH-6); 134.33 (C-8b); 135.98 (C-7); 140.05 (C-10); 14.31 (C-12b); 153.31 (C-2); 162.48 (C-4). IR: 1724, 1692, 1653, 1621, 1587, 1514, 1443, 1369, 1317, 1295, 1264, 1233, 1192, 1168, 1111,

1011. MS (ESI$^+$), *m/z* (% relative intensity): 319 (M$^+$+H, 8), 341 (M$^+$+Na, 100), 359 (2M$^+$+Na, 17). HR MS (M$^+$+Na): 341.12606 (calcd for $C_{20}H_{18}O_2N_2Na$ 341.12605).

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (43)



Dry DMF (1 mL) was added through a septum to an argon purged vial containing 1,3-dimethyl-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**35**) (25 mg, 0.12 mmol, 1.0 equiv) and Cs_2CO_3 (98 mg, 0.30 mmol, 2.5 equiv). The reaction mixture was heated at 160 °C until the reaction was complete (3 h). After cooling to r.t., DMF was evaporated under reduced pressure. The residue was dissolved in H_2O and acidified by HCl forming precipitate. The product was isolated by filtration as a white powder, mp 185 - 187 °C (lit[180] mp 188 - 189 °C). ^{1}H NMR (499.8 MHz, D_2O): 3.34 (s, 3H, CH_3-3); 3.54 (s, 3H, CH_3-1); 8.65 (s, 1H, H-6). ^{13}C NMR (125.7 MHz, D_2O): 30.84 (CH_3-3); 40.84 (CH_3-1); 103.49 (C-5); 154.65 (C-2); 155.88 (CH-6); 167.68 (C-4); 169.22 (COOH). IR: 1745, 1720, 1634, 1529, 1495, 1459, 1425, 1404, 1367, 1339, 1208, 1156, 1077, 1033, 1004. MS (ESI$^+$), *m/z* (% relative intensity): 185 (M$^+$+H, 100), 207 (M$^+$+Na, 27), 391 (2M$^+$+Na, 14). HR MS (M$^+$+Na): 207.03768 (calcd for $C_7H_8O_4N_2Na$ 207.03763).

5.7. Single-crystal X-ray structure analysis

(Performed by Dr. Blanka Klepetářová)

Single-crystal diffraction data of 5-(4-metoxyphenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**3c**), 1,3-dimethyl-6-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4a**), 1,3-dimethyl-6-(pyren-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (**4e**), 4-phenyl-2-(*p*-tolyl)pyrimidine **33ab**, 2,4-bis(4-methoxyphenyl)pyrimidine **33cc**, 2-(3-fluoro-4-methoxyphenyl)-4-(4-methoxyphenyl)pyrimidine **33cd**, 4-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)pyrimidine **33cf**, 4-(3-fluoro-4-methoxyphenyl)-2-(4-methoxyphenyl)pyrimidine **33dc** and 2,4-bis(3,4,5-trimethoxyphenyl)pyrimidine **33ff**, 1,3-dimethyl-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**35**), 1,3-dimethyl-6-(*p*-tolyl)-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**41**) were collected on Xcalibur

X-ray diffractometr with CuK$_\alpha$ (λ=1.54180 Å) at 170 K (**33ab**, **33cc**, **33dc** and **33ff**), at 190 K (**4a, 33cd**, **33cf**, **35** and **41**) and at 150 K (**3c, 4e**). The structures were solved by direct methods with SIR92[183] (**3c**, **4a**, **4e**, **33ab**, **33cf**, **33ff**) and by charge flipping with SUPERFLIP[184] (**33cc**, **33cd**, **33dc**) and refined by full-matrix least-squares on F with CRYSTALS[185]. The structures **35** and **41** were solved by direct methods with SIR92[183] and by charge flipping with SUPERFLIP[184] and refined by full-matrix least-squares on F with CRYSTALS[185]. The hydrogen atoms were all located in a difference map and recalculated into idealized positions. All hydrogen atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry after which the positions were refined with riding constraints, while all other atoms were refined with anisotropic displacement parameters.

Crystal data for 3c (light brown block, 0.23 x 0.31 x 0.52 mm): $C_{13}H_{14}N_2O_3$, monoclinic, space group $P2_1/c$, $a = 18.489(2)$ Å, $b = 7.1077(6)$ Å, $c = 22.2051(3)$ Å, $\beta = 126.622(3)°$, $V = 2342.0(4)$ Å^3, $Z = 8$, $M = 492.53$, 72357 reflections measured, 4950 independent reflections. Final $R = 0.059$, $wR = 0.069$, $GoF = 1.061$ for 3814 reflections with $I > 2\sigma(I)$ and 326 parameters.

Crystal data for 4a (colourless plate, 0.05 x 0.4 x 0.5 mm): $C_{13}H_{14}N_2O_2$, monoclinic, space group $P2_1/c$, $a = 10.2426(2)$ Å, $b = 8.20001(13)$ Å, $c = 13.8733(3)$ Å, $\beta = 99.8298(18)°$, $V = 1148.11(4)$ Å^3, $Z = 4$, $M = 230.27$, 9372 reflections measured, 2334 independent reflections. Final $R = 0.047$, $wR = 0.059$, $GoF = 1.019$ for 2173 reflections with $I > 2\sigma(I)$ and 155 parameters.

Crystal data for 4e (orange prism, 0.11 x 0.22 x 0.29 mm): $C_{22}H_{16}N_2O_2$, monoclinic, space group $C2/c$, $a = 27.683(2)$ Å, $b = 7.7554(5)$ Å, $c = 15.2520(8)$ Å, $\beta = 99.240(7)°$, $V = 3232.0(4)$ Å^3, $Z = 8$, $M = 340.38$, 90576 reflections measured, 3433 independent reflections. Final $R = 0.054$, $wR = 0.062$, $GoF = 1.081$ for 2039 reflections with $I > 2\sigma(I)$ and 235 parameters.

Crystal data for 33ab (colourless plate, 0.06 x 0.31 x 0.38 mm): $C_{17}H_{14}N_2$, monoclinic, space group $P2_1/c$, $a = 9.9361(5)$ Å, $b = 16.6333(5)$ Å, $c = 8.2531(3)$ Å, $\beta = 108.873(5)°$, $V = 1290.66(10)$ Å^3, $Z = 4$, $M = 246.31$, 13686 reflections measured, 2706 independent reflections. Final $R = 0.043$, $wR = 0.051$, $GoF = 1.058$ for 1854 reflections with $I > 2\sigma(I)$ and 173 parameters.

Crystal data for 33cc (colourless plate, 0.02 x 0.50 x 0.59 mm): $C_{18}H_{16}N_2O_2$, monoclinic, space group $P2_1$, $a = 7.3477(15)$ Å, $b = 6.5001(16)$ Å, $c = 15.615(3)$ Å, *β* = 103.51(2)°, *V* = 725.1(3) Å^3, *Z* = 2, *M* = 292.34, 7870 reflections measured, 2824 independent reflections. Final *R* = 0.050, *wR* = 0.059, *GoF* = 0.993 for 2345 reflections with $I > 2\sigma(I)$ and 218 parameters, Flack parameter *x* = -0.1(2). The pyrimidine ring contains substitutional disorder in which N1 and C1 occupy the same position (site occupation factors being 0.625 and 0.375) and was therefore refined with several vibration and thermal similarity restraints.

Crystal data for 33cd (colourless plate, 0.08 x 0.27 x 0.39 mm)**:** $C_{18}H_{15}F_1N_2O_2$, monoclinic, space group *Pa*, *a* = 12.3731(3) Å, *b* = 3.91704(9) Å, *c* = 15.2461(4) Å, *β* = 101.551(2)°, *V* = 723.95(3) Å^3, *Z* = 2, *M* = 310.33, 5624 reflections measured, 2031 independent reflections. Final *R* = 0.075, *wR* = 0.087, *GoF* = 1.004 for 1985 reflections with $I > 2\sigma(I)$ and 236 parameters. The pyrimidine ring contains substitutional disorder in which N1 and C1 occupy the same position (with site occupation factors of 0.5 and 0.5) and the fluorine atom is correspondingly disordered over two positions (with site occupancies of 0.5 and 0.5).

Crystal data for 33cf (colourless thick plate, 0.21 x 0.38 x 0.40 mm)**:** $C_{20}H_{20}N_2O_4$, monoclinic, space group $P2_1/c$, *a* = 16.5714(9) Å, *b* = 5.1278(2) Å, *c* = 20.9130(15) Å, *β* = 101.243(6)°, *V* = 1742.97(18) Å^3, *Z* = 4, *M* = 352.39, 14349 reflections measured, 3602 independent reflections. Final *R* = 0.043, *wR* = 0.054, *GoF* = 1.002 for 3231 reflections with $I > 2\sigma(I)$ and 236 parameters.

Crystal data for 33dc (colourless thick plate, 0.19 x 0.49 x 0.58 mm)**:** $C_{18}H_{15}F_1N_2O_2$, monoclinic, space group *Pc*, *a* = 15.2380(12) Å, *b* = 3.9061(3) Å, *c* = 12.3890(8) Å, *β* = 101.509(7)°, *V* = 722.57(10) Å^3, *Z* = 2, *M* = 310.33, 5895 reflections measured, 1895 independent reflections. Final *R* = 0.074, *wR* = 0.093, *GoF* = 1.105 for 1809 reflections with $I > 2\sigma(I)$ and 245 parameters. The crystal used for data collection was a twin with the twin law (-1 0 -0.491, 0 1 0, 0 0 1), as disclosed by ROTAX[186] and a refined component ratio of 0.542 (5):0.458 (5). Furthermore, the pyrimidine ring and the fluorine atoms were found to be disordered over two positions with an occupancy ratio of 0.5: 0.5.

Crystal data for 33ff (colourless block, 0.56 x 0.58 x 0.59 mm): $C_{22}H_{24}N_2O_6$, monoclinic, space group $P2_1/c$, *a* = 16.1130(2) Å, *b* = 11.38894(15) Å, *c* = 11.8681(2) Å, *β* = 110.7558(19)°, *V* = 2036.57(6) Å^3, *Z* = 4, *M* = 412.44, 18026 reflections measured, 4142 independent reflections. Final *R* = 0.040, *wR* = 0.045, *GoF* = 1.042 for 3909 reflections with $I > 2\sigma(I)$ and 272 parameters.

Crystal data for 35 (colorless, 0.27 x 0.32 x 0.78 mm)**:** $C_7H_7F_3N_2O_2$, orthorhombic, space group $P2_12_12_1$, a = 6.19806(12) Å, b = 10.53566(18) Å, c = 13.2460(2) Å, V = 864.97(3) Å^3, Z = 4, M = 208.14, 3031 reflections measured, 1759 independent reflections. Final R = 0.046, wR = 0.051, GoF = 1.110 for 1730 reflections with $I > 2\sigma(I)$ and 129 parameters, Flack parameter x = 0.0(2). CCDC 945178.

Crystal data for 41 (0.07x 0.61x 0.79 mm)**:** $C_{14}H_{13}F_3N_2O_2$, monoclinic, space group $P2_1/n$, a = 8.2089(5) Å, b = 12.4775(6) Å, c = 13.4481(7) Å, β = 97.690(5)°, V = 1365.05(12) Å^3, Z = 4, M = 298.26, 8971 reflections measured, 2770 independent reflections. Final R = 0.131, wR = 0.141, GoF = 0.876 for 2590 reflections with $I > 2\sigma(I)$ and 191 parameters. CCDC 945179. Unfortunately, the crystals of **41** were of rather poor quality and did not diffract strongly, which led to higher R factor value. The precision of the structure determination is therefore not excellent, but it still describes reasonably well all the main structural features of **41**.

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