Novel P,N-Ligand Stabilized Transition Metal Complexes as Efficient Catalysts for Organic Syntheses

DISSERTATION

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Dipl. Chemiker Benoît Blank
geboren in Frankfurt/Main

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Examination Committee:

First referee:	Prof. Dr. Rhett Kempe
Second referee:	Prof. Dr. Rainer Schobert
Third referee:	Prof. Dr. Jürgen Senker
Chairman:	Prof. Dr. Thomas Hellweg

This work was carried out from October 2006 to May 2009 at the Chair of Inorganic Chemistry II at the University of Bayreuth, Germany under the supervision of Professor Dr. Rhett Kempe.

To my parents, for their constant support

and

to Uli, for her endless patience, encouragement and love…

Abbreviations

Ar	aryl
Å	Ångström
Bn	benzyl
Bu	butyl
br	broad
°C	degree celsius
cod	cis-1,5-cyclooctadiene
d	doublet
diglyme	diethylene glycol dimethyl ether
δ	chemical shift (ppm)
equiv	equivalent
g	gram
GC	gas chromatography
h	hours
Hz	Hertz
Het	*N*-heteroaromatics
J	coupling constant (Hz)
K	Kelvin
m	multiplet
Me	methyl
min	minute
mL	milliliter
mmol	millimol
NMR	nuclear magnetic resonance
Ph	phenyl
Py	2-pyridyl
q	quartet
rt	room temperature
s	singlet
t	triplet
µL	microliter

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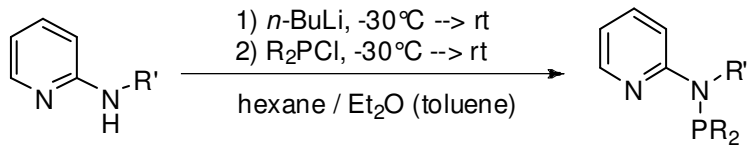
1. Summary

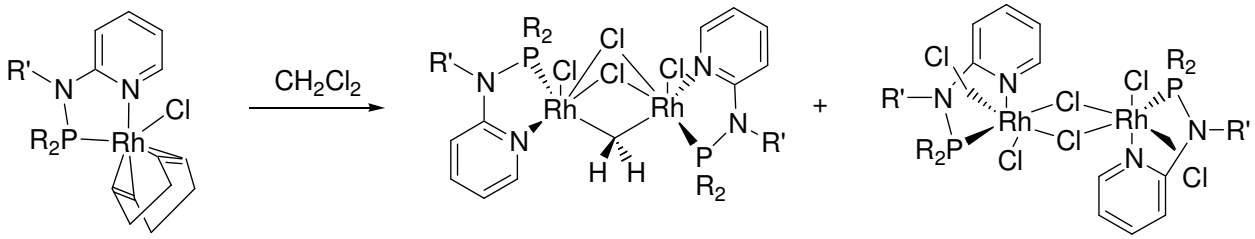
In the context of this work a library of novel P,N-ligands was synthesized and reacted with several transition metals with the aim to prepare active complexes for the efficient application in the field of homogeneous catalysis. Besides the synthesis and full characterization of these P,N-ligand stabilized transition metal complexes, further important aspects, such as the elucidation of mechanistic pathways and the development of novel catalytic methodologies for organic syntheses were covered.

The preparation of the P,N-ligands is carried out in a one-pot reaction, in which first the amine is selectively deprotonated with *n*-BuLi and subsequently treated with the corresponding chlorophosphine. The desired ligand is thus obtained in excellent yields and the reaction can readily be performed on a multi-gram scale.



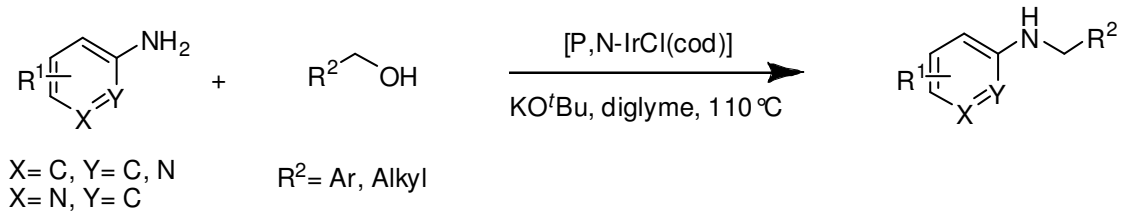
Scheme 1. Synthesis of the P-functionalized aminopyridine ligands (P,N-ligands).

P,N-ligand stabilized transition metal complexes can usually be prepared and isolated by adding stoichiometric amounts of the corresponding ligand to a metal precursor complex. However, a highly dynamic behavior was observed for the formation of P,N-rhodium complexes, which was dependent on the employed ligand and the used solvent. In the case of methylene chloride, these complexes even reacted with the solvent and for the first time the single and double activation of the rather stable C–Cl bonds of methylene chloride were observed simultaneously, affording both a dimeric Rh^{III} complex with terminal chloromethyl groups and a dinuclear Rh^{III} complex with a bridging μ-CH_2 group. The obtained activation products were characterized with single crystal X-ray analysis, and further synthetic as well as NMR kinetic experiments were carried out to identify the active species for this reaction. A most-likely fivefold-coordinated Rh^{I} complex was determined to be responsible for the activation of the solvent and a possible reaction mechanism that includes the formation of both activation products was postulated.



Scheme 2. Single and double C–Cl bond activation with P,N-rhodium complexes.

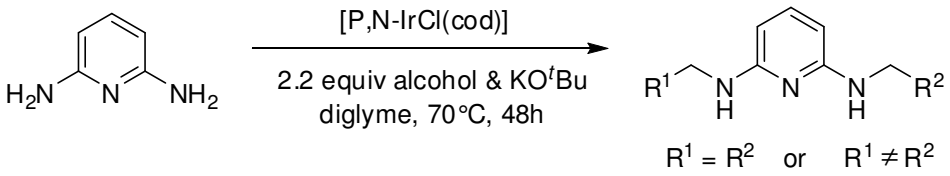
The isolation of a single crystal of this fivefold-coordinated rhodium species, suitable for X-ray analysis, could not be achieved due to its high reactivity and instability, whereas analogous complexes with iridium were readily prepared in quantitative yields and fully characterized. These P,N-ligand stabilized iridium complexes were hence evaluated as potential catalysts for the *N*-alkylation of amines with alcohols.



Scheme 3. Iridium-catalyzed *N*-alkylation of amines with alcohols.

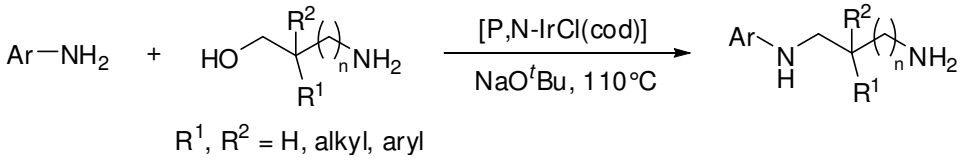
For this purpose, the reaction conditions were first optimized by systematic variation of important parameters such as solvents, bases or catalyst loadings. Later on the possible substrate scope of this method was demonstrated. The obtained results showed that our P,N-iridium catalyst has an excellent activity in this reaction and also a very narrow selectivity profile, because in all reactions only the selective monoalkylation of the corresponding amine was observed without any side-product formation. In addition, only aromatic amines can be alkylated with this catalyst, whereas no conversion is observed with aliphatic amines.

Further optimization of the reaction conditions for the *N*-alkylation of amines with alcohols led to a significant improvement, so that such a reaction could for the first time be performed at a temperature of only 70°C, along with a catalyst loading as low as 0.1 mol% Ir. Moreover, the excellent selectivity of the catalyst for monoalkylation was successfully exploited for the symmetric and non-symmetric *N,N'*-dialkylation of diamines under mild reaction conditions.



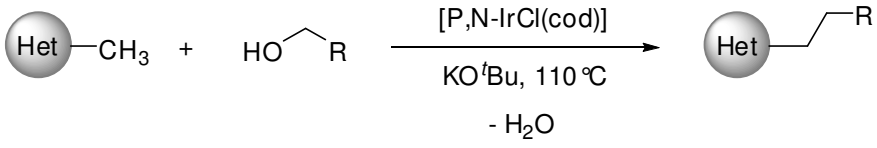
Scheme 4. Selective Ir-catalyzed *N,N'*-dialkylation of diamines under mild reaction conditions.

Next, the specific selectivity of the P,N-iridium catalyst for the preferred alkylation of aromatic amines in comparison to aliphatic amines was exploited in order to develop the first simple method for the selective preparation of mono-*N*-aryl aliphatic diamines by using commercially available amino alcohols. However, an adaptation of the reaction conditions was necessary with amino alcohols and the reaction had to be performed with NaO^{t}Bu instead of KO^{t}Bu in order to obtain good conversions of the substrates. The presented synthetic protocol allows the preparation of *N*-aryl alipatic diamines with a branched alkyl backbone that were hitherto highly difficult to obtain or not accessible at all. The general applicability of the method was shown for a variety branched and linear amino alcohols and with several (hetero)aromatic amines affording the expected diamines in yields up to 93%.



Scheme 5. Synthesis of mono-*N*-aryl aliphatic diamines with amino alcohols.

In the last chapter of the present work, the selective formation of C–C bonds by alkylation of methyl-substituted heteroaromatic substrates with alcohols was examined. This reaction can be seen as a completely new extension of the so-called "borrowing hydrogen" mechanism. A reaction of heteroaromatic substrates bearing acidic methyl groups with alcohols, leading to the selective alkylation of the methyl group, has to our best knowledge hitherto not been described in the literature and was therefore intensively studied and fully developed. We could show that a large variety of substituted benzylic as well as aliphatic alcohols can be employed and that many methyl-substituted *N*-heteroaromatic substrates such as pyridimidines, pyrazines, pyridazines and even pyridines are perfectly tolerated.

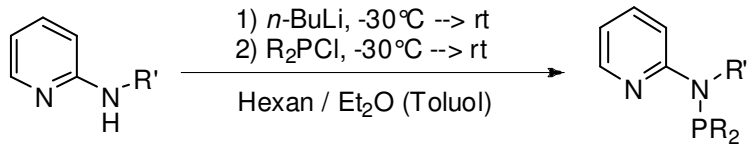


Scheme 6. Catalytic alkylation of methyl-substituted heteroaromatics with alcohols.

Zusammenfassung

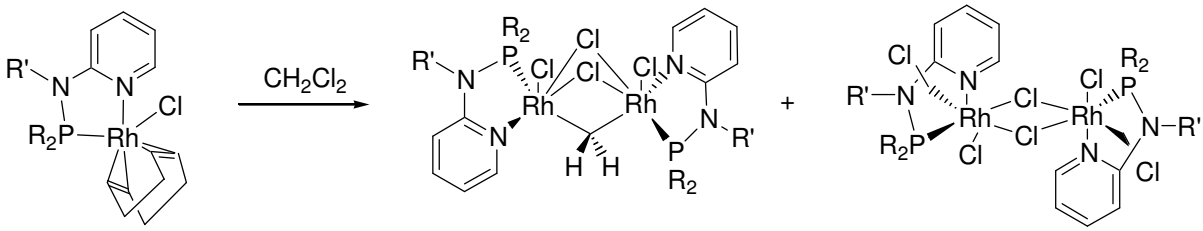
Im Rahmen der vorliegenden Arbeit wurde eine Bibliothek neuer P,N-Liganden synthetisiert und mit verschiedenen späten Übergangsmetallen umgesetzt, mit dem Ziel aktive Komplexe für den effizienten Einsatz in der homogenen Katalyse herzustellen. Neben der Synthese und vollständigen Charakterisierung dieser P,N-Ligand stabilisierten Übergangsmetallkomplexe waren die Aufklärung mechanistischer Fragen sowie die Ausarbeitung neuer katalytischer Methoden für die organische Synthese weitere wichtige Aspekte dieser Arbeit.

Die Synthese der P,N-Liganden erfolgt in einer Eintopfreaktion, bei der im ersten Schritt das Amin mit *n*-BuLi selektiv deprotoniert und anschließend mit dem entsprechenden Chlorophosphan umgesetzt wird. Die gewünschten Liganden werden hierbei in sehr guten Ausbeuten erhalten und können somit auf einfache Weise im multi-gramm Maßstab hergestellt werden.



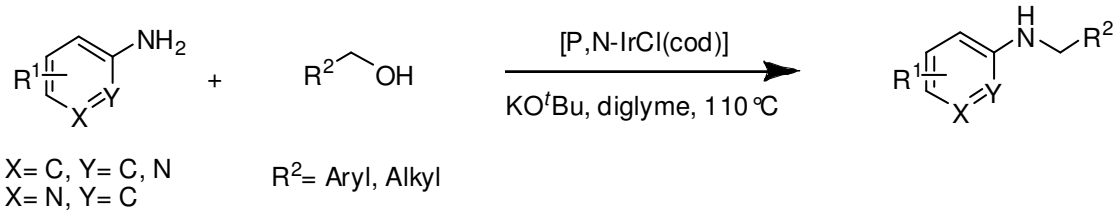
Schema 1. Synthese der P,N-Liganden.

P,N-Ligand stabilisierte Übergangsmetallkomplexe können meist durch stöchiometrische Zugabe des Liganden zu einem Übergangsmetall Precursorkomplex hergestellt und isoliert werden. Im Fall von Rhodiumverbindungen zeigte sich jedoch, dass die Bildung der gewünschten Komplexe sehr stark vom Lösungsmittel, sowie vom jeweiligen Liganden abhängig ist und dass die gebildeten Komplexe dazu tendieren, mit dem Lösungsmittel Methylenchlorid selbst zu reagieren. Hierbei wurde erstmals gleichzeitig die einfache und doppelte Aktivierung der sehr stabilen C–Cl Bindungen von Methylenchlorid beobachtet unter Bildung eines dinuklearen Rh^{III}-Komplexes mit einer verbrückenden μ-CH_2-Gruppe, sowie eines dimeren Rh^{III} Komplexes mit terminalen Chloromethylgruppen. Die erhaltenen Aktivierungsprodukte wurden mittels Einkristallröntgenstrukturanalyse charakterisiert und weitere Versuche wurden unternommen, um mit Hilfe von synthetischen Untersuchungen und kinetischen NMR Experimenten die aktive Komplexspezies der Reaktion zu ermitteln. Hierbei zeigte sich, dass höchstwahrscheinlich ein fünffach-koordinierter Rh^{I}-Komplex für die Aktivierung des Lösungsmittels verantwortlich ist und ein möglicher Reaktionsmechanismus für die Bildung der beiden Aktivierungsprodukte wurde postuliert.



Schema 2. Einfache und doppelte C–Cl Bindungsaktivierung mit P,N-Rhodiumkomplexen.

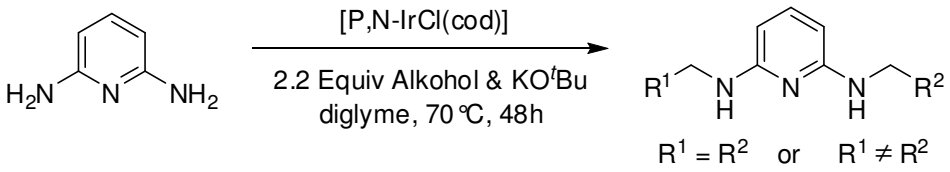
Die Isolierung eines Einkristalls dieses fünffach-koodinierten Rhodiumkomplexes für eine Röntgenstrukturanalyse konnte wegen dessen hoher Reaktivität und Instabilität nicht erreicht werden, wohingegen analoge Komplexe mit Iridium als Zentralatom in quantitativen Ausbeuten erhalten wurden und vollständig charakterisiert werden konnten. Diese P,N-Ligand stabilisierten Iridiumkomplexe wurden dann als Katalysatoren für die *N*-Alkylierung von Aminen mit Alkoholen eingesetzt und auf ihre Aktivität hin überprüft.



Schema 3. Iridium-katalysierte *N*-Alkylierung von Aminen mit Alkoholen.

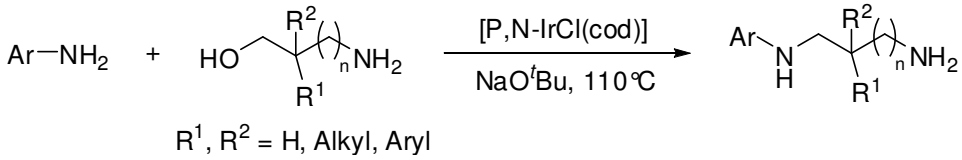
Hierfür wurden zuerst die Reaktionsbedingungen durch systematische Variation verschiedener Parameter, wie z. B. Lösungsmittel, Basen und Katalysatorbeladung optimiert und anschließend die mögliche Substratbreite der entwickelten Methode aufgezeigt. Es stellte sich heraus, dass unsere P,N-Iridium Komplexe eine sehr gute katalytische Aktivität sowie ein sehr enges Selektivitätsprofil besitzen, da in allen durchgeführten Reaktionen immer eine selektive Monoalkylierung des Amins erzielt wurde, ohne dass unerwünschte Nebenprodukte entstehen. Desweiteren können nur aromatische Amine alkyliert werden, während bei aliphatischen Aminen keine Umsetzung beobachtet werden konnte.

Durch Optimierung der Reaktionsbedingungen für die *N*-Alkylierung von Aminen mit Alkoholen konnten anschließend weitere signifikante Verbesserungen erzielt werden, so dass die Reaktion erstmals bei nur 70°C und mit niedrigen Katalysatorbeladungen von 0.1 mol% Ir durchgeführt werden konnte. Außerdem wurde die exzellente Selektivität des Katalysators bezüglich der Monoalkylierung ausgenutzt, um erstmals eine einfache und effiziente Methode für die symmetrische und nicht-symmetrische *N,N'*-Dialkylierung von Diaminen unter milden Reaktionsbedingungen zu entwickeln.



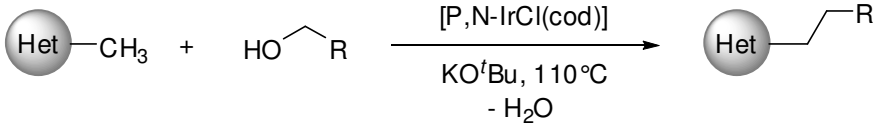
Schema 4. Selektive Ir-katalysierte *N,N'*-Dialkylierung von Diaminen unter milden Bedingungen.

In einem weiteren Schritt wurde die hohe Selektivität unseres P,N-Iridiumkatalysators für die Alkylierung von aromatischen gegenüber aliphatischen Aminen ausgenutzt, um erstmals eine einfache Methode für die selektive Synthese von mono-*N*-aryl aliphatischen Diaminen mit kommerziell erhältlichen Aminoalkoholen zu entwickeln. Eine Anpassung der Reaktionsbedingungen auf die eingesetzten Aminoalkohole war jedoch nötig und es konnte gezeigt werden, dass in diesem Fall die Reaktion mit NaO^{t}Bu weitaus besser abläuft als mit der bisher verwendeten Base KO^{t}Bu. Das hier beschriebene Syntheseprotokoll ermöglicht die Synthese von *N*-Aryl Diaminen mit einem verzweigten Alkylrückgrat, die bisher nur sehr schwierig oder gar nicht zugänglich waren. Die generelle Anwendbarkeit der Methode konnte für eine Vielzahl verschiedener Aminoalkohole und (hetero)aromatischer Amine gezeigt werden und liefert die gewünschten Diamine in Ausbeuten von bis zu 93%.



Schema 5. Synthese von mono-*N*-aryl aliphatischen Diaminen mit Aminoalkoholen.

Im letzten Kapitel dieser Arbeit wird die selektive Knüpfung von C–C Bindungen durch Alkylierung methylsubstituierter Heteroaromaten mit Alkoholen beschrieben. Hierbei handelt es sich um eine Erweiterung des von Williams et al. benannten „borrowing-hydrogen“ Mechanismus.
Eine Reaktion methylsubstituierter heteroaromatischer Substrate mit Alkoholen unter Knüpfung einer C–C Bindung ist bislang in der Literatur noch nicht beschrieben worden und wurde daher genauer untersucht und gezielt weiterentwickelt. Es zeigte sich, dass sowohl substituierte Benzylalkohole als auch aliphatische Alkohole eingesetzt werden können und eine Vielzahl an *N*-heteroaromatischen Substraten, wie z. B. Pyrimidine, Pyrazine, Pyridazine und sogar nur sehr gering aktivierte Pyridine toleriert werden.



Schema 6. Katalytische Alkylierung methylsubstituierter Heteroaromaten mit Alkoholen.

2. Introduction

The age of modern chemistry is marked by an effort to employ the available resources in an efficient and sustainable manner. Thus, catalysis plays an important role within the field of modern chemical synthesis. The first mention and definition of the term "catalysis" goes back to J. Berzelius, who used the Greek term "*κατάλυσις*", which means as much as "breakup" and gives a first hint of the basic functioning of a catalytic reaction. Hence, a catalyst allows the reaction of two starting materials (A + B) and their subsequent transformation into new products (C + D) by the reduction of the activation energy barrier (ΔE_a) for that reaction, which does otherwise not take place. A catalyst takes part in the reaction, but does not appear in the final products and should therefore theoretically not be consumed.

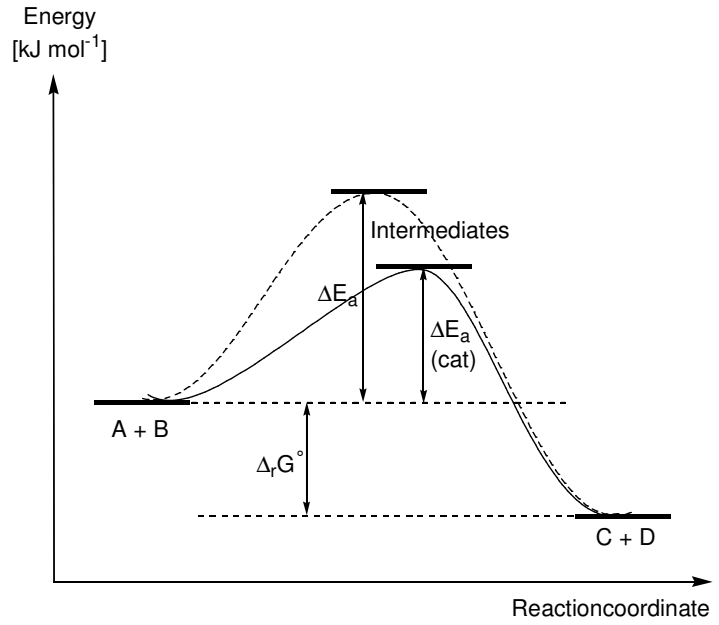


Fig. 1. Thermodynamic profile of a catalytic (plain) and non-catalytic reaction (dashed). In the catalyzed reaction the necessary activation energy ΔE_a(cat) is lowered and the reaction rendered possible.

One can differenciate between two major types of catalysis:

1) Heterogeneous catalysis, in which the catalyst is present in a solid state (mainly metal particles dispersed on a solid surface or a porous material) and the reagents are applied in a solid, liquid or gaseous form, therefore innately separating reagents and catalyst into two different phases.[1]
2) Homogeneous catalysis, in which the starting materials, the catalyst and even the formed products are all present in the same phase, mostly in a dissolved state.[2]

Both types of catalysts have their advantages and inconveniences and are thus used in different fields of application. While heterogeneous catalysts usually have a lower activity and selectivity compared to their homogeneous relatives and usually require drastic reaction conditions, the former can score with a much longer lifetime, simple regneration and excellent separation from the reagents and products.[3] Heterogeneous catalyst systems are mostly employed in the large-scale bulk-chemicals synthesis, whereas homogeneous systems are mainly used in the area of fine- and agrochemicals as well as for pharmaceutical syntheses.[4]

The field of homogeneous catalysis is especially marked by the chemistry of transition metals, because the employed catalysts are well-defined and fully characterized transition metal complexes, which can be tailored to the corresponding reaction, due to a better understanding of the mechanistic pathways for the catalytic sub-steps of any reaction. The area of homogeneous catalysis therefore requires constant advancements in the field of organometallic synthesis, in order to prepare novel transition metal complexes that have better catalytic activities and selectivities, but also to gain a better understanding of the mechanistic apects of catalytic reactions, so that even better tailored catalyst systems can be produced.[5]

The catalytic properties of a transition metal complex are not only dependent on the employed metal atom, but also mainly rely on the used coordinating ligands, which on the one hand help to stabilize the metal atom, but also enhance the activity of the latter due to electronic effects, so that the newly formed ligand-metal complex can interact with organic molecules in a more efficient way. For that reason, in the last decades the main research in homogeneous catalysis has been focused on the development of novel ligand systems to allow the preparation of even more efficient catalysts with a very narrow selectivity profile in order to minimize unwanted side-reactions. Many research groups around the world have therefore developed a multitude of novel mono- and polydentate phosphorus-[6] or nitrogen-containing ligands[7] as well as hybrid P,N-ligands[7] or N-heterocyclic carbene ligands[8] that can efficiently be employed with various transition metals for the preparation of new catalyst complexes.

However, not only the development of novel transition metal catalysts was promoted, but also the development of new catalytic methodologies for the preparation of organic compounds, which heretofore required many synthetic steps or were even impossible to prepare. Excellent examples are the palladium-catalyzed Suzuki cross-coupling reaction[9,10] and the Buchwald-Hartwig arylamination reaction,[11,12] which for the first time allowed a much simpler preparation of biaryls and *N*-arylamines, respectively. The continuous development of novel catalysts for these reactions has nowadays rendered these methodologies a mature synthetic tool and allowed them to find application not only in academia but also in an industrial context.[13]

The focus of current research lies on the development of novel catalytic protocols that are characterized by an excellent atom-efficiency and produce less molecular waste.[14] Recently, the direct arylation of arenes with haloarenes has emerged as a potential substitute for the Suzuki cross-coupling reaction, because it does not require the introduction of an activating elementorganic group in one of the coupling partners and therefore generates less waste. Although this reaction has gained a lot of attention in recent years and reached an interesting application scope, it is still in its infancy because it still requires high catalyst loadings and is mostly limited to activated substrates.[15,16]

A new class of P-functionalized aminopyridine ligands (P,N-ligands) developed by Kempe et al. has already proved to be of great interest due to the simple preparation, high flexibility and excellent efficiency in a first combinatorial study for the Suzuki cross-coupling reaction.[17] Furthermore, a novel bimetallic P,N-ligand stabilized rhodium complex could be prepared that efficiently catalyzes the non-directed direct arylation of unactivated arenes with aryl chlorides.[18] Based on these very promising preliminary studies, one of the objectives of this work was the synthesis of a multitude of P,N-ligands to build a P,N-ligand library and the reaction of the latter with several transition metal precursors in order to prepare novel P,N-ligand stabilized transition metal complexes which can be used as catalysts for organic syntheses. Besides detailed synthetic and mechanistic studies for the activation of C–Cl bonds with P,N-ligand stabilized rhodium complexes, this work also covers the development of novel P,N-iridium complexes and their application as highly efficient and selective catalysts for the formation of C–N and C–C bonds using simple alcohols.[19,20]

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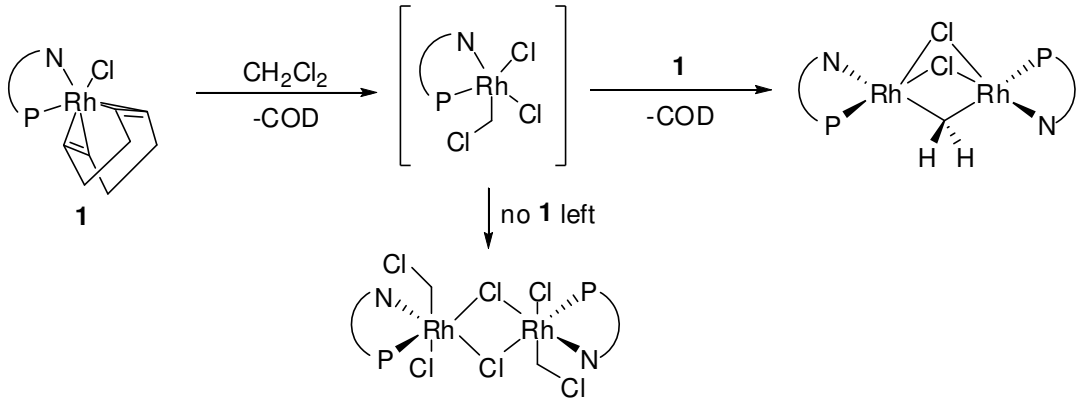
3. Overview of Thesis Results

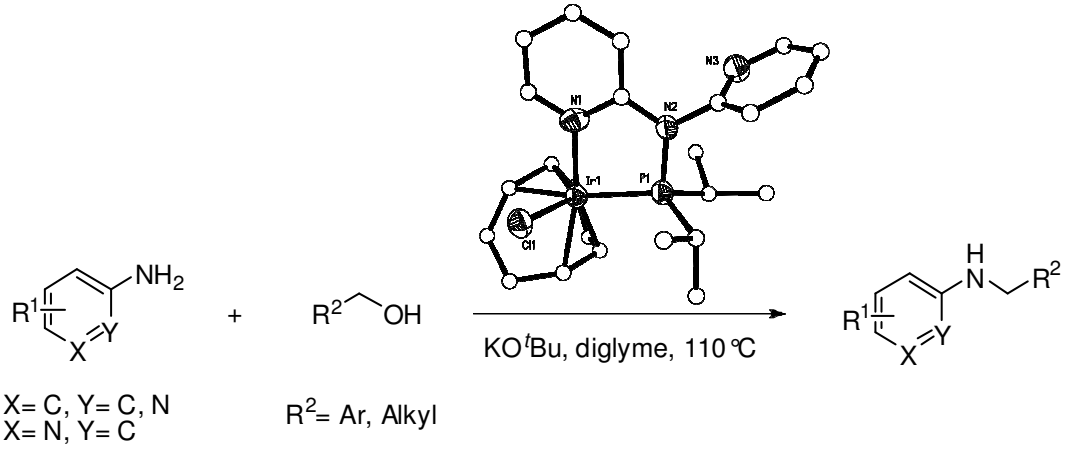
This thesis comprises five publications which are presented in chapter 4-8.

3.1. Single and Double C–Cl-Activation of Methylene Chloride by P,N-ligand Coordinated Rhodium Complexes



Recently, our group reported a novel P,N-ligand stabilized bimetallic rhodium catalyst that efficiently performs the direct arylation of unactivated arenes with haloarenes. For the first time even chloroarenes could be employed for these transformations, which implies that the P,N-rhodium complex is reactive enough for the cleavage of C–Cl bonds. Hence, our goal was to synthesize a library of different P,N-ligands and prepare distinct rhodium complexes with the latter in order to improve the catalyst efficiency for the direct arylation reaction. In our attempt to prepare Rh^{I} complexes with different P,N-ligands we observed the activation of the quite stable C–Cl bonds of the solvent methylene chloride. Simultaneously, the single and double activation of C–Cl bonds of methylene chloride took place, affording both a dimeric Rh^{III} complex bearing terminal CH_2Cl groups in addition to a binuclear Rh^{III} complex with a bridging μ-CH_2 group. The structures of the oxidative addition products were obtained by X-ray diffraction studies and further experiments were carried out in order to determine the active species of the reaction. Several ^{31}P NMR kinetic experiments were performed to gain a better understanding of the complex formation in solution. A most-likely fivefold-coordinated and highly reactive Rh^{I} species was determined to be the active complex for the activation of methylene chloride. Furthermore, a mechanism for the simultaneous formation of the single and double C–Cl activation products was developed.

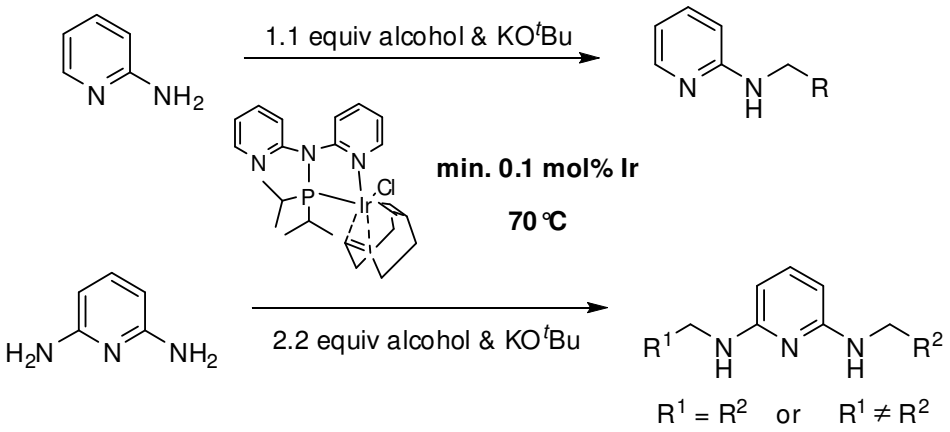
3.2. An Efficient Method for the Selective Iridium-Catalyzed Monoalkylation of (Hetero)Aromatic Amines with Primary Alcohols



In the course of our investigations concerning the active species for the activation of C–Cl bonds with P,N-rhodium complexes we were able to prepare analogous fivefold-coordinated P,N-iridium complexes in quantitative yields by simple mixing of the P,N-ligand with $[IrCl(cod)]_2$. In contrast to the rather difficult rhodium complex chemistry, stable iridium complexes could be prepared regardless of the ligand or the used solvent. Inspired by a recent report of Fujita et al., who reported $[Cp^*IrCl_2]_2$ to be the first efficient iridium catalyst for the *N*-alkylation of amines with alcohols, we attempted to test our P,N-ligand stabilized iridium complex as a catalyst for this reaction. First, the catalyst system was optimized by studying eight different P,N-ligands, nine different solvents and fourteen different bases. Then the systematic variation of the substrate to base and the amine to alcohol ratios as well as the catalyst loading led to optimized catalytic reaction conditions. The substrate scope of the developed catalytic protocol was shown by synthesizing twenty different amines in isolated yields up to 97 %.

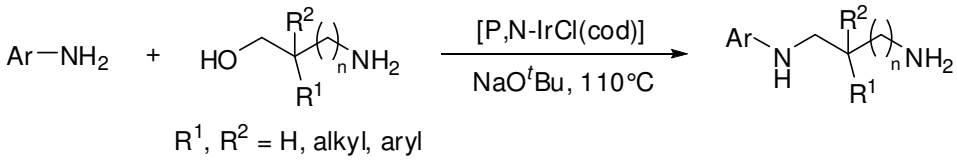
Interestingly, the present iridium catalyst exhibits a very narrow selectivity profile. In all reactions, only the monoalkylated compounds were obtained without any formation of tertiary amines. Moreover, only the alkylation of aromatic amines is possible, whereas aliphatic amines react rather poorly. Furthermore, this is the first catalystic protocol that allows the efficient alkylation of heteroaromatic amines using simple alcohols.

3.3. Selective Iridium-Catalyzed Alkylation of (Hetero)Aromatic Amines and Diamines with Alcohols under Mild Reaction Conditions



By further variation of several reaction parameters, a significant improvement of the above presented iridium-catalyzed amine alkylation method was achieved, such that it can be performed at a temperature of 70°C and with catalyst loadings as low as 0.1 mol% Ir, while still affording excellent yields of secondary amines. Furthermore, the above mentioned high selectivity of the present catalyst for the monoalkylation of aromatic amines has been successfully exploited for the alkylation of diamines in both symmetric and nonsymmetric fashions, providing a novel and very efficient synthetic tool for the preparation of *N*,*N'*-dialkylated aromatic diamines.

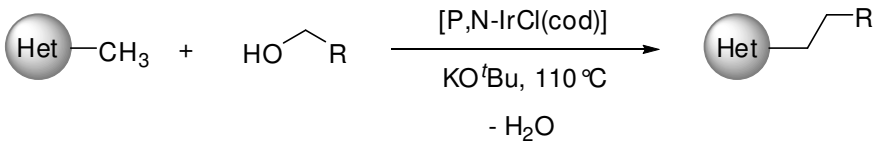
3.4. Synthesis of Selectively Mono-*N*-Arylated Aliphatic Diamines via Iridium-Catalyzed Amine Alkylation



Our next goal was to further exploit the selectivity profile of our P,N-iridium catalyst for the preparation of yet unaccessible mono-*N*-arylated aliphatic diamines. As a consequence of the observation that the present iridium complex only poorly catalyzes the reaction with aliphatic amines, it should be possible to selectively react readily available aminoalcohols with (hetero)aromatic amines. However, initial experiments showed that under the so far used reaction conditions the reaction proceeds rather poorly. A re-examination of several reaction parameters revealed that an exchange of KO^{t}Bu for NaO^{t}Bu is necessary to obtain full conversions. A variety

of branched and linear aminoalcohols as well as several (hetero)aromatic amines was employed to demonstrate the general applicability of this method for the preparation of novel mono-*N*-aryl aliphatic diamines.

3.5. Catalytic Alkylation of Methyl-*N*-Heteroaromatics with Alcohols



In the course of our initial investigations with P,N-iridium complexes for the alkylation of aromatic amines with alcohols described in chapter 5, an interesting observation was made, when 2-amino-4-methylpyrimidine was employed as a substrate. Next to the expected alkylation of the amino group, a further reaction with the methyl group of the heteroaromatic substrate was observed. Since such a reactivity was hitherto unprecedented, it was further investigated and a method for the selective Ir-catalyzed formation of C–C bonds by using methyl-substituted heteroaromatic substrates with alcohols was successfully developed. A variety of substituted benzylic and also aliphatic alcohols is perfectly tolerated and the method can be extended to several methyl-substituted *N*-heteroaromatic substrates, such as pyrimidines, pyridazines, pyrazines and even fairly activated pyridines.

The alkylation of methyl-substituted *N*-heteroaromatic compounds can be seen as a further development of the "borrowing hydrogen" methodology, which uses alcohols for the catalytic formation of C–N or C–C bonds in a very efficient way, with water as the only by-product.

3.6. Individual Contribution to Joint Publications

The results presented in this thesis were obtained in collaboration with others and are published, submitted or are to be submitted as indicated below. In the following, the contributions of all the co-authors to the different publications are specified. The asterisk denotes the corresponding author.

Chapter 4

This work is published in *Chem. Asian J.* **2009**, *4*, 321–327, with the title
"Single and Double C–Cl-Activation of Methylene Chloride by P,N-ligand Coordinated Rhodium Complexes"
Benoît Blank, Germund Glatz, and Rhett Kempe*

I synthesized all complexes presented in this work and carried out the NMR-experiments. Also, the publication was written by me. Germund Glatz performed the X-ray analyses and solved the crystal structures of the compounds published in this work. Rhett Kempe supervised this work and was involved in scientific discussions, comments and correction of the manuscript.

Chapter 5

This work is published in *Adv. Synth. Catal.* **2008**, *350*, 749–758 with the title
"An Efficient Method for the Selective Iridium-Catalyzed Monoalkylation of (Hetero)aromatic Amines with Primary Alcohols"
Benoît Blank, Martyna Madalska, and Rhett Kempe*

I prepared all ligands and complexes presented in this work and developed the catalytic methodology. Also, the publication was written by me. Martyna Madalska helped with the development of the catalytic protocol during her ERASMUS stay in Bayreuth. Rhett Kempe supervised this work and was involved in scientific discussions, comments and correction of the manuscript.

Chapter 6

This work is published in *Chem. Eur. J.* **2009**, *15*, 3790–3799 with the title
"Selective Iridium-Catalyzed Alkylation of (Hetero)Aromatic Amines and Diamines with Alcohols under Mild Reaction Conditions"
Benoît Blank, Stefan Michlik, and Rhett Kempe*

All catalytic studies in this work were performed by me and the publication was written by me. Stefan Michlik helped with the development of the catalytic protocol in the course of his B. Sc. thesis in our group. Rhett Kempe supervised this work and was involved in scientific discussions, comments and correction of the manuscript.

Chapter 7

This work has been accepted for publication in *Adv. Synth. Catal.* with the title
"Synthesis of Selectively Mono-*N*-Arylated Aliphatic Diamines via Iridium-Catalyzed Amine Alkylation"
Benoît Blank, Stefan Michlik, and Rhett Kempe*

The catalytic studies in this work were performed by me and the publication was written by me. Stefan Michlik helped with the development of the catalytic protocol in the course of his B. Sc. thesis in our group. Rhett Kempe supervised this work and was involved in scientific discussions, comments and correction of the manuscript.

Chapter 8

This manuscript is to be submitted with the title
"Catalytic Alkylation of Methyl-*N*-Heteroaromatics with Alcohols"
Benoît Blank, and Rhett Kempe*

I performed all catalytic studies and syntheses presented in this work and wrote the publication. Rhett Kempe supervised this work and was involved in scientific discussions, comments and correction of the manuscript.

4. Single and Double C–Cl-Activation of Methylene Chloride by P,N-ligand Coordinated Rhodium Complexes

Benoît Blank,[a] Germund Glatz,[a] and Rhett Kempe* [a]

[a] Lehrstuhl für Anorganische Chemie II, Universitätsstraße 30, NW I, 95440 Bayreuth, Germany. Fax: +49 (0) 921-55-2157, E-mail: kempe@uni-bayreuth.de

Keywords: C–Cl activation, NMR spectroscopy, P,N-ligand, rhodium, X-ray diffraction

Published in: *Chem. Asian J.* **2009**, *4*, 321–327.

Abstract: The synthesis of Rh^{I} complexes with P-functionalized aminopyridine ligands is reported as well as the first simultaneous observation of a single and double activation of C–Cl bonds of methylene chloride affording both a dimeric Rh^{III} complex bearing terminal CH_2Cl groups in addition to a binuclear Rh^{III} complex with a bridging μ-CH_2 group. The structures of the oxidative addition products were obtained by X-ray diffraction studies and NMR experiments were performed to elucidate some aspects of the reaction pathway.

Abstract in German: Die Synthese von Rh^{I} Komplexen mit P-funktionalisierten Aminopyridinliganden und die erste gleichzeitige Beobachtung einer einfachen und doppelten C–Cl Bindungsaktivierung von Dichlormethan wird beschrieben. Diese Bindungsaktivierung führt sowohl zu einem dimeren Rh^{III} Komplex mit terminalen CH_2Cl Gruppen, als auch zu einem binuklearen Rh^{III} Komplex mit einer verbrückenden Methylengruppe. Die Strukturen der oxidativen Additionsprodukte wurden mittels Einkristallröntgenstrukturanalyse charakterisiert. Außerdem wurden detaillierte NMR Experimente durchgeführt, um gewisse Aspekte des Reaktionsmechanismus aufzuklären.

4.1. Introduction

The oxidative addition of molecules containing a C–X bond (X = I, Br, Cl) to low-valent transition metals is of great academic and industrial interest as the resulting compounds are key intermediates in many catalytic cycles. Moreover, the activation of the C–X bond is often the rate determining step of the overall reaction, especially when X = Cl.[1] Therefore, a detailed knowledge of this oxidative addition step is of great interest.

The addition of CH_3X (X = I, Br, Cl), CH_2I_2 and CH_2Br_2 to various transition metal centers is well documented in the literature.[2] However, the activation of the relatively inert C–Cl bond (bond dissociation energy ≈ 338 $kJmol^{-1}$),[3] especially in CH_2Cl_2 is more challenging than for C–Br or C–I bonds. Hence, fewer examples for the oxidative addition of CH_2Cl_2 under mild conditions have been reported so far. The most widely known reaction is the simple oxidative addition of one molecule of CH_2Cl_2 to electron-rich transition metal complexes stabilized by mono-[4,5,6] and polydentate[7] phosphorous ligands, mono-[8], bi-[9,10] and polydentate [11,12,13] nitrogen ligands, hybrid nitrogen-phosphorus ligands,[14,15,16] sulphur macrocycles[17] and pyridine/phosphine functionalized NHCs[18,19] affording complexes with a terminal CH_2Cl group.

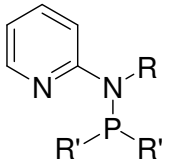
The double activation of one molecule of CH_2Cl_2 to two distinct rhodium centers affording bridging μ-methylene complexes is rare and has only been reported for the basic Rh^I complexes $[(dppe)Rh(\mu\text{-}Cl)]_2$[20] (dppe = 1,2-bis(diphenylphosphino)-ethane), $[(PR_3)_2Rh(\mu\text{-}Cl)]_2$ (R = Et, Ph_2Me)[21] as well as for the isocyanide complexes $[Rh(CN^tBu)(\mu\text{-}pz)]_2$[22] (Bu = butyl, pz = pyrazolate), $[Rh(CN^tBu)(\mu\text{-}S^tBu)]_2$,[23] *syn*-$[Rh(\mu\text{-}NH\{p\text{-}toluyl\})(CN^tBu)_2]_2$[23] and *syn*-$[(cod)Rh(\mu\text{-}NH\{p\text{-}toluyl\})_2Rh(CN^tBu)_2]$[24] (cod = 1,5-cyclootadiene).

To date, the reaction conditions determining the formation of either the terminal or the bridging binding mode are still unknown. In light of the first discovery of the dimeric Rh^{III} complex containing a bridging μ-CH_2 group, Fryzuk et al. suggested that only basic and chelating ligands such as dppe could afford such compounds.[20] However, this assumption was refuted by Brunet et al. who performed detailed NMR experiments with monophosphine-containing complexes and showed that the formation of a μ-methylene species is not limited to binuclear Rh^I starting complexes stabilized by chelating phosphine ligands, but could also be obtained from mononuclear as well as binuclear monophosphine-ligand complexes.[21] Herein, we report on the synthesis of Rh^I complexes with P-functionalized aminopyridine ligands[25] and their potential for the activation of methylene chloride. For the first time, the formation of both a Rh^{III} complex bearing a terminal CH_2Cl group and a binuclear Rh^{III} complex with a bridging μ-CH_2 group are observed

simultaneously. X-ray single crystal structures of the oxidative addition products are provided and NMR experiments are performed in order to elucidate some aspects of the reaction pathway.

4.2. Results and Discussion

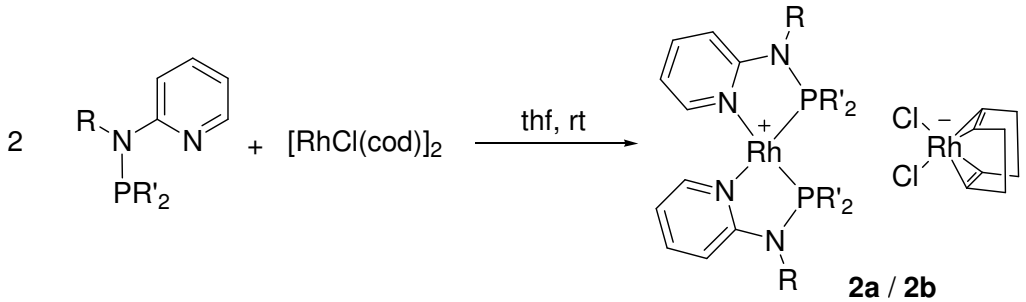
We recently reported a multi-gram synthesis protocol for the preparation of a variety of P,N-ligands and the preparation of their corresponding iridium complexes.[26] These ligands (see Scheme 1) were also used to stabilize rhodium complexes and we discovered that in contrast to iridium a rather unexpected chemistry takes place depending on the solvent as well as the nature of the P,N-ligand.



R = 2-pyridyl	R' = Ph	Py_2NPPh_2	**(1a)**
R = Me	R' = Ph	$PyMeNPPh_2$	**(1b)**
R = 2-pyridyl	R' = Cy	Py_2NPCy_2	**(1c)**
R = 2-pyridyl	R' = *t*-Bu	$Py_2NP(t\text{-}Bu)_2$	**(1d)**
R = 2-pyridyl	R' = *i*-Pr	$Py_2NP(i\text{-}Pr)_2$	**(1e)**

Scheme 1. Nomenclature of the P,N-ligands.

As previously reported,[27] two equivalents of P,N-ligand **1a** react with $[RhCl(cod)]_2$ in THF to form the ionic bimetallic Rh complex **2a** [$^{31}P\{^1H\}$ NMR, δ (CD_2Cl_2) = 126.9 ppm, $J_{P\text{-}Rh}$ = 174.8 Hz] (Scheme 2). When this reaction is performed with P,N-ligand **1b** a similar ionic Rh complex **2b** [$^{31}P\{^1H\}$ NMR, δ (CD_2Cl_2) = 128.4 ppm, $J_{P\text{-}Rh}$ = 173.3 Hz] is obtained in quantitative yield as a yellow solid which is almost insoluble in THF, diethylether and benzene but very soluble in chlorinated solvents such as CH_2Cl_2. The crystal structure of complex **2b** is shown in Figure 1.



Scheme 2. Formation of bimetallic ionic Rh complexes **2a** (R = 2-Py, R' = Ph) and **2b** (R = Me, R' = Ph).

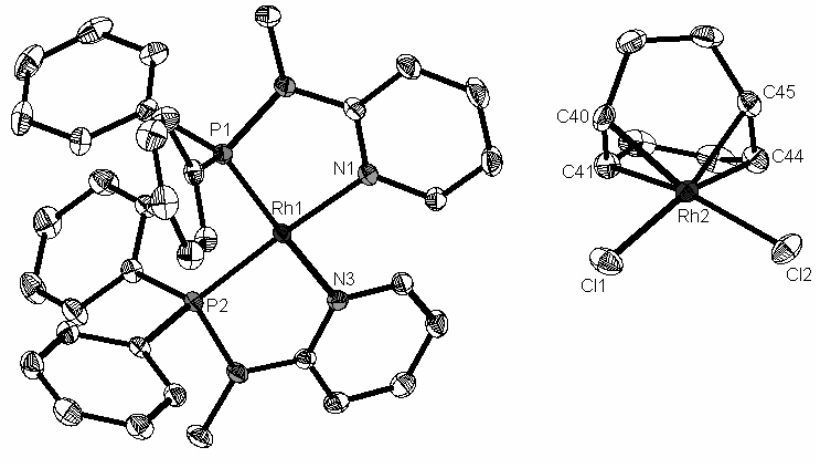


Figure 1. Molecular structure of $[(PyMeNPPh_2)_2Rh][RhCl_2(cod)]$ (**2b**). Hydrogen atoms and solvent molecules omitted for clarity; ellipsoids set to 40% probability level. Selected bond lengths [Å] and angles [°]: N1–Rh1 2.1274(19), N3–Rh1 2.1269(18), P1–Rh1 2.1809(6), P2–Rh1 2.1844(6), Cl1–Rh2 2.3797(7), Cl2–Rh2 2.3706(7), C40–Rh2 2.092(3), C41–Rh2 2.098(3), C45–Rh2 2.100(3), C44–Rh2 2.095(2), P1–Rh1–P2 99.90(2), N1–Rh1–P1 80.62(5), N3–Rh1–P2 81.07(5), N3–Rh1–N1 99.25(7), Cl2–Rh2–Cl1 91.19(3), C40–Rh2–Cl1 88.59(9), C41–Rh2–Cl1 92.29(9), C44–Rh2–Cl2 87.30(8), C45–Rh2–Cl2 92.39(7).

However, the formation of this ionic bimetallic species seems to be highly dependent on the substituents at the phosphorus center, since only P,N-ligands carrying phenyl substituents (regardless of the amine substitution pattern) afford these ionic Rh complexes. When two equivalents of a P,N-ligand with cyclohexyl (**1c**), isopropyl (**1e**) or *tert*-butyl (**1d**) substituents are reacted with $[RhCl(cod)]_2$ in THF no well-defined complexes can be obtained, but merely a mixture of unidentified products as observed by ^{31}P NMR spectroscopy.

In order to elaborate a general method for the preparation of distinct Rh complexes with our P,N-ligands we changed the solvent from THF to CH_2Cl_2 and were very pleased to find that well-defined complexes could be prepared with all ligands, except for **1a** and **1b** bearing phenyl substituents on the phosphorus atom. Dropwise addition of a solution of **1a** or **1b** in CH_2Cl_2 to a solution of $[RhCl(cod)]_2$ always affords a mixture of two compounds as determined by ^{31}P NMR spectroscopy. In the case of **1b**, the minor signal [$^{31}P\{^1H\}$ NMR, δ (CD_2Cl_2) = 128.2 ppm, $J_{P\text{-}Rh}$ = 173.1 Hz] could be attributed to the bimetallic ionic Rh complex **2b**, whereas the major signal [$^{31}P\{^1H\}$ NMR, δ (CD_2Cl_2) = 105.5 ppm, $J_{P\text{-}Rh}$ = 162.9 Hz] belonged to a yet unknown complex **5b**. However, after a few days crystalline material had precipitated from the solution and a mixture of deep orange (major) (**3b**) and pale yellow (minor) (**4b**) crystals were obtained and both were

analyzed by single crystal X-ray diffraction analysis. The molecular structures of **3b** and **4b** are shown in Figures 2 and 3, respectively.

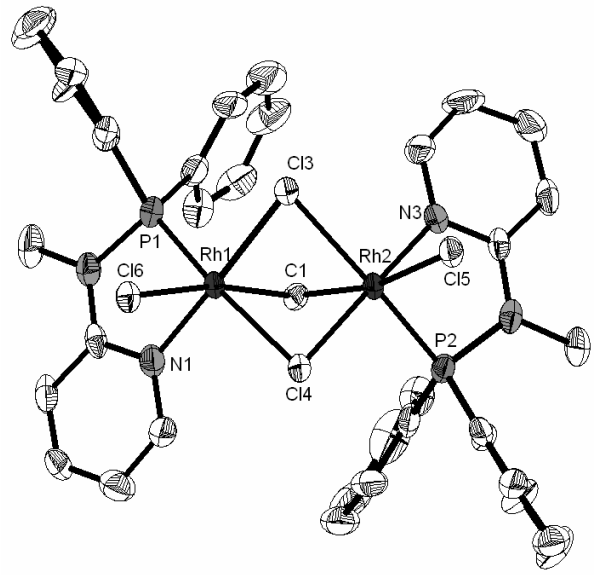


Figure 2. Molecular structure of $[(PyMeNPPh_2RhCl)_2(\mu\text{-}Cl)_2(\mu\text{-}CH_2)]$ (**3b**). Hydrogen atoms and solvent molecules omitted for clarity; ellipsoids set to 40% probability level. Selected bond lengths [Å] and angles [°]: C1–Rh2 2.036(10), C1–Rh1 2.041(9), N1–Rh1 2.017(9), N3–Rh2 2.040(8), P1–Rh1 2.169(3), P2–Rh2 2.174(3), Cl3–Rh1 2.358(3), Cl3–Rh2 2.514(3), Cl4–Rh2 2.378(2), Cl4–Rh1 2.550(3), Cl5–Rh2 2.503(3), Cl6–Rh1 2.531(2), Rh2–C1–Rh1 92.7(4), Cl5–Rh2–Cl3 86.72(8), Cl4–Rh2–Cl3 85.10(8), P2–Rh2–Cl5 98.63(9), N3–Rh2–Cl5 86.7(2), Cl4–Rh2–Cl5 95.55(9), Cl6–Rh1–Cl4 86.92(8), Cl3–Rh1–Cl4 84.72(9), Cl3–Rh1–Cl6 97.88(9), P1–Rh1–Cl6 99.17(9), N1–Rh1–Cl6 85.1(2).

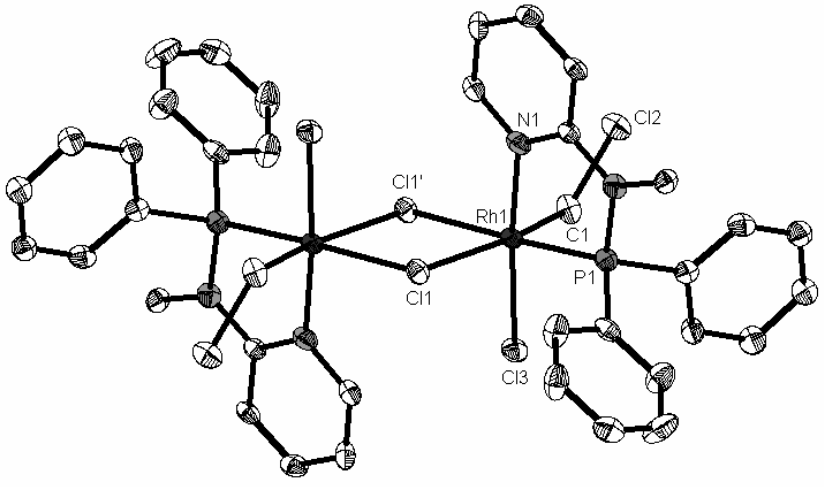


Figure 3. Molecular structure of $[\{PyMeNPPh_2Rh(CH_2Cl)Cl(\mu\text{-}Cl)\}_2]$ (**4b**). Hydrogen-atoms and solvent molecules omitted for clarity; ellipsoids set to 40% probability level. Selected bond lengths [Å] and angles [°]: N1–Rh1 2.031(7), P1–Rh1 2.160(2), Cl1–Rh1 2.511(2), Cl1'–Rh1 2.468(2),

Cl3–Rh1 2.318(2), C1–Rh1 2.010(8), C1–Cl2 1.801(9), P1–Rh1–Cl3 90.28(8), P1–Rh1–Cl1 101.22(8), P1–Rh1–Cl1' 178.19(9), N1–Rh1–P1 83.2(2), C1–Rh1–P1 91.6(3), N1–Rh1–Cl3 173.5(2), N1–Rh1–Cl1 89.0(2), N1–Rh1–Cl1' 95.9(2), C1–Rh1–N1 94.2(3), Cl3–Rh1–Cl1 92.13(7), Cl3–Rh1–Cl1' 90.56(8).

The results of the single crystal analysis showed that the obtained crystals belong to two distinct complexes in which the activation of C–Cl bonds had taken place. The activation of methylene chloride by Rh-complexes affording μ-methylene bridged bimetallic complexes[20-22] or dimeric Rh^{III} complexes with two activated molecules of CH_2Cl_2[19] has been reported before. However, the simultaneous formation of both compounds has to our knowledge not been described previously. In order to gain a better understanding of the reaction and determine the active species involved in the activation of methylene chloride we performed ^{31}P NMR kinetic experiments with Ph_3PO as an internal standard (Figure 4).

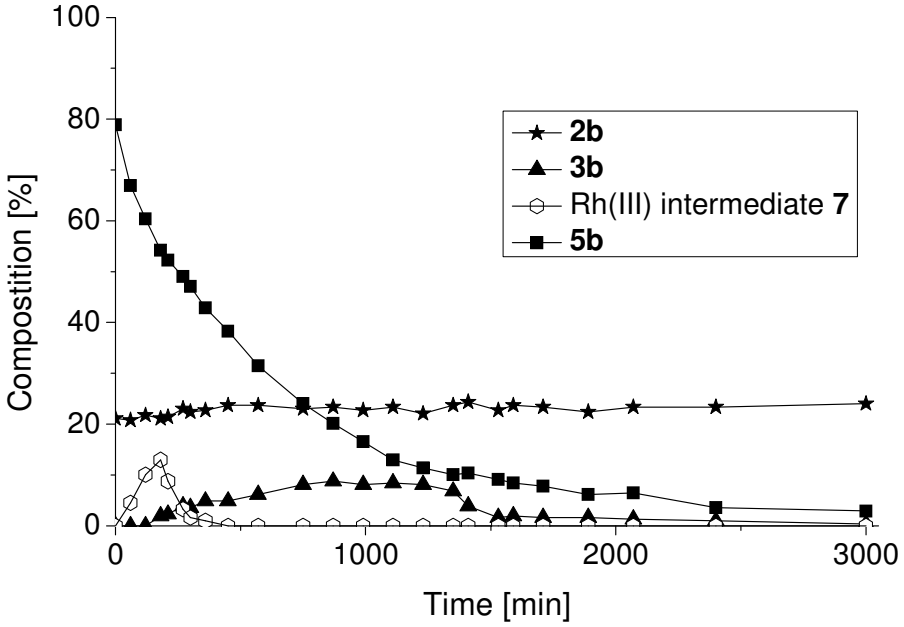
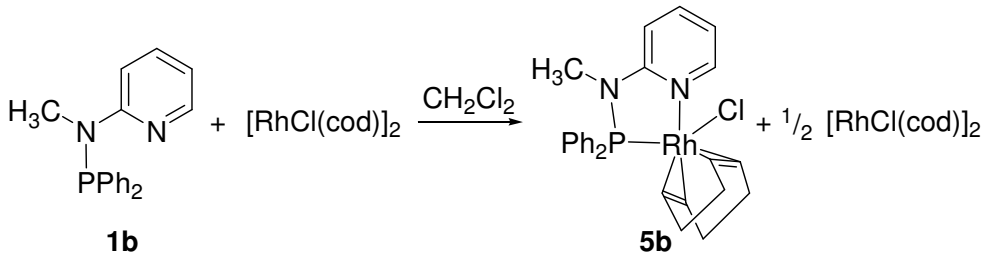


Figure 4: Time-resolved ^{31}P NMR experiment of the CH_2Cl_2 activation.

As determined by these NMR experiments the active species for the activation of methylene chloride is compound **5b**, whereas the bimetallic ionic complex **2b** does not react with CH_2Cl_2 and stays unchanged in the reaction mixture. Therefore, further attempts were made to prepare a pure sample of **5b** and suppress the formation of **2b**. However, the only way to suppress the formation of **2b** was to perform the reaction with an excess of Rh precursor, affording a 1:1 mixture of **5b** and unreacted starting material (Scheme 3). The information obtained from NMR experiments show that the Rh center in **5b** is coordinated by one molecule of ligand **1b** as well as one chelating

molecule of cyclooctadiene, comparable to the already reported equivalent iridium complexes of this type.[26]

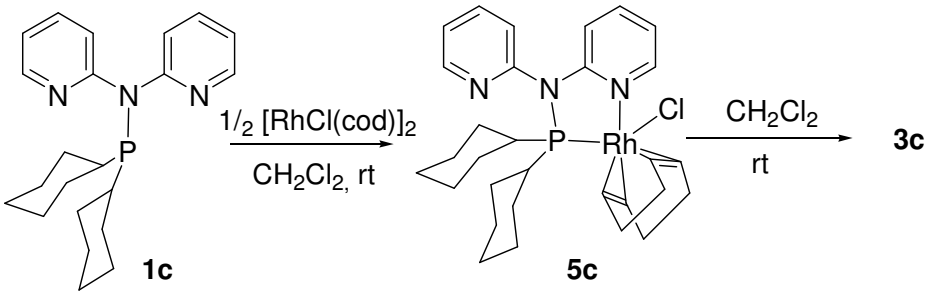


1b **5b**

Scheme 3. Preparation of **5b** with an excess of rhodium precursor.

We therefore assumed that in solution, **5b** must be an equilibrium between a four- or fivefold coordinated Rh^{I} complex which is highly reactive. A similar complex has been reported by Danopoulos et al., but a crystal structure analysis revealed that the pyridine moiety of the ligand does not coordinate to the metal center, reducing the coordination number to four. Hence, we were interested in determining whether the pyridyl part in our P,N-ligands really coordinates to the metal center or not, since this is not obvious for complex **5b**. Use of ligand **1c** with two pyridyl groups in the molecule should, in the case of a pyridyl coordination to the transition metal center, lead to inequivalent and clearly distinguishable pyridyl rings in a ^{1}H NMR spectrum.

Interestingly, in the case of the cyclohexyl ligand **1c**, when reacted with $[RhCl(cod)]_2$ in CH_2Cl_2, no byproducts similar to **2b** were formed and a sharp signal [$^{31}P\{^{1}H\}$ NMR, δ (CD_2Cl_2) = 125.8 ppm, $J_{P\text{-}Rh}$ = 157.6 Hz] similar to **5b** was observed. The obtained complex **5c** was isolated in quantitative yields and extensively characterized by NMR spectroscopy and elemental analysis, which revealed a most likely fivefold-coordinated structure with a coordinated P,N-ligand as well as one coordinated cyclooctadiene unit and a chlorine atom in the molecule (Scheme 4). The ^{1}H NMR data shows the tight coordination of one pyridyl unit to the metal center (an exchange of the pyridyl rings is not observed) as well as an analogy of the olefinic C–H_{cod} signals in **5c** to its corresponding fivefold-coordinated Ir complex.[26] Both complexes exhibit only one broad signal for all four olefinic C–H_{cod} protons at δ = 4.96 and 3.90 ppm, respectively. However, all attempts to prepare single crystals suitable for X-ray analysis were unsuccessful since **5c** could only be prepared in methylene chloride, which also reacts with the latter, leading to the μ-methylene bridged complex **3c** (Figure 5).



Scheme 4. Preparation of **5c** and reaction with CH_2Cl_2 affording μ-methylene complex **3c**.

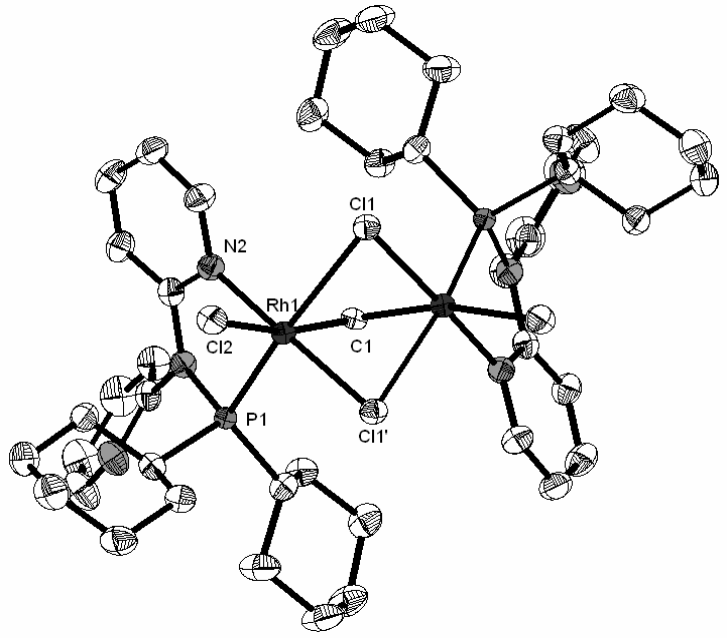


Figure 5. Molecular structure of $[(Py_2NPCy_2RhCl)_2(\mu\text{-}Cl)_2(\mu\text{-}CH_2]$ (**3c**). Hydrogen atoms and solvent molecules omitted for clarity; ellipsoids set to 40% probability level. Selected bond lengths [Å] and angles [°]: N2–Rh1 2.005(3), P1–Rh1 2.1853(11), C1–Rh1 2.023(4), Cl1–Rh1 2.6253(10), Cl1'–Rh1 2.3617(9), Cl2–Rh1 2.5143(10), N2–Rh1–P1 83.28(10), C1–Rh1–P1 90.54(9), N2–Rh1–Cl2 89.73(10), N2–Rh1–C1 89.52(13), P1–Rh1–Cl2 104.77(4), Cl2–Rh1–Cl1 85.78(3), Cl1'–Rh1–Cl2 95.41(3), Cl1–Rh1–Cl1' 85.05(4).

Moreover, **5c** is much less reactive for the activation of C–Cl bonds than complex **5b** as determined by further time-resolved NMR experiments. In order to obtain a full conversion of **5c** into **3c** it takes about a month (Figure 6), whereas complex **5b** completely reacts with CH_2Cl_2 in less than 3 days.

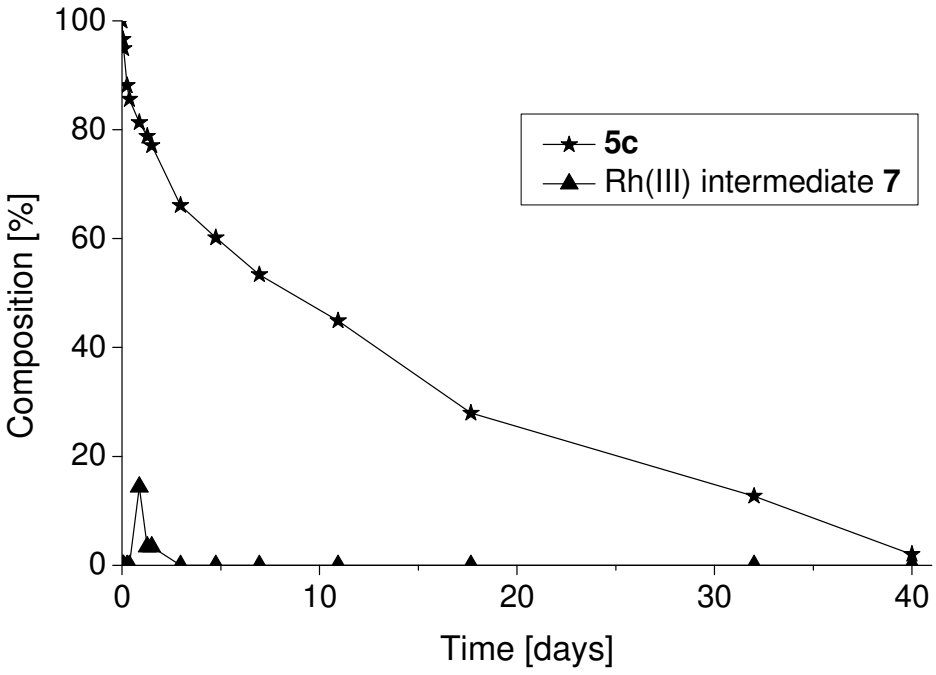
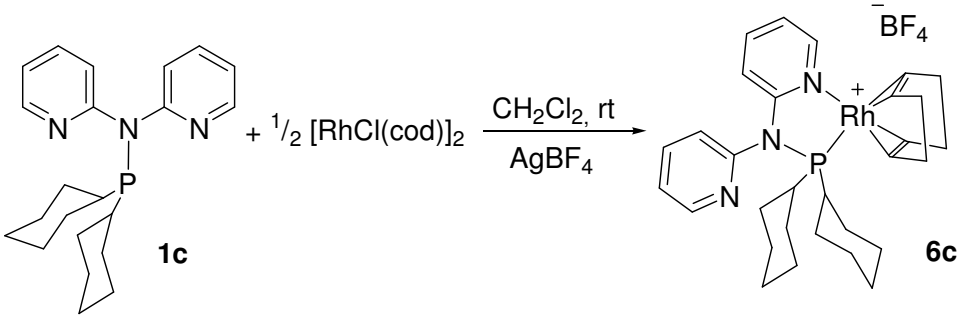


Figure 6: ^{31}P NMR experiment of the CH_2Cl_2 activation of **5c**.

Since we were unable to crystallize the active but unstable monomer, thought to be the fivefold-coordinated Rh complex **5c**, we performed an indirect experiment to determine its structural nature. We prepared **5c** by addition of ligand **1c** to a solution of $[RhCl(cod)]_2$ in CH_2Cl_2 and subsequently treated the resulting complex with $AgBF_4$ in order to remove the chlorine atom and obtain the stable fourfold-coordinated ionic complex **6c** (Scheme 5) which could easily be crystallized and characterized by single crystal X-ray analysis (Figure 7). Complex **6c** is stable in CH_2Cl_2 and does not lead to an activation of the solvent. In the ^{1}H NMR spectrum **6c** exhibits two separate sets of signals for the olefinic C–H_{cod} protons at δ = 5.55 and 4.38 ppm whereas **5c** affords only one broad signal for all these protons at δ = 4.96 ppm. Even at a temperature of –20°C this broad signal does not resolve into two separate signal sets as observed for **6c**, which brings us to the conclusion that for the complexes of type **5** in solution the chlorine atom is probably coordinating to the metal center and does not act as a dissociated counterion. Nevertheless, an equilibrium of five-coordinated **5c** and a highly reactive 3- or 4-coordinated intermediate that results from temporary de-coordination of either the pyridyl or the cyclooctadiene unit from the metal center is possible, though we have no direct evidence for this.



Scheme 5. In-situ preparation of **5c** and subsequent treatment with 1 equiv of $AgBF_4$ affording stable ionic complex **6c**.

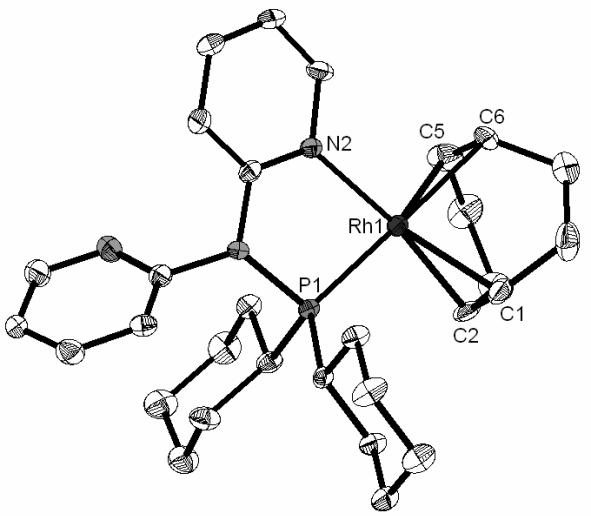
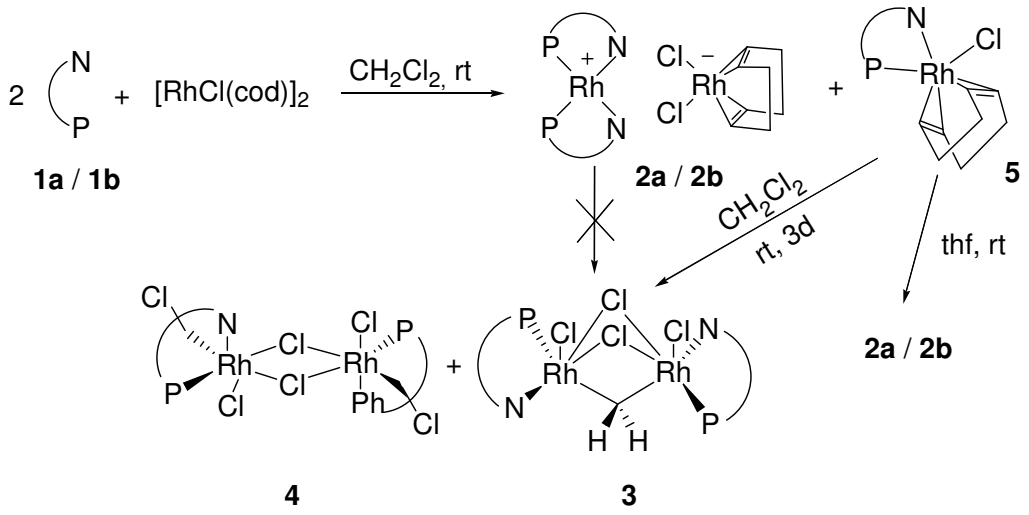


Figure 7. Molecular structure of $[Py_2NPCy_2)Rh(cod)]BF_4$ (**6c**). Hydrogen atoms, solvent molecules and BF_4-anion omitted for clarity; ellipsoids set to 40% probability level. Selected bond lengths [Å] and angles [°]: P1–Rh1 2.2566(10), N2–Rh1 2.108(3), C1–C2 1.386(6), C2–Rh1 2.162(4), C5–C6 1.339(9), C5–Rh1 2.201(4), C6–Rh1 2.265(4), N2–Rh1–P1 81.58(9), C1–Rh1–C2 37.45(17), C5–Rh1–C6 34.8(2), P1–Rh1–C6 177.10(15), C1–Rh1–P1 100.73(12), C2–Rh1–P1 93.28(11), C5–Rh1–P1 147.56(18), N2–Rh1–P1 81.58(9), N2–Rh1–C5 95.62(16), N2–Rh1–C1 157.54(16), N2–Rh1–C2 164.83(15), N2–Rh1–C6 96.86(15).

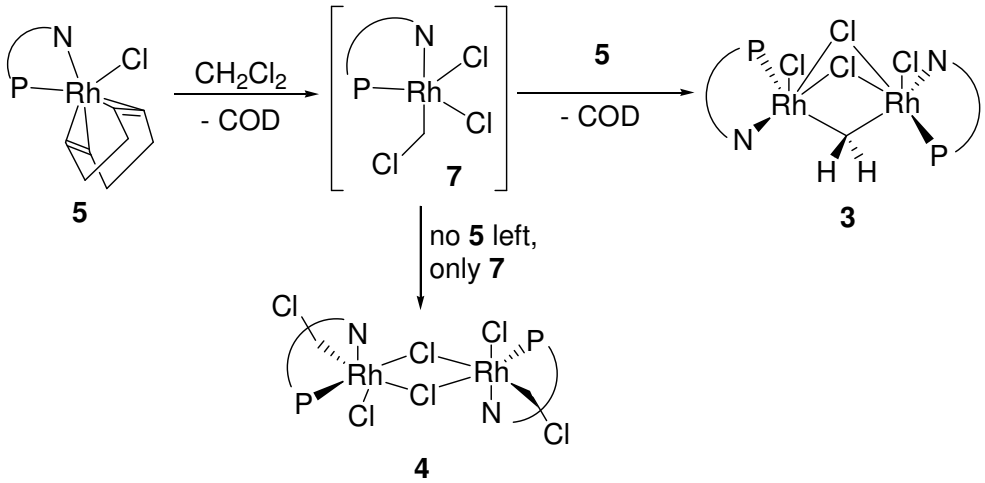
Arising from the high activity of complex **5b** towards the oxidative addition of CH_2Cl_2 we focussed on this complex for further experiments. As mentioned above, the reaction of the P,N-ligands with $[RhCl(cod)]_2$ is highly dependent on the solvent. Therefore, we wanted to understand the formation of the bimetallic ionic complex **2b** and determine whether it results from the monomeric complex **5b** as well. An aliquot of isolated **5b** (containing 85% **5b**) was redissolved in a small quantity of THF and a yellow precipitate rapidly developed, which was washed twice with hexane, dried in vacuum and analyzed by NMR spectroscopy. The ^{31}P NMR signal δ = 128.4 ppm ($J_{P\text{-}Rh}$ = 173.3 Hz)

corresponds exactly to complex **2b**. It seems that in polar donor solvents such as THF a quick rearrangement of the chlorine atom as well as a redistribution of the ligands occur, affording an equilibrium of different Rh species, which in the case of phenyl-substituted ligands **1a** and **1b,** is shifted towards the formation of the sparingly soluble (in THF) complexes **2a** and **2b,** respectively (Scheme 6). The latter are the thermodynamically stable species that precipitate from the solution and can only be redissolved in methylene chloride. However, **2a** and **2b** do not activate CH_2Cl_2, even upon heating of the reaction mixture and long reaction times (2 months).



Scheme 6. Preparation and reactivity of complexes **2a/b** and **5**.

Having determined the most likely fivefold-coordinated complexes of type **5** to be the active species for the activation of C–Cl bonds, we were furthermore interested to find out how both CH_2Cl_2 activation products **3** and **4** can form simultaneously. Scheme 7 depicts a possible reaction pathway that could be an explanation for the formation of both compounds based on our experimental findings. The NMR experiments in Figure 4 and Figure 6 exhibit the rapid formation of an uncharacterized intermediate **7** that might instantly react with a further equivalent of **5** to afford the μ-methylene bridged Rh complex **3**. Since the latter is almost insoluble it rapidly crystallizes from the solution as bright orange crystals. This reaction takes place as long as the concentration of compound **5** is sufficiently high to enable a quick reaction with intermediate **7**. At the end of the reaction when most of **5** has been consumed, the reactive and unstable Rh^{III}-intermediate **7** dimerizes in order to obtain a stable octahedral coordination sphere, affording complex **4**. The latter is also poorly soluble in CH_2Cl_2 and crystallizes from the solution as a pale yellow solid.



Scheme 7. Suggested mechanism for the simultaneous formation of **3** and **4**.

4.3. Conclusions

In summary, we have synthesized new rhodium complexes bearing P,N-ligands that can activate up to two C–Cl bonds of methylene chloride and form μ-methylene bridged Rh^{III} complexes as well as dimeric Rh^{III} complexes with terminal chloromethyl groups. This is the first example of the simultaneous formation of both CH_2Cl_2 activation products. Furthermore, detailed NMR studies were carried out to determine the active species involved in the oxidative addition of the solvent and to gain a better understanding of its possible mechanistic pathway.

4.4. Experimental Section

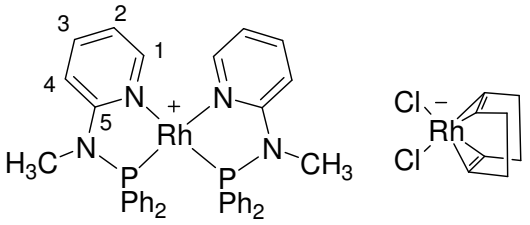
All reactions and manipulations involving air-sensitive compounds were performed under dry argon, using standard Schlenk and glovebox techniques. Non-halogenated solvents were distilled over sodium benzophenone ketyl and halogenated solvents over P_2O_5. Deuterated solvents were obtained from Cambridge Isotope Laboratories and were degassed, dried using molecular sieves and distilled prior to use. All chemicals were purchased from commercial sources in purities > 97% and used without further purification, unless stated otherwise in the synthetic procedure. NMR spectra were obtained using a Varian INOVA 300 or a Varian INOVA 400 spectrometer at 298 K unless stated otherwise. Chemical shifts are reported in ppm relative to the deuterated solvent. Elemental analyses were performed on a Vario elementar EL *III*. X-ray crystal structure analysis of all compounds was performed by using a STOE-IPDS II equipped with an Oxford Cryostream low-temperature unit. Structure solution and refinement were accomplished using SIR97,[28] SHELXL-97[29] and WinGX.[30] CCDC 700638 (compound **3c**), 700639 (compound **3b**), 700640 (compound **2b**), 700641 (compound **4b**) and 700642 (compound **6c**), contain the supplementary

crystallographic data for this publication. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: + 44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

All P,N-ligands were prepared according to the literature procedure.[26]

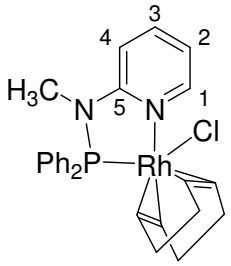
Complex Synthesis

Synthesis of [(PyMeNPPh$_2$)$_2$Rh][RhCl$_2$(cod)] (2b):



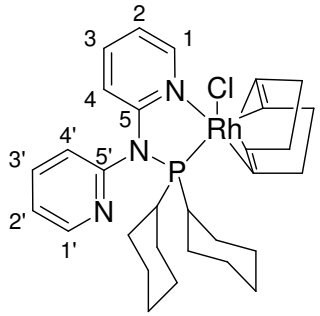
[RhCl(cod)]$_2$ (0.098 g, 0.20 mmol) was dissolved in THF (10 mL) and a solution of PyMeNPPh$_2$ (**1b**) (0.117 g, 0.40 mmol) in THF (5 mL) was slowly added at rt under vigorous stirring. Rapidly a yellow solid precipitated and the suspension was stirred overnight. Then, the solvent was decanted, the solid washed twice with hexane (15 mL) and dried in vacuo, affording **2b** as a bright yellow solid (0.336 g, 87%). – ^{1}H NMR (400 MHz, CD_2Cl_2, 296K): δ = 8.30 (d, *J* = 5.5 Hz, 2H, H_1), 7.89 (t, *J* = 7.9 Hz, 2H, H_3), 7.36-7.26 (m, 12H, H_{Ph}), 7.19-7.10 (m, 8H, H_{Ph}), 7.06 (t, *J* = 5.9 Hz, 2H, H_2), 6.84 (d, *J* = 8.4 Hz, 2H, H_4), 4.10 (m, 4H, H_{CHcod}), 2.82 (t, *J* = 2.2 Hz, 6H, H_{CH_3}), 2.39-2.28 (m, 4H, H_{CH_2cod}), 1.65-1.54 (m, 4H, H_{CH_2cod}); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 161.5 (ddd, *J*= 7.1, 7.1, 1.6 Hz, C_5), 149.9 (s, C_1), 140.6 (s, C_3), 132.9 (t, *J*= 6.9 Hz, $C_{o, Ph}$), 131.6 (s, $C_{p, Ph}$), 130.5 (ddd, *J*= 26.7, 22.9, 2.6 Hz, $C_{q, Ph}$), 129.0 (t, *J*= 5.5 Hz, $C_{m, Ph}$), 117.0 (s, C_2), 110.0 (t, *J*= 4.2 Hz, C_4), 76.8 (br, C_{CHcod}) 33.9 (t, *J*= 2.5 Hz, C_{CH_3}), 31.6 (s, C_{CH_2cod}); ^{31}P NMR (161 MHz, CD_2Cl_2): δ = 128.3 (d, *J*= 173.4 Hz); elemental analysis: calcd (%) for $C_{44}H_{42}Cl_2N_4P_2Rh_2$: C 54.74, H 4.38, N 5.80; found: C 54.98, H 4.77, N 5.79.

Synthesis of [PyMeNPPh$_2$RhCl(cod)] (5b):



To a solution of [RhCl(cod)]$_2$ (0.148 g, 0.30 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of PyMeNPPh$_2$ (**1b**) (0.088g, 0.30 mmol) in CH_2Cl_2 (5 mL) under stirring. The reaction mixture was stirred for 15 min at room temperature and the solvent removed in vacuo. The residue was washed twice with hexane (15 mL) and dried in vacuo, affording a 1:1 mixture of the title compound and residual [RhCl(cod)]$_2$ in quantitative yields - ^{1}H NMR (400 MHz, CD_2Cl_2, 296K): δ = 7.97 (t, *J*= 7.5 Hz, 1H, H_3), 7.80 (d, *J*= 5.9 Hz, 1H, H_1), 7.72-7.64 (m, 6H, H_{Ph}), 7.62-7.59 (m, 4H, H_{Ph}), 7.09 (t, *J*= 6.2 Hz, 1H, H_2), 7.06 (d, *J*= 8.8 Hz, 1H, H_4), 4.74 (s_br, 4H, H_{CHcod}), 4.08 (s_br, 4H, $H_{CH[RhCl(cod)]_2}$), 2.94 (d, *J*= 5.1 Hz, 3H, H_{CH_3}), 2.48-2.37 (m, 4H, $H_{CH_2[RhCl(cod)]_2}$), 2.37-2.26 (m, 8H, H_{CH_2cod}), 1.59 (d, *J*= 7.7 Hz, 4H, $H_{CH_2[RhCl(cod)]_2}$); ^{13}C NMR (100 MHz, CD_2Cl_2, 296K): δ = 162.6 (d, *J*= 18.0 Hz, C_5), 148.9 (s, C_1), 142.6 (s, C_3), 133.1 (d, *J*= 1.9 Hz, $C_{p,\,Ph}$), 132.9 (d, *J*= 13.5 Hz, $C_{o,\,Ph}$), 130.1 (d, *J*= 10.9, $C_{m,\,Ph}$), 128.1 (dd, *J*= 51.5, 1.9 Hz, $C_{q,\,Ph}$), 117.8 (s, C_2), 111.4 (d, *J*= 8.1 Hz, C_4), 77.1 (br, C_{CHcod} + $C_{CH[RhCl(cod)]_2}$), 34.4 (d, *J*= 5.2 Hz, C_{CH_3}), 31.5 (s, C_{CH_2cod}), 30.4 (s, $C_{CH_2[RhCl(cod)]_2}$); ^{31}P NMR (162 MHz, CD_2Cl_2, 296K): δ = 106.0 (d, *J*= 166.8 Hz); no elemental analysis due to mixture of compounds.

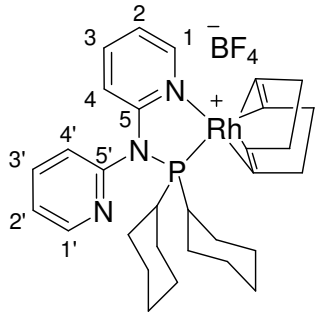
Synthesis of [Py$_2$NPCy$_2$Rh(cod)Cl] (5c):



To a solution of [RhCl(cod)]$_2$ (0.098 g, 0.20 mmol) in CH_2Cl_2 (10 mL) was slowly added a solution of Py$_2$NPCy$_2$ (**1c**) (0.147 g, 0.40 mmol) in CH_2Cl_2 (2 mL). The solution was stirred for 10 min at rt and subsequently the solvent was removed in vacuo. The residue was washed with hexane (2 x 10 mL) and dried in vacuo, affording the title compound as an orange solid (0.230 g, 92 %). – ^{1}H

NMR (400 MHz, CD_2Cl_2, 296K): δ = 8.64 (s, 1H, H_1), 8.01 (t, *J*= 6.6 Hz, 1H, H_3), 7.74 (d, *J*= 4.0 Hz, 1H, $H_{1'}$), 7.66 (t, *J*= 6.3 Hz, 1H, $H_{3'}$), 7.51 (t, *J*= 4.8 Hz, 1H, H_2), 7.27 (d, *J*= 7.3 Hz, 1H, H_4), 7.03 (t, *J*= 5.9 Hz, 1H, $H_{2'}$), 6.33 (d, *J*= 8.1 Hz, 1H, $H_{4'}$), 4.96 (br, 4H, H_{CHcod}), 2.54 (br, 5H, H_{CH_Cy} + H_{CH_2cod}), 2.43-2.30 (m, 5H, H_{CH_Cy} + H_{CH_2cod}), 2.12-1.94 (m, 2H, $H_{CH_2\_Cy}$), 1.90-1.81 (m, 3H, $H_{CH_2\_Cy}$), 1.78-1.56 (m, 5H, $H_{CH_2\_Cy}$), 1.36-0.79 (m, 10H, $H_{CH_2\_Cy}$); ^{13}C NMR (100 MHz, CD_2Cl_2, 296K): δ = 164.2 (d, *J*= 14.5 Hz, C_5), 152.7 (s, $C_{5'}$), 151.1 (s, C_1), 148.2 (s, $C_{1'}$), 141.7 (s, $C_{3'}$), 140.6 (s, C_3), 125.0 (s, C_2), 124.2 (s, C_4), 118.2 (s, $C_{2'}$), 112.3 (d, *J*= 4.5 Hz, $C_{4'}$), 110.0 (br, $C_{CHcod/trans-P}$), 79.8 (br, $C_{CHcod\ /cis-P}$), 40.3 (m, C_{CH_Cy}), 37.0 (m, C_{CH_Cy}), 31.5 (m, C_{CH_2cod}), 31.3-29.5 (m, C_{CH_2cod}), 28.9-27.5 (m, $C_{CH_2\_Cy}$), 27.3-26.7 (m, $C_{CH_2\_Cy}$), 26.3 (d, *J*= 0.7 Hz, $C_{CH_2\_Cy}$); ^{31}P NMR (162 MHz, CD_2Cl_2, 296K): δ = 125.8 (d, *J*= 157.2 Hz); elemental analysis: calcd (%) for $C_{30}H_{42}ClN_3PRh \times 0.5\ CH_2Cl_2$: C 55.80, H 6.60, N 6.40; found: C 55.70, H 6.50, N 6.47.

Synthesis of [$Py_2NPCy_2Rh(cod)$] BF_4 (6c):



To a solution of $[RhCl(cod)]_2$ (0.148 g, 0.30 mmol) in CH_2Cl_2 (10 mL) was slowly added a solution of Py_2NPCy_2 (**1c**) (0.220 g, 0.60 mmol) in CH_2Cl_2 (4 mL). The solution was stirred for 10 min at rt and subsequently a solution of $AgBF_4$ (0.123 g, 0.63 mmol) in acetone (1 mL) was added. After stirring for 30 min, the white precipitate (AgCl) was filtered over a glass frit filled with Celite (2 cm). The frit was washed with CH_2Cl_2 (2 x 10 mL). The solvent was removed in vacuo, the yellow solid washed with hexane (1 x 20 mL) and dried in vacuo (0.340 g, 85%). – ^{1}H NMR (400 MHz, CD_2Cl_2, 296K): δ = 8.67 (d, *J*= 2.6 Hz, 1H, H_1), 7.99 (t, *J*= 7.3 Hz, 1H, H_3), 7.71-7.69 (m, 2H, $H_{1'}$ + $H_{3'}$), 7.50 (t, *J*= 5.1 Hz, 1H, H_2), 7.26 (d, *J*= 7.7 Hz, 1H, H_4), 6.97 (t, *J*= 6.0 Hz, 1H, $H_{2'}$), 6.31 (d, *J*= 8.8 Hz, 1H, $H_{4'}$), 5.55 (s_br, 2H, H_{CHcod}), 4.38 (s_br, 2H, H_{CHcod}), 2.88-2.40 (m, 7H, H_{CH_Cy} + H_{CH_2cod}), 2.38-2.24 (m, 3H, H_{CH_2cod}), 2.19-0.60 (m, 20H, $H_{CH_2\_Cy}$); ^{13}C NMR (100 MHz, CD_2Cl_2, 296K): δ = 164.6 (d, *J*= 15.5 Hz, C_5), 152.8 (s, $C_{5'}$), 151.3 (s, C_1), 148.0 (s, $C_{1'}$), 141.8 (s, $C_{3'}$), 140.6 (s, C_3), 125.2 (s, C_2), 124.4 (s, C_4), 118.1 (s, $C_{2'}$), 112.6 (s, $C_{4'}$), 108.3-107.6 (m, C_{CHcod}), 80.8-78.7 (m, C_{CHcod}), 78.3-76.2 (m, C_{CHcod}), 41.2-39.3 (m, C_{CH_Cy}), 37.8-36.1 (m, C_{CH_Cy}), 33.6-

32.0 (m, C_{CH_2cod}), 30.2 (s, C_{CH_2cod}), 29.3-27.8 (m, C_{CH_2cod} + $C_{CH_2\_Cy}$), 27.5-27.0 (m, $C_{CH_2\_Cy}$), 26.5 (m, $C_{CH_2\_Cy}$); ^{31}P NMR (162 MHz, CD_2Cl_2, 296K): δ = 126.0 (d, *J*= 157.7 Hz); ^{19}F NMR (376 MHz, CD_2Cl_2, 296K): δ = -153.7; elemental analysis: calcd (%) for $C_{30}H_{42}N_3PRhBF_4$: C 54.15, H 6.36, N 6.32; found: C 53.60, H 6.57, N 5.94.

General procedure for the activation of CH_2Cl_2 with P,N-rhodium complexes

$[RhCl(cod)]_2$ (1.0 equiv) was dissolved in 0.4 mL CH_2Cl_2 and a solution of P,N-ligand (2.0 equiv) in 0.2 mL CH_2Cl_2 was added dropwise at rt under stirring. The orange solution was left for several days until crystallization was complete. The supernatant solution was decanted, the crystalline material washed twice with CH_2Cl_2 and dried in vacuo.

Due to the poor solubility of the CH_2Cl_2 activation compounds **3b**, **4b** and **3c** in common solvents no NMR-characterization could be obtained. Since the CH_2Cl_2 activation with **5b** is too fast no pure sample of the μ-methylene complex **3b** as well as the dimeric chloromethyl complex **4b** could be isolated for elemental analysis. However, the reaction with ligand **1c** is slow enough to be able to obtain a pure sample of μ-methylene compound **5c** for elemental analysis by aborting the reaction after only a few days and washing the crystalline material with CH_2Cl_2. Elemental analysis: calcd (%) for $C_{45}H_{62}Cl_4N_6P_2Rh_2 \times 1\ CH_2Cl_2$: C 46.76, H 5.46, N 7.11; found: C 46.43, H 5.39, N 7.08.

Table 1. Crystal parameters for all analyzed compounds.

Compound	**2b**	**3b**	**4b**	**3c**	**6c**
Formula	$C_{44}H_{46}Cl_2N_4P_2Rh_2$ × 0.5 THF	$C_{37}H_{36}Cl_4N_4P_2Rh_2$ × 3 CH_2Cl_2	$C_{38}H_{38}Cl_4N_4P_2Rh_2$	$C_{45}H_{62}Cl_4N_6P_2Rh_2$ × 3 CH_2Cl_2	$C_{30}H_{42}BF_4N_3PRh$
Crystal system	triclinic	triclinic	triclinic	monoclinic	orthorhombic
Space group	P-1	P-1	P-1	C2/c	Pna2(1)
a [Å]	9.5610(6)	10.8080(12)	9.1840(11)	18.4140(6)	18.5830(10)
b [Å]	14.2130(8)	11.1800(11)	10.8320(12)	11.3250(6)	10.6640(5)
c [Å]	16.0760(10)	20.693(2)	12.4680(15)	27.5170(14)	14.6970(8)
α [°]	77.014(5)	100.962(8)	96.882(9)	90.00	90.00
β [°]	83.227(5)	99.008(8)	100.357(9)	96.664(4)	90.00
γ [°]	87.635(5)	92.987(8)	101.756(9)	90.00	90.00
V [Å^3]	2113.6(2)	2415.8(4)	1178.7(2)	5699.6(5)	2912.5(3)
Crystal size [mm]	0.68×0.68×0.61	0.29×0.13×0.12	0.26×0.17×0.11	0.34×0.15×0.11	0.39×0.18×0.16
$\rho_{calcd.}$ [g cm^{-3}]	1.577	1.651	1.453	1.584	1.517
μ [mm^{-1}] (Mo-K$_\alpha$)	1.023	1.337	1.137	1.143	0.693
T [K]	173(2)	173(2)	133(2)	191(2)	133(2)
θ range [°]	1.31–26.11	1.86–25.93	1.69–26.08	1.49–26.07	1.39–26.14
No. of unique refl.	7979	9095	4435	5377	5497
No. of obsd. refl. [$I > 2\sigma(I)$]	7537	4622	3514	4360	4889
No. of parameters	534	525	236	422	361
wR_2 (all data)	0.0693	0.1788	0.1777	0.1019	0.0818
R value [$I > 2\sigma(I)$]	0.0264	0.0673	0.0649	0.0427	0.0346

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4.5. References

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5. An Efficient Method for the Selective Iridium-Catalyzed Monoalkylation of (Hetero)Aromatic Amines with Primary Alcohols

Benoît Blank[a], Martyna Madalska[a], and Rhett Kempe[a]*

[a] Lehrstuhl für Anorganische Chemie II, Universität Bayreuth, 95440 Bayreuth, Germany.
Fax: (+49)-921-55-2157; e-mail: kempe@uni-bayreuth.de

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Abstract: An efficient multi-gram scale synthesis protocol of a variety of P,N-ligands is described. The synthesis is achieved in a two step reaction. First, the amine is deprotonated and subsequently the chlorophosphine is added to yield the corresponding P,N-ligand. Deprotonation of the amine is normally achieved with *n*-BuLi at low temperature, but for the preparation of ligands with a 2,2'-dipyridylamino backbone and phosphines with a high steric demand KH has to be employed in combination with reaction temperatures of 110°C for the salt metathesis step. The reaction of two equivalents of a selected P,N-ligand with one equivalent $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene) affords P,N-ligand coorddinated iridium complexes in quantitative yield. X-Ray single-crystal structure analysis of one of these complexes reveals a monomeric five-coordinated structure in the solid state. The iridium complexes were used to form catalysts for the *N*-alkylation of aromatic amines with alcohols. The catalyst system was optimized by studying 8 different P,N-ligands, 9 different solvents and 14 different bases. Systematic variation of the substrate to base and the amine to alcohol ratios as well as the catalyst loading led to optimized catalytic reaction conditions. The substrate scope of the developed catalytic protocol was shown by synthesizing 20 different amines of which 12 could be obtained in isolated yields higher than 90 %. A new efficient catalyst system for the selective monoalkylation of primary aromatic and heteroaromatic amines with primary aromatic, heteroaromatic as well as aliphatic alcohols has been established. The reaction proceeds with rather moderate catalyst loadings.

5.1. Introduction

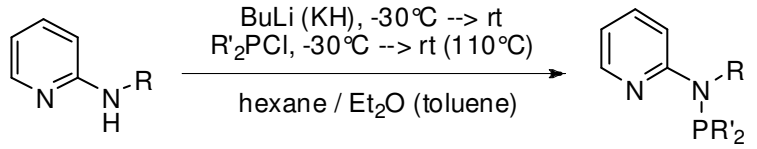
Nitrogen-containing molecules and especially amines are intermediates and products of enormous importance for chemical and life science applications. In the last decade, catalytic amine syntheses such as, for instance, Pd-catalyzed aminations of aryl halides,[1] hydroaminations[2] and hydroaminomethylations[3] have received particular attention and many new applications have emerged due to the broadening of the scope of these methods. A well-known method for the preparation of *N*-alkyl-amines is the reaction of amines with alkyl halides.[4] Such reactions are difficult to run selectively due to increasing nucleophilicity/reactivity of the amine after the first alkylation step. The alkylation of primary amines with alcohols is an attractive and promising alternative since the starting materials are inexpensive and readily available and the selectivity of the reaction can be controlled with the catalyst. The first homogeneous catalysts for this reaction were introduced by Grigg et al.[5] and Watanabe et al.[6] in 1981. Most of them required very high reaction temperatures and the scope of applicable substrates was rather limited. To the present day, catalytic systems employing ruthenium,[7] rhodium,[8] platinum[9] and iridium,[8],[10],[11] complexes have been reported for the alkylation of primary amines with alcohols. In the last few years, research has mainly been focussed on ruthenium-catalyzed *N*-alkylation reactions and has helped to extend the applicability of this reaction towards a broad range of substrates.[12],[13],[14] However, the selective alkylation of aromatic amines with primary and secondary alcohols remains challenging. In this regard, Fujita et al. reported an interesting system for the *N*-alkylation of amines with alcohols catalyzed by a Cp*Ir complex (Cp* = pentamethylcyclopentadienyl anion)[11],[15] and inspired us to develop an easily accessible iridium-based catalyst system. Herein, we report on novel P,N-ligand coorddinated iridium complexes and the use of these compounds as catalysts for the *N*-alkylation of (hetero)aromatic amines with primary alcohols.

5.2. Results and Discussion

Ligand/Catalyst Synthesis

P-Functionalized aminopyridines were reported to be effective ligands for a variety of transition-metal catalyzed coupling reactions.[16],[17] These P,N-ligands are bidentate, form strongly bonded five-membered chelates and are modular due to extensive variations of the substituents at the amino as well as the phosphorus centers. These ligands were so far essentially prepared in-situ from the corresponding amine and chlorophosphine precursors for combinatorial screenings.[16] Thus, within this study we first developed efficient multi-gram scale synthesis protocols for these ligands. The synthesis is achieved in a two step reaction. First, the amine is deprotonated and subsequently the

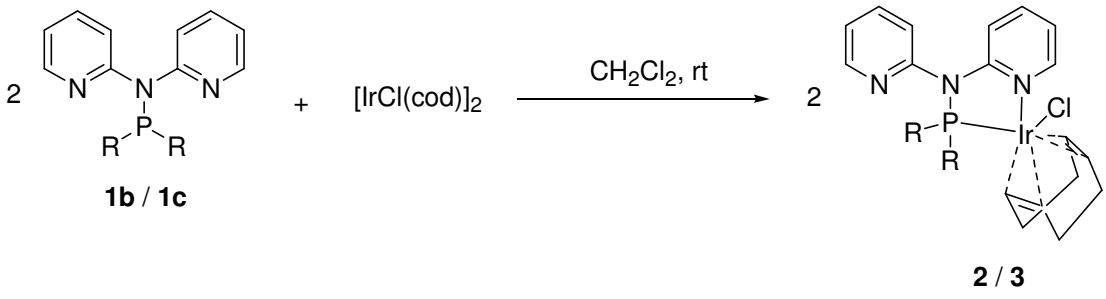
chlorophosphine is added to yield the corresponding P,N-ligand. Deprotonation of the amine is normally achieved with *n*-BuLi at low temperature, but for the preparation of ligands with a 2,2'-dipyridylamino backbone and phosphines with a high steric demand, for instance, *tert*-butyl substituents KH has to be employed in combination with reaction temperatures of 110°C to obtain a full conversion. The reaction and abbreviation scheme of the P,N-ligands synthesized and used in this study are presented in Scheme 1.



R=2-pyridyl, R'=Ph, Py_2NPPh_2 **(1a)**
R=2-pyridyl, R'=Cy, Py_2NPCy_2 **(1b)**
R=2-pyridyl, R'=*i*-Pr, Py_2NPiPr_2 **(1c)**
R=2-pyridyl, R'=*t*-Bu, Py_2NPtBu_2 **(1d)**
R=Me, R'=Ph, $PyMeNPPh_2$ **(1e)**
R=Me, R'=Cy, $PyMeNPCy_2$ **(1f)**
R=Me, R'=*i*-Pr, $PyMeNPiPr_2$ **(1g)**
R=Me, R'=*t*-Bu, $PyMeNPtBu_2$ **(1h)**

Scheme 1. Synthesis of the used P,N-ligands.

The reaction of two equivalents of a selected P,N-ligand (**1b** and **1c**) with one equivalent $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene) in CH_2Cl_2 affords P,N-ligand coordinated iridium complexes in quantitative yields (Scheme 2).



1b / **1c**

2 / **3**

Scheme 2. Synthesis of **2** (R = cyclohexyl) and **3** (R = isopropyl).

An X-ray single-crystal structure analysis of **2** revealed a monomeric five-coordinated structure in the solid state. Selected bond lengths and angles as well as the molecular structure of **2** are given in Figure 1.

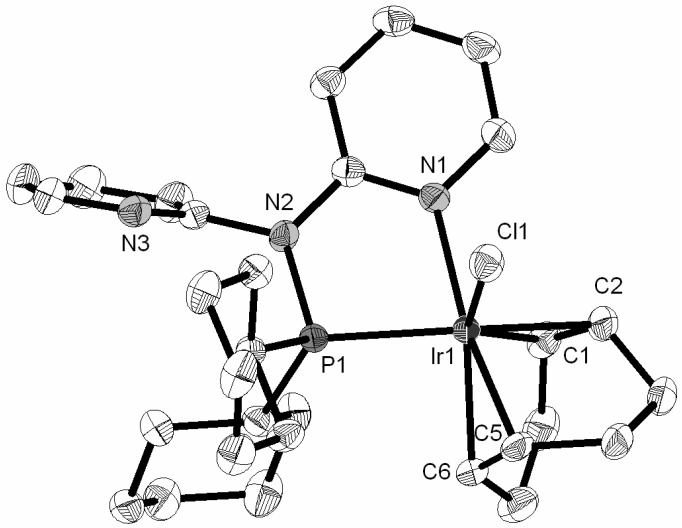
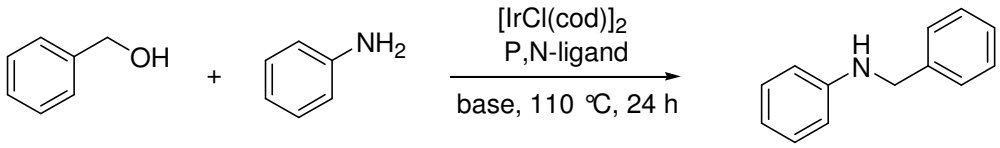


Figure 1. Molecular structure of monomeric [Py_2NPCy_2)Ir(cod)Cl] (**2**). Selected bond lengths [Å] and angles [°] : N1–Ir1 2.118(3), P1–Ir1 2.3024(11), Cl1–Ir1 2.5707(10), C1–Ir1 2.112(4), C2–Ir1 2.157(4), C5–Ir1 2.137(4), C6–Ir1 2.153(4), C1–C2 1.427(6), C5–C6 1.406(7), N1–Ir1–P1 80.57(10), P1–Ir1–Cl1 96.52(4), N1–Ir1–Cl1 85.31(9), C1–Ir1–C2 39.04(17), C5–Ir1–C6 38.26(17), C1–Ir1–N1 88.03(16), C2–Ir1–Cl1 98.48(13), C6–Ir1–P1 89.45(12), C5–Ir1–Cl1 82.71(13).

The P,N-ligand forms a five-membered ring in addition to cyclooctadiene and Cl ligand coordination. The coordination geometry of the metal is distorted square pyramidal with the chlorine atom as the axial ligand. The base is defined by P1, N1 and the centers of the two olefinic cyclooctadiene bonds. We were surprized not to find examples of structural similarity. To our best knowledge, no iridium complex stabilized by a N–P–Cl-donor set and two additional olefinic bonds has yet been reported. However, complexes containing phosphorous (mono- and bidentate), nitrogen, sulfur or carbene donors in such an arrangement are known.[18] The Ir–Cl distance in **2** [2.571(1) Å] matches the average value of the Ir–Cl bond in these compounds (2.57 Å). NMR studies of **2** and **3** reveal a similar structure in solution. Two separate signal sets for the pyridyl moieties most likely for the coordinating as well as non-coordinating were observed. At room temperature, the isopropyl groups of **3** exhibit only broad ^{1}H NMR signals that can easily be resolved into the corresponding multiplets at lower temperatures (–20°C). These results are indicative of the dynamic behavior of the isopropyl groups of **3** in solution and underline the crowded nature of the compound.

Catalytic Studies

Based on the pioneering work of Fujita et al., where $[Cp^*IrCl_2]_2$ was employed as a catalyst for the alkylation of aromatic amines with several primary and secondary alcohols,[11,15] we chose to determine the catalytic potential of iridium-P,N complexes for such reactions. The alkylation of aniline with alcohols has proved to be challenging with ruthenium-based catalysts and often affording mixtures of mono- and dialkylated amines.[6,7g,9] Our investigation was started with the alkylation of aniline with benzyl alcohol as a model reaction (Scheme 3). In general, the screening reactions were performed using 0.5 mmol of substrates at 110°C for 24 h and the catalyst was prepared in-situ from stock solutions of $[IrCl(cod)]_2$ and P,N-ligand.



Scheme 3. Model reaction used to optimize the reaction conditions for the alkylation of aromatic amines.

Optimization of the Reaction Conditions

First, the influence of the substrate/base ratio using various amounts of K_2CO_3 under the same reaction conditions as in the literature was studied.[15] The results (Table 1, entries 1-3) exhibit only very low yields (1-2 %) of the expected benzylated aniline. Therefore K_2CO_3 was exchanged with the stronger and better soluble base KO^{t}Bu. The results of these reactions (Table 1, entries 4-7) show that KO^{t}Bu is much more effective and leads to better yields. Surprisingly, full conversion of the amine into benzylphenyl-amine could only be obtained when stoichiometric amounts of base were employed. Interestingly, use of 50 mol% of base still led to full conversion of the amine, but to a mixture of alkylated amine as well as the corresponding imine.

Table 1. Influence of substrate/base ratio.

Entry	Base	Substrate:Base	Yield [%][a]
1	K_2CO_3	1:1	2
2	K_2CO_3	2:1	2
3	K_2CO_3	5:1	1
4	KO^{t}Bu	50:1	1
5	KO^{t}Bu	5:1	29
6	KO^{t}Bu	2:1	78
7	KO^{t}Bu	1:1	92

Reaction conditions: 0.50 mmol aniline, 0.50 mmol benzyl alcohol, 5.0 mol % $[IrCl(cod)]_2$, 10.0 mol % $PyMeNPPh_2$ (**1e**), 0.01-0.50 mmol base, 1 mL toluene, 110°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard.

In order to optimize the reaction conditions the catalyst loading was lowered from 10 to 2 mol% and several organic solvents were screened (Table 2). The highest yields were obtained in diglyme (86 %) or THF (77 %) (Table 2, entries 4 and 8). Alkaline solvents such as pyridine and triethyl-amine were also used (Table 2, entries 6 and 9), but without further addition of KO^{t}Bu. In both cases no conversion of was observed.

Table 2. Solvent screening.

Entry	Solvent	Temperature	Yield [%][a]
1	Toluene	110°C	36
2	DMF	110°C	60
3	Dioxane	110°C	42
4	Diglyme	110°C	86
5	DMSO	110°C	2
6	Pyridine	110°C	0[b]
7	DME	110°C	62
8	THF	70°C	77
9	Et_3N	110°C	0[b]

Reaction conditions*:* 0.50 mmol aniline, 0.50 mmol benzyl alcohol, 1.0 mol % $[IrCl(cod)]_2$, 2.0 mol % $PyMeNPPh_2$ (**1e**), 0.50 mmol KO^{t}Bu, 1 mL solvent, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard. [b] Reaction without KO^{t}Bu.

In a next step various organic and inorganic bases were examined in order to determine the best reaction conditions and see if the results obtained with KO^{t}Bu could be improved. The results summarized in Table 3 show that only a few bases led to acceptable conversions and yields. In most cases only poor conversions were achieved and the corresponding imine was obtained as a by-product, except in the run with $KN(SiMe_3)_2$ where more undefined by-products were observed. KO^{t}Bu was once again found to be the best base, leading to best conversions and highest yield of *N*-benzylphenylamine (Table 3, entry 1). The reaction with KH or $NaN(SiMe_3)_2$ also led to satisfying results (Table 3, entries 10 and 14), but the yields using other bases were much lower. For example, K_2CO_3, Na_2CO_3, NaOAc, KOAc, AgF_3OAc, $Mg(OEt)_2$ and N(*i*-Pr)$_2$Et did not lead to any conversion of the reaction.

Table 3. Base screening.

Entry	Base	Yield [%][a]
1	KO^{t}Bu	79
2	K_3PO_4	37
3	K_2CO_3	0
4	Na_2CO_3	0
5	NaOAc	0
6	KOAc	<1
7	Cs_2CO_3	12
8	AgF_3OAc	<1
9	$KN(SiMe_3)_2$	48
10	$NaN(SiMe_3)_2$	59
11	$Mg(OEt)_2$	0
12	$KOSiMe_3$	20
13	N(*i*-Pr)$_2$Et	0
14	KH	67

Reaction conditions: 0.50 mmol aniline, 0.50 mmol benzyl alcohol, 1.0 mol % $[IrCl(cod)]_2$, 2.0 mol % $PyMeNPPh_2$ (**1e**), 0.50 mmol base, 1 mL diglyme, 110°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard.

It was of special interest to us to know how important the influence of the P,N-ligand is for the outcome of the reaction and to determine a trend of reactivity for the different ligands. Therefore, screening of all the mentioned ligands described in Scheme 1 was accomplished. The results show, that all ligands have an activating influence on the metal center, as the obtained yields were significantly higher compared to the reaction without ligand (Table 4, entry 9). Three ligands were

found to be very activating (Table 4, entries 4, 7, 8) since they afforded yields from 77 % up to 81 %. All these ligands contain electron-donating *i*-Pr or *t*-Bu substituents on the phosphorus center and hence provide a strong basicity of the latter. These ligands are also the most bulky ones and thus ligand bulkiness may also play an important role in terms of catalyst efficiency or in terms of the generation of the catalytically active species. Compared with the results of Fujita, when only $[IrCl(cod)]_2$ was used as the catalyst with 5 mol % K_2CO_3 in toluene – affording only 3 % yield,[15] our results show that the loading and the nature of the added base play an important role.

Table 4. Ligand screening.

Entry	Ligand	Yield [%][a]
1	$PyMeNPPh_2$ (**1e**)	68
2	$PyMeNPCy_2$ (**1f**)	67
3	$PyMeNP(i\text{-}Pr)_2$ (**1g**)	67
4	$PyMeNP(t\text{-}Bu)_2$ (**1h**)	79
5	Py_2NPPh_2 (**1a**)	66
6	Py_2NPCy_2 (**1b**)	66
7	$Py_2NP(i\text{-}Pr)_2$ (**1c**)	81
8	$Py_2NP(t\text{-}Bu)_2$ (**1d**)	77
9	without ligand	34

Reaction conditions: 0.50 mmol aniline, 0.50 mmol benzyl alcohol, 1.0 mol% $[IrCl(cod)]_2$, 2.0 mol% ligand, 0.50 mmol KO^tBu, 1 mL diglyme, 110°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard.

Having optimized important reaction parameters (solvent, ligand, and base), it was of interest to know whether the amount of KO^tBu could be reduced without loss of performance. When catalytic amounts of base were employed (Table 5, entries 1-3) only poor conversions were observed as well as the formation of the corresponding imine as a major by-product. The same result was obtained when 50 mol% of base were introduced, affording good conversions, but also mostly imine as by-product (Table 5, entry 4). The highest yields were obtained when stoichiometric amounts of KO^tBu were used and it also seems that a 10 % excess of base is necessary to form the product quantitatively (Table 5, entry 6).

Finally, in order to obtain 100% conversion (GC) and thus to allow optimized product isolation, the influence of the amine/alcohol ratio on the *N*-alkylation reaction was studied. Our investigations showed that a large excess of alcohol leads to decreasing yields (Table 6, entries 2-4), whereas a

10 % excess of alcohol (Table 6, entry 5) is beneficial in order to achieve full conversion and to decrease the amount of corresponding imine.

Table 5. Influence of substrate/base ratio.

Entry	Base	Substrate : Base	Yield [%][a]
1	KO^{t}Bu	50:1	1
2	KO^{t}Bu	20:1	7
3	KO^{t}Bu	10:1	19
4	KO^{t}Bu	2:1	79
5	KO^{t}Bu	1:1	90
6	KO^{t}Bu	1:1.1	98 (92[b])

Reaction conditions: 1.00 mmol aniline, 1.10 mmol benzyl alcohol, 1.0 mol % $[IrCl(cod)]_2$, 2.0 mol % $Py_2NP(i\text{-}Pr)_2$ (**1c**), 1.10-0.02 mmol KO^{t}Bu, 1 mL diglyme, 110°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard. [b] Isolated yield.

Table 6. Influence of amine/alcohol ratio.

Entry	Amine : Alcohol	Yield [%][a]
1	1:1	75
2	1:2	68
3	1:3	65
4	1:4	57
5	1:1.1	100

Reaction conditions: 0.50 mmol aniline, 0.50-2.50 mmol benzyl alcohol, 1.0 mol % $[IrCl(cod)]_2$, 2.0 mol % $Py_2NP(i\text{-}Pr)_2$ (**1c**), 0.55 mmol KO^{t}Bu, 1 mL diglyme, 110°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard.

Having determined the best reaction conditions [1.0 equiv amine, 1.1 equiv alcohol, 1.1 equiv KO^{t}Bu, diglyme, 110°C and $[IrCl(cod)]_2$ with $Py_2NP(i\text{-}Pr)_2$ (**1c**)], the catalyst loading was varied. Compared with the results of our first investigation where 10 mol% iridium catalyst had been employed (Table 1), it could be shown that a catalyst loading of 2 mol% is sufficient to obtain excellent yields (Table 7, entry 1) with the optimized reaction conditions. However, further reduction of the iridium complex concentration led to a decrease of yield within the 24 h time window (Table 7, entries 2-5). Finally, a catalyst concentration of 1 mol% $[IrCl(cod)]_2$ and 2 mol% $Py_2NP(i\text{-}Pr)_2$ (**1c**) was found to be optimal.

Table 7. Influence of catalyst loading.

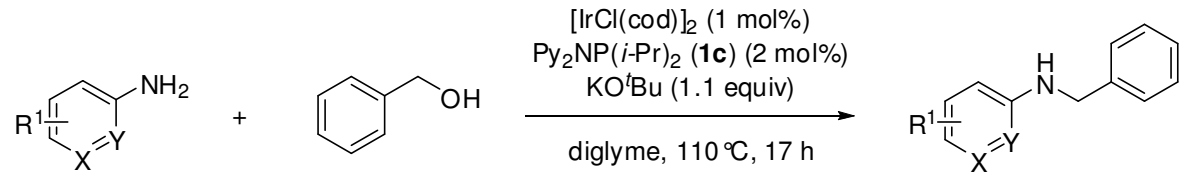
Entry	Ir loading (mol%)	Yield [%][a]
1	2.0	98
2	1.0	82
3	0.5	65
4	0.25	33
5	0	4

Reaction conditions: 0.50 mmol aniline, 0.55 mmol benzyl alcohol, $[IrCl(cod)]_2$, $Py_2NP(i\text{-}Pr)_2$ (**1c**), 0.55 mmol KO^{t}Bu, 1 mL diglyme, 110°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard.

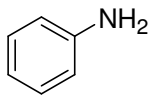
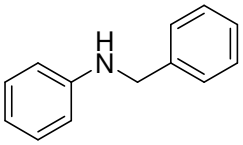
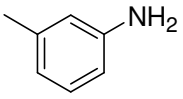
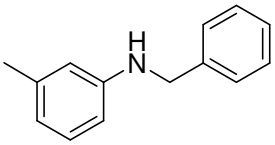
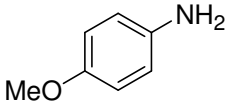
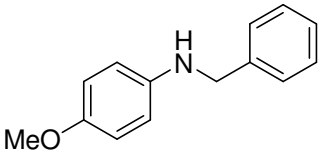
N-Alkylation Reactions of Substituted Anilines with Primary Alcohols

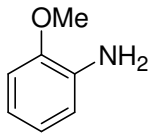
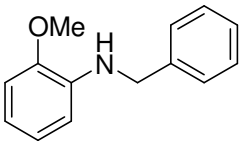
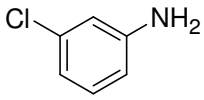
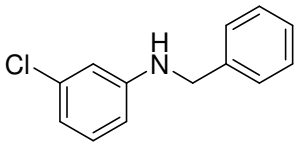
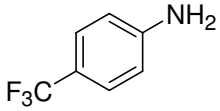
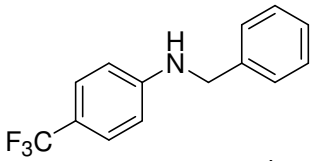
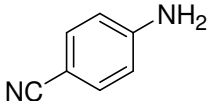
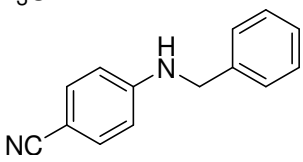
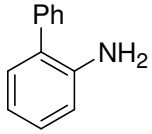
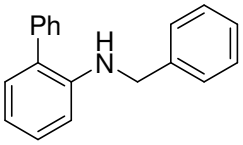
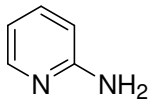
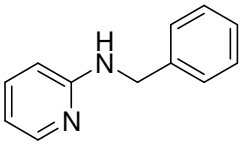
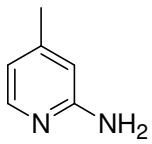
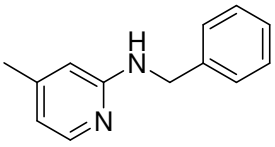
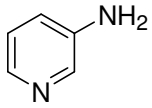
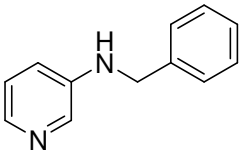
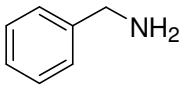
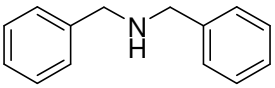
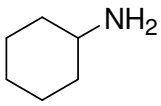
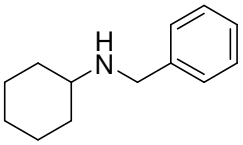
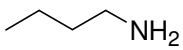
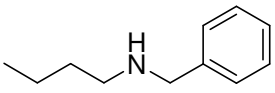
In order to point out the general applicability of this improved iridium-catalyzed *N*-alkylation reaction, various substituted aromatic amines were alkylated with benzyl alcohol with the above-mentioned optimal reaction parameters (Table 8).

Table 8. Catalytic *N*-alkylation of primary aromatic amines with benzyl alcohol.



X= C, Y= C, N
X= N, Y= C

Entry	Amine	Product	Yield [%][a]
1			92
2			92
3			97

4			79
5			96
6			67[b]
7			69[c]
8			92
9			93
10			94
11			97
12			3
13			0
14			0

Reaction conditions: 1.00 mmol amine, 1.10 mmol benzyl alcohol, 1.0 mol % $[IrCl(cod)]_2$, 2.0 mol % $Py_2NP(i\text{-}Pr)_2$ (**1c**), 1.10 mmol KO^tBu, 1 mL diglyme, 110°C, 17 h (reaction times were not optimized). [a] Isolated yield. [b] Reaction time: 3 h. [c] Reaction time: 20 min.

The results show that electron-donating (Table 8, entries 2, 3, 4, 8) as well as electron-withdrawing (Table 8, entries 5, 6, 7) substituents in *ortho*, *meta* and *para* positions of the aromatic ring are perfectly tolerated and most products were isolated in very good to excellent yields. However, the use of a strong base such as KO^{t}Bu has disadvantages concerning the tolerance for base-sensitive functional groups. For example the alkylation of 4-aminobenzonitrile had to be monitored by thin layer chromatography (TLC). However, the alkylation of the aminobenzonitrile is very fast and full conversion was obtained after only 20 min. The reaction was then rapidly quenched to prevent the formation of 4-benzylaminobenzamide, which forms quantitatively after a few hours.

The *N*-alkylation reaction of 4-(trifluoromethyl)-aniline, carrying a usually very stable CF_3 group, surprisingly afforded many non-identifiable side-products and only led to moderate yields (34%) when reacted for 17 h. In order to avoid the decomposition of the product the reaction was also monitored by TLC and quenched after 3 h when full conversion was observed. By doing so benzyl-(4-trifluoromethylphenyl)amine could be isolated in good yields (67%) (Table 8, entry 6). The *N*-alkylation of amines bearing nitro and ester groups was unsuccessful and did not afford the expected secondary amines. Instead, mainly the degradation products of the starting materials were observed. This degradation can be assigned to the use of stoichiometric amounts of the strong base KO^{t}Bu, since the catalytic system of Fujita et al. in which K_2CO_3 (in catalytic amount) was added as a base perfectly tolerates nitro-substituted aromatic amines.[15]

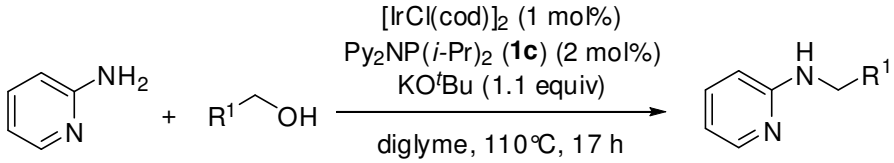
Interestingly, not only the derivatives of aniline but also the even more deactivated heteroaromatic amines could generally be alkylated with benzyl alcohol in excellent yields (Table 8, entries 9-11). To our best knowledge, there is no reported general method for the *N*-alkylation of aminopyridines with alcohols and an iridium catalyst. Merely two ruthenium-based protocols have been reported for the *N*-alkylation of aminopyridines.[7b],[14] However these protocols have also disadvantages, especially the selectivity towards mono- and dialkylation of the amine. In contrast, with our iridium catalyst system excellent yields of monoalkylated 2- and 3-aminopyridines could be obtained with lower catalyst loadings.

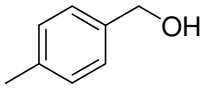
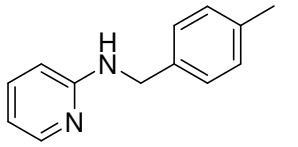
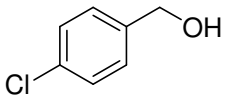
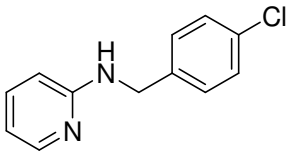
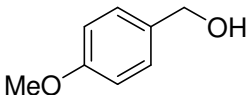
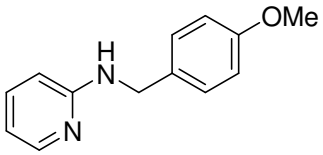
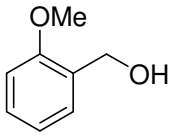
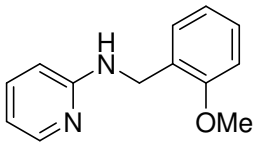
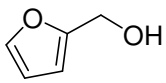
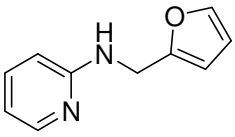
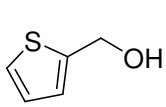
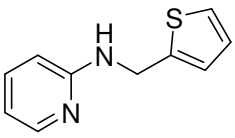
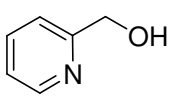
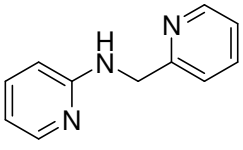
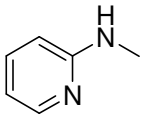
The reactions were also carried out with aliphatic amines such as benzylamine, *n*-butylamine and cyclohexylamine, but in all cases low conversions were observed and almost no product could be detected (Table 8, entries 12, 13, 14). These results show the necessity of a direct connection of the amino group to the aromatic ring, in order to obtain a good nucleophilic attack at the carbonyl center, fast formation of the corresponding imine and hydrogen-transfer from the iridium complex to the imine.

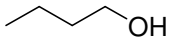
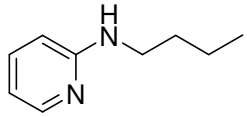
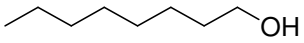
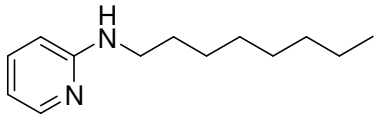
N-Alkylation of Aminopyridines with Primary Alcohols

In order to show the general applicability of this method for the alkylation of aminopyridines a broad scope of substituted benzyl alcohol derivatives as well as aliphatic alcohols and heteroaromatic alcohols were employed, selectively affording the monoalkylated compounds in good to excellent yields.

Table 9. Catalytic *N*-alkylation of 2-aminopyridine with various primary alcohols.



Entry	Alcohol	Product	Yield [%][a]
1			94
2			82[b]
3			97
4			95
5			71
6			69
7			44
8	CH_3OH		63[c]

9			75
10			72

Reaction conditions: 1.00 mmol 2-aminopyridine, 1.10 mmol alcohol, 1.0 mol % $[IrCl(cod)]_2$, 2.0 mol % $Py_2NP(i\text{-}Pr)_2$ (**1c**), 1.10 mmol KO^tBu, 1 mL diglyme, 110°C, 17 h (reaction times were not optimized). [a] Isolated yield. [b] Reaction time 4 h. [c] 1.6 equiv of MeOH, Yield determined by GC analysis with dodecane as internal standard.

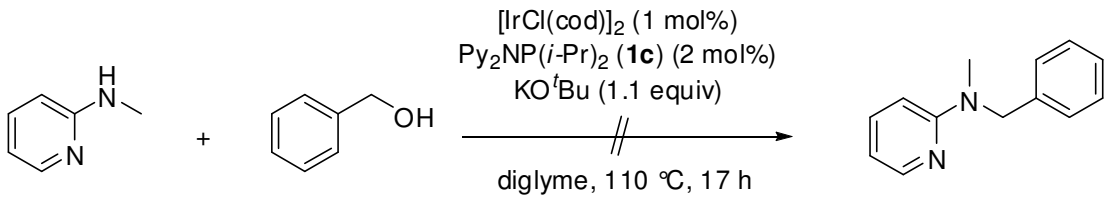
The results in Table 9 show that the *N*-alkylation of aminopyridines with several substituted benzyl alcohols works perfectly and that electron-donating (Table 9, entries 1, 3, 4) as well as electron-withdrawing (Table 9, entry 2) substituents in *ortho* and *para* position of the aromatic ring are tolerated. All obtained products were isolated in good to excellent yields. However, the reaction of 2-aminopyridine with 4-chlorobenzyl alcohol (Table 9, entry 2) is more complicated due to the fact that the product can partially lose its chlorine atom and form *N*-benzylaminopyridine as by-product. Therefore, the reaction had to be quenched after four hours when full conversion was obtained and decomposition had not yet started.

The reaction of heteroaromatic alcohols also proceeds efficiently and the corresponding *N*-alkylated aminopyridines were obtained in moderate to good yields (Table 9, entries 5-7). Monitoring of these reactions showed that they are slower than the reactions with benzyl alcohol derivatives. The reaction of pyridin-2-ylmethanol did not afford a full conversion of the starting material even after 17 h and 2-aminopyridine as well as the corresponding product were present in the reaction mixture. To the present day there has been no report for such an *N*-alkylation reaction of heteroaromatic amines with heteroaromatic primary alcohols, except for the *N*-alkylation of aliphatic amines with several heteroaromatic alcohols using a ruthenium catalyst and higher catalyst loadings.[12]

Especially interesting is the fact that our catalyst system described here is not only restricted to benzyl alcohols but that aliphatic alcohols can also be used as alkylating agents, particularly methanol. The reaction of 2-aminopyridine with 1-octanol or 1-butanol affords the expected *N*-alkylated aminopyridines in good yields (Table 9, entries 9 and 10). We could also show that our catalyst system is very useful for the selective *N*-methylation of aminoarenes (Table 9, entry 8), affording good yields of monoalkylated product without any traces of *N*,*N*-dimethylated amine. Such a selective catalytic monomethylation of aminoarenes is difficult as earlier investigations have

shown, because an excess of the alcohol has to be used, leading to unwanted dimethylated tertiary amines.[6],[7g]

In order to understand the high selectivity towards monoalkylation of primary aromatic amines, the *N*-alkylation of a secondary (aryl, alkyl)-amine was investigated. However, in the reaction of 2-(methylamino)pyridine with benzyl alcohol no conversion of the amine was observed (Scheme 4).[15]



Scheme 4. *N*-alkylation of secondary amines with benzyl alcohol.

This result shows that our catalyst is highly selective towards monoalkylation in the reaction of primary amines with alcohols and stops after one alkylation of the amine. This selectivity is not a matter of catalyst deactivation, because no dialkylated amine was observed even with higher catalyst loadings (10 mol%) and higher loadings of base. This selectivity renders our catalytic protocol a useful tool for organic synthesis because the selective monoalkylation, especially the monomethylation, of aromatic amines is difficult to accomplish.

5.3. Conclusions

Summarized, we have developed an efficient protocol for the synthesis of P-functionalized aminopyridine ligands and their iridium complexes as well as an efficient catalytic application of the latter for the alkylation of primary aromatic and heteroaromatic amines with primary aromatic, heteroaromatic as well as aliphatic alcohols. It is noteworthy that this process is highly selective towards monoalkylation and proceeds with rather moderate catalyst loadings.

5.4. Experimental Section

General Considerations

Please see Supporting Information.

P,N-ligand synthesis

For analytical and spectroscopic data please see Supporting Information. Py_2NPPh_2 (**1a**) was prepared according to the literature procedure.[16]

General Procedure for the Preparation of P-Functionalized Aminopyridines with *n*-BuLi.

Py_2NPCy_2 (1b): Di(2-pyridyl)amine (2.47 g, 14.4 mmol) was suspended in 50 mL hexane and the solution was cooled to −20°C. Then *n*-BuLi (9.0 mL, 14.4 mmol) was added dropwise with a syringe. The reaction mixture was stirred at −20°C for 30 min, allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to −20°C and chlorodicyclohexylphosphine (3.18 mL, 14.4 mmol) added drop wise with a syringe. The yellow solution was then left to warm to room temperature and stirred overnight. The yellow suspension was filtered on a glass filter frit with a celite pad (3 cm) and washed with 100 mL pentane. The solvents were concentrated in vacuo to 10 mL and the product was left to crystallize at −20°C. The supernatant solution was decanted, the solid washed with 3 mL cold pentane and subsequently dried in vacuo yielding the title compound as a beige solid; yield: 3.291 g (64 %).

General Procedure for the Preparation of P-functionalized Aminopyridines with KH.

$Py_2NP(t\text{-}Bu)_2$ (1d): Potassium hydride (0.48 g, 12.0 mmol) was suspended in 30 mL toluene and the solution was cooled to −40°C. Then di(2-pyridyl)amine (2.05 g, 12.0 mmol), dissolved in 30 mL toluene was added drop wise with a dropping funnel. The reaction mixture was stirred at −20°C for 30 min, allowed to warm to room temperature and stirred overnight. Then the reaction mixture was cooled to −20°C and chloro-di-*tert*-butylphosphine (2.3 mL, 12.0 mmol) was added drop wise with a syringe. The yellow soluteon was then stirred overnight at room temperature and subsequently heated to 100°C for 4 days. The clear yellow solution was filtered on a glass filter frit with a celite pad (3 cm) and washed with 30 mL toluene. The solvent was removed in vacuo and the resulting brown oil left to crystallize at −20°C. The solid was dried in vacuo yielding the title compound as a pale brown solid; yield: 3.301 g (87 %).

$Py_2NP(i\text{-}Pr)_2$ (1c): Following the general procedure employed for the synthesis of **1b**, the product was obtained as an orange / red solid; yield: 3.017 g (87 %).

$PyMeNPPh_2$ (1e): Following the general procedure employed for the synthesis of **1b**, the product was obtained as a beige solid; yield: 3.96 g (90 %).

PyMeNPCy$_2$ (1f): Following the general procedure employed for the synthesis of **1d**, without heating after the addition of the chlorophosphine, the product was obtained as a colourless very viscous liquid after distillation; yield: 3.722 g (82 %).

PyMeNP(*i*-Pr)$_2$ (1g): Following the general procedure employed for the synthesis of **1d**, without heating after the addition of the chlorophosphine, the product was obtained as a pale yellow liquid after distillation; yield: 2.388 g (71 %).

PyMeNP(*t*-Bu)$_2$ (1h): Following the general procedure employed for the synthesis of **1b**, the product was obtained as a yellow liquid after distillation; yield: 2.42 g (73 %).

Complex Synthesis; General Method

[IrCl(cod)]$_2$ (1.0 equiv) was dissolved in 15 mL CH_2Cl_2 and subsequently a solution of P,N-ligand (2.0 equiv) in 5 mL CH_2Cl_2 was added dropwise. A red solution was obtained and after 15 min the solvent was removed under vacuum, affording the complex in quantitative yields. For analytical and spectroscopic data please see Supporting Information.

General procedure for screening reactions

In a pressure tube, stock solutions of [IrCl(cod)]$_2$ (80 µL, 0.005 mmol, 0.0625 M in THF) and Py$_2$NP(*i*-Pr)$_2$ (**1c**) (80 µL, 0.01 mmol, 0.125 M in THF) were mixed. Then aniline (45.9 µL, 0.50 mmol), benzyl alcohol (56.8 µL, 0.55 mmol) and 1 mL diethylene glycol dimethyl ether (diglyme) as solvent were added. Last, KO^{t}Bu (0.56 g, 0.55 mmol) was dissolved in the reaction mixture and the pressure tube was fitted with a Teflon® cap and stirred at 110°C for 24 h. The reaction mixture was cooled to room temperature. Then water (15 mL), diethyl ether (15 mL) and dodecane (56.8 µL, 0.25 mmol) were added. After stirring, an aliquot of the organic phase was analyzed by gas chromatography.

General procedure for the *N*-alkylation reactions

In a pressure tube, stock solutions of [IrCl(cod)]$_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) and Py$_2$NP(*i*-Pr)$_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF) were mixed. Then the amine (1.00 equiv), the alcohol (1.10 equiv) and 1 mL diethylene glycol dimethyl ether (diglyme) as solvent were added. Last, KO^{t}Bu (1.10 equiv) was dissolved in the reaction mixture and the pressure tube was fitted with a Teflon® cap and stirred at 110°C for 17 h. The reaction mixture was cooled to room temperature and all volatiles were removed under vacuum. Then water (40 mL) was added to the

residue and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and the solvent removed under vacuum. Finally, the residue was purified by column chromatography.

Crystallographic Data

X-ray crystal structure analysis of **2** was performed by using a STOE-IPDS II equipped with an Oxford Cryostream low-temperature unit. Structure solution and refinement were accomplished using SIR97,[19] SHELXL-97[20] and WinGX.[21] Crystal system: triclinic, space group: $P\bar{1}$, lattice constants[Å,°]: a 9.5370(6), b 10.9370(7), c 15.2230(9), α 100.393(5), β 96.344(5), γ 94.013(5), V [Å^3]: 1545.66(17), crystal size [mm]: 0.35 × 0.32 × 0.15, $\rho_{calcd.}$ [g cm^{-3}]: 1.694, μ [mm^{-1}] (Mo-K$_\alpha$): 4.656, T [K]: 173(2), θ range [°]: 1.37–26.13, no. of unique refl.: 5822, no. of obsd. refl. [$I > 2\sigma(I)$]: 5104, no. of parameters: 352, wR^2 (all data): 0.0626, R value [$I > 2\sigma(I)$]: 0.0298. CCDC 670063 (compound **2**) contains the supplementary crystallographic data for this publication. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: + 44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Supporting Information Available

Detailed synthesis and characterization data of all ligands, complexes and products.

Acknowledgments

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5.6. Supporting Information

General considerations

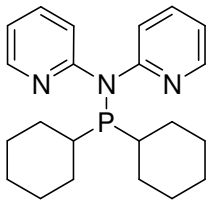
All reactions and manipulations with air-sensitive compounds were performed under dry argon, using standard Schlenk and glovebox techniques. Non-halogenated solvents were distilled over sodium benzophenone ketyl and halogenated solvents over P_2O_5. Deuterated solvents were obtained from Cambridge Isotope Laboratories and were degassed, dried using molecular sieves and distilled prior to use.

All chemicals were purchased from commercial sources in purities > 97% and used without further purification if not otherwise mentioned in the synthetic procedure. NMR spectra were obtained using a Varian INOVA 300 or a Varian INOVA 400 spectrometer at 298 K if not stated otherwise. Chemical shifts are reported in ppm relative to the deuterated solvent. Elemental analyses were performed on a Vario elementar EL *III*. GC analyses were performed on an Agilent 6890N Network GC-System equipped with a HP-5 column (30 m × 0.32 µm × 0.25 µm) and GC-MS analyses on a Thermo Focus GC with a DSQ MS-unit equipped with a HP-5-MS column (30 m × 0.32 µm × 0.25 µm).

P,N-ligand synthesis

Py_2NPPh_2 was prepared according to the literature procedure.

Synthesis of Py_2NPCy_2 (1b)



Di(2-pyridyl)amine (2.47 g, 14.4 mmol) was suspended in 50 mL hexane and the solution was cooled to -20°C. Then *n*-BuLi (9.0 mL, 14.4 mmol) was added dropwise with a syringe. The reaction mixture was stirred at -20°C for 30 min, allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to -20°C and chlorodicyclohexylphosphine (3.18 mL, 14.4 mmol) added dropwise with a syringe. The yellow solution was then left to warm to room temperature and stirred overnight. The yellow suspension was filtered on a glass filter frit with a celite pad (3 cm) and washed with 100 mL pentane. The solvents were concentrated in vacuo to 10

mL and the product was left to crystallize at -20°C. The supernatant solution was decanted, the solid washed with 3 mL cold pentane and subsequently dried in vacuo yielding Py_2NPCy_2 as a beige solid (3.291 g, 64 %).

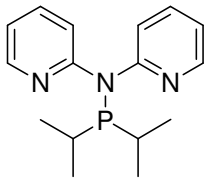
^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.29 (ddd, *J*= 5.0, 2.1, 0.9 Hz, 2H), 7.53 (ddd, *J*= 8.5, 7.3, 2.1 Hz, 2H), 6.97 (d, *J*= 7.3 Hz, 2H), 6.91 (ddd, *J*= 7.2, 4.8, 0.9 Hz, 2H), 2.58-2.44 (m, 2H), 1.91-1.56 (m, 12H), 1.31-1.13 (m, 8H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ = 161.0 (d, *J*= 7.9 Hz), 148.5, 137.6, 118.9 (d, *J*= 7.8 Hz), 118.4, 38.0 (d, *J*= 16.6 Hz), 30.7 (d, *J*= 26.0 Hz), 28.9 (d, *J*= 9.4 Hz), 27.3 (d, *J*= 6.1 Hz), 27.3 (d, *J*= 28.7 Hz), 27.0 (d, *J*= 1.1 Hz).

^{31}P NMR (121 MHz, CD_2Cl_2): δ = 77.8.

Elemental analysis found for **$C_{22}H_{30}N_3P$** (calc.): C 72.06 (71.91), H 8.68 (8.23), N 11.44 (11.40).

Synthesis of $Py_2NP(i\text{-}Pr)_2$ (1c)



Di(2-pyridyl)amine (2.57 g, 15.0 mmol) was suspended in 60 mL pentane/diethyl ether (2:1) and the solution was cooled to -20°C. Then *n*-BuLi (9.4 mL, 15.0 mmol) was added dropwise with a syringe. The reaction mixture was stirred at -20°C for 30 min, allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to -20°C and chlorodiisopropylphosphine (3.40 mL, 15.0 mmol) added dropwise with a syringe. The yellow solution was then left to warm to room temperature and stirred overnight. The yellow suspension was filtered on a glass filter frit with a celite pad (3 cm) and washed with 30 mL diethyl ether. The solvents were concentrated in vacuo, affording a red oil. 5 mL of a 1:1 hexane:diethyl ether mixture were added and the residue left to crystallize at -20°C. The supernatant solution was decanted and the solid subsequently dried in vacuo yielding $Py_2NP(i\text{-}Pr)_2$ as an orange / red solid (3.017 g, 87 %).

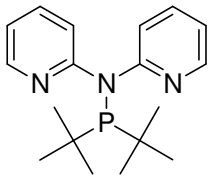
^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.28 (ddd, *J*= 5.0, 2.1, 0.9 Hz, 2H), 7.54 (ddd, *J*= 8.9, 6.8, 1.9 Hz, 2H), 6.99 (d, *J*= 8.2 Hz, 2H), 6.92 (ddd, *J*= 7.2, 4.8, 0.9 Hz, 2H), 2.78-2.62 (m, 2H), 1.13-1.00 (m, 12H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ = 161.0 (d, *J*= 5.0 Hz), 148.5, 137.6, 119.0 (d, *J*= 6.9 Hz), 118.6, 27.8 (d, *J*= 15.8 Hz), 20.6 (d, *J*= 11.4 Hz), 20.1 (d, *J*= 29.7 Hz).

^{31}P NMR (121 MHz, CD_2Cl_2): δ = 87.2.

Elemental analysis found for **$C_{16}H_{22}N_3P$** (calc.): C 67.05 (66.88), H 7.53 (7.72), N 14.54 (14.62).

Synthesis of Py_2NPtBu_2 (1d)



Potassium hydride (0.48 g, 12.0 mmol) was suspended in 30 mL toluene and the solution was cooled to -40°C. Then di(2-pyridyl)amine (2.05 g, 12.0 mmol), dissolved in 30 mL toluene was added dropwise with a dropping funnel. The reaction mixture was stirred at -20°C for 30 min, allowed to warm to room temperature and stirred overnight. Then the reaction mixture was cooled to -20°C and chloro-di-tertbutylphosphine (2.3 mL, 12.0 mmol) was added dropwise with a syringe. The yellow solution was then stirred overnight at rt and subsequently heated to 100°C for 4 days. The clear yellow solution was filtered on a glass filter frit with a celite pad (3 cm) and washed with 30 mL toluene. The solvent was removed in vacuo and the resulting brown oil left to crystallize at -20°C. The solid was dried in vacuo yielding Py_2NPtBu_2 as a pale brown solid (3.301 g, 87 %).

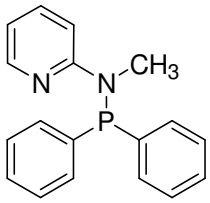
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35-8.25 (m, 2H), 7.58-7.33 (m, 3H), 6.99-6.79 (m, 2H), 6.75-6.58 (m, 1H), 1.22 (d, *J*= 13.2 Hz, 18H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 159.6, 148.3, 148.0, 137.5, 137.0, 120.3, 119.0, 118.9, 117.9, 36.7 (d, *J*= 30.6 Hz), 30.0 (d, *J*= 17.7 Hz).

^{31}P NMR (161 MHz, $CDCl_3$): δ = 101.1.

Elemental analysis found for **$C_{18}H_{26}N_3P$** (calc.): C 68.39 (68.55), H 8.68 (8.31), N 13.37 (13.32).

Synthesis of $PyMeNPPh_2$ (1e)



2-(Methylamino)pyridine (1.622 g, 15.0 mmol) was dissolved in 50 mL hexane / 30 mL diethyl ether and the solution was cooled to -30°C. Then *n*-BuLi (9.4 mL, 15.0 mmol) was added dropwise with a syringe. The reaction mixture was stirred at -20°C for 30 min, allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to -20°C and chlorodiphenylphosphine (3.3 mL, 15.0 mmol) added dropwise with a syringe. The yellow solution was then left to warm to room temperature and stirred overnight. The yellow suspension was filtered on a glass filter frit with a celite pad (3 cm) and washed with 40 mL diethyl ether. The solvents were concentrated in vacuo until precipitation occurred and the solution was left to crystallize at -20°C. The supernatant colored solution was decanted and the solid was then dried in vacuo yielding $PyMeNPPh_2$ as a beige solid (3.96 g, 90 %).

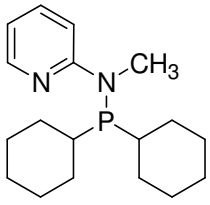
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.22 (ddd, *J*= 4.9, 2.0, 1.1 Hz, 1H), 7.54 (ddd, *J*= 8.8, 7.0, 1.9 Hz, 1H), 7.46-7.39 (m, 11H), 6.76 (ddd, *J*= 7.0, 4.9, 0.9 Hz, 1H), 2.92 (d, *J*= 1.5 Hz, 3H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 161.8 (d, *J*= 26.4 Hz), 148.1 (d, *J*= 1.6 Hz), 137.5 (d, *J*= 3.2 Hz), 137.4 (d, *J*= 15.3 Hz), 132.5 (d, *J*= 20.6 Hz), 129.5, 129.0 (d, *J*= 5.8 Hz), 115.1, 110.9 (d, *J*= 20.6 Hz), 34.7 (d, *J*= 8.4 Hz).

^{31}P NMR (161 MHz, CD_2Cl_2): δ = 51.9.

Elemental analysis found for **$C_{18}H_{17}N_2P$** (calc.): C 73.95 (73.96); H 5.78 (5.86); N 9.51 (9.58).

Synthesis of $PyMeNPCy_2$ (1f)



Potassium hydride (0.601 g, 15.0 mmol) was suspended in 100 mL toluene, the solution cooled to -40°C and 2-(methylamino)pyridine (1.622 g, 15.0 mmol) added dropwise with a syringe. The

reaction mixture was stirred at -40°C for 30 min, allowed to warm to room temperature and stirred for further 3 h until it became pale green. Then the reaction mixture was again cooled to -30°C and chloro-dicyclohexylphosphine (3.49 g, 15.0 mmol) added dropwise with a syringe. The solution was stirred for further 30 min at -30°C, the left to warm to rt and stirred overnight. The colorless but viscous solution was filtered on a glass filter frit with a celite pad (3 cm) and washed with 40 mL toluene. The solvent was removed in vacuo and the resulting colorless oil distilled under reduced pressure (0.06 mbar) at 180°C to yield PyMeNPCy$_2$ as a colorless very viscous liquid (3.722 g, 82 %).

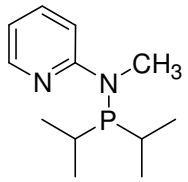
^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.10 (d, *J*= 4.1 Hz, 1H), 7.55-7.44 (m, 1H), 7.38 (ddd, *J*= 8.9, 7.0, 2.1 Hz, 1H), 6.62-6.54 (m, 1H), 3.04 (d, *J*= 1.2 Hz, 3H), 1.96 (d, *J*= 10.8 Hz, 2H), 1.80-1.60 (m, 10H), 1.36-1.13 (m, 10H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ = 163.2 (d, *J*= 24.1 Hz), 147.7, 136.5, 113.7, 111.5 (d, *J*= 27.4 Hz), 37.0 (d, *J*= 15.6 Hz), 30.3 (d, *J*= 23.1 Hz), 29.6 (d, *J*= 8.5 Hz), 27.3 (d, *J*= 20.8 Hz), 27.2 (d, *J*= 26.4 Hz).

^{31}P NMR (121 MHz, CD_2Cl_2): δ = 63.0.

Elemental analysis found for **$C_{18}H_{29}N_2P$** (calc.): C 70.58 (71.02); H 9.52 (9.60); N 9.32 (9.20).

Synthesis of PyMeNP(*i*-Pr)$_2$ (1g)



Potassium hydride (0.601 g, 15.0 mmol) was suspended in 100 mL toluene, the solution cooled to -40°C and 2-(methylamino)pyridine (1.622 g, 15.0 mmol) added dropwise with a syringe. The reaction mixture was stirred at -40°C for 30 min, allowed to warm to room temperature and stirred for further 3 h until it became pale green. Then the reaction mixture was again cooled to -30°C and chloro-diisopropylphosphine (2.4 mL, 2.289 g, 15.0 mmol) added dropwise with a syringe. The solution was stirred for further 30 min at -30°C, the left to warm to rt and stirred overnight. The solution was filtered on a glass filter frit with a celite pad (3 cm) and washed with 30 mL toluene. The solvents were removed in vacuo and the resulting colorless liquid distilled under reduced pressure (0.06 mbar) at 72°C to yield PyMeNP(*i*-Pr)$_2$ as a pale yellow liquid (2.388 g, 71 %).

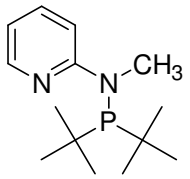
^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.11 (d, *J*= 4.4 Hz, 1H), 7.52-7.44 (m, 1H), 7.40 (ddd, *J*= 8.7, 6.8, 2.1 Hz, 1H), 6.60 (ddd, *J*= 6.7, 5.2, 1.0 Hz, 1H), 3.04 (d, *J*= 1.8 Hz, 3H), 2.22-2.08 (m, 2H), 1.11 (dd, *J*= 16.8, 6.9 Hz, 6H), 0.99 (dd, *J*= 12.0, 7.0 Hz, 6H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ = 153.1 (d, *J*= 22.6 Hz), 147.7, 136.5, 113.9, 111.5 (d, *J*= 26.0 Hz), 26.8 (d, *J*= 15.5 Hz), 19.9, 19.6 (d, *J*= 17.7 Hz).

^{31}P NMR (121 MHz, CD_2Cl_2): δ = 72.3.

Elemental analysis found for **$C_{12}H_{21}N_2P$** (calc.): C 63.98 (64.26); H 9.56 (9.44); N 12.24 (12.49).

Synthesis of PyMeNP*t*Bu$_2$ (1h)



2-(Methylamino)pyridine (1.406 g, 13.0 mmol) was dissolved in 80 mL diethyl ether and the solution was cooled to -30°C. Then *n*-BuLi (8.1 mL, 13.0 mmol) was added dropwise with a syringe. The reaction mixture was stirred at -30°C for 30 min, allowed to warm to room temperature and stirred for 3 h. The reaction mixture was cooled to -20°C and chlorodi-tert-butylphosphine (2.348 g, 13.0 mmol) added dropwise with a syringe. The yellow solution was then left to warm to room temperature and stirred overnight. The yellow suspension was filtered on a glass filter frit with a celite pad (3 cm) and washed with 40 mL diethyl ether. The solvents were concentrated in vacuo and the obtained yellow liquid was then distilled under reduced pressure (0.06 mbar) to yield PyMeNP*t*Bu$_2$ as a yellow liquid (2.42 g, 73 %).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.12 (dd, *J*= 4.9, 0.9 Hz, 1H), 7.72 (ddd, *J*= 8.7, 4.6, 0.7 Hz, 1H), 7.39 (ddd, *J*= 8.7, 6.8, 2.1 Hz, 1H), 6.64-6.56 (m, 1H), 3.27 (s, 3H), 1.24 (d, *J*= 12.6 Hz, 18H).

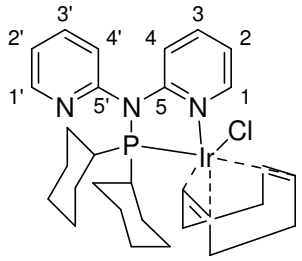
^{13}C NMR (100 MHz, CD_2Cl_2): δ = 163.0 (d, *J*= 27.4 Hz), 147.0, 135.9 (d, *J*= 3.9 Hz), 113.4, 111.8 (d, *J*= 30.3 Hz), 36.9 (d, *J*= 8.4 Hz), 36,0 (d, *J*= 27.7 Hz), 29.8 (d, *J*= 17.1 Hz).

^{31}P NMR (161 MHz, CD_2Cl_2): δ = 86.1.

Elemental analysis found for **$C_{14}H_{25}N_2P$** (calc.): C 66.15 (66.64); H 9.519 (9.99); N 11.21 (11.10).

Complex Synthesis

Preparation of [(Py_2NPCy_2)IrCl(cod)] (2)



$[IrCl(cod)]_2$ (0.134 g, 0.2 mmol) was dissolved in 15 mL CH_2Cl_2 and subsequently a solution of Py_2NPCy_2 (**1b**) (0.147 g, 0.4 mmol) in 5 mL CH_2Cl_2 was added added dropwise. A red solution was obtained and after 15 min the solvent was removed in vacuo, affording **2** as an orange solid in quantitative yields.

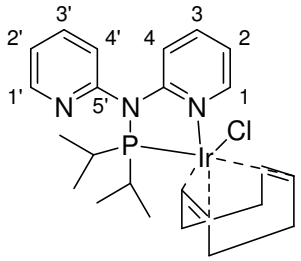
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.66 (d, *J*= 4.4 Hz, 1H, H^1), 8.05 (d, *J*= 5.5 Hz, 1H, $H^{1'}$), 7.91 (t, *J*= 7.7 Hz, 1H, H^3), 7.47 (t, *J*= 7.7 Hz, 1H, $H^{3'}$), 7.42 (dd, *J*= 6.6, 4.0 Hz, 1H, H^2), 7.28 (d, *J*= 7.7 Hz, 1H, H^4), 6.76 (t, *J*= 6.2 Hz, 1H, $H^{2'}$), 6.24 (d, *J*= 8.8 Hz, 1H, $H^{4'}$), 3.90 (s_br, 4H, H_{CHcod}), 2.71 (s_br, 1H, $H_{CHcyclohexyl}$), 2.39 (m, 4H, H_{CH_2cod}), 2.27 (s_br, 1H, $H_{CHcyclohexyl}$), 1.97-1.58 (m, 10H, $H_{CH_2cyclohexyl}$ + 4H, H_{CH_2cod}), 1.45-0.9 (m, 10H, $H_{CH_2cyclohexyl}$).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 164.9 (d, *J*= 15.1 Hz, C^5), 154.3 (d, *J*= 6.0 Hz, $C^{5'}$), 151.0 (s, C^1), 148.5 (s, $C^{1'}$), 139.9 (s, C^3), 139.4 (s, $C^{3'}$), 124.5 (s, C^2), 124.2 (s, C^4), 117.4 (s, $C^{2'}$), 111.7 (d, *J*= 5.2 Hz, $C^{4'}$), 67.3 (br, C_{CHcod}), 66.0 (br, C_{CHcod}), 42.1 (br, $C_{CHcyclohexyl}$), 39.4 (br, $C_{CHcyclohexyl}$), 33.4 (br, C_{CH_2cod}), 31.9 (br, C_{CH_2cod}), 28.0 (d, *J*= 5.0 Hz, $C_{CH_2cyclohexyl}$), 27.7 (d, *J*= 12.9 Hz, $C_{CH_2cyclohexyl}$), 27.5 (d, *J*= 11.3 Hz, $C_{CH_2cyclohexyl}$) 26.7 (s, $C_{CH_2cyclohexyl}$).

^{31}P NMR (161 MHz, CD_2Cl_2): δ= 103.6.

Elemental analysis found for **$C_{30}H_{42}ClIrN_3P$** (calc.): C 51.72 (51.23); H 6.23 (6.02); N 5.68 (5.97).

Preparation of [($Py_2NP(i\text{-}Pr)_2$)IrCl(cod)] (3)



$[IrCl(cod)]_2$ (0.269 g, 0.4 mmol) was dissolved in 15 mL CH_2Cl_2 and subsequently a solution of $Py_2NP(i\text{-}Pr)_2$ (**1c**) (0.230 g, 0.8 mmol) in 5 mL CH_2Cl_2 was added added dropwise. A red solution was obtained and after 15 min the solvent was removed in vacuo, affording **3** as an orange solid in quantitative yields.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.63 (d, *J*= 4.8 Hz, 1H, H^1), 8.09 (d, *J*= 5.9 Hz, 1H, $H^{1'}$), 7.89 (td, *J*= 7.8, 1.7 Hz, 1H, H^3), 7.45 (t, *J*= 8.1 Hz, 1H, $H^{3'}$), 7.39 (dd, *J*= 7.0, 5.1 Hz, 1H, H^2), 7.29 (d, *J*= 7.7 Hz, 1H, H^4), 6.74 (t, *J*= 6.6 Hz, 1H, $H^{2'}$), 6.23 (d, *J*= 8.8 Hz, 1H, $H^{4'}$), 3.85 (s_br, 4H, H_{CHcod}), 3.01 (s_br, 1H, $H_{CH\textit{i}Pr}$), 2.55 (s_br, 1H, $H_{CH\textit{i}Pr}$), 2.44-2.33 (m, 4H, H_{CH_2cod}), 1.91-1.81 (m, 4H, H_{CH_2cod}), 1.34-1.10 (m, 12H, $H_{CH_3\textit{i}Pr}$).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 164.5 (d, *J*= 15.8 Hz, C^5), 154.3 (d, *J*= 5.8 Hz, $C^{5'}$), 150.9 (s, C^1), 148.7 (d, *J*= 1.3 Hz, $C^{1'}$), 139.9 (s, C^3), 139.1 (s, $C^{3'}$), 124.4 (s, C^2), 124.0 (s, C^4), 117.3 (s, $C^{2'}$), 111.4 (d, *J*= 5.2 Hz, $C^{4'}$), 67.2 (br, C_{CHcod}), 66.3 (br, C_{CHcod}), 32.7 (br, C_{CH_2cod}), 28.9 (br, $C_{CH\textit{i}Pr}$), 18.2 (s, $C_{CH_3\textit{i}Pr}$), 18.1 (s, $C_{CH_3\textit{i}Pr}$), 17.6 (s, $C_{CH_3\textit{i}Pr}$), 17.5 (s, $C_{CH_3\textit{i}Pr}$).

^{31}P NMR (161 MHz, CD_2Cl_2): δ= 110.4.

Elemental analysis found for **$C_{24}H_{34}ClIrN_3P$** x 0.5 **CH_2Cl_2** (calc.): C 44.41 (44.21); H 5.36 (5.30); N 6.05 (6.31).

General procedure for screening reactions

In a pressure tube, stock solutions of $[IrCl(cod)]_2$ (80 µL, 0.005 mmol, 0.0625 M in THF) and $Py_2NP(i\text{-}Pr)_2$ (**1c**) (80 µL, 0.01 mmol, 0.125 M in THF) were mixed. Then aniline (45.9 µL, 0.50 mmol), benzyl alcohol (56.8 µL, 0.55 mmol) and 1 mL diethylene glycol dimethyl ether (diglyme) as solvent were added. Last, KO^{t}Bu (0.56 g, 0.55 mmol) was dissolved in the reaction mixture and the pressure tube was fitted with a Teflon® cap and stirred at 110°C for 24 h. The reaction mixture was cooled to room temperature. Then water (15 mL), diethyl ether (15 mL) and

dodecane (56.8 µL, 0.25 mmol) were added. After stirring, an aliquot of the organic phase was analyzed by gas chromatography.

General procedure for the *N*-alkylation reactions

In a pressure tube, stock solutions of $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) and $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF) were mixed. Then the amine (1.00 equiv), the alcohol (1.10 equiv) and 1 mL diethylene glycol dimethyl ether (diglyme) as solvent were added. Last, KO^tBu (1.10 equiv) was dissolved in the reaction mixture and the pressure tube was fitted with a Teflon® cap and stirred at 110°C for 17 h. The reaction mixture was cooled to room temperature and all volatiles were removed in vacuo. Then water (40 mL) was added to the residue and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and the solvent removed in vacuo. Finally, the residue was purified by column chromatography.

Benzylphenylamine (Table 8, entry 1): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), aniline (90.9 µL, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^tBu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 5:1) and gave 0.169 g (92%) benzyl-phenyl-amine as a yellow solid.

^{1}**H NMR** (400 MHz $CDCl_3$): δ = 7.37-7.24 (m, 5H), 7.16 (t, *J*= 8.4 Hz, 2H), 6.70 (t, *J*= 7.2 Hz, 1H), 6.63 (d, *J*= 5.9 Hz, 2H), 4.32 (s, 2H), 4.01 (s_br, 1H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 148.3, 139.6, 129.5, 128.9, 127.7, 127.5, 117.8, 113.1, 48.6.

Benzyl-*m*-tolylamine (Table 8, entry 2): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), m-tolyl-amine (109 µL, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^tBu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 5:1) afforded 0.182 g (92%) benzyl-*m*-tolyl-amine as a brown liquid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 7.43-7.32 (m, 5H), 7.11 (t, *J*= 7.6 Hz, 1H), 6.59 (d, *J*= 7.9 Hz, 1H), 6.51 (s, 1H), 6.49 (d, *J*= 8.4 Hz, 1H), 4.35 8(s, 2H), 3.98 (s_br, 1H), 2.32 (s, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 148.4, 139.7, 139.2, 129.3, 128.8, 127.7, 127.4, 118.7, 113.8, 110.1, 48.5, 21.8.

Benzyl-(4-methoxyphenyl)amine (Table 8, entry 3): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), *p*-anisidine (0.123 g, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 5:1) afforded 0.208 g (98%) benzyl-(4-methoxy-phenyl)-amine as an yellow solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 7.37-7.24 (m, 5H), 6.77 (dd, *J*= 9.2, 4.0 Hz, 2H), 6.61 (dd, *J*= 8.8, 4.8 Hz, 2H), 4.27 (s, 2H), 3.93 (s_br, 1H), 3.73 (s, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 152.6, 142.3, 139.7, 128.8, 127.8, 127.4, 115.1, 114.6, 56.0, 49.6.

Benzyl-(2-methoxyphenyl)amine (Table 8, entry 4): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), *o*-anisidine (112.8 µL, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 20:1) afforded 0.169 g (79%) benzyl-(2-methoxy-phenyl)-amine as a brown liquid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 7.47-7.34 (m, 5H), 6.91 (t, *J*= 9.2Hz, 1H), 6.86 (d, *J*= 3.9 Hz, 1H), 6.77 (t, *J*= 6.4 Hz, 1H), 6.68 (d, *J*= 7.2 Hz, 1H), 4.71 (s_br, 1H), 4.42 (s, 2H), 3.90 (s, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 146.9, 139.7, 138.3, 128.7, 127.6, 127.2, 121.4, 116.8, 110.2, 109.5, 55.5, 48.2.

Benzyl-(3-chlorophenyl)amine (Table 8, entry 5): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), 3-chloro-phenyl-amine (108.3 µL, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 5:1) afforded 0.209 g (96%) benzyl-(3-chloro-phenyl)-amine as a yellow liquid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 7.27-7.17 (m, 4H), 6.97 (t, *J*= 8.4 Hz, 1H), 6.58 (d, *J*= 8.8 Hz, 1H), 6.50 (d, *J*= 1.6 Hz, 1H), 6.37 (dd, *J*= 10.4, 6.4 Hz, 1H), 4.17 (s, 2H), 3.97 (s_br, 1H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 149.4, 138.9, 135.1, 130.4, 128.9, 127.6, 127.5, 117.5, 112.7, 111.3, 48.2.

Benzyl-(4-trifluoromethylphenyl)amine (Table 8, entry 6): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), 4-trifluoromethyl-phenyl-amine (124.3 µL, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. **Reaction time: 3h!!** Purification by column

chromatography (pentane/ethyl acetate, 5:1) afforded 0.169g (67 %) benzyl-(4-trifluoromethyl-phenyl)-amine as a brown solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 7.40 (d, *J*= 8.8 Hz, 2H), 7.37 (d, *J*= 1.8 Hz, 2H), 7.35 (s, 2H), 7.32-7.28 (m, 1H), 6.63 (d, *J*= 8.8 Hz, 2H), 4.43-4.34 (m, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 150.4, 138.4, 128.8, 127.5, 127.3, 126.6 (q, *J*= 3.9 Hz), 124.9 (q, *J*= 270.4 Hz), 119.0 (q, *J*= 23.5 Hz), 111.9, 44.8.

4-Benzylaminobenzonitrile (Table 8, entry 7): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), 4-amino-benzonitrile (0.118 g, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. **Reaction time: 20 min!!** Purification by column chromatography (pentane/diethyl ether, 1:1) afforded 0.144 g (69 %) 4-benzylamino-benzonitrile as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 7.41-7.29 (m, 7H), 6.57 (d, *J*= 8.8 Hz, 2H), 4.59 (s_br, 1H), 4.36 (d, *J*= 4.8 Hz, 2H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 151.3, 138.0, 133.9, 129.1, 127.9, 127.5, 120.6, 112.6, 47.7.

Benzylbiphenyl-2-yl-amine (Table 8, entry 8): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), biphenyl-2-yl-amine (0.173 g, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 30:1) afforded 0.238 g (92%) benzyl-biphenyl-2-yl-amine as a colorless solid.

^{1}**H NMR** (400 MHZ, $CDCl_3$): δ = 7.48-7.38 (m, 5H), 7.35-7.23 (m, 5H), 7.18 (t, *J*= 8.8 Hz, 1H), 7.11 (dd, *J*= 9.2, 6.0 Hz, 1H), 6.77 (t, *J*= 8.4 Hz, 1H), 6.65 (d, *J*= 8.0 Hz, 1H), 4.39 (s_br, 1H), 4.32 (d, *J*= 4.0 Hz, 2H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ= 145.0, 139.6, 139.6, 130.4, 129.6, 129.3, 129.2, 128.9, 128.8, 127.9, 127.5, 127.3, 117.5, 111.0, 48.4.

Benzylpyridin-2-yl-amine (Table 8, entry 9): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.094 g, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 5:1) afforded 0.171 g (93%) 2- benzyl-pyridin-2-yl-amine as a colorless solid.

^{1}**H NMR** (400 MHz $CDCl_3$): δ = 8.05 (ddd, *J* = 3.9, 1.1, 0.9 Hz, 1H), 7.39-7.24 (m, 6H), 6.56 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 4.99 (s_br, 1H), 4.46 (d, *J* = 5.9 Hz, 2H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 158.8, 148.5, 139.4, 137.7, 128.9, 127.6, 127.5, 113.4, 107.0, 46.6.

Benzyl-(4-methylpyridin-2-yl)amine (Table 8, entry 10): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), 4-methyl-pyridin-2-yl amine (0.110 g, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (diethyl ether) afforded 1.187 g (94%) benzyl-(4-methyl-pyridin-2-yl)-amine as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 7.96 (d, *J*= 5.9 Hz, 1H), 7.35-7.24 (m, 5H), 6.42 (d, *J*= 5.2 Hz, 1H), 6.19 (s, 1H), 4.78 (s_br, 1H), 4.48 (d, *J*= 5.6 Hz, 2H), 2.19 (s, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 159.0, 148.8, 147.9, 139.5, 128.8, 127.6, 127.4, 115.0, 107.3, 46.6, 21.4.

Benzylpyridin-3-yl-amine (Table 8, entry 11): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-3-yl-amine (0.097 g, 1.00 mmol), benzyl alcohol (113.6 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (ethyl acetate) afforded g 0.178 g (97%) benzyl-pyridin-3-yl-amine as a yellow solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.5 (d, *J*= 2.8 Hz, 1H), 7.94 (d, *J*= 4.8 Hz, 1H), 7.34-7.26 (m, 5H), 7.4 (dd, *J*= 4.4, 3.9 Hz, 1H), 6.84 (dd, *J*= 10.4, 5.6 Hz, 1H)4.32 (d, *J*= 4.4 Hz, 2H), 4.19 (s_br, 1H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 144.2, 139.1, 138.7, 136.4, 128.9, 127.7, 127.6, 123.9, 118.7, 48.0.

(4-Methylbenzyl)pyridin-2-yl-amine (Table 9, entry 1): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.095 g, 1.00 mmol), p-tolyl-methanol (0.137 g, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (diethyl ether) afforded 0.183 g (92%) (4-methyl-benzyl)-pyridin-2-yl-amine as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.09 (d, *J*= 4.8 Hz, 1H), 7.39 (t, *J*= 7.6 Hz, 1H), 7.26 (d, *J*= 1.2 Hz, 2H), 7.14 (d, *J*= 8.0 Hz, 2H), 6.58 (t, *J*= 6.4 Hz, 1H), 6.36 (d, *J*= 8.4 Hz, 1H), 4.85 (s_br, 1H), 4.45 (d, *J*= 5.6 Hz, 2H), 2.34 (s, 3H).

^{13}**C NMR** (100 MHz. $CDCl_3$): δ = 158.9, 148.4, 137.7, 137.1, 136.3, 129.5, 127.6, 113.3, 106.9, 46.3, 21.3.

(4-Chlorobenzyl)pyridin-2-yl-amine (Table 9, entry 2): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.095 g, 1.00 mmol), (4-chloro-phenyl)-methanol (0.158 g, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (diethyl ether) afforded 0.207 g (97%) (4-chloro-benzyl)-pyridin-2-yl-amine as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.09 (d, *J*=4.4 Hz, 1H), 7.40-7.27 (m, 5H), 6.58 (d, *J*= 7.2 Hz, 1H), 6.33 (d, *J*= 8.4 Hz, 1H), 4.87 (s_br, 1H), 4.47 (d, *J*= 4.0 Hz, 2H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 158.6, 148.6, 138.0, 137.7, 133.1, 129.0, 128.9, 113.6, 107.1, 45.7.

(4-Methoxybenzyl)pyridin-2-yl-amine (Table 9, entry 3): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.095 g, 1.00 mmol), (4-methoxy-phenyl)-methanol (0.154 g, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (diethyl ether) afforded 0.207 g (97%) (2-methoxy-benzyl)-pyridin-2-yl-amine as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.06 (d, *J*= 5.2 Hz, 1H), 7.36 (t, *J*= 7.2 Hz, 1H), 7.25 (d, *J*= 8.4 Hz, 2H), 6.84 (d, *J*= 6.8 Hz, 2H), 6.55 (t, *J*= 6.8 Hz, 1H), 6.33 (d, *J*= 8.4 Hz, 1H), 4.84 (s_br, 1H), 4.39 (d, J= 5.6 Hz, 2H), 3.76 (s, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 159.0, 158.8, 148.4, 137.6, 131.4, 128.9, 114.2, 113.3, 107.0, 55.5, 46.0.

(2-Methoxybenzyl)pyridin-2-yl-amine (Table 9, entry 4): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.095 g, 1.00 mmol), (2-methoxy-phenyl)-methanol (147.70 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (diethyl ether) afforded 0.203 g (95%) (2-methoxy-benzyl)-pyridin-2-yl-amine as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.08 (d, *J*= 5.6 Hz, 1H), 7.36 (dt, *J*= 8.4, 6.8 Hz, 1H), 7.29 (d, *J*= 7.6 Hz, 1H), 7.23 (dt, *J*= 8.6, 8.0 Hz, 1H), 6.86 (m, 2H), 6.53 (t, *J*= 6.0 Hz, 1H), 6.37 (d, *J*= 8.4 Hz, 1H), 4.95 (s_br, 1H), 4.47 (d, *J*= 6.39, 2H), 3.84 (s, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 159.1, 157.7, 148.4, 137.6, 128.9, 129.6, 127.3, 120.7, 113.0, 110.4, 106.9, 55.5, 41.9.

Furan-2-yl-methylpyridin-2-yl-amine (Table 9, entry 5): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.095 g, 1.00 mmol), furan-2-yl-methanol (97.4 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 1:1) afforded 0.123 g (71%) furan-2-ylmethyl-pyridin-2-yl-amine as a brown solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.09 (d, *J*= 5.6 Hz, 1H), 7.39 (t, *J*= 7.2 Hz, 1H), 7.33 (d, *J*= 1.0 Hz, 1H), 6.58 (t, *J*= 6.0 Hz, 1H), 6.14 (d, *J*= 8.4 Hz, 1H), 6.29 (t, *J*= 2.8 Hz, 1H), 6.21 (d, *J*= 3.2 Hz, 1H), 4.88 (s_br, 1H), 4.49 (d, *J*= 5.6 Hz, 2H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ= 158.4, 152.8, 148.3, 142.1, 137.6, 113.6, 110.5, 107.5, 107.1, 39.5.

Pyridin-2-yl-tiophen-2-yl-methylamine (Table 9, entry 6): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.095 g, 1.00 mmol), thiophen-2-yl-methanol (140.9 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 1:1) afforded 0.131 g (69%) pyridin-2-yl-tiophen-2-ylmethyl-amine as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.11 (d, *J*= 5.2 Hz, 1H), 7.40 (t, *J*= 8.4, 1H), 7.18 (d, *J*= 6.4 Hz, 1H), 6.99 (d, *J*= 2.8 Hz, 1H), 6.94 (t, *J*= 3.4 Hz, 1H), 6.59 (t, *J*= 4.6 Hz, 1H), 6.41 (d, *J*= 8.4, 1H), 4.85 (s_br, 1H), 4.68 (d, *J*= 5.6 Hz, 2H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 158.3, 148.4, 142.8, 137.6, 127.0, 125.4, 124.9, 113.7, 107.6, 41.5.

Pyridin-2-yl-pyridin-2-yl-methylamine (Table 9, entry 7): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.095 g, 1.00 mmol), pyridin-2-yl-methanol (108.4 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether/THF, 1:1:1) afforded 0.082 g (44%) pyridin-2-yl-pyridin-2-ylmethyl-amine as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.53 (d, *J*= 4.8 Hz, 1H), 8.08 (d, *J*= 4.8 Hz, 1H), 7.59 (dt, *J*= 7.6, 1.6 Hz, 1H), 7.35 (dt, *J*= 8.8, 1.6 Hz, 1H), 7.29 (d, *J*= 7.6 Hz, 1H), 7.13 (t, *J*= 5.2 Hz, 1H), 6.54 (t, *J*= 5.2 Hz, 1H),. 6.42 (d, *J*= 8.4 Hz, 1H), 5.66 (s_br, 1H), 4.62 (d, *J*= 5.2 Hz, 2H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 158.6, 158.3, 149,.2, 148.3, 137.4, 136.8, 122.2, 121.8, 113.2, 107.9, 47.4.

Butylpyridin-2-yl-amine (Table 9, entry 9): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.095 g, 1.00 mmol), butan-1-ol (102.54 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 1:1) afforded 0.113 g (75%) butyl-pyridin-2-yl-amine as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.04 (d, *J*= 4.0 Hz, 1H), 7.37 (dt, *J*= 8.4, 6.8 Hz, 1H), 6.51 (t, *J*= 6.0 Hz, H), 6.33 (d, *J*= 8.4 Hz, 1H); 4.52 (s_br, 1H), 3.21 (q, *J*= 6.8 Hz, 2H), 1.61-1.53 (m, 2H), 1.42-1.38 (m, 2H), 0.92 (t, *J*= 7.2 Hz, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 159.2, 148.4, 137.5, 112.7, 106.4, 42.2, 31.8, 20.4, 14.0.

Octylpyridin-2-yl-amine (Table 9, entry 10): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (**1c**) (160 µL, 0.02 mmol, 0.125 M in THF), pyridin-2-yl-amine (0.095 g, 1.00 mmol), octan-1-ol (175.0 µL, 1.10 mmol), KO^{t}Bu (0.123 g, 1.10 mmol) and 1 mL diglyme. Purification by column chromatography (pentane/diethyl ether, 1:1) afforded 0.149 g (72%) octyl-pyridin-2-yl-amine as a colorless solid.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.04 (dd, *J*= 6.4, 4.0 Hz, 1H), 7.38 (dt, *J*= 7.2, 6.8 Hz, 1H), 6.52 (t, *J*= 4.8 Hz, 1H), 6.33 (d, *J*= 8.4 Hz, 1H), 4.48 (s_br, 1H), 3.21 (q, *J*= 7.2 Hz, 2H), 1.59 (m, 2H), 1.36-1.24 (m, 10H), 0.85 (t, *J*=6.8 Hz, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 159.2, 148.4, 137.6, 112.8, 106.5, 42.5, 32.0, 29.8, 29.6, 29.5, 27.3, 22.9, 14.3.

6. Selective Iridium-Catalyzed Alkylation of (Hetero)Aromatic Amines and Diamines with Alcohols under Mild Reaction Conditions

Benoît Blank, Stefan Michlik, and Rhett Kempe*[a]

[a] Benoît Blank, Stefan Michlik, Prof. Dr. Rhett Kempe, Lehrstuhl für Anorganische Chemie II, Universitätsstraße 30, NW I, 95440 Bayreuth, Germany. Fax: +49 (0) 921-55-2157, E-mail: kempe@uni-bayreuth.de

Abstract: A P,N-ligand coordinated iridium complex has been employed as an efficient catalyst for the selective monoalkylation of (hetero)aromatic amines with alcohols. A significant improvement of this alkylation method has been achieved, such that it can be performed at a temperature of 70°C and with catalyst loadings as low as 0.1 mol% Ir, while still affording excellent yields of secondary amines. Furthermore, the high selectivity of this catalyst for the monoalkylation of aromatic amino functions has been successfully exploited for the alkylation of diamines in both symmetric and nonsymmetric fashions, providing a novel and very efficient synthetic tool for the preparation of *N*,*N'*-dialkylated aromatic diamines.

Keywords: alkylation, amines, iridium, P,N-ligands

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6.1. Introduction

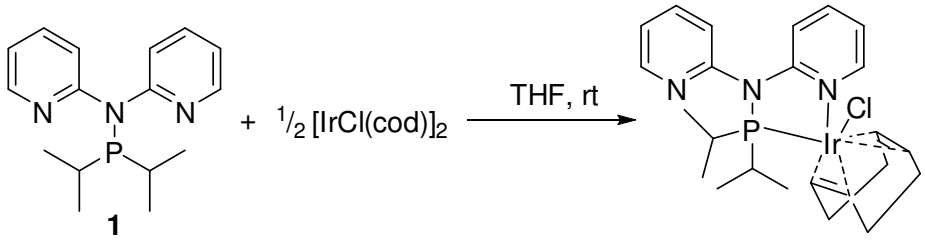
Nitrogen-containing molecules and especially amines are a very important class of compounds. They find widespread application in both the bulk and fine chemical industries as basic intermediates, additives, dyes, and agrochemicals, as well as in the pharmaceutical industry.[1] The development of simple methods for the selective formation of C–N-bonds is therefore of great importance. The best known method for the alkylation of amines is their nucleophilic substitution reaction with haloalkanes.[2] However, this reaction is only moderately selective and the mono-, di-, and trialkylated amines as well as quaternary ammonium salts are obtained. Therefore, several synthetic protocols for the selective alkylation of amines have been developed in the last decades, such as the reductive amination of carbonyl compounds[3] or the hydroamination[4] and hydroaminomethylation[5] of C–C multiple bonds. However, these methods have certain

inconveniences. The direct reductive amination of carbonyl compounds is still rather difficult to accomplish and this reaction is therefore mostly performed in two steps, by reduction of a previously prepared imine. Compared to the well-established intramolecular hydroamination reaction, the intermolecular coupling of alkenes and amines is still very challenging. Hence, the catalytic alkylation of amines using alcohols is an interesting and promising method, since a great variety of inexpensive alcohols is commercially available and water is the only by-product of the reaction, rendering the reaction very atom-economic. Unfortunately, this reaction has a reputation of being rather problematic in terms of catalyst loading and reaction temperature. The first homogeneous catalysts employed for the alkylation of amines with alcohols were mainly based on ruthenium,[6] as well as rhodium,[7] iridium,[7] and platinum,[8] but were only moderately selective and needed very high reaction temperatures >180°C. In the last few years this type of reaction has again received widespread attention due to the development of a more selective Ru catalyst by Beller et al. that can be used for the alkylation of aliphatic amines with primary as well as secondary alcohols.[9] Another highly efficient Cp*Ir-based catalyst has been reported by Fujita et al., which allows the reaction of a great variety of aromatic as well as aliphatic amines with primary and secondary alcohols and a controlled selectivity in favor of monoalkylation.[10] The mechanism of this Ir-catalyzed amination reaction has also recently been studied by DFT calculations,[11] affording a better understanding of the reaction pathways. Significant contributions by Williams et al. have led to a broadened application scope for the amination of alcohols[12] and a better understanding of the "borrowing hydrogen" mechanism.[13] Following on from this mechanistic approach, Beller et al. recently reported a very efficient method for the synthesis of secondary amines starting directly from aliphatic amines and anilines using the Shvo catalyst.[14] Herein, we present an optimized method for the selective Ir-catalyzed monoalkylation of (hetero)aromatic amines that proceeds efficiently under rather mild conditions, at 70°C and with catalyst loadings as low as 0.1 mol% Ir. Also, a new protocol for the symmetric and nonsymmetric *N*,*N'*-dialkylation of diamines with alcohols is reported, demonstrating the potential of our catalyst towards a broad scope of substrates.

6.2. Results and Discussion

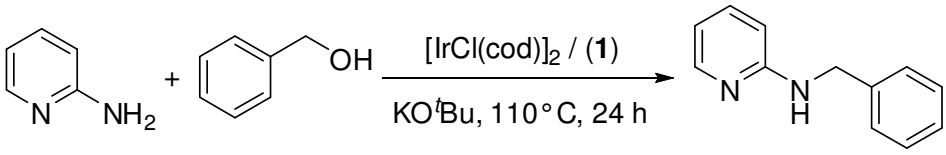
Optimization of the reaction conditions:

Recently, we reported on a novel P,N-ligand stabilized[15] iridium catalyst for the selective monoalkylation of amines with alcohols.[16] The complex was generated in-situ from $[IrCl(cod)]_2$ (cod = cis-1,5-cyclooctadiene) and the P,N-ligand $Py_2NP(i\text{-}Pr)_2$ (**1**) (Scheme 1).



Scheme 1. In-situ formation of the catalyst from $[IrCl(cod)]_2$ and P,N-ligand **1**.

In this first study the reaction conditions for the alkylation of anilines were optimized by the screening of several reaction parameters such as the addition of base, the use of different solvents, base/substrate and alcohol/substrate ratios, as well as the catalyst loading. As a result, we developed a very useful method not only for the selective monoalkylation of aromatic amines such as aniline, but also for heteroaromatic substrates such as aminopyridines, which are usually more difficult to alkylate.[17] In order to further improve this method for the alkylation of heteroaromatic substrates, several reaction parameters that had not been tested before, such as the amount of solvent and the temperature, were evaluated with regard to higher catalyst efficiencies as well as milder reaction conditions. In all former reactions 1 mL diglyme (diethylene glycol dimethyl ether) per mmol of substrate had been added to the reaction mixture, since this had afforded the best results in the first solvent screening. However, the quantity used had not been examined and so our goal here has been to determine the smallest possible amount of solvent, in anticipation of higher catalytic activity in a more concentrated reaction mixture. All optimization studies were carried out with 2-aminopyridine and benzyl alcohol as model substrates (Scheme 2).



Scheme 2. Model reaction used for the variation of several reaction parameters.

Table 1. Influence of the solvent quantity.

Entry	Solvent quantity (diglyme) [mL]	Yield [%][a]
1	2.0	77
2	1.0	83
3	0.8	78
4	0.5	83
5	0.4	81
6	0.2	90
7	0	85

Reaction conditions: 1.0 mmol 2-aminopyridine, 1.1 mmol benzyl alcohol, 1.0 mol% $[IrCl(cod)]_2$, 2.0 mol% $Py_2NP(i\text{-}Pr)_2$ (**1**), 1.1 mmol KO^tBu, 0-2 mL diglyme, 110°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard.

Interestingly, the results in Table 1 show that the yield of the reaction is not significantly dependent on the addition of diglyme to the reaction mixture, since even the reaction without the addition of diglyme (entry 7) afforded an excellent yield of the alkylated product. However, the use of 0.2 mL of diglyme was chosen for all further reactions (entry 6) since incomplete dissolution of the base in the very small amount of THF from the catalyst stock solutions could thereby be avoided. Moreover, towards the end of the reaction, the solution otherwise became very viscous, which could lead to insufficient stirring.

Having successfully lowered the amount of added solvent to a fifth of the original quantity, we proceeded to determine the optimal catalyst loading for this reaction, since catalyst cost is a very important aspect for the application of a catalyst in organic synthesis (Table 2).

Table 2. Reduction of the catalyst loading.

Entry	Cat. loading [mol% Ir]	Yield [%][a]
1	2.0	90
2	1.0	87
3	0.6	92
4	0.2	85
5	0.1	90
6	0.05	74
7	0	10

Reaction conditions: 1.0 mmol 2-aminopyridine, 1.1 mmol benzyl alcohol, 0 – 1.0 mol% $[IrCl(cod)]_2$, 0 - 2.0 mol% $Py_2NP(i\text{-}Pr)_2$ (**1**), 1.1 mmol KO^tBu, 0.2 mL diglyme, 110°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard.

Screening of the catalyst loading showed that in the range from 2.0 to 0.1 mol% Ir (entries 1-5) the yield of the product remained relatively constant and that even with 0.05 mol% Ir (entry 6) a satisfactory yield could still be obtained. As expected, the higher concentration of the reaction mixture increased the efficiency of the catalyst and therefore 0.1 mol% Ir was determined as a minimum for all further reactions. Interestingly, the reaction also took place to some extent when no catalyst was used, affording about 10% of the alkylated product (entry 7). Lastly, the temperature for this alkylation reaction was also re-evaluated. Most recent protocols from the literature need elevated temperatures of at least 110°C in order to alkylate amines with alcohols.[9,10,12,16] A lower reaction temperature would not only be beneficial from a technical point of view, but would also allow the use of more sensitive substrates that would decompose at higher temperatures. In previously conducted reactions, decomposition of chloro-substituted benzyl alcohols had been observed at 110°C, leading to a partial loss of the chlorine atom in the final product. Also, the reaction of 4-(trifluoromethyl)benzyl alcohol with 2-aminopyridine could not be performed, since the starting materials easily decomposed. The effect of varying the temperature on the alkylation of 2-aminopyridine with benzyl alcohol is summarized in Table 3.

Table 3. Influence of the temperature.

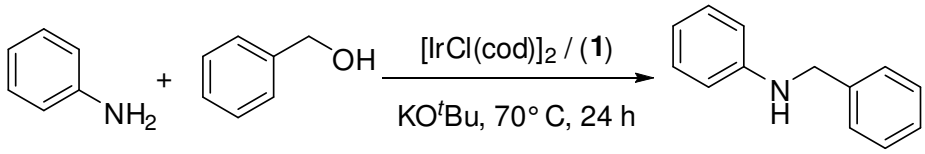
Entry	Temperature [°C]	Yield [%][a]
1	110	95
2	90	94
3	70	93
4	50	69
5	25	55

Reaction conditions: 1.0 mmol 2-aminopyridine, 1.1 mmol benzyl alcohol, 0.05 mol% $[IrCl(cod)]_2$, 0.1 mol% $Py_2NP(i\text{-}Pr)_2$ (**1**) , 1.1 mmol KO^{t}Bu, 0.2 mL diglyme, 25-110°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard.

These results show that the reaction could readily be performed at just 70°C (entry 3) affording the same results as at higher temperatures (entries 1 and 2). The efficiency of the catalytic system significantly decreases when the reaction is performed at 50°C, but moderate yields of the product could nevertheless be obtained even at room temperature. The above studies showed our catalyst to be especially efficient for the alkylation of heteroaromatic substrates such as aminopyridines, which prompted us to determine whether the mild reaction conditions and the low catalyst loadings were restricted to aminopyridines or whether they could also be applied for the alkylation of anilines. Since in our first study full conversions of the latter had only been obtained with 2 mol% of

catalyst, it was of interest to determine whether the reduction of the solvent quantity could also be beneficial for the alkylation anilines. Therefore, a further screening of the catalyst loading was performed with aniline and benzyl alcohol under the above optimized reaction conditions (Table 4).

Table 4. Reduction of the catalyst loading for the alkylation of anilines.



Entry	Cat. loading [mol% Ir]	Yield [%][a]
1	2.0	97
2	1.0	96
3	0.6	93
4	0.4	87
5	0.2	71
6	0.1	38

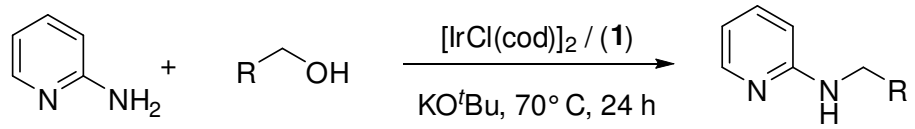
Reaction conditions: 1.0 mmol aniline, 1.1 mmol benzyl alcohol, 0.05-1.0 mol% $[IrCl(cod)]_2$, 0.1-2.0 mol% $Py_2NP(i\text{-}Pr)_2$ (**1**), 1.1 mmol KO^tBu, 0.2 mL diglyme, 70°C, 24 h. [a] Yield determined by GC analysis with dodecane as internal standard.

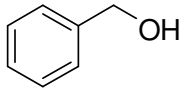
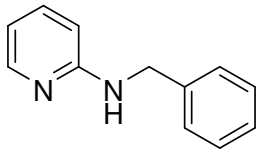
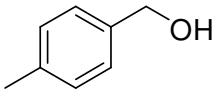
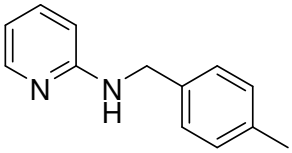
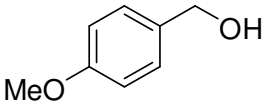
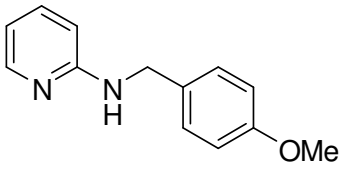
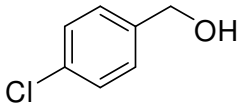
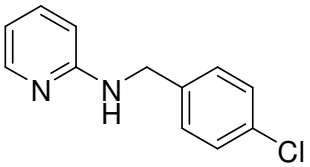
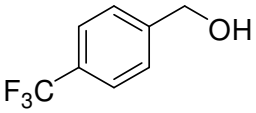
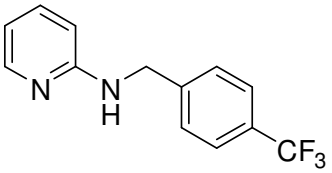
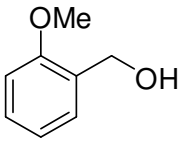
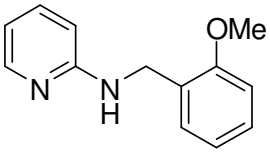
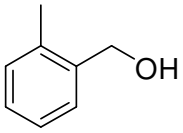
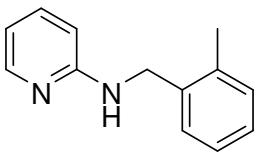
As expected, the optimized reaction conditions for 2-aminopyridine could also be applied for the alkylation of anilines. However, the results presented in Table 4 clearly show that anilines are less reactive compared to heteroaromatic amines and that catalyst loadings of at least 0.6 mol% Ir have to be employed (entry 3) to achieve full conversion of the substrate and excellent yields of the product. It seems that the catalyst is very sensitive to electronic effects, since electron-rich aliphatic amines cannot be alkylated at all, whereas the catalytic activity increases with decreasing electron density on the amine, heteroaromatic substrates therefore being most efficiently alkylated. Moreover, this catalytic system is the first reported to be highly efficient for the alkylation of heteroaromatic amines with alcohols, because these substrates can lead to the deactivation of other catalysts due to their strong coordinating potential. Deprotonated aminopyridines are a well described class of ligands.[18, 19]

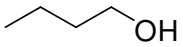
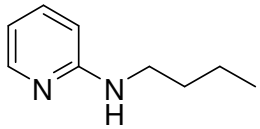
In summary, the efficiency of our catalytic system has been further increased through reduction of the amount of solvent and as a result catalyst loadings as low as 0.1 mol% Ir and milder reaction temperatures of only 70°C may be applied. The optimal reaction conditions for the alkylation of aromatic amines with alcohols are now: 1.0 mmol aminopyridine, 1.05 mmol alcohol, 1.1 mmol KO^tBu, 0.2 mL diglyme, 0.05 mol% $[IrCl(cod)]_2$, 0.1 mol% $Py_2NP(i\text{-}Pr)_2$ (**1**), reaction temperature: 70°C, time: 24h. Based on these optimized reaction conditions the general applicability of this

method for the monoalkylation of 2-aminopyridine with various substituted benzylic as well as aliphatic alcohols is presented in Table 5.

Table 5. Iridium-catalyzed *N*-alkylation of 2-aminopyridine with several alcohols.



Entry	Cat. loading [mol% Ir]	Alcohol	Product	Yield [%][a]
1	0.1		 **2a**	93
2	0.2		 **2b**	89
3	0.1		 **2c**	86
4	0.2		 **2d**	71
5	0.6		 **2e**	75
6	0.8		 **2f**	92[b]
7	0.3		 **2g**	90

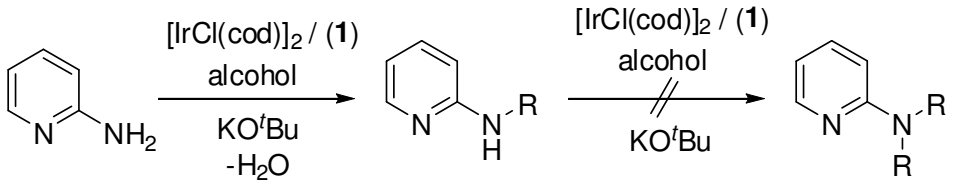
8	2.0		 **2h**	83[b]

Reaction conditions: 1.0 mmol 2-aminopyridine, 1.05 mmol alcohol, $[IrCl(cod)]_2$, $Py_2NP(i\text{-}Pr)_2$ (**1**), 1.1 mmol KO^tBu, 0.2 mL diglyme, 70°C, 24 h. [a] isolated yield. [b] 48 h.

These results show that under the optimized reaction conditions (hetero)aromatic amines can be efficiently alkylated with a variety of substituted benzyl alcohols bearing functional groups in their *para* (entries 2-5) or *ortho* position (entries 6 and 7), affording the expected secondary amines **2a-h** in yields ranging from 71% to 93%. Both electron-withdrawing (entries 4 and 5) and electron-donating substituents (entries 2, 3, 6 and 7) are well tolerated. However, in the case of 4-chlorobenzyl alcohol the catalyst loading had to be increased to 0.2 mol% Ir, otherwise a full conversion could not be observed, not even after a prolonged reaction time of 48 h. Loss of the chlorine atom in the final product, resulting in the formation of unwanted benzylpyridin-2-ylamine, did not occur, a fact that can certainly be attributed to the milder reaction temperature of 70°C. For the first time it was also possible to perform the alkylation reaction with 4-(trifluoromethyl)-benzyl alcohol, albeit with a higher catalyst loading of 0.6% Ir, affording the secondary amine **2e** in 75% yield (entry 5), which had hitherto not been possible due to decomposition of the starting material. Besides *para*-substituted benzyl alcohols *ortho*-substituted benzyl alcohols are also well tolerated and, with a slightly higher catalyst loading of 0.3 mol% Ir, the reaction with 2-methylbenzyl alcohol readily afforded the secondary amine **2g** in 90% yield (entry 7). The more sterically hindered substrate 2-methoxybenzyl alcohol also afforded the corresponding amine **2f** in excellent yield (entry 6). The need for a higher catalyst loading and longer reaction time with this substrate can be rationalized in terms of increased steric demand of the *ortho*-methoxy group compared to the smaller *ortho*-methyl group. In all of the reactions discussed thus far, substituted benzyl alcohols that innately favor the deprotonation of the alcohol function due to their electron-withdrawing nature were employed. Hence, the reaction was also performed with 1-butanol (entry 8) as a general example that the method can also be used with aliphatic alcohols, even though this required a higher catalyst loading of 2 mol% Ir and a longer reaction time of 48 h due to the electron-donating nature of the alkyl backbone and hence decreased proclivity for deprotonation of the alcohol.

Alkylation of diamines with alcohols:

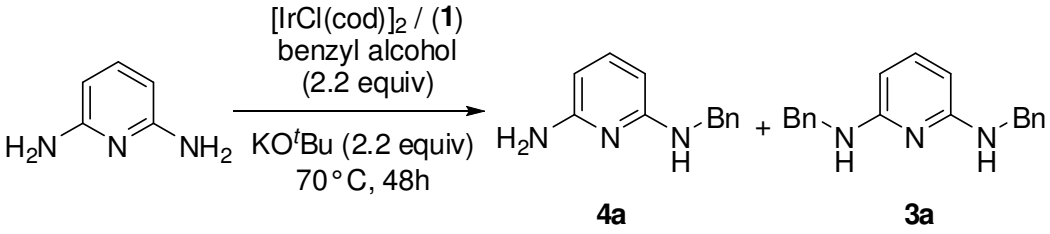
One of the outstanding properties of the present catalyst is its high selectivity for monoalkylation of (hetero)aromatic amines. There are of course other recently developed catalytic systems that provide good selectivity in favor of the monoalkylation of primary amines, but in most cases the alcohol cannot be added in excess, since this would favor the formation of the tertiary amine. On the contrary, with the present catalyst, no dialkylation of the amino function to afford the tertiary amine could be observed in any reaction, irrespective of the amount of alcohol or base added, even with high catalyst loadings and after very long reaction times (Scheme 3).



Scheme 3. High selectivity of the catalyst towards monoalkylation of amines.

Hence, it was of interest to determine whether this selectivity for the monoalkylation of primary aromatic amino functions could be used for the *N*,*N'*-dialkylation of diamines. Only very few synthetic procedures for the preparation of such compounds can be found in the literature, which variously require very high reaction temperatures (up to 250°C),[20] previous protection of the amino groups and subsequent treatment with alkyl halides[21] or a reductive amination pathway.[22] In most cases, these transformations are either not selective or have to be performed in several steps and thus lack general applicability towards a broad range of substrates. The reaction of 2,6-diaminopyridine with two equivalents of benzyl alcohol was chosen as a model reaction. Since the alkylation of both amino functions of the substrate is more demanding than that of simple aminopyridines the reaction time was increased to 48h and the catalyst loading was re-examined. The results of this study are summarized in Table 6.

Table 6. Determination of the optimal catalyst loading for the alkylation of 2,6-diaminopyridine.

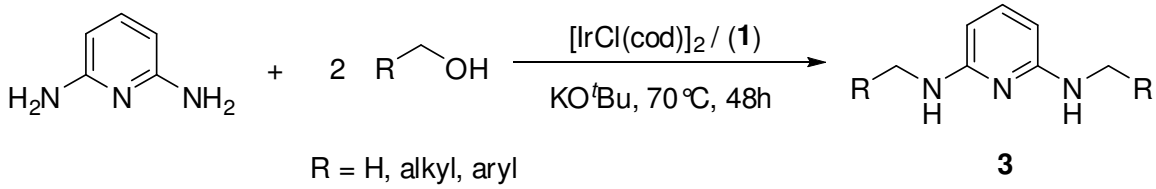


Entry	Cat. loading [mol% Ir]	Yield [%][a] 4a	Yield [%][a] 3a
1	2.0	0	89
2	1.0	1	86
3	0.8	1	84
4	0.6	1	81
5	0.5	8	76
6	0.4	13	75
7	0.3	15	66
8	0.2	23	58
9	0.1	48	20
10	0	1	0

Reaction conditions: 1.0 mmol 2,6-diaminopyridine, 2.1 mmol benzyl alcohol, 0-1.0 mol% $[IrCl(cod)]_2$, 0-2.0 mol% $Py_2NP(i\text{-}Pr)_2$ (**1**), 2.2 mmol KO^tBu, 0.2 mL diglyme, 70°C, 48 h. [a] Yield determined by GC analysis with dodecane as internal standard.

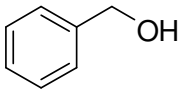
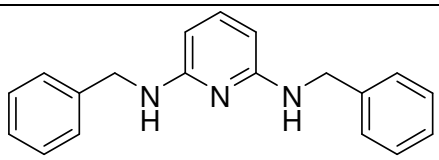
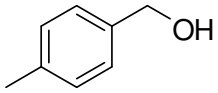
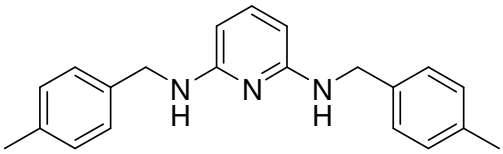
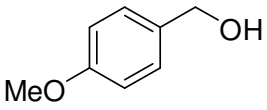
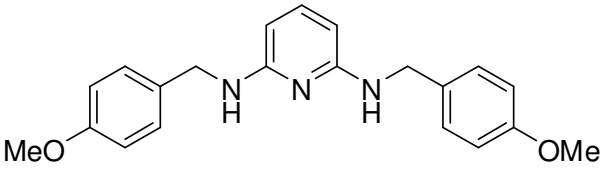
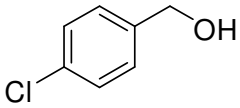
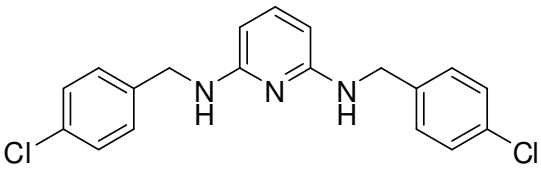
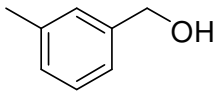
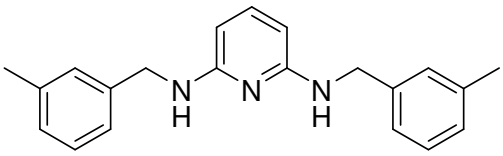
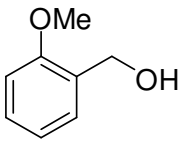
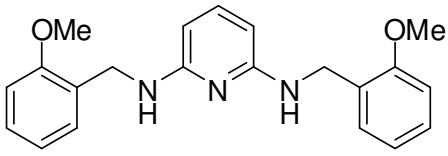
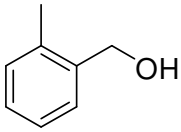
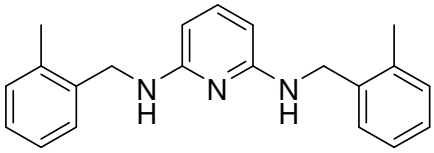
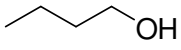
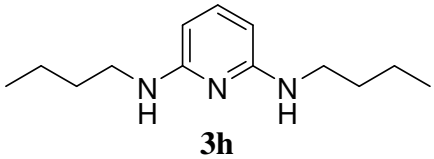
As is evident from the results in Table 6 it is possible to selectively monoalkylate both amino functions of the diamine affording the corresponding product **3a** in excellent yield. However, as expected, this reaction needs slightly elevated catalyst loadings in order to obtain full conversions. Moreover, the reaction occurs in two separate alkyation steps since, depending on the catalyst loading, the unilaterally monoalkylated diamine **4a** is observed as a by-product. The use of 0.6 mol% Ir represents a good compromise between catalyst loading and yield of the dialkylated diamine (Table 6, entry 4). In order to demonstrate the general applicability of this method 2,6-diaminopyridine was reacted with several substituted benzylic as well as aliphatic alcohols, affording the symmetrically *N*,*N'*-dialkylated diamines **3a-i** in excellent yields (Table 7).

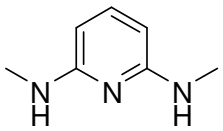
Table 7. Ir-catalyzed alkylation of 2,6-diaminopyridine with various alcohols.



R = H, alkyl, aryl

3

Entry	Cat. loading [mol% Ir]	Alcohol	Product	Yield [%][a]
1	0.6		 **3a**	94
2	0.6		 **3b**	90
3	0.6		 **3c**	97
4	0.6		 **3d**	87
5	0.6		 **3e**	93
6	1.4		 **3f**	82
7	1.4		 **3g**	86
8	0.6		 **3h**	90

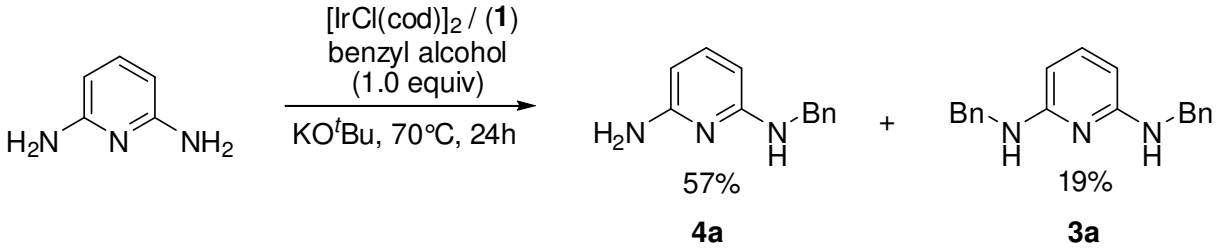
9	0.8	MeOH	 **3i**	88[b]

Reaction conditions: 1.0 mmol 2,6-diaminopyridine, 2.1 mmol alcohol, $[IrCl(cod)]_2$, $Py_2NP(i\text{-}Pr)_2$ (**1**), 0.2 mL diglyme, 0.35 mL THF, 2.2 mmol KO^{t}Bu 70°C 48 h. [a] isolated yield. [b] 4.0 mmol methanol.

First, 2,6-diaminopyridine was reacted with benzyl alcohol (entry 1), which afforded *N*,*N'*-dibenzyl-pyridine-2,6-diamine (**3a**) in 94% yield. Next, several substituted benzyl alcohols were employed (entries 2-7), and, as determined before for the alkylation of 2-aminopyridine (Table 5), both electron-donating (entries 2 and 3) and electron-withdrawing (entry 4) substituents in the *para* position are well tolerated, these reactions affording the dialkylated products in yields ranging from 87% to 97%. The excellent yield in the case of the reaction of 4-methoxybenzyl alcohol with 2,6-diaminopyridine (entry 3) can be attributed to the limited solubility of *N*,*N'*-bis(4-methoxybenzyl)pyridine-2,6-diamine (**3c**) in THF and diglyme; the product precipitates from the solution, thereby shifting the reaction equilibrium in its favor. Furthermore, benzyl alcohols bearing substituents in *meta* position may also be used in this reaction, affording excellent yields of the alkylated product (entry 5). However, in the case of *ortho*-substituted benzyl alcohols, for example with 2-methylbenzyl alcohol (entry 7) or 2-methoxybenzyl alcohol (entry 6), the reaction is more difficult and the catalyst loading had to be raised to 1.4 mol% Ir. Substituents in the *ortho* position have a higher steric demand and probably hamper the coordination of the imine to the catalyst and the transfer of the hydride to the latter. As is evident from entries 6 and 7, the reaction of 2-methylbenzyl alcohol with 2,6-diaminopyridine affords a better yield than that of 2-methoxybenzyl alcohol, since the methoxy group has a slightly greater steric demand compared to the methyl group. No such differentiation is observed when these substituents are in the *meta* or *para* positions. In addition, aliphatic alcohols could also be employed as substrates for this reaction. As a first example the reaction was performed with 1-butanol, which afforded *N*,*N'*-dibutylpyridine-2,6-diamine (**3h**) in 90% yield (entry 8). Methanol was also used for the alkylation reaction (entry 9), since the selective methylation of amines is of great synthetic interest. This interest stems for the fact, that highly toxic and carcinogenic methyl iodide is usually employed as the methylating agent, which leads to non-selective methylation of diamines. As shown in entry 9, it is possible to selectively dimethylate 2,6-diaminopyridine using methanol with a catalyst loading of 0.8 mol% Ir, affording **3i** in 88% yield. The excess of methanol used for this reaction was to ensure its good availability as a reagent because it might be in a state of reflux at a reaction temperature of 70°C.

However, due to the high selectivity of the catalyst for monoalkylation,this excess of methanol did not present a problem.

As stated before, the Ir-catalyzed dialkylation of diamines with alcohols is a two-step reaction, in which the starting diamine is first monoalkylated on one side and then the second amino function is alkylated. The possibility of nonsymmetrically alkylating diamines with different alcohols without having to first protect one amino group would be even more interesting than the preparation of symmetrically dialkylated substrates. The reaction was therefore repeated with exactly one equivalent of alcohol with the aim of selectively obtaining the unilaterally alkylated diamine **4a** (Scheme 4).



Scheme 4. Reaction of 2,6-diaminopyridine with one equiv benzyl alcohol affording the mono-*N*-alkylated (**4a**) and *N,N'*-dialkylated product (**3a**).

However, **4a** could only be obtained in 57% yield, along with the *N,N'*-dialkylated product **3a** (19%) as well as unreacted starting material (20%), rendering a one-pot preparation of nonsymmetrically alkylated diamines impossible. To gain a better understanding of this reaction, a kinetic experiment was performed in which the composition of the reaction mixture was monitored over time by gas chromatography (Fig. 1).

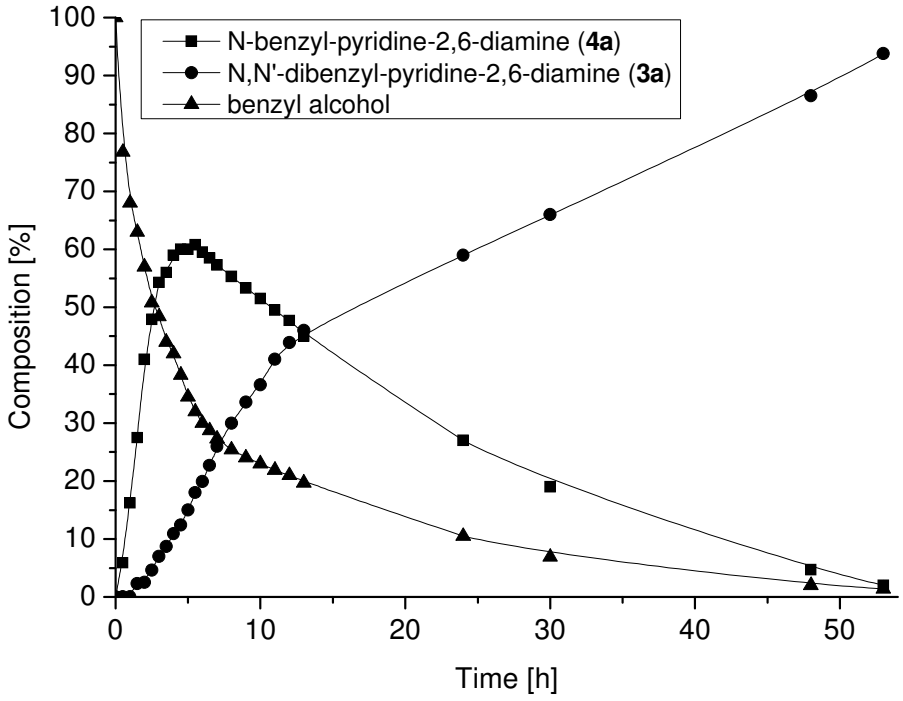
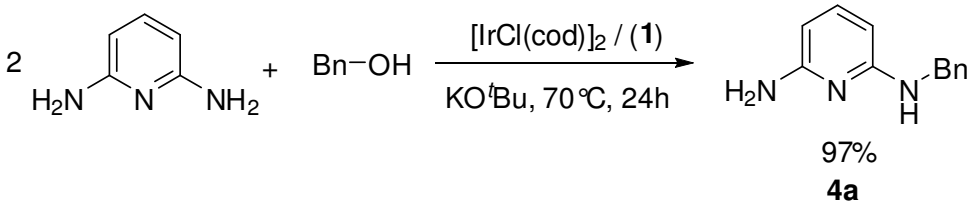


Fig. 1. Time-Conversion-Plot for the reaction of 2,6-diaminopyridine with benzyl alcohol. Reaction conditions: 4.0 mmol 2,6-diaminopyridine, 8.4 mmol benzyl alcohol, 0.3 mol% $[IrCl(cod)]_2$, 0.6 mol% $Py_2NP(i\text{-}Pr)_2$ (**1**), 0.8 mL diglyme, 4.4 mL THF, 8.8 mmol KO^tBu, 70°C, 53 h. Conversion and yields determined by GC analysis with dodecane as internal standard.

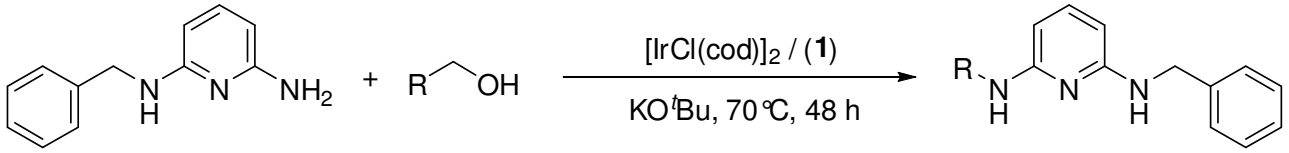
This experiment clearly showed that under the given circumstances it is not possible to obtain compound **4a** in yields higher than 60%, since its formation reaches a after around six hours. At the same time, around 20% of **4a** has already reacted with another equivalent of alcohol to afford the dialkylated product **3a.** This corroborates the earlier finding that the reaction with one equivalent of alcohol led to a 54% isolated yield of **4a** (Scheme 4). However, it is interesting to see that the alkylation of the second amino group is not kinetically inhibited, but that the favored reaction of 2,6-diaminopyridine with the alcohol in the first hours of the reaction is merely due to a higher concentration of starting material compared to that of the steadily forming intermediate **4a**. The alcohol was hence employed as the limiting substrate and the reaction was performed with an excess of the diamine. The addition of two equivalents of 2,6-diaminopyridine to only one equivalent of benzyl alcohol successfully led to a quantitative yield of *N*-benzylpyridine-2,6-diamine (**4a**) (Scheme 5).



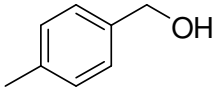
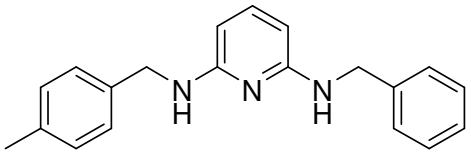
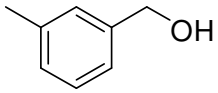
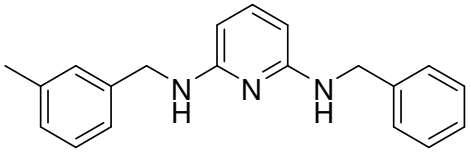
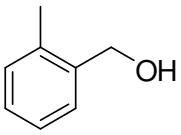
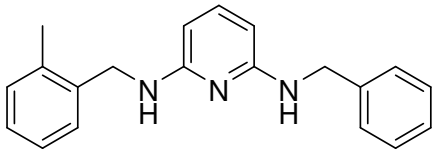
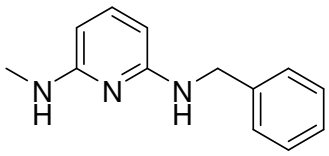
Scheme 5. Preparation of *N*-benzylpyridine-2,6-diamine (**4a**) using an excess of 2,6-diaminopyridine.

With the ability to selectively alkylate only one amino group of the diamine as shown in Scheme 5 and due to the excellent selectivity of the catalyst for the monoalkylation of amines, this method could be further employed to synthesize nonsymmetrically substituted diamines by treating the monoalkylated product **4a** with a different alcohol. To the best of our knowledge, no simple protocol has been reported in the literature that can be used for the selective preparation of such nonsymmetrically alkylated compounds without the need for several protection and deprotection steps of the amino functions. Therefore, this iridium-catalyzed two-step synthesis, in which one of the amino functions is first monoalkylated and then, after purification, the monoalkylated intermediate is further reacted with any other alcohol, leading to a nonsymmetrically substituted diamine, represents a great synthetic improvement. Table 8 shows some examples that demonstrate the general applicability of this synthetic method, in which the initially prepared compound **4a** was reacted with an equivalent of another alcohol, affording the expected nonsymmetrically dialkylated diamines **5a-d**.

Table 8. Ir-catalyzed *N*-alkylation of N-benzyl-pyridine-2,6-diamine with various alcohols.



4a **5**

Entry	Cat. loading [mol% Ir]	Alcohol	Product	Yield [%][a]
1	0.4		 **5a**	95
2	0.4		 **5b**	94
3	0.8		 **5c**	97
4	0.5	MeOH	 **5d**	98[b]

Reaction conditions: 1.0 mmol *N*-benzylpyridine-2,6-diamine, 1.1 mmol alcohol, $[IrCl(cod)]_2$, $Py_2NP(i\text{-}Pr)_2$ (**1**), 1.1 mmol KO^{t}Bu, 0.2 mL diglyme, 0.35 mL THF, 70°C, 48 h. [a] isolated yield. [b] 2.0 mmol methanol.

The above results further demonstrate that *para*-, *meta*- and *ortho*-substituted benzyl alcohols can readily be employed for the alkylation of *N*-benzylpyridine-2,6-diamine (**4a**) affording dialkylated products in yields of up to 97%. Generally, the alkylation of the second amino function of diamines is slightly more difficult and therefore the optimal catalyst loadings determined for the alkylation of 2-aminopyridine could not directly be adopted, with these quantities only incomplete conversions were observed. This might be due to a higher steric demand of the substrate, which renders the coordination to the catalyst more difficult and therefore reduces the activity of the catalyst. In the case of *ortho*-substituted benzyl alcohols (entry 3), this becomes even more apparent since a catalyst loading of 0.8 mol% Ir had to be employed to obtain full conversion of the substrate. As a

final example, methanol was used as the alkylating agent and the corresponding *N*-benzyl-*N'*-methylpyridine-2,6-diamine (**5d**) was obtained in 98% yield (entry 4).

6.3. Conclusions

In summary, we have developed an efficient and mild Ir-catalyzed protocol for the *N*-alkylation of (hetero)aromatic amines with alcohols, which proceeds at a reaction temperature of only 70°C and with catalyst loadings as low as 0.1 mol% Ir. Compared to the known protocols from the literature, which require temperatures in the range of 110 - 150°C and catalyst loadings of 2 - 6 mol%, these are the mildest reaction conditions ever reported for the alkylation of amines with alcohols. Furthermore, we have been able to exploit the selectivity of our catalyst system for the monoalkylation of amines for the preparation of symmetrically as well as nonsymmetrically *N*,*N'*-dialkylated diamines, providing the first simple and general protocol for the preparation of these compounds. Further investigations aimed at gaining a better understanding of the selectivity of the catalyst as well as the reaction mechanism are currently underway in our laboratories.

6.4. Experimental Section

General considerations: All reactions were carried out under a dry argon or nitrogen atmosphere, using standard Schlenk and glovebox techniques. Non-halogenated solvents were distilled over sodium benzophenone ketyl and halogenated solvents over P_2O_5. Diglyme was dried over molecular sieves. Deuterated solvents were obtained from Cambridge Isotope Laboratories and stored over molecular sieves. All chemicals were purchased from commercial sources in purities > 97% and used without further purification. In the case of 2,6-diaminopyridine the dark black unpurified compound was used only for the screening reactions whereas the recrystallized compound was used for all further reactions. NMR spectra were obtained using a Varian INOVA 300 or a Varian INOVA 400 spectrometer at 298 K. Chemical shifts are reported in ppm relative to the deuterated solvent. Elemental analyses were performed on a Vario elementar EL *III*. GC analyses were performed on an Agilent 6890N Network GC-System equipped with a HP-5 column (30 m × 0.32 µm × 0.25 µm Flash chromatography was performed over SiO_2 60 (0.040-0.063 mm) from Merck; all eluting solvents were freshly distilled prior to use.

Typical procedure for the Ir-catalyzed alkylation of (di)amines with alcohols: In a Schlenk-tube stock solutions of $[IrCl(cod)]_2$ and $Py_2NP(i\text{-}Pr)_2$ were mixed. Then the (di)amine (1.00 equiv), the alcohol (1.05 equiv or 2.1 equiv for diamines) and diglyme (200 µL) were added. Last, KO^tBu (1.10 equiv or 2.20 equiv for diamines) was dissolved in the reaction mixture, the reaction vessel

tightly closed and stirred at 70°C for the mentioned time. The reaction mixture was cooled to room temperature, quenched with water (2 mL) and diethyl ether (7–8 mL), and subsequently extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (15 mL), and dried over Na_2SO_4, and the solvent was removed in vacuo. Finally, the residue was purified by column chromatography and dried in vacuo.

Benzylpyridin-2-yl-amine (2a):[23] $[IrCl(cod)]_2$ (80 µL, 0.0005 mmol, 0.00625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (80 µL, 0.001 mmol, 0.0125 M in THF). The substrates were added and the reaction was allowed to proceed for 24 h at 70°C. Column chromatography (pentane/diethyl ether, 1:1) Yield: 161 mg = 0.88 mmol = 88% - ^{1}H NMR (400 MHz $CDCl_3$): δ = 8.05 (ddd, *J* = 3.9, 1.1, 0.9 Hz, 1H), 7.39-7.24 (m, 6H), 6.56 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 4.99 (s_br, 1H), 4.46 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 148.1, 139.1, 137.5, 128.6, 127.3, 127.1, 113.1, 106.7, 46.3.

(4-Methylbenzyl)pyridin-2-yl-amine (2b):[16] $[IrCl(cod)]_2$ (160 µL, 0.001 mmol, 0.00625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (160 µL, 0.002 mmol, 0.0125 M in THF). The substrates were added and the reaction was allowed to proceed for 24 h at 70°C. Column chromatography (pentane/diethyl ether, 1:1) Yield: 177 mg = 0.89 mmol = 89%;^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (ddd, *J* = 5.1, 1.8, 1.1 Hz, 1H), 7.38 (ddd, *J* = 8.5, 6.8, 1.8 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1Hz, 2H), 6.57 (ddd, *J* = 7.1, 4.9, 1.1 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 4.83 (s_br, 1H), 4.45 (d, *J* = 5.9 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) : δ =158.6, 148.2, 137.4, 136.9, 136.0, 129.3, 127.4, 113.1, 106.7, 46.1, 21.1.

(4-Methoxybenzyl)pyridin-2-yl-amine (2c):[16] $[IrCl(cod)]_2$ (80 µL, 0.0005 mmol, 0.00625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (80 µL, 0.001 mmol, 0.0125 M in THF). The substrates were added and the reaction was allowed to proceed for 24 h at 70°C. Column chromatography (pentane/diethyl ether, 2:1) Yield: 184 mg = 0.86 mmol = 86% ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 5.2 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 6.8 Hz, 2H), 6.55 (t, *J* = 6.8 Hz, 1H), 6.33 (d, *J* = 8.4 Hz, 1H), 4.84 (s_br, 1H), 4.39 (d, *J* = 5.6 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 158.8, 148.4, 137.6, 131.4, 128.9, 114.2, 113.3, 107.0, 55.5, 46.0.

(4-Chlorobenzyl)pyridin-2-yl-amine (2d):[16] $[IrCl(cod)]_2$ (160 µL, 0.001 mmol, 0.00625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (160 µL, 0.002 mmol, 0.0125 M in THF). The substrates

were added and the reaction was allowed to proceed for 24 h at 70°C. Column chromatography (pentane/diethyl ether, 1:1); Yield: 155 mg = 0.71 mmol = 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (ddd, *J* = 5.1, 1.8, 0.7 Hz, 1H), 7.36 (ddd, *J* = 8.5, 6.9, 1.8 Hz, 1H), 7.25-7.20 (m, 4H), 6.56 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.31 (dd, *J* = 8.1 Hz, 1H), 4.84 (s_br, 1H), 4.44 (d, *J* = 6.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 148.2, 137.8, 137.5, 132.9, 128.7, 128.6, 113.4, 106.9, 45.5.

Pyridin-2-yl-(4-trifluoromethylbenzyl)amine (2e): $[IrCl(cod)]_2$ (48 µL, 0.003 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (48 µL, 0.006 mmol, 0.125 M in THF). The substrates were added and the reaction was allowed to proceed for 24 h at 70°C; Column chromatography (pentane/diethyl ether, 1:1); Yield: 189 mg = 0.75 mmol = 75%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (ddd, *J* = 5.1, 1.8, 0.7 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.45-7.35 (m, 1H), 6.57 (ddd, *J* = 7.3, 5.1, 1.1 Hz, 1H), 6.60 (d, *J*= 8.4 Hz, 1H), 4. 99 (s_br, 1H), 4.59 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 147.9, 143.5, 137.7, 129.4 (q, *J* = 32.2 Hz), 127.4, 125.5 (q, *J* = 3.6 Hz), 124.2 (q, *J* = 272.0 Hz), 113.5, 107.0, 45.6; elemental analysis (%) calcd: C 61.90, H 4.40, N 11.11; found: C 61.40, H 4.436, N 11.02.

(2-Methoxybenzyl)pyridin-2-yl-amine (2f): $[IrCl(cod)]_2$ (64 µL, 0.004 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (64 µL, 0.008 mmol, 0.125 M in THF). The substrates were added and the reaction was allowed to proceed for 48 h at 70°C. Column chromatography (pentane/diethyl ether, 1:1); Yield: 197 mg = 0.92 mmol = 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (ddd, *J* = 5.1, 1.8, 0.7 Hz, 1H), 7.37 (ddd, *J* = 8.6, 7.0, 2.1 Hz, 1H), 7.24 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.24 (dt, *J* = 7.8, 1.6 Hz, 1H), 6.85-6.80 (m, 2H), 6.54 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 4.84 (s_br, 1H), 4.48 (d, *J* = 6.2 Hz, 2H), 4.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =158.9, 157.42, 148.2, 137.3, 128.8, 128.3, 127.1, 120.4, 112.8, 110.2, 106.7, 55.3, 41.7; elemental analysis (%) calcd: C 72.87, H 6.59, N 13.07; found: C 72.83, H 6.671, N 13.10.

(2-Methylbenzyl)pyridin-2-yl-amine (2g): $[IrCl(cod)]_2$ (240 µL, 0.0015 mmol, 0.00625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (240 µL, 0.003 mmol, 0.0125 M in THF). The substrates were added and the reaction was allowed to proceed for 24 h at 70°C; Column chromatography (pentane/diethyl ether, 1:1); Yield: 179 mg = 0.9 mmol = 90%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.4 (ddd, J = 8.4, 7.0, 1.8 Hz, 1H), 7.31 (d, *J* = 6.6 Hz, 1H), 7.21-7.15 (m, 3H), 6.58 (ddd, *J* = 7.3, 5.1, 0.7 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 4.74 (s_br, 1H), 4.45 (d, *J* = 5.5 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 148.4, 137.7, 136.9, 136.5,

130.6, 128.2, 127.6, 126.3, 113.2, 107.0, 63.6, 44.6, 19.2; elemental analysis (%) calcd: C 78.75, H 7.12, N 14.13; found: C 78.70, H 7.266, N 14.09.

Butylpyridin-2-yl-amine (2h):[24] $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (160 µL, 0.02 mmol, 0.125 M in THF), THF instead of diglyme (200 µL). 48 h at 70°C; Column chromatography (pentane/diethyl ether, 1:1); Yield: 123 mg = 0.82 mmol = 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (ddd, *J* = 4.8, 1.8, 0.7 Hz, 1H), 7.39 (ddd, *J* = 8.5, 6.9, 1.8 Hz, 1H), 6.53 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 4.46 (s_br, 1H), 3.23 (td, *J* = 7.0, 5.9 Hz, 2H), 1.59-1.55 (m, 2H), 1.42-1.37 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 148.2, 137.3, 112.6, 106.3, 42.0, 31.7, 20.2, 13.9.

***N,N′*-Dibenzylpyridine-2,6-diamine (3a)**: $[IrCl(cod)]_2$ (48 µL, 0.003 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (48 µL, 0.006 mmol, 0.125 M in THF), add. THF (160 µL). 48 h at 70°C. Column chromatography (pentane/diethyl ether, 4:1); Yield: 271 mg = 0.94 mmol = 94%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.16 (m, 11H), 5.72 (d, *J* = 7.7 Hz, 2H), 4.62 (s_br, 2H), 4.43 (d, *J* = 5.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 139.7, 139.1, 128.5, 127.4, 127.0, 95.2, 46.3; elemental analysis (%) calcd: C 78.86, H 6.62, N 14.52; found: C 78.53, H 6.75, N 14.58.

***N,N′*-Bis-(4-methylbenzyl)pyridine-2,6-diamine (3b)**: $[IrCl(cod)]_2$ (48 µL, 0.003 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (48 µL, 0.006 mmol, 0.125 M in THF), add. THF (160 µL). 48 h at 70°C; Column chromatography (pentane/diethyl ether, 3:1) - Yield: 286 mg = 0.90 mmol = 90%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27(s, 4H), 7.21 (t, *J* = 7.87 Hz, 1H), 7.15 (d, *J* = 7.69 Hz, 4H), 5.74 (dt, *J* = 8.05 Hz, 2H), 4. 61 (t, *J* = 5.49 Hz, 2H), 4.41 (d, *J* = 5.86 Hz, 4H), 2.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 139.0, 136.6, 136.6, 129.2, 127.4, 95.0, 46.1, 21.1; elemental analysis (%) calcd: C 79.46, H 7.30, N 13.24; found: C 79.26, H 7.20, N 13.52.

***N,N′*-Bis-(4-methoxybenzyl)pyridine-2,6-diamine (3c)**: $[IrCl(cod)]_2$ (48 µL, 0.003 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (48 µL, 0.006 mmol, 0.125 M in THF), add. THF (160 µL). 48 h at 70°C. Column chromatography (CH_2Cl_2: ethyl acetate, 60:1); Yield: 337 mg = 0.97 mmol = 97%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.24 (m, 4H), 7.20 (t, *J* = 7.9 Hz 1H), 6.85 (ddd, *J* = 9.2, 2.9, 2.6 Hz, 4H), 5.72 (d, *J* = 7.7 Hz, 2H), 4. 58 (t, *J* = 5.3, 2H), 4.36 (d, *J* = 5.86 Hz, 4H), 3.79 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 157.9, 139.1, 131.7, 128.7, 113.9,

95.1, 55.3, 45.8; elemental analysis (%) calcd: C 72.18, H 6.63, N 12.03; found: C 71.98, H 6.602, N 11.86.

***N,N'*-Bis-(4-chlorobenzyl)pyridine-2,6-diamine (3d)**: $[IrCl(cod)]_2$ (48 µL, 0.003 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (48 µL, 0.006 mmol, 0.125 M in THF), add. THF (160 µL). 48 h at 70°C. Column chromatography (pentane/diethyl ether, 3:1) - Yield: 312 mg = 0.87 mmol = 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 8H), 7.18 (t, *J* = 8.05 Hz, 1H), 5.70 (d, *J* = 7.69Hz, 2H), 4.61 (t, *J* = 5.67 Hz, 2H), 4.40 (d, *J* = 5.86 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 139.1, 138.4, 132.6, 128.6, 128.6, 95.5, 45.5; elemental analysis (%) calcd: C 63.80, H 4.78, N 11.73; found: C 64.05, H 4.72, N 12.06.

***N,N'*-Bis-(3-methylbenzyl)pyridine-2,6-diamine (3e)**: $[IrCl(cod)]_2$ (48 µL, 0.003 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{Pr}_2$ (48 µL, 0.006 mmol, 0.125 M in THF), add. THF (350 µL). 48 h at 70°C; Column chromatography (CH_2Cl_2: ethyl acetate, 40:1); Yield: 294 mg = 0.93 mmol = 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.17 (m, 7H), 7.11 (d, *J* = 7.3 Hz, 2H), 5.77 (d, *J* = 8.1 Hz, 2H), 4.67 (t, *J* = 5.7 Hz, 2H), 4.44 (d, *J* = 5.9 Hz, 4H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 139.6, 139.1, 138.1, 128.2, 128.1, 127.8, 124.5, 95.0, 46.3, 21.4; elemental analysis (%) calcd: C 79.46, H 7.30, N 13.24; found: C 79.11, H 7.156, N 13.20.

***N,N'*-Bis-(2-methoxybenzyl)pyridine-2,6-diamine (3f)**: $[IrCl(cod)]_2$ (80 µL, 0.005 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (80 µL, 0.01 mmol, 0.125 M in THF), add. THF (350 µL). 48 h at 70°C; Column chromatography (pentane/diethyl ether, 1:1); Yield: 239 mg = 0.68 mmol = 68%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 7.5, 1.6 Hz, 2H), 7.23 (td, *J* = 8.1, 1.8 Hz, 2H), 7.18 (t, *J* = 7.9 Hz, 1H), 6.89 (ddd, *J* = 14.6, 7.3, 1.1 Hz, 4H), 5.73 (d, *J* = 7.7 Hz, 2H), 4.73 (t, *J* = 6.2 Hz, 2H) 4.45 (d, *J* = 6.2 Hz, 4H) 3.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 157.3, 138.9, 128.8, 128.0, 127.7, 120.4, 110.0, 94.8, 55.2, 41.5; elemental analysis (%) calcd: C 72.18, H 6.63, N 12.03; found: C 71.94, H 6.592, N 12.00.

***N,N'*-Bis-(2-methylbenzyl)pyridine-2,6-diamine (3g)**: $[IrCl(cod)]_2$ (80 µL, 0.005 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (80 µL, 0.01 mmol, 0.125 M in THF), add. THF (350 µL). 48 h at 70°C; Column chromatography (pentane/diethyl ether, 3:1) - Yield: 223 mg = 0.70 mmol = 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.31 (m, 2H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.20-7.18 (m, 6H), 5.75 (d, *J* = 8.1 Hz, 2H), 4.47 (s_br, 2H), 4.40 (d, *J* = 5.5 Hz, 4H) 2.36 (s, 6H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ = 158.1, 139.0, 137.2, 136.2, 130.2, 128.0, 127.2, 126.0, 94.9, 44.4, 19.0; elemental analysis (%) calcd: C 79.46, H 7.30, N 13.24; found: C 79.24, H 7.312, N 13.23.

***N,N′*-Dibutylpyridine-2,6-diamine (3h)**: $[IrCl(cod)]_2$ (48 µL, 0.003 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (48 µL, 0.006 mmol, 0.125 M in THF), add. THF (350 µL). 48 h at 70°C; Column chromatography (pentane/diethyl ether, 1:1); Yield: 199 mg = 0.90 mmol = 90%; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (t, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 4.21 (s_br, 2H), 3.16 (q, *J* = 6.95 Hz, 4H), 1.56 (t, *J* = 7.23 Hz, 4H), 1.41-1.37 (m, 4H) 0.93 (t, *J* = 7.3, Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 138.9, 94.0, 42.0, 31.7, 20.2, 13.8; elemental analysis (%) calcd: C 70.54, H 10.47, N 18.98; found: C 70.99, H 10.59, N 19.13.

***N,N′*-Dimethylpyridine-2,6-diamine (3i)**: $[IrCl(cod)]_2$ (64 µL, 0.004 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (64 µL, 0.008 mmol, 0.125 M in THF), add. THF (350 µL). 48 h at 70°C; Column chromatography (Diethylether); Yield: 121 mg = 0.88 mmol = 88%; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (t, *J* = 7.9 Hz, 1H), 5.71 (d, *J* = 8.1Hz, 2H), 4.31 (s_br, 2H), 2.83 (d, *J* = 5.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 139.0, 94.0, 29.1; elemental analysis (%) calcd: C 61.29, H 8.08, N 30.62; found: C 61.04, H 8.035, N 30.24.

***N*-Benzylpyridine-2,6-diamine (4a)**: $[IrCl(cod)]_2$ (320 µL, 0.002 mmol, 0.00625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (320 µL, 0.004 mmol, 0.0125 M in THF), add. THF (160 µL). 24 h; 70°C; Column chromatography (pentane/diethyl ether, 1:1); Yield: 207 mg = 0.97 mmol = 97%; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26-7.17 (m, 4H), 7.16-7.10 (m, 1H), 7.1 (t, *J* = 7.9 Hz, 1H), 5.73 (d, *J* = 7.7 Hz, 1H), 5.65 (d, *J* = 7.7 Hz, 1H), 4.57 (s_br, 1H), 4.32 (d, *J* = 5.9 Hz, 2H), 4.07 (s_br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 157.6, 139.4, 139.4, 128.5, 127.3, 127.1, 97.1, 95.6, 46.4; elemental analysis (%) calcd: C 72.33, H 6.58, N 21.09; found: C 72.33, H 6.58, N 21.09.

***N*-Benzyl-*N′*-(4-methylbenzyl)pyridine-2,6-diamine (5a)**: $[IrCl(cod)]_2$ (320 µL, 0.002 mmol, 0.00625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (320 µL, 0.004 mmol, 0.0125 M in THF). The substrates were added and the reaction was allowed to proceed for 48 h at 70°C; Column chromatography (pentane/diethyl ether, 10:1); Yield: 288 mg = 0.95 mmol = 95%; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.28 (m, 4H), 7.27-7.17 (m, 4H), 7.12 (d, *J* = 7.7 Hz, 2H), 5.72 (d, *J* = 8.1 Hz, 2H), 4.64 (s_br, 2H), 4.41 (dd, *J* = 20.5, 4.0 Hz, 4H) 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 157.9, 139.7, 139.2, 136.7, 136.6, 129.2, 128.5, 127.4, 127.0, 95.1, 95.1, 46.3,

46.1, 21.1; elemental analysis (%) calcd: C 79.17, H 6.98, N 13.85; found: C 78.79, H 6.99, N 13.74.

***N*-Benzyl-*N′*-(3-methylbenzyl)pyridine-2,6-diamine (5b)**: $[IrCl(cod)]_2$ (320 µL, 0.002 mmol, 0.00625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (320 µL, 0.004 mmol, 0.0125 M in THF). The substrates were added and the reaction was allowed to proceed for 48 h at 70°C; Column chromatography (pentane/diethyl ether, 10:1); Yield: 285 mg = 0.94 mmol = 94%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.14 (m, 9H), 7.07 (d, *J* = 7.3 Hz, 1H), 5.74 (d, *J* = 7.7 Hz, 2H), 4.65 (s_br, 2H), 4.42 (dd, *J* = 18.3, 5.9 Hz, 4H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 157.9, 139.7, 139.6, 139.2, 138.2, 128.5, 128.4, 128.2, 127.8, 127.4, 127.0, 124.5, 95.1, 95.1, 46.3, 21.4; elemental analysis (%) calcd: C 79.17, H 6.98, N 13.85; found: C 78.60, H 6.913, N 13.83.

***N*-Benzyl-*N′*-(2-methylbenzyl)pyridine-2,6-diamine (5c)**: $[IrCl(cod)]_2$ (64 µL, 0.004 mmol, 0.0625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (64 µL, 0.008 mmol, 0.125 M in THF). The substrates were added and the reaction was allowed to proceed for 48 h at 70°C; Column chromatography (pentane/diethyl ether, 4:1); Yield: 295 mg = 0.97 mmol = 97%; ^{1}H NMR (400 MHz, $CDCl_3$): δ =7.37-7.29 (m, 5H), 7.27-7.15 (m, 5H), 5.74 (d, *J* = 8.1 Hz, 2H), 4.64 (s_br, 1H), 5.45-4.39 (m, 5H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 139.7, 139.1, 137.2, 136.2, 130.3, 128.5, 128.1, 127.4, 127.2, 127.0 126.0, 95.1, 95.0, 46.4, 44.4, 19.0; elemental analysis (%) calcd: C 79.17, H 6.98, N 13.85; found: C 78.88, H 6.940, N 13.79.

***N*-Benzyl-*N′*-methylpyridine-2,6-diamine (5d)**: $[IrCl(cod)]_2$ (400 µL, 0.0025 mmol, 0.00625 M in THF) was combined with $Py_2NP(i\text{-}Pr)_2$ (400 µL, 0.005 mmol, 0.0125 M in THF). The substrates were added and the reaction was allowed to proceed for 48 h at 70°C; Column chromatography (pentane/diethyl ether, 1:1); Yield: 209 mg = 0.98 mmol = 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.27 (m, 4H), 7.27-7.21 (m, 2H), 5.72 (dd, *J* = 7.7, 5.5 Hz, 2H), 4.65 (s_br, 1H), 4.44 (d, *J* = 5.5 Hz, 2H), 4.30 (s_br, 1H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 158.0, 139.7, 139.1, 128.5, 127.4, 127.0, 94.8, 94.3, 46.3; elemental analysis (%) calcd: C 73.21, H 7.09, N 19.70; found: C 72.97, H 7.047, N 19.76.

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7. Synthesis of Selectively Mono-*N*-Arylated Aliphatic Diamines via Iridium-Catalyzed Amine Alkylation

Benoît Blank,[a] Stefan Michlik,[a] and Rhett Kempe[a]*

[a] Lehrstuhl für Anorganische Chemie II, Universitätsstraße 30, 95440 Bayreuth, Germany.
Fax: +49 (0) 921-55-2157; Tel: +49 (0)921-55-2541; E-mail: kempe@uni-bayreuth.de

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Abstract. A highly selective P,N-ligand stabilized iridium complex efficiently catalyzes the reaction of aryl amines with unprotected amino alcohols, yielding *N*-arylated aliphatic diamines with a branched or linear alkyl backbone in yields up to 93%. The reaction can be performed with a large variety of branched and linear amino alcohols in combination with various aminopyridines or substituted anilines.

7.1. Introduction

Amines are a very important class of compounds. They are the basis of many bulk and fine chemical intermediates, additives, dyes, agrochemicals and pharmaceutical products.[1] Especially di- and polyamines are of great interest since such motifs can be found in many pharmacologically active compounds.[2] In addition, such compounds are used intensively as ligands for catalysts, organometallic reagents and coordination compounds.[3] The development of novel methods for the selective preparation of secondary amines of is hence of general interest. The best-known reaction for the alkylation of amines is the nucleophilic substitution reaction of amines with haloalkanes,[4] which is only fairly selective and affords mono, di- and trialkylated amines as well as quaternary ammonium salts. More selective methods are (a) the reductive amination of carbonyl compounds,[5] which is usually performed in two separate steps, (b) the transition-metal catalyzed hydroamination,[6] which is still very challenging for the intermolecular coupling of alkenes with amines, and (c) the hydroaminomethylation[7] of alkenes which requires high-pressures equipment

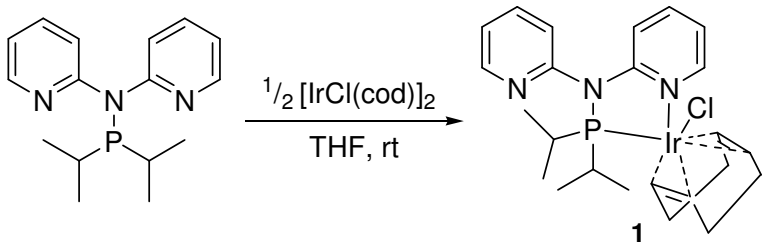
and often lacks a satisfactory regio-selectivity in the hydroformylation step. A promising development in this field which has received a lot of attention recently is the direct Ru-[8] or Ir-catalyzed[9,10,16,17] alkylation of amines using alcohols.[11]

The selective preparation of alkyl diamines bearing one *N*-aryl moiety and one primary amino function is still very challenging. The Pd-catalyzed aryl-amination, which is a very well developed and highly efficient method for the formation of *N*-aryl bonds,[12] is not really suited for the preparation of selectively mono-*N*-arylated aliphatic diamines. The main problem is the preferred *N,N'*-diarylation of the employed aliphatic diamine.[12] In order to establish monoarylation via catalytic aryl-amination pathways the diamine has to be used in large excess compared to the aryl halide.[13] The selective catalytic arylations of diamines with chemically inequivalent amine functionalities (branched alkyl backbone) have, to the best of our knowledge, not yet been described. Similar inconveniences as above also apply to the thermic reaction of aryl halides with aliphatic diamines, lacking a selective reaction pathway.[14]

Herein we present a simple and highly selective protocol for the preparation of mono-*N*-arylated aliphatic diamines via Ir-catalyzed alkylation of aromatic amines with unprotected amino alcohols.

7.2. Results and Discussion

We recently reported on a novel class of P,N-ligand[15] stabilized iridium catalysts[16] that efficiently perform the alkylation of (hetero)aromatic amines with alcohols under rather mild reaction conditions. The catalyst is generated in-situ by simply mixing the corresponding P,N-ligand with $[IrCl(cod)]_2$ in THF (Scheme 1).



Scheme 2. Preparation of the catalyst **1**.

P,N-iridium complex **1**, bearing isopropyl substituents on the phosphorus center, was in former studies determined to have the best activity for the selective alkylation of aromatic amines with alcohols. The molecular structure of **1** is shown in Fig. 1.

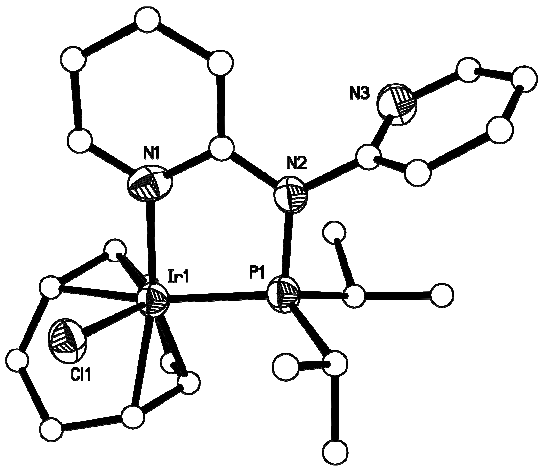
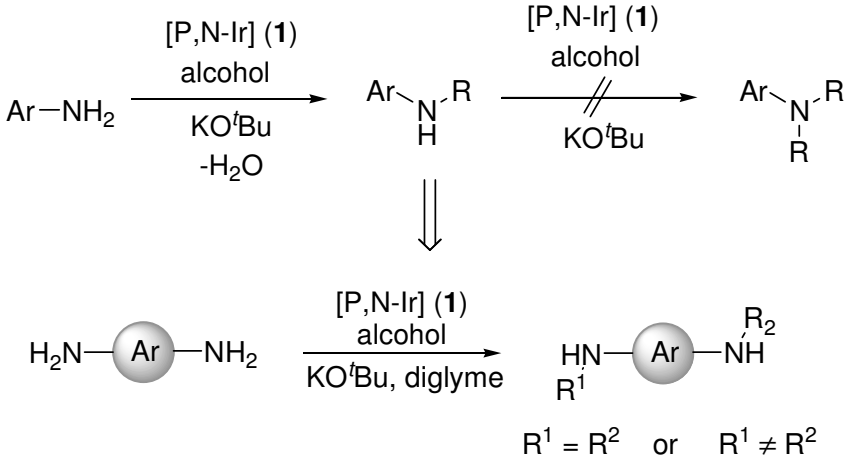


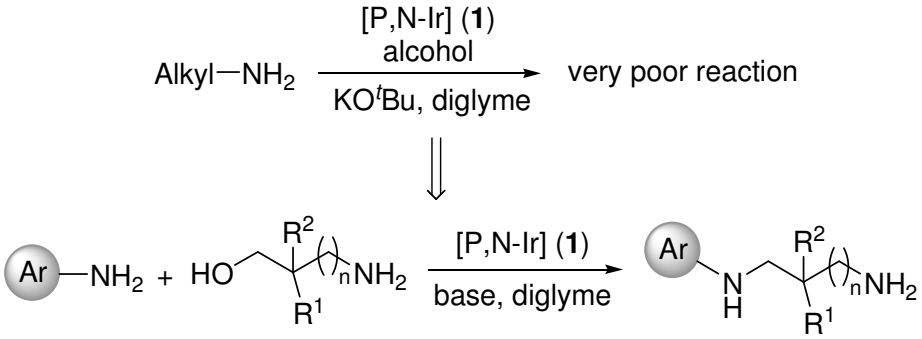
Fig. 1. Molecular structure of [$Py_2NP(i\text{-}Pr)_2Ir(cod)Cl$] (**1**). Selected bond lengths [Å] and angles [°]: Ir1–N1 2.119(3), Ir1–P1 2.2830(10), Ir1–Cl1 2.5459(10), P1–N2 1.730(3), N1–Ir1–P1 80.86(9), N1–Ir1–Cl1 82.93 (9), P1–Ir1–Cl1 103.78(3); N2–P1–Ir1 101.72(11).

This P,N-iridium complex does not only exhibit an excellent catalytic activity and efficiency for the alkylation of amines with simple alcohols (catalyst loadings as low as 0.1 mol% are possible), but also allows the reaction to be performed under mild reaction temperatures of only 70°C,[17] which is unprecedented since other catalytic systems require temperatures from 110 to 150°C for the same reaction. Next to this efficiency, in our former studies we also observed that complex **1** has a very narrow selectivity profile and always leads to a selective monoalkylation of the amine, regardless of the amount of added alcohol, since the secondary amine formed in the reaction does not react further. This selectivity for monoalkylation was hence already exploited in the development of a simple and efficient method for the preparation of symmetric and non-symmetric *N,N'*-dialkylated aromatic diamines (Scheme 2).[17] Interestingly, catalyst **1** allows only primary alcohols to be used for these transformations whereas secondary alcohols do not react.



Scheme 2. Selectivity of **1** for monoalkylation of amines and preparation of *N,N'*-dialkylated diamines.

We also observed a second selectivity profile of catalyst **1** allowing only the efficient alkylation of aromatic amines, whereas the reaction with aliphatic amines proceeded rather poorly.[16] Since such aliphatic amino functions cannot be alkylated with the catalyst system based on **1** we wanted to exploit this selectivity by employing readily available amino alcohols in combination with aromatic amines in order to prepare selectively mono-*N*-arylated aliphatic diamines that are yet inaccessible (Scheme 3).



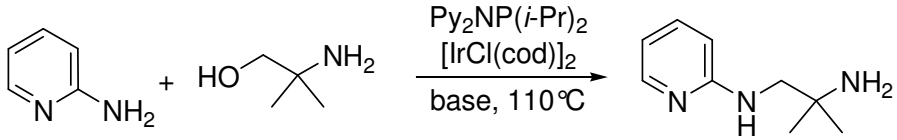
Scheme 3. Preparation of mono-*N*-aryl aliphatic diamines.

Evaluation of the reaction conditions:

The first reaction for the alkylation of aromatic amines using amino alcohols was carried out under the previously optimized reaction conditions[16] with catalyst **1**, now employing 2-aminopyridine and 2-amino-2-methyl-1-propanol as test substrates.

Although the high selectivity of **1** for the alkylation of only the aromatic amino function was maintained in the first run, only a poor conversion and yield was obtained (Table 1, entry 1). Therefore a systematic re-evaluation of the reaction conditions was performed (Table 1).

Table 1. Optimization of the reaction conditions for the use of amino alcohols.



Entry	Cat. Loading [mol% 1]	Equiv. Base	Base	Equiv. Amino Alcohol	Yield [%][a]
1	2.0	1.1	KO^{t}Bu	1.1	14
2	5.0	3.3	KO^{t}Bu	1.5	60
3	5.0	3.3	NaO^{t}Bu	1.5	85
4	5.0	3.3	NaO^{t}Bu	1.5	49[b]
5	1.0	1.1	NaO^{t}Bu	1.1	84
6	0.5	1.1	NaO^{t}Bu	1.1	61

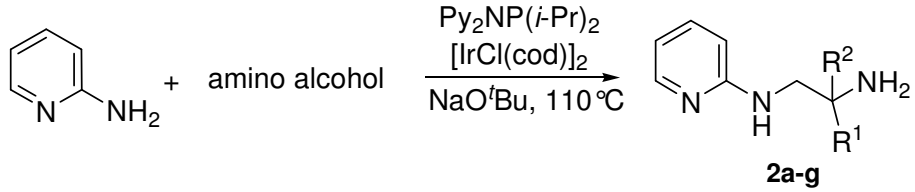
Reaction conditions: 1.0 mmol 2-aminopyridine, 1.1-1.5 mmol amino alcohol, 0.25-2.5 mol% $[IrCl(cod)]_2$, 0.5-5.0 mol% $Py_2NP(i\text{-}Pr)_2$, 1.1-3.3 mmol base, 0.3 mL diglyme, 0.2 mL THF, 110°C, 24 h. [a] Isolated yield. [b] Temperature: 70°C.

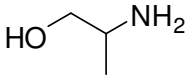
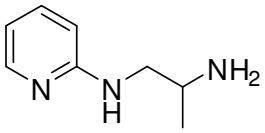
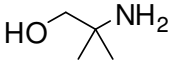
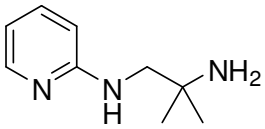
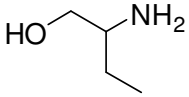
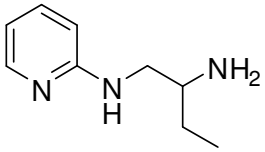
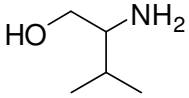
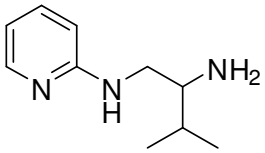
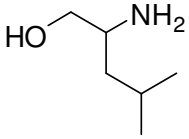
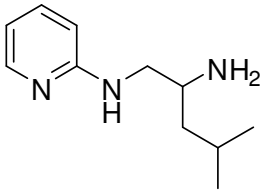
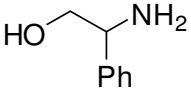
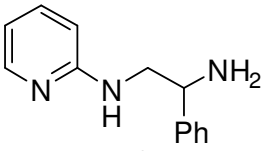
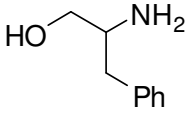
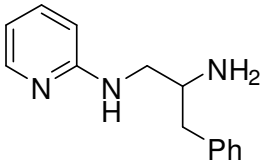
In order to determine whether the low yield resulted from a wrong stoichiometry of starting materials or a higher catalyst deactivation, the reaction was repeated using an excess of base and amino alcohol along with an increased catalyst loading of 5 mol% **1**. The expected diamine was now obtained in 60% yield (Table 1, entry 2), which shows that the reaction is generally possible, but still not very efficient. The base was therefore replaced by NaO^tBu. Interestingly, this simple exchange now allowed the isolation of the expected diamine in good yield (Table 1, entry 3). Next we tried to perform the reaction under milder reaction conditions at a temperature of 70°C, which unfortunately led to a decrease of the yield (Table 1, entry 4). It seems that the reaction with amino alcohols requires more drastic conditions than for simple alcohols and therefore a temperature of 110°C was used for further reactions. Since the low yield of the first run was simply due to the use of KO^tBu, now using NaO^tBu the amount of base and amino alcohol could again be reduced to 1.1 equivalents along with a lowered catalyst loading of 1.0 mol% **1**, still affording good yields of the *N*-arylated diamine (Table 1, entry 5). Further reduction of the catalyst loading to 0.5 mol% **1** was not possible, as a significant decrease of yield was observed (Table 1, entry 6).

Alkylation of aromatic amines with amino alcohols:

Having successfully optimized the reaction conditions a variety of different branched amino alcohols was employed in combination with 2-aminopyridine in order to show the applicability of this method. As depicted in Table 2 the corresponding *N*-arylated diamines **2a-g** were obtained in yields up to 93%.

Table 2. General application of several branched amino alcohols.



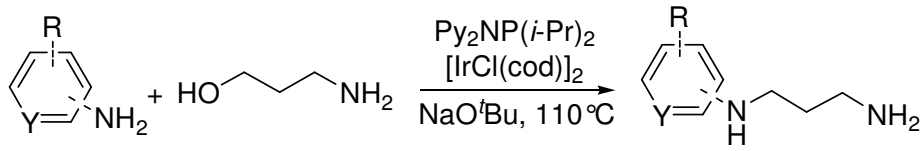
Entry	Amino Alcohol	Product	Yield [%][a]
1		 **2a**	81
2		 **2b**	84
3		 **2c**	70
4		 **2d**	93
5		 **2e**	89
6		 **2f**	93
7		 **2g**	77

Reaction conditions*:* 2.0 mmol 2-aminopyridine, 2.2 mmol amino alcohol, 0.5 mol% $[IrCl(cod)]_2$, 1.0 mol% $Py_2NP(i\text{-}Pr)_2$, 2.2 mmol NaO^tBu, 0.6 mL diglyme, 0.4 mL THF, 110°C, 24 h. [a] Isolated yield.

The presented results show that this method is rather efficient for the preparation of diamines with a branched aminoalkyl backbone using a variety of commercially available amino alcohols, which were hitherto unaccessible via an arylamination pathway due to a lack of selectivity with alkyl diamines. It is however noteworthy to mention that even though chiral β-amino alcohols can be employed, the stereoinformation is lost in the course of the reaction, due to a keto-enol tautomerization of the intermediately formed aldehyde, and therefore only racemic *N*-arylated diamines are obtained.

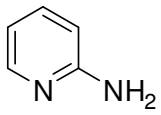
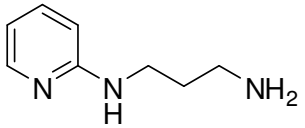
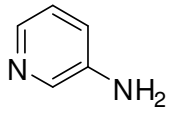
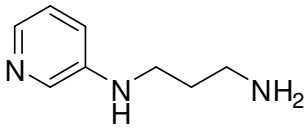
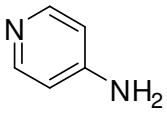
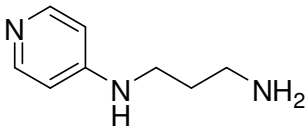
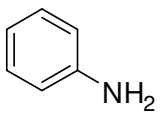
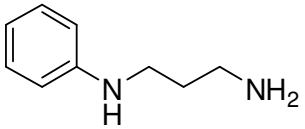
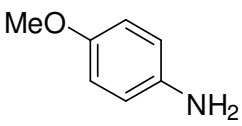
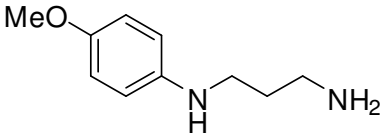
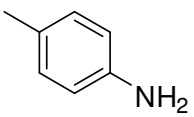
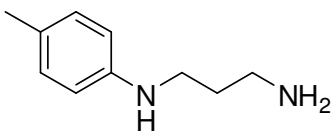
In a next step several heteroaromatic amines and functionalized anilines were tested in order to demonstrate the general applicability of this method (Table 3).

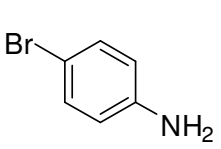
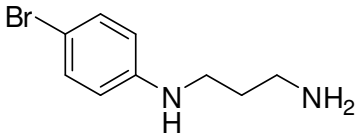
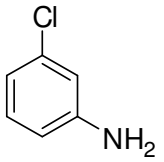
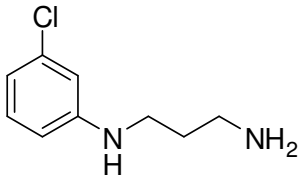
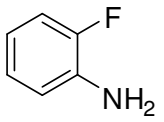
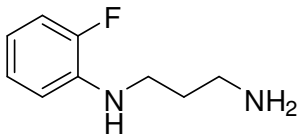
Table 3. Variation of the (hetero)aromatic substrate.



Y = C, N

3a-i

Entry	Cat. Loading (mol% Ir)	Amine	Product	Yield [%][a]
1	1.0		 **3a**	91
2	2.0		 **3b**	75
3	4.0		 **3c**	68
4	5.0		 **3d**	71
5	5.0		 **3e**	78
6	5.0		 **3f**	71

7	5.0		 **3g**	83
8	5.0		 **3h**	86
9	5.0		 **3i**	63

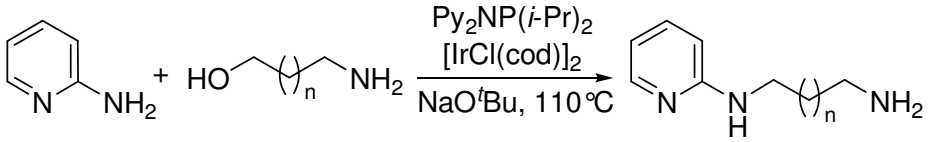
Reaction conditions: 2.0 mmol amine, 2.2 mmol 3-amino-1-propanol, 0.5-2.5 mol% $[IrCl(cod)]_2$, 1.0-5.0 mol% $Py_2NP(i\text{-}Pr)_2$, 2.2 mmol NaO^tBu, 0.6 mL diglyme, 0.4 mL THF, 110°C, 24 h. [a] Isolated yield.

The best catalytic activity of **1** is observed with 2-aminopyridine, whereas the yield decreases with the pyridine nitrogen moving from the 3- to the 4-position, since the catalyst loadings had to be raised to 2 and 4 mol% **1**, respectively (Table 3, entries 2, 3). Although **1** is especially efficient with heteroaromatic substrates, substituted anilines are also tolerated and afford the corresponding N-arylated diamines **3d-i** in yields from 63% to 86%, however with a higher catalyst loading of 5 mol% **1**. Substituents in *ortho*, *meta* and *para* positions are tolerated, although substituents in *ortho* position seem to slightly hinder the reaction as can be determined from entry 9. As observed before,[17,18] catalyst **1** seems to be slightly more efficient when electron-poor (hetero)aromatic amines are employed which is consistent with the results in Table 3, where electron-withdrawing substituents (entries 7-9) seem to have an activating effect on the reaction, in comparison to the reactions with electron-donating substituents (entries 5 and 6).

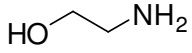
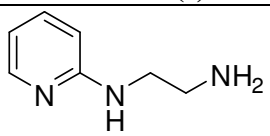
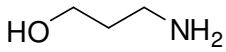
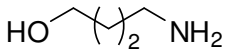
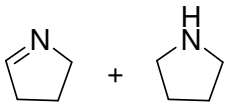
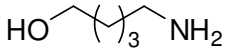
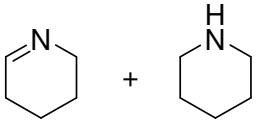
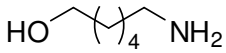
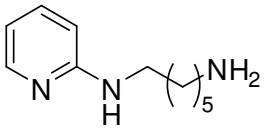
As shown in Table 2 and 3, it is possible to employ linear, as well as branched amino alcohols for this alkylation reaction. Interestingly, the length of the alkyl chain also plays an important role as can be concluded from the results shown in Table 4. With a growing chain-length, from 2-amino-1-ethanol to 3-amino-1-propanol, the yield significantly increases due to a greater distance of the electron-rich amino function from the alcohol, which facilitates the oxidation of the latter (Table 4, entries 1, 2). However, when the number of CH_2 groups in the alcohol is four or five, only traces of the expected diamine were observed, because the intramolecular cyclization of the formed amino aldehyde is favoured, mainly affording a mixture of 3,4-dihydro-2*H*-pyrrole and pyrrolidine or 2,3,4,5-tetrahydro-pyridine and piperidine, respectively (Table 4, entries 3 and 4).

The intramolecular formation of a five- or six-membered ring seems to be kinetically favoured compared to the intermolecular reaction with the aromatic amine. Experiments using up to a fivefold excess of 2-aminopyridine and catalyst loadings of 5 mol% **1**, in order to favour the intermolecular reaction, were nevertheless unsuccessful and it was not possible to obtain reasonable amounts of these *N*-arylated diamines. However, use of 6-amino-1-hexanol again afforded the expected diamine in good yields because the formation of seven-membered rings is more difficult and the intermolecular reaction with the aromatic amine is therefore favoured (Table 4, entry 5).

Table 4. Variation of the chain-length of the amino alcohol.



3j-k

Entry	Alcohol	Product(s)	Yield [%][a]
1		 **3j**	71
2		**3a**	91
3			n.d.
4			n.d.
5		 **3k**	82

Reaction conditions: 2.0 mmol 2-aminopyridine, 2.2 mmol amino alcohol, 0.5 mol% $[IrCl(cod)]_2$, 1.0 mol% $Py_2NP(i\text{-}Pr)_2$, 2.2 mmol NaO^tBu, 0.6 mL diglyme, 0.4 mL THF, 110°C, 24 h. [a] Isolated yield.

7.3. Conclusions

In conclusion, we have successfully used the chemo-selectivity profile, preference for aromatic amines, of our iridium catalyst system based on **1** to develop a novel and general method for the preparation of mono-*N*-arylated aliphatic diamines. The procedure bases on amine alkylation

chemistry using unprotected linear or branched amino alcohols as alkylating agents and also allows the synthesis of selectively mono-*N*-arylated aliphatic diamines.

7.4. Experimental Section

General considerations: All reactions were carried out under a dry argon or nitrogen atmosphere, using standard Schlenk and glovebox techniques. All chemicals were purchased from commercial sources in purities > 97% and used without further purification if not otherwise mentioned in the synthetic procedure. NMR spectra were obtained on a Varian INOVA 400 spectrometer at 300 K. Chemical shifts are reported in ppm relative to the deuterated solvent. Elemental analyses were performed on a Vario elementar EL *III*. GC-MS analyses on a Thermo Focus GC with a DSQ MS-unit equipped with a HP-5-MS column (30 m × 0.32 µm × 0.25 µm). Flash chromatography was performed over SiO_2 60 (0.040-0.063 mm) from Merck and all used solvents freshly distilled prior to use.

Typical procedure: In a Schlenk tube stock solutions of $[IrCl(cod)]_2$ (0.0625 M in THF) and $Py_2NP(i\text{-}Pr)_2$ (0.125 M in THF) were mixed in order to generate the catalyst in-situ. Then the amine (1.0 equiv), the amino alcohol (1.1 equiv) diglyme (300 µL/mmol amine), THF (200 µL/mmol amine) were added. Last, NaO^tBu (1.1 equiv) was dissolved in the reaction mixture, the reaction vessel tightly closed and stirred at 110°C for 24h. The reaction mixture was cooled to room temperature and quenched with water (2 mL) and CH_2Cl_2 (7-8 mL). Then, 15 mL brine were added and the aqueous layer extracted with CH_2Cl_2 (6 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed in vacuo. Finally, the residue was purified by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1) and dried in vacuo.

***N*^{1}-Pyridin-2-yl-propane-1,2-diamine (2a):** $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 2-amino-2-methyl-1-propanol (171 µL, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^tBu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 81%. bp: 97°C at 1.3×10^{-1} mbar. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (ddd, *J* = 5.1, 1.8, 0.7 Hz, 1H), 7.35 (ddd, *J* = 8.6, 7.0, 2.0 Hz, 1H), 6.51 (ddd, *J* = 7.1, 5.0, 0.7 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 4.83 (s_br, 1H),

3.29 (ddd, *J* = 12.6, 6.0, 4.4 Hz, 1H), 3.16-3.07 (m, 1H), 3.06-2.95 (m, 1H), 1.24 (s_br, 2H), 1.11 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 148.1, 137.3, 112.7, 107.1, 50.1, 46.4, 22.0; MS (70 eV, EI); m/z (%): 151 (2, M^+), 119 (2), 108 (100), 95 (18), 79 (38), 51 (6), 44 (4). elemental analysis (%) for $C_8H_{13}N_3$ calc: C 63.54, H 8.67, N 27.79; found: C 63.29, H 8.770, N 27.75.

2-Methyl-*N*^{1}-pyridin-2-yl-propane-1,2-diamine (2b): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 2-amino-2-methyl-1-propanol (211 µL, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 84%. bp: 85°C at 1.0×10^{-1} mbar; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (ddd, *J* = 5.1, 1.8, 0.7 Hz, 1H), 7.34 (ddd, *J* = 8.6, 7.0, 2.0 Hz, 1H), 6.50 (ddd, *J* = 7.1, 5.0, 0.7 Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 4.84 (s, 1H), 3.17 (d, *J* = 6.2 Hz, 2H), 1.14 (s_br, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 148.0 137.2, 112.6, 107.3, 53.4, 50.2, 28.9; MS (70 eV, EI); m/z (%): 165 (4, M^+), 133 (4), 108 (56), 79 (20), 58 (100), 42 (6). elemental analysis (%) for $C_9H_{15}N_3$ calc: C 65.42, H 9.15, N 25.43; found: C 65.81, H 9.561, N 25.61.

***N*^{1}-Pyridin-2-yl-butane-1,2-diamine (2c):** $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 2-amino-butan-1-ol (208 µL, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 70%. bp: 83°C at 7.2×10^{-2} mbar; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (ddd, *J* = 5.1, 1.8, 0.7 Hz, 1H), 7.35 (ddd, *J* = 8.8, 7.0, 1.8 Hz, 1H), 6.51 (ddd, *J* = 7.1, 5.0 1.1 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 4.87 (s_br 1H), 3.41-3.30 (m, 1H), 3.03-2.95 (m, 1H), 2.89-2.80 (m, 1H) 1.58-1.47(m, 1H), 1.37-1.15 (m, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 148.1, 137.2, 112.7, 107.2, 52.4, 48.1, 29.0, 10.5; MS (70 eV, EI); m/z (%): 165 (2, M^+), 108 (100), 95 (15), 80 (30), 58 (32); elemental analysis (%) for $C_9H_{15}N_3$ calc: C 65.42, H 9.15, N 25.43; found: C 65.42, H 9.508, N 24.87.

3-Methyl-*N*^{1}-pyridin-2-yl-butane-1,2-diamine (2d): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 2-amino-3-methyl-butan-1-ol (244 µL, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl

ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 93%. bp: 84°C at 1.1×10^{-1}mbar; ^{1}H NMR (400 MHz, $CDCl_3$): δ =8.04 (ddd, *J* = 5.1, 2.0, 0.9 Hz, 1H), 7.35 (ddd, *J* = 8.6, 7.0, 2.0 Hz, 1H), 6.50 (ddd, *J* = 7.1, 5.0, 1.1 Hz, 1H), 6.37 (dt, *J* = 8.4, 0.9 Hz, 1H), 4.94 (s_br, 1H), 3.44-3.35 (m, 1H), 3.04-2.94 (m, 1H), 2.72-2.67 (m, 1H), 1.69-1.61 (m, 1H), 1.34 (s_br, 2H), 0.94-0.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 148.1, 137.2, 112.6, 107.3, 56.3, 46.1, 32.4, 19.4, 17.7; MS (70 eV, EI); m/z (%): 179 (1, M^+), 136 (5), 119 (8), 108 (100), 95 (11), 80 (25), 72 (29), 55 (14). elemental analysis (%) for $C_{10}H_{17}N_3$ calc: C 67.00, H 9.56, N 23.44; found: C 66.57, H 9.841, N 23.37.

4-Methyl-N^1-pyridin-2-yl-pentane-1,2-diamine (2e): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 2-amino-4-methyl-pentan-1-ol (284 µL, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 89%. bp: 102°C at 8.7×10^{-2} mbar; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (ddd, *J* = 5.1, 1.8, 0.7 Hz, 1H), 7.34 (ddd, *J* = 8.8, 7.0, 1.8 Hz, 1H), 6.50 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.37 (dt, *J* = 8.4, 0.9 Hz, 1H), 4.97 (s_br, 1H), 3.39-3.31 (m, 1H), 3.04-2.94 (m, 2H), 1.75-1.66 (m, 3H) 1.31-1.18 (m, 2H), 0.91-0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 148.0, 137.2, 112.7, 107.2, 48.7, 48.7, 45.3, 24.7, 23.3, 22.1; MS (70 eV, EI); m/z (%): 193 (1, M^+), 136 (2), 108 (100), 80 (24), 44 (8); elemental analysis (%) for $C_{10}H_{16}N_3$ calc: C 68.35, H 9.91, N 21.74; found: C 68.38, H 10.34, N 21.39.

1-Phenyl-N^2-pyridin-2-yl-ethane-1,2-diamine (2f): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 2-amino-2-phenyl-ethanol (301 mg, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.40-7.32 (m, 5H), 7.27 (dt, *J* = 5.3, 2.4 Hz, 1H), 6.55 (dd, *J* = 6.8, 5.3 Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 4.82 (s_br, 1H), 4.19 (dd, *J* = 7.9, 5.3 Hz, 1H) 3.57-3.51 (m, 1H) 3.45-3.38 (m, 1H), 1.64 (s_br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 148.1, 143.9, 137.3, 128.6, 127.4, 126.4, 113.0, 107.2, 55.2, 49.8; MS (70 eV, EI); m/z (%): 213 (3, M^+), 106 (100), 79 (45), 51 (9), 28 (12); elemental analysis (%) for $C_{13}H_{15}N_3$ calc: C 73.21, H 7.09, N 19.70; found: C 72.71, H 7.147, N 19.63.

3-Phenyl-N^1-pyridin-2-yl-propane-1,2-diamine (2g): $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 2-amino-3-phenyl-propan-1-ol (332 µL, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^tBu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 77%. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (ddd, *J* = 5.1, 1.8, 0.7 Hz, 1H), 7.36 (ddd, *J* = 8.5, 7.1, 2.0 Hz, 1H), 7.31-7.25 (m, 2H), 7.22-7.16 (m, 3H), 6.53 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 4.89 (s_br,1H), 3.45-3.40 (m, 1H) 3.28-3.20 (m, 1H) 3.16-3.09 (m, 1H), 2.87 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.53 (dd, *J* = 13.4, 8.6 Hz, 1H), 1.22 (s_br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 148.1, 138.8, 137.3, 129.2, 128.6, 126.4, 112.8, 107.2, 52.4, 48.1, 42.6; MS (70 eV, EI); m/z (%): 227 (0.5 M^+), 136 (16), 120 (35), 108 (100), 91 (10), 80 (20); elemental analysis (%) for $C_{11}H_{19}N_3$ calc: C 73.98, H 7.54, N 18.49; found: C 74.14, H 7.506, N 18.20.

***N*^{1}-Pyridin-2-yl-propane-1,3-diamine (3a):** $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 3-amino-propan-1-ol (168 µL, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^tBu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 91%. bp: 103°C at 1.3×10^{-1} mbar; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.39-7.32 (m, 1H), 6.53-6.50 (m, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 4.80 (s_br, 1H), 3.36-3.30 (m, 2H), 2.81 (t, *J* = 6.6 Hz, 2H), 1.79-1.69 (m, 2H), 1.27 (s_br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 148.2, 137.3, 112.6, 106.7, 40.2, 40.1, 33.0; MS (70 eV, EI); m/z (%): 151 (38, M^+), 121 (100), 108 (98), 94 (26), 78 (68), 67 (16), 30 (22); elemental analysis (%) for $C_8H_{13}N_3$ calc: C 63.54, H 8.67, N 27.79; found: C 63.55, H 9.166, N 27.45.

***N*^{1}-Pyridin-3-yl-propane-1,3-diamine (3b):** $IrCl(cod)]_2$ (320 µL, 0.02 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (320 µL, 0.04 mmol, 0.125 M in THF), 3-aminopyridine (188 mg, 2.0 mmol), 3-amino-propan-1-ol (168 µL, 2.2 mmol), diglyme (600 µL), THF (180 µL) and NaO^tBu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 75%. bp: 135°C at 7.4×10^{-2} mbar; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (dd, *J* = 2.9, 0.7 Hz, 1H), 7.90 (dd, *J* = 4.6, 1.3 Hz, 1H), 7.03 (ddd, *J* = 8.4, 4.8, 0.7 Hz, 1H), 6.82 (ddd, *J* = 8.1, 2.9, 1.5 Hz, 1H), 4.23 (s_br, 1H), 3.18 (t, *J* = 6.6 Hz, 2H), 2.84 (t, *J* = 6.6 Hz, 2H) 1.79-1.69 (m, 2H), 1.26 (s_br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 138.5, 136.0, 123.6, 118.2, 42.0, 40.3, 32.4; MS (70 eV, EI); m/z (%): 151 (48, M^+), 133

(72), 119 (15), 107 (100), 95 (42), 78 (31), 56 (17), 30 (21); elemental analysis (%) for $C_8H_{13}N_3$ calc: C 63.54, H 8.67, N 27.79; found: C 63.91, H 8.931, N 27.40.

***N*^{1}-Pyridin-4-yl-propane-1,3-diamine (3c):** $[IrCl(cod)]_2$ (27 mg, 0.04 mmol), $Py_2NP(i\text{-}Pr_2)$ (23 mg, 0.08 mmol), THF (400µL), 4-aminopyridine (188 mg, 2.0 mmol), 3-amino-propan-1-ol (168 µL, 2.2 mmol), diglyme (600 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:5, then: diethyl ether/methanol/triethyl amine, 2:10:1). Yield: 68%. bp: 110°C at 2.4×10^{-2} mbar; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 5.5 Hz, 2H), 6.38 (d, *J* = 6.2 Hz, 2H), 4.90 (s_br, 1H), 3.24-3.17 (m, 2H), 2.84 (t, *J* = 6.4 Hz, 2H), 1.76-1.69 (m, 2H), 1.18 (s_br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 150.0, 107.4, 41.3, 40.4, 31.9; MS (70 eV, EI); m/z (%): 151 (30, M^+), 133 (100), 107 (99), 95 (54), 78 (27), 56 (25), 51 (19), 30 (33), 28 (48); elemental analysis (%) for $C_8H_{13}N_3$ calc: C 63.54, H 8.67, N 27.79; found: C 62.89, H 9.078, N 27.45.

***N*^{1}-Phenylpropane-1,3-diamine (3d):**[13c] $[IrCl(cod)]_2$ (34 mg, 0.05 mmol), $Py_2NP(i\text{-}Pr_2)$ (29 mg, 0.1 mmol), THF (400µL), aniline (182 µL, 2.0 mmol), 3-amino-propan-1-ol (168 µL, 2.2 mmol), diglyme (600 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.14 (t, *J* = 7.2 Hz, 2H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 2H), 3.17 (t, *J* = 6.7 Hz, 2H), 2.83 (t, *J* = 6.7 Hz, 2H), 2.15 (s_br, 2H), 1.78-1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 148.5, 129.2, 117.2, 112.7, 42.1, 40.3, 32.9; MS (70 eV, EI); m/z (%): 150 (42, M^+), 132 (40), 106 (100), 93 (25), 77 (30), 57 (27), 51 (10), 30 (17), 28 (17).

***N*^{1}-(4-Methoxyphenyl)propane-1,3-diamine (3e):**[13b] $[IrCl(cod)]_2$ (34 mg, 0.05 mmol), $Py_2NP(i\text{-}Pr_2)$ (29 mg, 0.1 mmol), THF (400µL), 4-methoxyaniline (247 mg, 2.0 mmol), 3-amino-propan-1-ol (168 µL, 2.2 mmol), diglyme (600 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): 6.74 (d, *J* = 8.8 Hz, 2H), 6.55 (d, *J* = 8.8 Hz, 2H), 3.71 (s, 3H), 3.12 (t, *J* = 6.8 Hz, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.59 (s_br, 3H), 1.77-1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.0, 142.7, 114.9, 114.0, 55.8, 43.0, 40.1, 32.6; MS (70 eV, EI); m/z (%): 180 (M^+, 47), 162 (10), 148 (15), 136 (100), 123 (30), 108 (28), 77 (12), 57 (13).

***N*^{1}-(4-Methylphenyl)propane-1,3-diamine (3f):**[13b] $[IrCl(cod)]_2$ (34 mg, 0.05 mmol), $Py_2NP(i\text{-}Pr_2)$ (29 mg, 0.1 mmol), THF (400µL), 4-methylaniline (215 mg, 2.0 mmol), 3-amino-propan-1-ol (168 µL, 2.2 mmol), diglyme (600 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$): 6.95 (d, *J* = 8.1 Hz, 2H), 6.51 (d, *J* = 8.4 Hz, 2H), 3.15 (t, *J* = 6.8 Hz, 2H), 2.82 (t, *J* = 6.6 Hz, 2H), 2.38 (s_br, 3H), 2.29 (s, 3H), 1.78-1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 146.2, 129.7, 126.4, 112.9, 42.4, 40.2, 32.7, 20.4; MS (70 eV, EI); m/z (%): 164 (M^+, 36), 146 (15), 132 (26), 120 (100), 107 (32), 91 (33), 77 (21), 65 (17), 57 (19).

***N*^{1}-(4-Bromophenyl)propane-1,3-diamine (3g):**[13b] $[IrCl(cod)]_2$ (34 mg, 0.05 mmol), $Py_2NP(i\text{-}Pr_2)$ (29 mg, 0.1 mmol), THF (400µL), 4-bromoaniline (345 mg, 2.0 mmol), 3-amino-propan-1-ol (168 µL, 2.2 mmol), diglyme (600 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (d, *J* = 8.8 Hz, 2H), 6.45 (d, *J* = 8.8 Hz, 2H), 3.14 (t, *J* = 6.6 Hz, 2H), 2.84 (t, *J* = 6.6 Hz, 2H), 2.74 (s_br, 3H), 1.80-1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 147.4, 131.9, 114.2, 108.7, 42.1, 40.0, 31.8; MS (70 eV, EI); m/z (%): 230 (24), 228 (M^+, 28), 186 (49), 184 (61), 132 (61), 118 (22), 105 (36), 91 (26), 57 (86), 45 (36), 30 (100).

***N*^{1}-(3-Chlorophenyl)propane-1,3-diamine (3h):** $[IrCl(cod)]_2$ (34 mg, 0.05 mmol), $Py_2NP(i\text{-}Pr_2)$ (29 mg, 0.1 mmol), THF (400µL), 3-chloroaniline (212 µL, 2.0 mmol), 3-amino-propan-1-ol (168 µL, 2.2 mmol), diglyme (600 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.02 (t, *J* = 8.1 Hz, 1H), 6.60 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.53 (dd, *J* = 2.2, 2.2 Hz, 1H), 6.42 (dd, *J* = 8.0, 2.3 Hz, 1H), 3.13 (t, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H), 1.76-1.67 (m, 2H), NH signals are not given; ^{13}C NMR (100 MHz, $CDCl_3$): 149.5, 134.9, 130.1, 116.8, 112.1, 111.0, 42.0, 40.2, 32.2; MS (70 eV, EI); m/z (%): 184 (M^+, 37), 166 (32), 140 (100), 132 (37), 111 (23), 75 (25), 57 (79) 45 (28); elemental analysis (%) for $C_9H_{13}ClN_2$ calc: C 58.54, H 7.10, N 15.17; found: C 58.14, H 7.013, N 14.69.

***N*^{1}-(2-Fluorophenyl)propane-1,3-diamine (3i):** $[IrCl(cod)]_2$ (34 mg, 0.05 mmol), $Py_2NP(i\text{-}Pr_2)$ (29 mg, 0.1 mmol), THF (400µL), 2-fluoroaniline (194 µL, 2.0 mmol), 3-amino-propan-1-ol (168 µL, 2.2 mmol), diglyme (600 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by

column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 63%; ^{1}H NMR (400 MHz, $CDCl_3$): 6.99-6.89 (m, 2H), 6.70-6.63 (m, 1H), 6.62-6.54 (m, 1H), 3.21 (t, *J* = 6.8 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 1.82-1.73 (m, 2H), NH signals are not given; ^{13}C NMR (100 MHz, $CDCl_3$): 151.9 (d, *J* = 133.6 Hz), 124.5 (d, *J* = 3.5 Hz), 116.3 (d, *J* = 7.1 Hz), 114.4, 114.2, 111.9 (d, *J* = 3.5 Hz), 41.7, 40.1, 32.7; MS (70 eV, EI); m/z (%): 168 (M^+, 37), 151 (35), 150 (36), 124 (100), 111 (34), 83 (28), 77 (50), 57 (78), 56 (52); elemental analysis (%) for $C_9H_{13}FN_2$ x 0.33 H_2O calc: C 62.05, H 7.91, N 16.08; found: C 62.47 , H 7.690, N 15.63.

***N*^{1}-Pyridin-2-yl-ethane-1,2-diamine (3j):** $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 2-amino-ethanol (124 µL, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 71%. bp: 90°C at 1.2×10^{-1} mbar; ^{1}H NMR (400 MHz, $CDCl_3$): 8.05 (ddd, *J* = 5.1, 1.8, 0.7 Hz, 1H), 7.36 (ddd, *J* = 8.6, 7.0, 2.0 Hz, 1H), 6.52 (ddd, *J* = 7.1, 5.0, 1.0 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 4.77 (s_br, 1H), 3.35-3.31 (m, 2H), 2.94-2.88 (m, 2H), 1.17 (s_br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 158.9, 148.1, 137.3, 112.8, 107.1, 44.8, 41.5; MS (70 eV, EI); m/z (%): 137 (7, M^+), 109 (4), 107 (100), 95 (36), 78 (46), 51 (8), 30 (9); elemental analysis (%) for $C_7H_{11}N_3$ calc: C 61.29, H 8.08, N 30.63; found: C 60.90, H 8.332, N 30.22.

***N*^{1}-Pyridin-2-yl-hexane-1,6-diamine (3k):** $[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-aminopyridine (188 mg, 2.0 mmol), 6-amino-1-hexanol (124 µL, 2.2 mmol), diglyme (600 µL), THF (400 µL) and NaO^{t}Bu (212 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (first: diethyl ether/methanol, 1:1, then: diethyl ether/methanol/triethyl amine, 5:5:1). Yield: 82%. bp: 119°C at 1.1×10^{-1} mbar; ^{1}H NMR (400 MHz, $CDCl_3$): 8.03 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.37 (ddd, , *J* = 8.5, 6.9, 1.8 Hz, 1H), 6.51 (ddd, , *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.33 (dd, *J* = 8.4, 0.9 Hz, 1H), 4.46 (s_br, 1H), 3.25-3.18 (m, 2H), 2.65 (t, *J* = 7.0 Hz, 2H), 1.63-1.56 (m, 2H), 1.45-1.30 (m, 6H), 1.21 (s_br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 158.9, 148.2, 137.4, 112.6, 106.3, 42.2, 42.1, 33.8, 29.5, 26.9, 26.7; MS (70 eV, EI); m/z (%): 193 (17, M^+), 177 (13), 163 (17), 121 (41), 107 (100), 94 (48), 78 (35), 67 (7), 30 (18), 28 (25); elemental analysis (%) for $C_{11}H_{19}N_3$ calc: C 68.35, H 9.91, N 21.74; found: C 67.99, H 10.41, N 21.38.

Crystallographic Data: X-ray crystal structure analysis of **1** was performed by using a STOE-IPDS II equipped with an Oxford Cryostream low-temperature unit. Structure solution and refinement were accomplished using SIR97,[19] SHELXL-97[20] and WinGX.[21] Crystal system: monoclinic, space group: P2(1)/c, lattice constants[Å,°]: *a* 11.8250(6), *b* 23.8930(12), *c* 10.0800(5), α 90.00, β 101.079(4), γ 90.00, *V* [Å^3]: 2794.9(2), crystal size [mm]: 0.32 × 0.16 × 0.13, $\rho_{calcd.}$ [g cm^{-3}]: 1.652, μ [mm^{-1}] (Mo-K$_\alpha$): 4.946, *T* [K]: 133(2), θ range [°]: 52.28–3.41, no. of unique refl.: 5261, no. of obsd. refl. [$I > 2\sigma(I)$]: 4293, no. of parameters: 316, wR^2 (all data): 0.0536, *R* value [$I > 2\sigma(I)$]: 0.0349. CCDC 742977 contains the supplementary crystallographic data for this publication. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: + 44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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7.5. References

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8. Catalytic Alkylation of Methyl-*N*-Heteroaromatics with Alcohols

Benoît Blank,[a] and Rhett Kempe[a]*

[a] Lehrstuhl für Anorganische Chemie II, Universität Bayreuth, Universitätsstraße 30, 95440 Bayreuth, Germany. E-mail: kempe@uni-bayreuth.de

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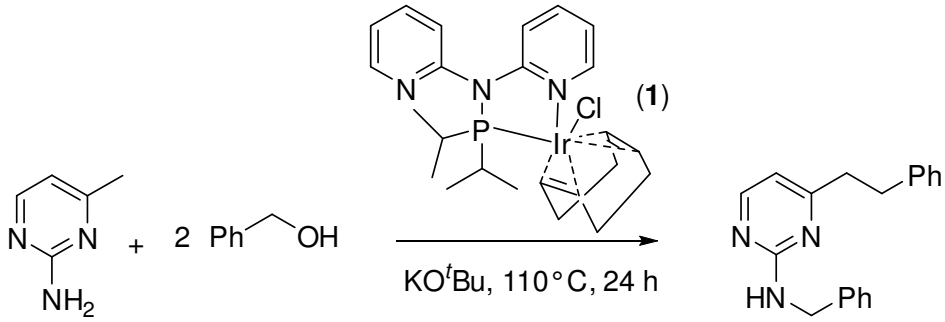
8.1. Main Text

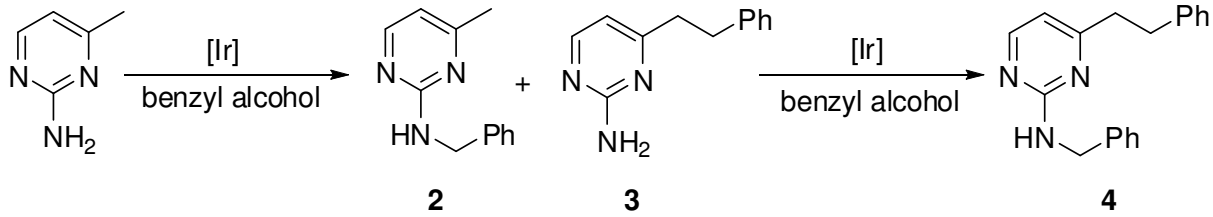
The chemistry of heterocycles plays a very important role in countless domains of human life. As a major part of the DNA especially nitrogen-containing heterocycles are indispensable, but they also have an enormous industrial importance for the pharmaceutical industries as building blocks for vitamins, hormones, antibiotics and many other pharmaceuticals or in the domain of agro- and fine-chemicals as pesticides, insecticides, dyes, solvents or synthesis intermediates.[1] The chemistry of these heterocycles has a long and rich history in which many classical synthetic methods have been developed for the preparation of simple and substituted ring systems.[2] Due to the importance of these compounds there is a great demand for novel and catalytic methods which allow the simple and selective preparation of highly functionalized *N*-heterocycles.

For some time now, our group has intensively been studying the selective *N*-alkylation of primary (hetero)aromatic amines with alcohols[3] employing a novel P,N-ligand stabilized[4] iridium catalyst, and in due course an intriguing side-reaction was observed when 2-amino-4-methylpyrimidine was employed as the amine substrate. A detailed analysis of the formed products revealed that in this case not only the amino function, but also the methyl group in 4-position of the heteroaromatic substrate was alkylated (Scheme 1). This reaction was therefore further examined and we report here on a novel C–C bond formation reaction, namely the catalytic alkylation of *N*-heteroaromatic substituted methyl groups using simple alcohols.



Scheme 1. Successive *N*- and *C*-alkylation with alcohols.

Since in the case of the employed substrate both a C–N and a C–C bond are formed successively a detailed time-conversion plot was realized in order to gain a better understanding of the reaction (Fig. 1).



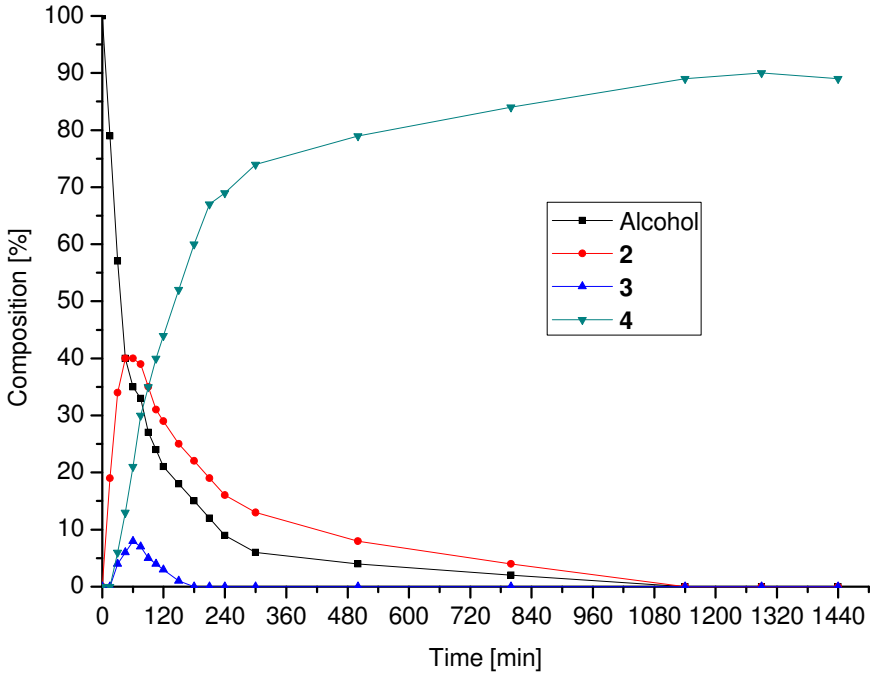
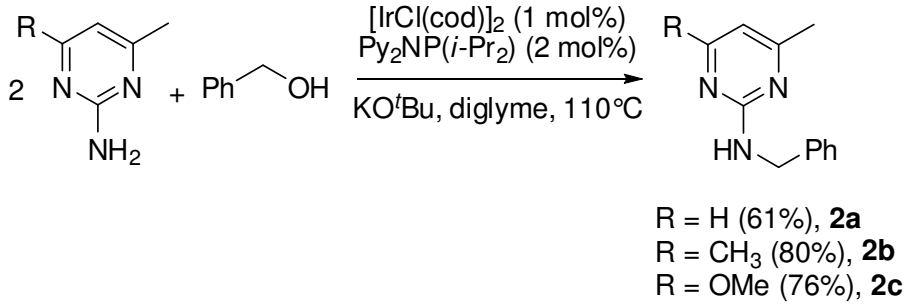


Fig. 1. Time-conversion-plot for the reaction of 2-amino-4-methylpyrimidine with benzyl alcohol.

The results show that our iridium catalyst (**1**) first rather efficiently alkylates the amino function (40%) in comparison to the methyl group (8%). Then, after around 2h under the given reaction conditions a maximum in the concentration of the intermediates **2** and **3** is attained and the latter are

quantitatively transformed into the final *N*- and *C*-alkylated product **4**. The increased selectivity of our catalyst towards the alkylation of the amino function can be exploited and, with the use of an excess of amine, allows the preparation of a variety of only *N*-alkylated intermediates **2a-c** (Scheme 2).



Scheme 2. Selective *N*-alkylation with benzyl alcohol.

Since the so far used reaction conditions had especially been optimized for the *N*-alkylation of amines[3] with our catalyst (**1**) we were further interested to determine the optimal reaction conditions for the alkylation of the methyl group using alcohols. Therefore, the beforehand *N*-alkylated substrate **2a** was employed and several reaction parameters were varied (the details of the optimization can be found in the supporting information). The results showed that for the functionalization of the methyl group diglyme (diethylene glycol dimethyl ether) is the best solvent and that a reaction temperature of 110°C is necessary, since at 70°C only low yields of product (**4a**) were obtained (38%). The screening of several organic and inorganic bases showed that the reaction works best with KO^{t}Bu (95%), but it can also be performed with KOH or NaO^{t}Bu, though with around 20% lower yields of the corresponding product. Most important is the fact that for the functionalization of the methyl group stoichiometric amounts of base have to be added to the reaction mixture in order to obtain full conversions. Also, a study with variable catalyst loadings showed that 2 mol% Ir are necessary to obtain full conversions. Last, a variety of P,N-ligands were tested in a catalyst/ligand-screening at low catalyst loadings (0.3 mol%) in order to determine most efficient catalyst for this reaction (Table 1).

Table 1. Ligand/catalyst screening.

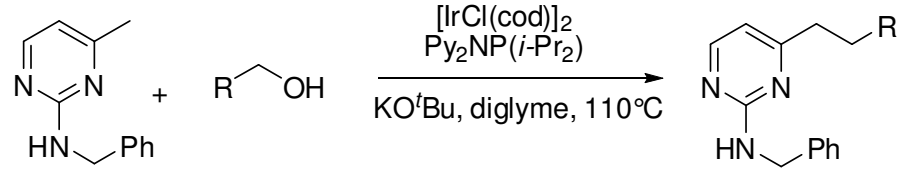
Entry	Catalyst	Yield [%][a]
1	[(Py_2NP**Ph**$_2$)IrCl(cod)]	42
2	[(Py_2NP**Cy**$_2$)IrCl(cod)]	69
3	[(Py_2NP(***i*-Pr**)$_2$)IrCl(cod)]	73
4	[(Py_2NP(***t*-Bu**)$_2$)IrCl(cod)]	70
5	$[IrCl(cod)]_2$	68

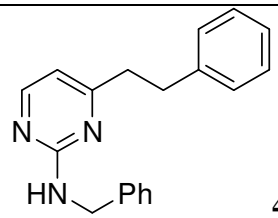
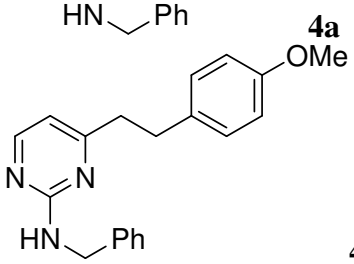
Reaction conditions: 1.0 mmol (**2a**), 1.1 mmol benzyl alcohol, 0.0015 mmol $[IrCl(cod)]_2$, 0.003 mmol P,N-ligand, diglyme, 1.1 mmol KO^{t}Bu, 24 h, 110°C. [a] Yield determined by GC-analysis with dodecane as internal standard.

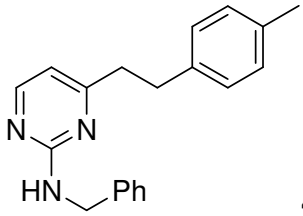
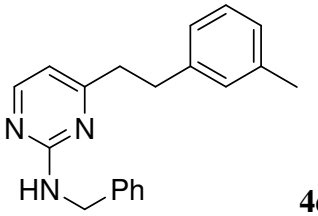
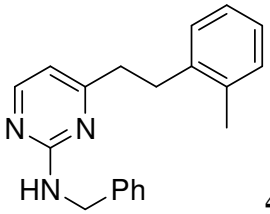
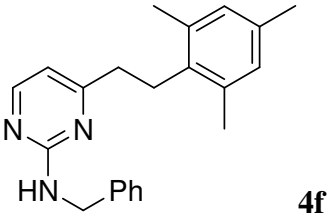
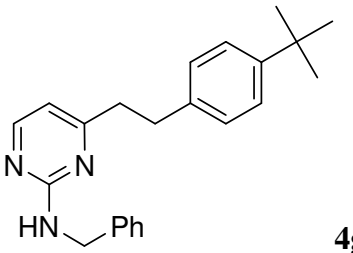
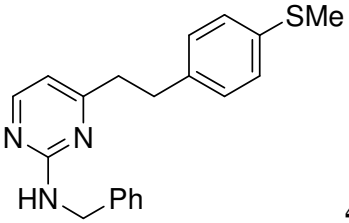
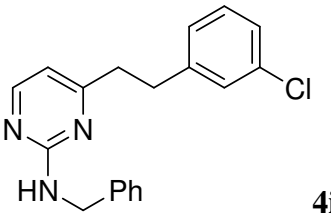
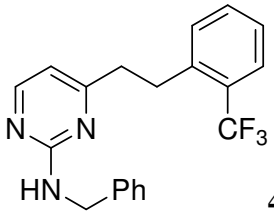
The obtained results show that the diisopropylphosphino-substituted P,N-ligand $Py_2NP(i\text{-}Pr)_2$ affords the best results for the catalytic alkylation of the methyl group. Most interestingly, the reaction can also be performed with neat $[IrCl(cod)]_2$ (COD = cycloocta-1,5-diene), although slightly lower product yields are obtained. Possibly, the substrate **2a**, in a deprotonated form, could itself act as a quasi- aminopyridinato ligand, a class of ligands that has extensively been studied in our group.[5]

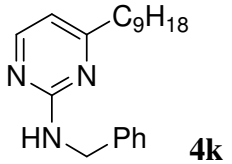
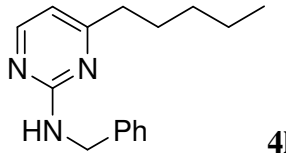
To show the general applicability of this novel *C*-alkylation methodology, **2a** was reacted with a variety of alcohols (Table 2).

Table 2. General application of several substituted benzylic and aliphatic alcohols.



Entry	R =	Product	Yield [%][a]
1	Ph	 **4a**	98 (87)
2	4-OMe-C_6H_4	 **4b**	95 (78)

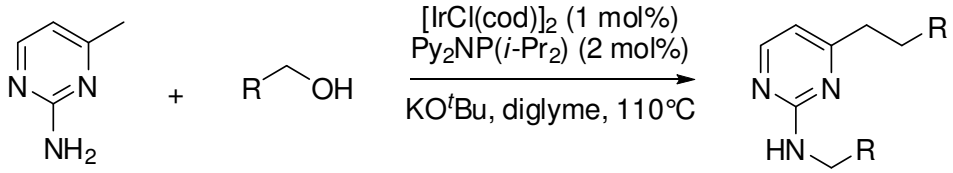
3	4-Me-C_6H_4	 **4c**	90 (77)
4	3-Me-C_6H_4	 **4d**	91
5	2-Me-C_6H_4	 **4e**	92
6	2,4,6-TriMe-C_6H_4	 **4f**	94
7	4-*t*-Bu-C_6H_4	 **4g**	91
8	4-SMe-C_6H_4	 **4h**	73
9	3-Cl-C_6H_4	 **4i**	78
10	2-CF_3-C_6H_4	 **4j**	62[b]

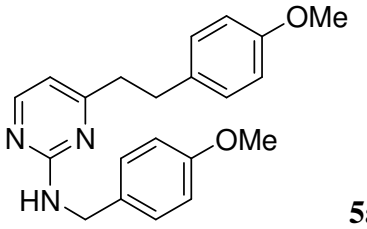
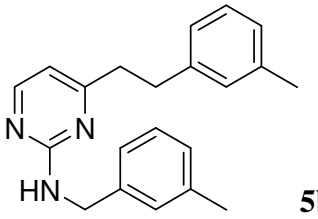
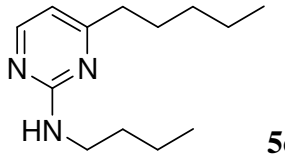
11	alcohol = 1-octanol	 **4k**	74
12	alcohol = 1-butanol	 **4l**	86

Reaction conditions: 1.0 mmol (**2a**), 1.1 mmol alcohol, 1 mol% $[IrCl(cod)]_2$, 2 mol% $Py_2NP(i\text{-}Pr)_2$, diglyme, 1.1 mmol KO^tBu, 24 h, 110°C. [a] Isolated yield; yields in bracket correspond to the reaction with neat $[IrCl(cod)]_2$. [b] 8 mol% Ir.

The results in Table 2 show that a multitude of functional groups are tolerated and that benzylic (entries 1-10) and aliphatic alcohols (entries 11 and 12) can be employed. The reaction works especially well with electron-donating substituents in *ortho*, *meta* and *para* positions and even with rather bulky substrates such as 2,4,6-trimethyl benzylic alcohol. The reaction with electron-withdrawing substituents is slightly more difficult and higher catalyst loadings are necessary in order to obtain full conversions (entry 10). This is somehow a contradiction to literature-known result for the condensation of aldehydes with methylheteroaromatics where a higher efficiency was observed for electron-poor aldehydes.[6] This implies that not the condensation step, but rather the successive hydrogenation of the formed olefin is hampered by electron-withdrawing substituents.
As determined before, the reaction can also be performed without the addition of P,N-ligand, using neat $[IrCl(cod)]_2$, but as shown for entries 1-3 the expected products are obtained in 10-20% lower yields in comparison to **1**. Further, the simultaneous *N*- and *C*-alkylation of 2-amino-4-methylpyrimidine with alcohols cannot be performed using $[IrCl(cod)]_2$ since only poor yields of the corresponding product are obtained, whereas this reaction can perfectly be carried out with **1**, affording excellent yields of the corresponding products as shown in Table 3.

Table 3. Simultaneous *C*- and *N*-alkylation with alcohols.



Entry	R =	Product	Yield [%][a]
1	Ph	**4a**	85
2	4-OMe-C_6H_4	 **5a**	83
3	3-Me-C_6H_4	 **5b**	81
4	alcohol = 1-butanol	 **5c**	62[b]

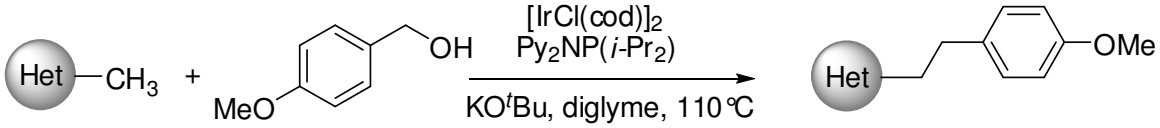
Reaction conditions: 1.0 mmol amine, 2.2 mmol alcohol, 1 mol% $[IrCl(cod)]_2$, 2 mol% $Py_2NP(i\text{-}Pr)_2$, diglyme, 2.2 mmol KO^{t}Bu, 24 h, 110°C. [a] Isolated yield. [b] 3.0 mmol 1-butanol; 48h.

Furthermore, a broad range of methyl-substituted heteroaromatic substrates was tested in order to show the general applicability of this novel method (Table 4). First, the influence of different substituents at the amine moiety was investigated and showed that next to *N*-benzyl and *N*-methyl groups (entry 2) even *N,N*-dibenzylamines are tolerated (entry 1). The reactivity of the latter is however reduced and an excess of alcohol has to be used to reach full conversions. Reactions with *N*-Boc- or *N*-TMS protected substrates were not successful, due to rapid cleavage of the protecting groups under these reaction conditions, affording only the alkylation of the amino function instead of the expected *C*–C bond formation product. The reaction could also be performed with the beforehand *N*-benzylated heteroaromatic substrate **2b**, bearing more than one methyl group. However, we made the observation that electron-donating substituents on the heteroaromatic core lead to a decreased reactivity of the substrates. In the case of the 4,6-dimethyl-substituted compound **2b** a C–C bond formation can nevertheless be achieved for both methyl groups (Table 4, entry 3), but the reaction needs increased catalyst loadings since the second alkylation step is

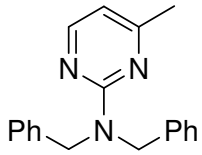
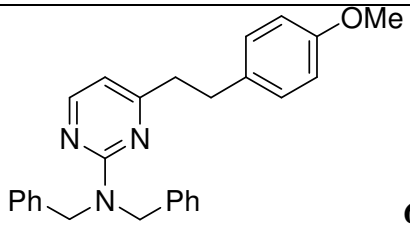
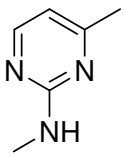
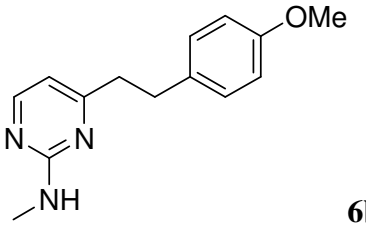
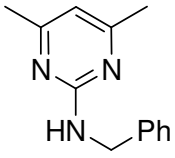
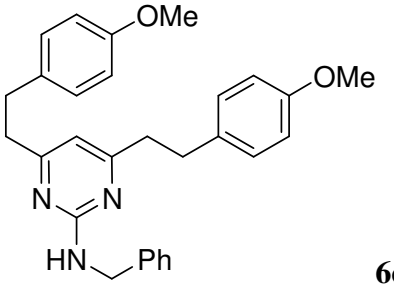
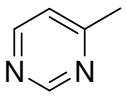
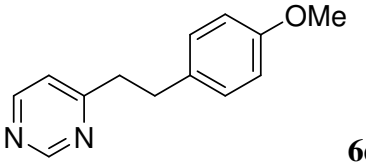
already more difficult due to a reduced reactivity. In the case of methoxy-substituted substrate **2c** the reactivity is already so low that, even with high catalyst loadings, the reaction proceeds only poorly.

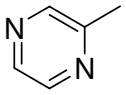
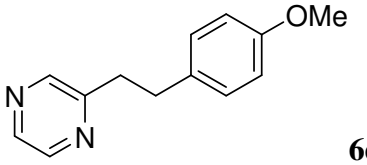
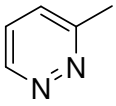
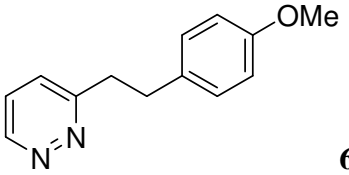
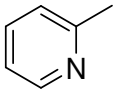
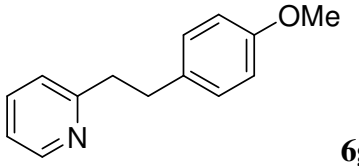
As shown with entries 4 to 7, not only methyl-substituted pyrimidines can be used as substrates, but also pyrazines, pyridazines and even pyridines. However, a similar trend as for **2b** and **2c** was observed here. With decreasing acidity of the methyl protons[7] from 4-methylpyrimidine and 2-methylpyrazine towards the chemically resembling substrates 3-methylpyridazine[8] and 2-methylpyridine the reaction proceeds less efficiently and affords lower yields of the *C*-alkylated products. It is however very interesting that the alkylation of 2-methylpyridine with alcohols is still possible, even though the latter is only a poorly activated substrate.

Table 4. Variation of the heteroaromatic substrates.



6

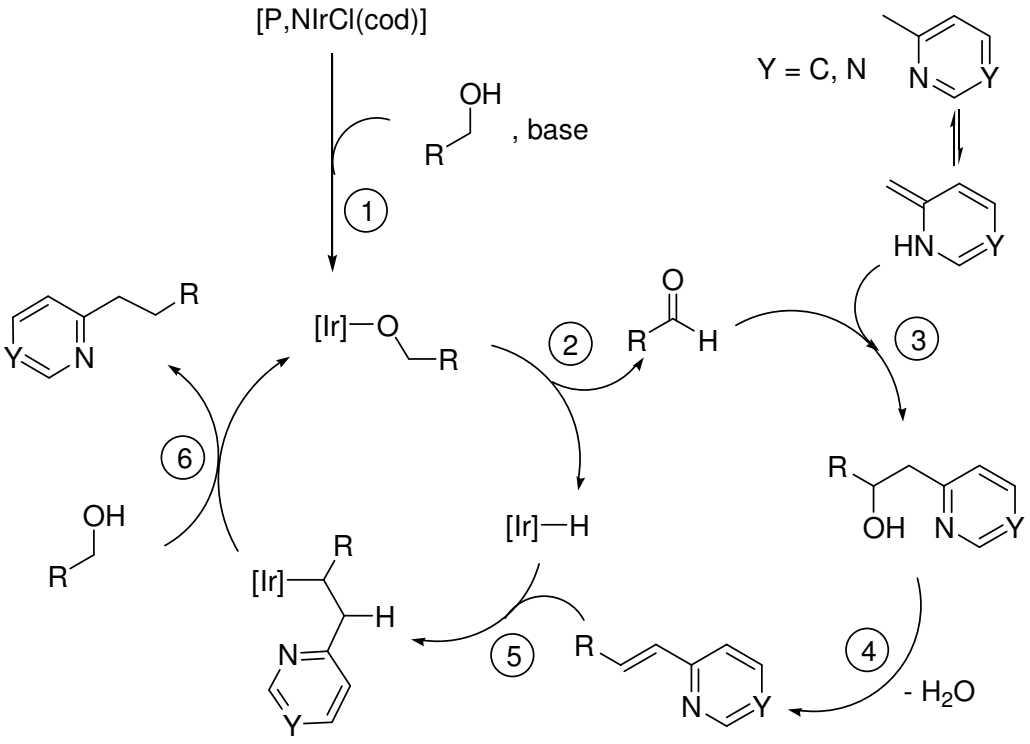
Entry	Cat. Loading [mol% Ir]	Heteroaromatic	Product	Yield [%][a]
1	2.0		 **6a**	56[b]
2	2.0		 **6b**	90
3	4.0		 **6c**	62[b]
4	5.0		 **6d**	71[c]

5	5.0		 **6e**	74[c]
6	5.0		 **6f**	38[c]
7	5.0		 **6g**	33[c]

Reaction conditions: 1.0 mmol heteroaromatic substrate, 1.1 mmol alkohol, 1-2.5 mol% $[IrCl(cod)]_2$, 2-5 mol% $Py_2NP(i\text{-}Pr)_2$, diglyme, 1.1 mmol KO^tBu, 24 h, 110°C. [a] Isolated yield. [b] 2.2 mmol alcohol & base. [c] 3.0 mmol heteroaromatic substrate, 1.0 mmol alcohol; 48h.

The alkylation of methyl-*N*-heteroaromatics with alcohols can be seen as an extension of the "borrowing hydrogen" mechanism named by Williams et al.[9] The latter allows for example the use of commercially available and non-toxic primary alcohols for the (selective) alkylation of amines[3,10,11]. Primary alcohols have also been employed for the formation of C–C bonds for example in the β-alkylation of secondary alcohols[12] or the alkylation of methylketones[13] which rely on an aldol condensation. To our best knowledge, the catalytic *C*-alkylation of heteroaromatic methyl groups using alcohols has not been reported yet.

Scheme 3 depicts the postulated catalytic cycle for this reaction. Based on our knowledge of the *N*-alkylation reaction with alcohols, the first step would comprise the formation of an iridium-alkoxy species which subsequently affords an aldehyde via oxidation of the alcohol and transmission hydrogen equivalent onto the metal complex (dehydrogenation). The in-situ formed aldehyde can further react with the tautomerized form of the heteroaromatic substrate and affords an olefinic intermediate in a condensation step[16] under elimination of water. The latter is finally hydrogenated by retransmission of the "borrowed" hydrogen equivalent from the metal complex and another equivalent of alcohol to the substrate, affording the expected *C*-alkylated aliphatic product.



Scheme 3. Postulated reaction mechanism for the *C*-alkylation reaction with alcohols.

In conclusion, we have developed a novel protocol, allowing the alkylation of methyl groups in *N*-heteroaromatic substrates using simple alcohols in a C–C bond formation reaction. This iridium-catalyzed protocol extends the application scope of the so-called "borrowing hydrogen" methodology towards a new class of substrates and gives an idea about the still hidden potential of catalytic reactions using alcohols.

8.2. Experimental Section

General procedure for the catalytic reactions: In a Schlenk tube stock solutions of $[IrCl(cod)]_2$ (0.0625 M in THF) and $Py_2NP(i\text{-}Pr)_2$ (0.125 M in THF) were mixed in order to generate the catalyst in-situ. Then the heterocycle (1.0 equiv), the alcohol (1.1 equiv) and diglyme (500 µL) were added. Last, KO^tBu (1.1 equiv) was dissolved in the reaction mixture, the reaction vessel tightly closed and stirred at 110°C for 24h. The reaction mixture was cooled to room temperature and quenched with water (20 mL) and diethyl ether (20 mL). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 x 30 mL). The combined organic fractions were washed with brine (10mL), dried over Na_2SO_4 and the solvent evaporated. The residue was purified by column chromatography and dried in vacuo.

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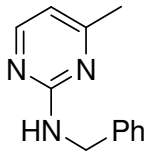
8.4. Supporting Information

General considerations: All reactions were carried out under a dry argon or nitrogen atmosphere, using standard Schlenk and glovebox techniques. Non-halogenated solvents were distilled over sodium benzophenone ketyl and halogenated solvents over P_2O_5. Diglyme was dried over molecular sieves. Deuterated solvents were obtained from Cambridge Isotope Laboratories and stored over molecular sieves. All chemicals were purchased from commercial sources in purities > 97% and used without further purification if not otherwise mentioned in the synthetic procedure. NMR spectra were obtained using a Varian INOVA 400 spectrometer at 300 K. Chemical shifts are reported in ppm relative to the deuterated solvent. Elemental analyses were performed on a Vario

elementar EL *III*. GC analyses were performed on an Agilent 6890N Network GC-System equipped with a HP-5 column (30 m × 0.32 µm × 0.25 µm) and GC-MS analyses on a Thermo Focus GC with a DSQ MS-unit equipped with a HP-5-MS column (30 m × 0.32 µm × 0.25 µm). Flash chromatography was performed over SiO_2 60 (0.040-0.063 mm) from Merck and all used solvents freshly distilled prior to use.

Typical procedure for the selective *N*-alkylation of methyl-substituted *N*-heteroaromatic amines: In a Schlenk tube stock solutions of $[IrCl(cod)]_2$ (0.0625 M in THF) and $Py_2NP(i\text{-}Pr)_2$ (0.125 M in THF) were mixed in order to generate the catalyst in-situ. Then the amine (2.0 equiv), the alcohol (1.0 equiv) and diglyme were added. Last, KO^{t}Bu (1.0 equiv) was dissolved in the reaction mixture, the reaction vessel tightly closed and stirred at 110°C for 6h. The reaction mixture was cooled to room temperature and quenched with water (20 mL) and diethyl ether (20 mL). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 x 30 mL). The combined organic fractions were washed with brine (10mL), dried over Na_2SO_4 and the solvent evaporated. The residue was purified by column chromatography and dried in vacuo.

Benzyl-(4-methylpyrimidin-2-yl)amine (2a)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-amino-4-methylpyrimidine (218 mg, 2.0 mmol), benzyl alcohol (104 µL, 1.0 mmol), diglyme (500 µL) and KO^{t}Bu (112 mg, 1.0 mmol), 6 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 122 mg = 61%

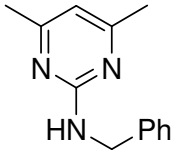
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 4.4 Hz, 1H), 7.34-7.27 (m, 4H), 7.25-7.22 (m, 1H), 6.40 (d, *J* = 5.1 Hz, 1H), 5.71 (s_br, 1H), 4.62 (d, *J* = 6.2 Hz, 2H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 162.0, 157.4, 139.2, 128.5, 128.3, 127.4, 127.1, 110.4, 45.4, 24.0.

MS (70 eV, EI); m/z (%): 199 (M^+, 100), 198 (68), 122 (12), 106 (62), 91 (20), 79 (10), 65 (10).

Elemental Analysis calcd (%) for $C_{12}H_{13}N_3$ (199.3): C 72.33, H 6.58, N 21.09; found: C 71.90, H 6.588, N 20.83.

Benzyl-(4,6-dimethylpyrimidin-2-yl)amine (2b)



$[IrCl(cod)]_2$ (480 µL, 0.03 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (480 µL, 0.06 mmol, 0.125 M in THF), 2-amino-4,6-dimethylpyrimidine (739 mg, 6.0 mmol), benzyl alcohol (310 µL, 3.0 mmol), diglyme (1.5 mL) and KO^{t}Bu (336 mg, 3.0 mmol), 6 h at 110°C. Workup with methylene chloride!! Purification by column chromatography (gradient: pentane/ethyl acetate, 3:1→ 1:1). Yield: 513 mg = 80%

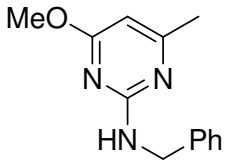
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.26 (m, 4H), 7.24-7.20 (m, 1H), 6.30 (s, 1H), 5.47 (s_br, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 2.26 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 161.9, 139.4, 128.4, 127.5, 127.1, 109.9, 45.4, 23.8.

MS (70 eV, EI); m/z (%): 213 (M^+, 46), 108 (30), 106 (100), 91 (34), 77 (23), 65 (34).

Elemental Analysis calcd (%) for $C_{13}H_{15}N_3$ (213.3): C 73.21, H 7.09, N 19.70; found: C 73.22, H 7.173, N 19.70.

Benzyl-(4-methoxy-6-methylpyrimidin-2-yl)amine (2c)



$[IrCl(cod)]_2$ (640 µL, 0.04 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (640 µL, 0.08 mmol, 0.125 M in THF), 2-amino-4-methoxy-6-methylpyrimidine (1.113 g, 8.0 mmol), benzyl alcohol (414 µL, 4.0 mmol), diglyme (2000 mL) and KO^{t}Bu (448 mg, 4.0 mmol), 6 h at 110°C. Workup with diethyl ether. Purification by column chromatography (pentane/ethyl acetate, 3:1). Yield: 693 mg, 76%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.26 (m ,4H), 7.25-7.19 (m, 1H), 5.86 (s, 1H), 5.68 (s_br, 1H), 4.60 (d, *J* = 6.2 Hz, 2H), 3.81 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 167.8, 162.1, 139.6, 128.4, 127.4, 127.0, 95.8, 53.0, 45.4, 23.7.

MS (70 eV, EI); m/z (%): 229 (M^+, 100), 214 (31), 152 (7), 124 (27), 16 (77), 91 (36), 83 (9), 65 (12).

Elemental Analysis calcd (%) for $C_{13}H_{15}N_3O$ (229.3): C 68.10, H 6.59, N 18.33; found: C 68.07, H 6.764, N 17.99.

Optimization of the reaction parameters

Typical Procedure for screening reactions: In a Schlenk tube stock solutions of $[IrCl(cod)]_2$ (0.0625 M in THF) and $Py_2NP(i\text{-}Pr)_2$ (0.125 M in THF) were mixed in order to generate the catalyst in-situ. Then **2a** (1.0 equiv), benzyl alcohol (1.1 equiv) and the solvent were added. Last, KO^{t}Bu was dissolved in the reaction mixture, the reaction vessel tightly closed and stirred at the given temperature for 24h. The reaction mixture was cooled to room temperature and quenched with water (2 mL) and diethyl ether (10 mL). Dodecane (227 µL, 1.0 mmol) was added and an aliquot of the organic phase was subsequently analyzed by GC-analysis.

Table 1. Solvent screening.

Entry	Solvent	Yield [%]
1	Toluol	55
2	Diglyme	92 (38[a])
3	DME	89
4	THF	36[a]

Reaction conditions: 1.0 mmol benzyl-(4-methylpyrimidin-2-yl)amine (**2a**), 1.1 mmol benzyl alcohol, 0.01 mmol $[IrCl(cod)]_2$, 0.02 mmol $Py_2NP(i\text{-}Pr)_2$, 600µL solvent, 1.1 mmol KO^{t}Bu, 24 h, 110°C. [a] 70°C.

Table 2. Base screening.

Entry	Base	Yield [%]
1	KO^{t}Bu	95
2	NaO^{t}Bu	73
3	KOH	75
4	NaOH	26
5	$KOSiMe_3$	50
6	K_2CO_3	0
7	K_3PO_4	0
8	NaOAc	0

Reaction conditions: 1.0 mmol benzyl-(4-methylpyrimidin-2-yl)amine (**2a**), 1.1 mmol benzyl alcohol, 0.01 mmol $[IrCl(cod)]_2$, 0.02 mmol $Py_2NP(i\text{-}Pr)_2$, 600µL diglyme, 1.1 mmol base, 24 h, 110°C.

Table 3. Base quantity screening.

Entry	Quantity of base [mol%]	Yield [%]
1	0	0
2	10	8
3	30	57
4	50	77
5	80	85
6	100	91
7	110	95

Reaction conditions: 1.0 mmol benzyl-(4-methylpyrimidin-2-yl)amine (**2a**), 1.1 mmol benzyl alcohol, 0.01 mmol $[IrCl(cod)]_2$, 0.02 mmol $Py_2NP(i\text{-}Pr)_2$, 600µL diglyme, 0–1.1 mmol KO^{t}Bu, 24 h, 110°C.

Table 4. Screening of the catalyst loading.

Entry	Catalyst Loading [mol% Ir]	Yield [%]
1	0	0
2	0.05	49
3	0.1	60
4	0.5	77
5	1.0	83
6	2.0	96

Reaction conditions: 1.0 mmol benzyl-(4-methylpyrimidin-2-yl)amine (**2a**), 1.1 mmol benzyl alcohol, 0–0.01 mmol $[IrCl(cod)]_2$, 0–0.02 mmol $Py_2NP(i\text{-}Pr)_2$, 300µL diglyme, 1.1 mmol KOtBu, 24 h, 110°C.

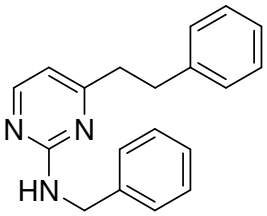
Table 5. Catalyst Screening.

Entry	Catalyst	Yield [%]
1	$[(Py_2NPPh_2)IrCl(cod)]$	42
2	$[(Py_2NPCy_2)IrCl(cod)]$	69
3	$[(Py_2NP(i\text{-}Pr)_2)IrCl(cod)]$	73
4	$[(Py_2NP(t\text{-}Bu)_2)IrCl(cod)]$	70
5	$[IrCl(cod)]_2$	68

Reaction conditions: 1.0 mmol benzyl-(4-methylpyrimidin-2-yl)amine (**2a**), 1.1 mmol benzyl alcohol, **0.0015 mmol $[IrCl(cod)]_2$**, **0.003 mmol P,N-ligand**, 300µL diglyme, 1.1 mmol KO^{t}Bu, 24 h, 110°C.

Typical procedure for the *C*-alkylation reaction: In a Schlenk tube stock solutions of $[IrCl(cod)]_2$ (0.0625 M in THF) and $Py_2NP(i\text{-}Pr)_2$ (0.125 M in THF) were mixed in order to generate the catalyst in-situ. Then the heterocycle (1.0 equiv), the alcohol (1.1 equiv) and diglyme (500 µL) were added. Last, KO^{t}Bu (1.1 equiv) was dissolved in the reaction mixture, the reaction vessel tightly closed and stirred at 110°C for 24h. The reaction mixture was cooled to room temperature and quenched with water (20 mL) and diethyl ether (20 mL). The organic phase was separated and the aqueous layer extracted with diethyl ether or ethyl acetate (3 x 30 mL). The combined organic fractions were washed with brine (10mL), dried over Na_2SO_4 and the solvent evaporated. The residue was purified by column chromatography and dried in vacuo.

Benzyl-(4-phenethylpyrimidin-2-yl)amine (4a)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), benzyl alcohol (114 µL, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 283 mg = 98%

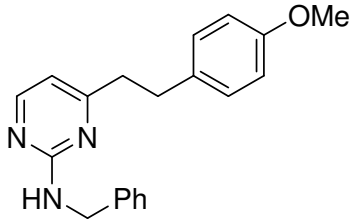
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 4.8 Hz, 1H), 7.36-7.27 (m, 4H), 7.26-7.22 (m, 3H), 7.18-7.13 (m, 3H), 6.36 (d, *J* = 4.8 Hz, 1H), 5.74 (s_br, 1H), 4.64 (d, *J* = 5.9 Hz, 2H), 3.02-2.97, (m, 2H), 2.90-2.86 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 161.8, 157.3, 140.1, 139.2, 128.5, 128.4, 128.4, 127.5, 127.2, 126.0, 110.0, 45.4, 39.3, 34.3.

MS (70 eV, EI); m/z (%): 289 (M^+, 39), 198 (41), 106 (35), 91 (100), 77 (10), 65 (32), 51 (8), 39 (11), 28 (20).

Elemental Analysis calcd (%) for $C_{19}H_{19}N_3$ (289.4): C 78.86, H 6.62, N 14.52; found: C 78.76, H 6.779, N 14.28.

Benzyl-{4-[2-(4-methoxyphenyl)ethyl]pyrimidin-2-yl}amine (4b)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 4-methoxybenzyl alcohol (130 µL, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 304 mg = 95%.

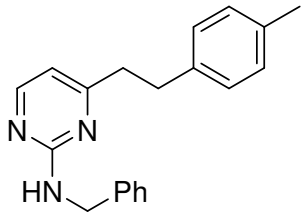
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 5.1 Hz, 1H), 7.36-7.28 (m, 4H), 7.26-7.21 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 4.8 Hz, 1H), 5.76 (s_br, 1H), 4.64 (d, *J* = 5.9 Hz, 2H), 3.75 (s, 3H), 2.96-2.89 (m, 2H), 2.86-2.80 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 157.9, 157.2, 139.1, 133.1, 129.3, 128.5, 127.5, 127.2, 113.8, 110.0, 55.2, 45.4, 39.6, 33.5.

MS (70 eV, EI); m/z (%): 319 (M^+, 57), 198 (29), 121 (100), 106 (18), 91 (51), 77 (12), 32 (10), 28 (33).

Elemental Analysis calcd (%) for $C_{20}H_{21}N_3O$ (319.4): C 75.21, H 6.63, N 13.16; found: C 75.19, H 6.642, N 13.08.

Benzyl-[4-(2-p-tolylethyl)pyrimidin-2-yl]amine (4c)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 4-methylbenzyl alcohol 134 mg, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 274 mg = 90%.

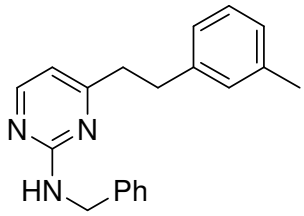
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 5.1 Hz, 1H), 7.36-7.28 (m, 4 H), 7.25 (d, *J* = 6.9 Hz, 1H), 7.08-7.02 (m, 4H), 6.37 (d, *J* = 5.1 Hz, 1H), 5.80 (s_br, 1H), 4.64 (d, *J* = 6.2 Hz, 2H), 2.97-2.91 (m, 2H), 2.89-2.82 (m, 2H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 161.5, 157.1, 139.0, 137.9, 135.5, 129.1, 128.5, 128.2, 127.5, 127.2, 110.0, 45.42, 39.5, 33.9, 21.0.

MS (70 eV, EI); m/z (%): 303 (M^+, 100), 212 (23), 198 (62), 105 (51), 91 (71), 77 (19), 65 (15), 32 (30), 28 (54).

Elemental Analysis calcd (%) for $C_{20}H_{21}N_3$ (303.4): C 79.17, H 6.98, N 13.85; found: C 79.11, H 7.035, N 13.69.

Benzyl-[4-(2-m-tolylethyl)pyrimidin-2-yl]amine (4d)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 3-methylbenzyl alcohol (132 µL, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 276 mg = 91%.

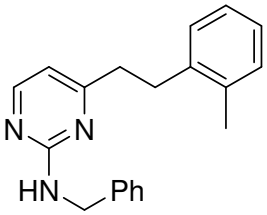
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1H), 7.39-7.29 (m, 4H), 7.26 (d, *J* = 6.9 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.03-6.96 (m, 3H), 6.36 (d, *J* = 4.8 Hz, 1H), 5.85 (s_br, 1H), 4.66 (d, *J* = 5.9 Hz, 2H), 3.00-2.92 (m, 2H), 2.90-2.82 (m, 2H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 162.1, 157.5, 141.1, 139.3, 137.9, 129.2, 128.5, 128.2, 127.5, 127.1, 126.7, 125.32, 109.88, 77.32, 76.68, 45.38, 39.40, 34.3, 21.3.

MS (70 eV, EI); m/z (%): 303 (M^+, 100), 212 (23), 198 (74), 106 (66), 91 (93), 77 (31), 65 (25), 51 (10), 39 (12), 28 (67).

Elemental Analysis calcd (%) for $C_{20}H_{21}N_3$ (303.4): C 79.17, H 6.98, N 13.85; found: C 79.07, H 6.926, N 13.71.

Benzyl-[4-(2-o-tolylethyl)pyrimidin-2-yl]amine (4e)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 2-methylbenzyl alcohol (134 mg, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 278 mg = 92%.

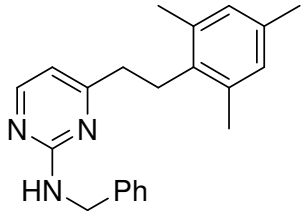
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 4.8 Hz, 1H), 7.36-7.29 (m, 4H), 7.25 (d, *J* = 7.3 Hz, 1H), 7.14-7.08 (m, 4H), 6.37 (d, *J* = 5.1 Hz, 1H), 5.72 (s_br, 1H), 4.65 (d, *J* = 5.9 Hz, 2H), 2.98-2.94 (m, 2H), 2.83-2.79 (m, 2H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 161.9, 157.4, 139.3, 139.2, 135.9, 130.2, 128.7, 128.5, 127.5, 127.2, 126.2, 126.0, 109.9, 45.3, 38.2, 31.8, 19.3.

MS (70 eV, EI); m/z (%): 303 (M^+, 95), 288 (12), 274 (7), 212 (27), 198 (47), 105 (64), 91 (100), 77 (34), 65 (26), 39 (12), 32 (15), 28 (94).

Elemental Analysis calcd (%) for $C_{20}H_{21}N_3$ (303.4): C 79.17, H 6.98, N 13.85; found: C 79.00, H 7.151, N 13.72.

Benzyl-{4-[2-(2,4,6-trimethylphenyl)ethyl]pyrimidin-2-yl}amine (4f)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 2,4,6-trimethylbenzyl alcohol (165 mg, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 312 mg = 94%.

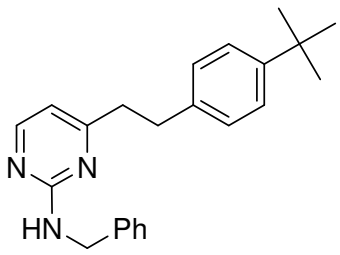
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 4.8 Hz, 1H), 7.38-7.28 (m, 4H), 7.25 (d, *J* = 7.3 Hz, 1H), 6.83 (s, 2H), 6.42 (d, *J* = 5.1 Hz, 1H), 5.84 (s_br, 1H), 4.65 (d, *J* = 6.2 Hz, 2H), 2.95-2.89 (m, 2H), 2.70-2.64 (m, 2H), 2.28 (s, 6H), 2.23 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 161.6, 157.1, 139.1, 136.1, 135.4, 134.8, 129.0, 128.5, 127.6, 127.2, 109.7, 45.4, 37.1, 28.4, 20.8, 19.7.

MS (70 eV, EI); m/z (%):331 (M^+, 100), 302 (16), 240 (17), 198 (31), 133 (77), 106 (18), 91 (78), 65 (11).

Elemental Analysis calcd (%) for $C_{22}H_{25}N_3$ (331.5): C 79.72, H 7.60, N 12.68; found: C 79.53, H 7.816, N 12.67.

Benzyl-{4-[2-(4-tert-butylphenyl)ethyl]pyrimidin-2-yl}amine (4g)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 4-tert-butylbenzyl alcohol (195 µL, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 314 mg = 91%.

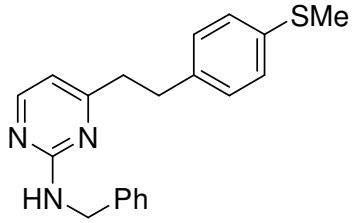
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 4.8 Hz, 1H), 7.36-7.24 (m, 7H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.40 (d, *J* = 5.1 Hz, 1H), 5.79 (s_br, 1H), 4.64 (d, *J* = 5.9 Hz, 2H), 2.99-2.92 (m, 2H), 2.90-2.84 (m, 2H), 1.28 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 161.6, 157.1, 148.9, 139.1, 138.0, 128.5, 128.0, 127.5, 127.2, 125.3, 109.9, 45.4, 39.3, 34.4, 33.8, 31.4.

MS (70 eV, EI); m/z (%):345 (M^+, 58), 288 (5), 254 (6), 212 (6), 198 (45), 131 (12), 117 (23), 106 (30), 92 (100), 65 (10), 28 (16).

Elemental Analysis calcd (%) for $C_{23}H_{27}N_3$ (345.5): C 79.96, H 7.88, N 12.16; found: C 79.69, H 7.991, N 12.07.

Benzyl-{4-[2-(4-methylsulfanylphenyl)ethyl]pyrimidin-2-yl}amine (4h)



$[IrCl(cod)]_2$ (160 μL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 μL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 4-methylthiobenzyl alcohol (201 mg, 1.3 mmol), diglyme (800 μL) and KO^{t}Bu (146 mg, 1.3 mmol), 24 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 3:1). Yield: 244 mg = 73%.

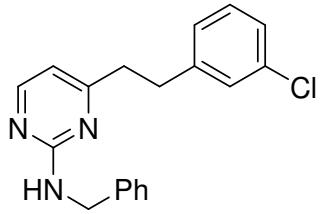
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 4.4 Hz, 1H), 7.36-7.27 (m, 4H), 7.27-7.22 (m, 1H), 7.16-7.12 (m, 2H), 7.08-7.03 (m, 2H), 6.34 (d, *J* = 5.1 Hz, 1H), 5.78 (s_br, 1H), 4.63 (d, 5.9 Hz, 2H), 2.97-2.91 (m, 2H), 2.86-2.80 (m, 2H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 161.8, 157.3, 139.1, 138.1, 135.6, 128.9, 128.5, 127.5, 127.2, 127.0, 110.0, 45.4, 39.2, 33.7, 16.2.

MS (70 eV, EI); m/z (%): 335 (M^+, 52), 244 (9), 198 (44), 137 (100), 122 (30), 106 (29), 91 (75), 78 (12), 65 (17), 28 (63).

Elemental Analysis calcd (%) for $C_{20}H_{21}N_3S$ (335.5): C 71.61, H 6.31, N 12.53; found: C 71.62, H 6.220, N 12.39.

Benzyl-{4-[2-(3-chlorophenyl)ethyl]pyrimidin-2-yl}amine (4i)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 3-chlorobenzyl alcohol (130 µL, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 3:1). Yield: 252 mg = 78%.

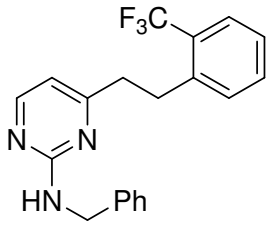
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 4.4 Hz, 1H), 7.36-7.28 (m, 4H), 7.26-7.22 (m, 1H), 7.18-7.12 (m, 3H), 7.03-6.98 (m, 1H), 6.33 (d, *J* = 5.1 Hz, 1H), 5.75 (s_br, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 2.99-2.93 (m, 2H), 2.87-2.80 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 161.9, 157.5, 143.2, 139.2, 134.1, 129.6, 128.5, 128.4, 127.5, 127.2, 126.6, 126.2, 110.0, 45.4, 38.9, 33.8.

MS (70 eV, EI); m/z (%): 323 (M^+, 100), 231 (10), 198 (89), 125 (14), 106 (66), 91 (53), 79 (9), 65 (15), 39 (5).

Elemental Analysis calcd (%) for $C_{19}H_{18}ClN_3$ (323.8): C 70.47, H 5.60, N 12.98; found: C 70.72, H 5.801, N 13.11.

Benzyl-{4-[2-(2-trifluoromethylphenyl)ethyl]pyrimidin-2-yl}amine (4j)



$[IrCl(cod)]_2$ (27 mg, 0.04 mmol) was dissolved in THF (200µL) and a solution of $Py_2NP(i\text{-}Pr_2)$ (23 mg, 0.08 mmol) in THF (200 µL) was added to the latter. Then, benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 2-(trifluoromethyl)benzyl alcohol (159 µL, 1.2 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol) were added and the reaction mixture stirred for 24 h at 110°C. Workup with ethyl acetate and purification by column chromatography (pentane/ethyl acetate, 8:1). Yield: 221 mg = 62%.

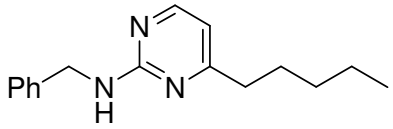
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 3.7 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.40 (t, = 7.5 Hz, 1H), 7.36-7.25 (m, 7H), 6.38 (d, *J* = 5.1 Hz, 1H), 5.86 (s_br, 1H), 4.64 (d, *J* = 5.9 Hz, 2H), 3.19-3.17 (m, 2H), 2.88-2.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 162.0, 157.6, 139.9, 139.2, 131.8, 131.0, 128.5, 128.4 (q, *J* = 29.6 Hz), 127.6, 127.2, 126.2, 126.0 (q, *J* = 5.7 Hz), 125.0 (q, *J* = 273.6 Hz), 109.9, 45.4, 39.2, 31.1.

MS (70 eV, EI); m/z (%): 357 (M^+, 76), 212 (14), 198 (88), 159 (25), 109 (26), 106 (85), 91 (100), 79 (20), 65 (3).

Elemental Analysis calcd (%) for $C_{20}H_{18}F_3N_3$ (357.4): C 67.22, H 5.08, N 11.76; found: C 67.10, H 4.978, N 11.61.

Benzyl-(4-pentylpyrimidin-2-yl)amine (4k)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 1-butanol (183 µL, 2.0 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 6:1). Yield: 219 mg = 86%.

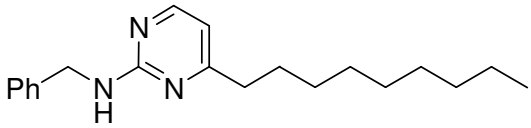
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 4.8 Hz, 1H), 7.35-7.27 (m, 4H), 7.25-7.20 (m, 1H), 6.41 (d, *J* = 5.1 Hz, 1H), 5.71 (s_br, 1H), 4.62 (d, *J* = 5.9 Hz, 2H), 2.53 (t, 7.9 Hz, 2H), 1.70-1.60 (m, 2H), 1.33-1.25 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 161.6, 157.2, 139.1, 128.5, 127.5, 127.2, 109.8, 45.4, 37.7, 31.5, 28.2, 22.5, 14.0.

MS (70 eV, EI); m/z (%): 255 (M^+, 24), 212 (13), 199 (96), 16 (46), 91 (100), 79 (13), 65 (20), 41 (19), 28 (23).

Elemental Analysis calcd (%) for $C_{16}H_{21}N_3$ (255.4): C 75.26, H 8.29, N 16.46; found: C 75.13, H 8.737, N 15.98.

Benzyl-(4-nonylpyrimidin-2-yl)amine (4l)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), benzyl-(4-methyl-pyrimidin-2-yl)-amine (199 mg, 1.0 mmol), 1-octanol (173 µL, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 8:1). Yield: 231 mg = 74%.

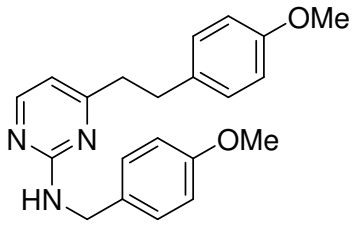
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1H), 7.35-7.28 (m, 4 H), 7.26-7.23 (m, 1H), 6.56 (s_br, 1H), 6.46 (d, *J* = 5.5 Hz, 1H), 4.65 (d, *J* = 5.9 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.70-1.62 (m, 2H), 1.33-1.23 (m, 12H), 0.85 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 156.2, 138.3, 128.6, 127.6, 127.4,109.5, 45.4, 31.8, 29.4, 29.3, 29.2, 29.2, 28.3, 22.7, 14.1.

MS (70 eV, EI); m/z (%): 311 (M^+, 12), 212 (15), 199 (100), 106 (26), 91 (79), 79 (8), 65 (10), 43 (25), 41 (33), 29 (25).

Elemental Analysis calcd (%) for $C_{20}H_{29}N_3$ (311.5): C 77.12, H 9.38, N 13.49; found: C 76.61, H 9.459, N 13.41.

(4-Methoxybenzyl)-{4-[2-(4-methoxyphenyl)ethyl]pyrimidin-2-yl}amine (5a)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-amino-4-methylpyrimidine (109 mg, 1.0 mmol), 4-methoxybenzyl alcohol (260 µL, 2.2 mmol), diglyme (500 µL) and KO^{t}Bu (246 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 290 mg = 83%

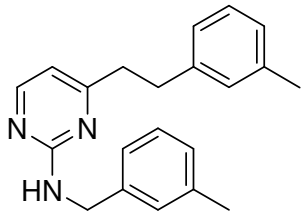
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 4.8 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.86-6.82 (m, 2H), 6.81-6.76 (m, 2H), 6.34 (d, *J* = 5.1 Hz, 1H), 5.71 (s_br, 1H), 4.56 (d, *J* = 5.5 Hz, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 2.96-2.90 (m, 2H), 2.85-2.80 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 158.8, 157.9, 157.2, 133.1, 131.1, 129.3, 128.9, 113.9, 113.8, 109.9, 55.3, 55.3, 44.9, 39.6, 33.5.

MS (70 eV, EI); m/z (%): 349 (M^+, 27), 241 (6), 228 (18), 136 (11), 121 (100), 91 (8), 77 (11), 28 (6).

Elemental Analysis calcd (%) for $C_{21}H_{23}N_3O_2$ (349.4): C 72.18, H 6.63, N 12.03; found: C 75.19, H 6.642, N 13.08

(3-Methylbenzyl)-[4-(2-m-tolylethyl)pyrimidin-2-yl]amine (5b)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-amino-4-methylpyrimidine (109 mg, 1.0 mmol), 3-methylbenzyl alcohol (265 µL, 2.2 mmol), diglyme (500 µL) and KO^{t}Bu (246 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (pentane/diethyl ether, 2:1). Yield: 258 mg = 81%.

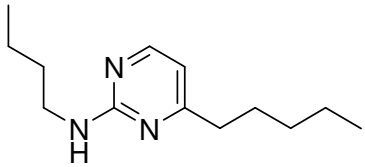
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 4.76 Hz, 1H), 7.22-7.13 (m, 4H), 7.06 (d, *J* = 7.3 Hz, 1H), 7.02-6.95 (m, 3H), 6.36 (d, *J* = 5.1 Hz, 1H), 5.67 (s_br, 1H), 4.61 (d, *J* = 5.9 Hz, 2H), 2.99-2.91 (m, 2H), 2.89-2.82 (m, 2H), 2.32 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 162.0, 157.4, 141.1, 139.1, 138.1, 137.9, 129.2, 128.4, 128.3, 128.2, 127.9, 126.7, 125.3, 124.6, 109.9, 45.4, 39.4, 34.3, 21.4.

MS (70 eV, EI); m/z (%): 317 (M^+, 100), 302 (8), 212 (76), 120 (49), 105 (61), 79 (16), 77 (19).

Elemental Analysis calcd (%) for $C_{21}H_{23}N_3$ (317.4): C 79.46, H 7.30, N 13.24; found: C 79.26, H 7.306, N 13.31.

Butyl-(4-pentylpyrimidin-2-yl)amine (5c)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), 2-amino-4-methylpyrimidine (109 mg, 1.0 mmol), 1-butanol (215 µL, 2.2 mmol), diglyme (500 µL) and KO^{t}Bu (246 mg, 2.2 mmol), 48 h at 110°C. Purification by column chromatography (pentane/ethyl acetate 3:1). Yield: 137 mg = 62%.

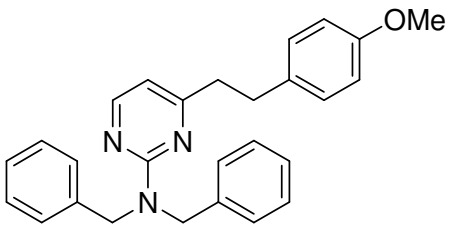
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 4.8 Hz, 1H), 6.37 (d, *J* = 5.1 Hz, 1H), 5.47 (s_br, 1H), 3.42-3.33 (m, 2H), 2.53 (t, *J* = 7.8 Hz, 2H), 1.69-1.60 (m, 2H), 1.60-1.52 (m, 2H), 1.43-1.34 (m, 2H), 1.33-1.27 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.88-0.83 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 157.1, 109.1, 41.2, 37.6, 31.7, 31.5, 28.2, 22.5, 20.1, 14.0, 13.8.

MS (70 eV, EI); m/z (%): 221 (M^+, 21), 192 (39), 178 (100), 165 (96), 136 (19), 123 (39), 109 (42), 94 (10), 41 (14).

Elemental Analysis calcd (%) for $C_{13}H_{23}N_3$ (221.3): C 70.54, H 10.47, N 18.98; found: C 70.39, H 10.58, N 18.99

Dibenzyl-{4-[2-(4-methoxyphenyl)ethyl]pyrimidin-2-yl}amine (6a)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), N,N-dibenzyl-4-methylpyrimidin-2-amine (289 mg, 1.0 mmol), 4-methoxybenzyl alcohol

(260 µL, 2.2 mmol), diglyme (1 mL) and KO^{t}Bu (246 mg, 2.2 mmol), 24 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 29:1). Yield: 229 mg = 56%.

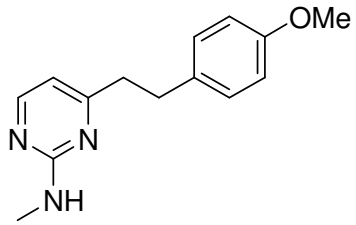
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 5.1 Hz, 1H), 7.31-7.26 (m, 4H), 7.25-7.21 (m, 6H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.34 (d, *J* = 5. 1 Hz, 1H), 4.87 (s, 4H), 3.75 (s, 3H), 2.96-2.90 (m, 2H), 2.88-2.83 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 157.8, 157.2, 138.5, 133.4, 129.3, 128.4, 127.7, 126.9, 113.7, 109.2, 55.2, 49.0, 39.7, 33.2.

MS (70 eV, EI); m/z (%): 409 (M^+, 4), 318 (71), 197 (8), 121 (100), 91 (75), 77 (11), 65 (17), 28 (21).

Elemental Analysis calcd (%) for $C_{27}H_{27}N_3O$ (409.5): C 79.19, H 6.65, N 10.26; found: C 79.13, H 6.613, N 10.19.

{4-[2-(4-Methoxyphenyl)ethyl]pyrimidin-2-yl}methylamine (6b)



$[IrCl(cod)]_2$ (160 µL, 0.01 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (160 µL, 0.02 mmol, 0.125 M in THF), methyl-(4-methyl-pyrimidin-2-yl)-amine[1] (123 mg, 1.0 mmol), 4-methoxybenzyl alcohol (130 µL, 1.1 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 24 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 1:1). Yield: 218 mg = 90%.

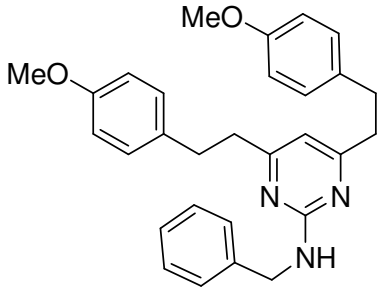
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 5.1 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.31 (d, *J* = 5.1 Hz, 1H), 5.30 (s_br, 1H), 3.75 (s, 3H), 2.98 (d, *J* = 5.1 Hz, 3H), 2.96-2.90 (m, 2H), 2.86-2.78 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 162.5, 157.9, 157.3, 133.2, 129.3, 113.8, 109.5, 55.2, 39.7, 33.6, 28.4.

MS (70 eV, EI); m/z (%): 243 (M^+, 32), 228 (6), 136 (7), 121 (100), 108 (7), 91 (10), 77 (12), 65 (5), 28 (11).

Elemental Analysis calcd (%) for $C_{14}H_{17}N_3O$ (243.3): C 69.11, H 7.04, N 17.27; found: C 68.94, H 7.100, N 17.26.

Benzyl-{4,6-bis-[2-(4-methoxyphenyl)ethyl]pyrimidin-2-yl}amine (6c)



$[IrCl(cod)]_2$ (320 µL, 0.02 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (320 µL, 0.04 mmol, 0.125 M in THF), benzyl-(4,6-dimethyl-pyrimidin-2-yl)-amine (213 mg, 1.0 mmol), 4-methoxybenzyl alcohol (260 µL, 2.2 mmol), diglyme (800 µL) and KO^{t}Bu (246 mg, 2.2 mmol), 48 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 7:1). Yield: 283 mg = 62%.

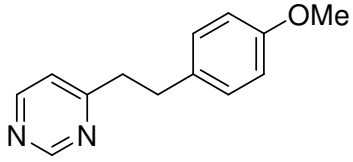
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.28 (m, 4H), 7.26-7.21 (m, 1H), 7.05 (d, *J* = 8.5 Hz, 4H), 6.78 (d, *J* = 8.6 Hz, 4H), 6.18 (s, 1H), 5.71 (s_br, 1H), 4.66 (d, *J* = 5.9 Hz, 2H), 3.75 (s, 6H), 2.93-2.86 (m, 4H), 2.81-2.75 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 161.6, 157.9, 139.4, 133.2, 129.3, 128.5, 127.6, 127.1, 113.7, 109.2, 55.2, 45.5, 39.5, 33.6.

MS (70 eV, EI); m/z (%): 453 (M^+, 0.3), 333 (47), 212 (31), 121 (100), 106 (22), 91 (78), 77 (16), 65 (15), 28 (49).

Elemental Analysis calcd (%) for $C_{29}H_{31}N_3O_2$ (453.6): C 76.79, H 6.89, N 9.26; found: C 76.36, H 6.958, N 9.557.

4-[2-(4-Methoxyphenyl)ethyl]pyrimidine (6d)



$[IrCl(cod)]_2$ (400 µL, 0.025 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (400 µL, 0.05 mmol, 0.125 M in THF), 4-methylpyrimidine (274 µL, 3.0 mmol), 4-methoxybenzyl alcohol (118 µL, 1.0 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 48 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 1:1). Yield: 153 mg = 71%.

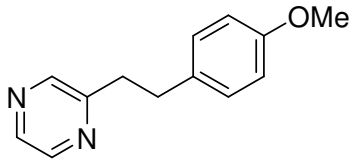
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 7.10-7.01 (m, 3H), 6.78 (d, *J* = 8.1 Hz, 2H), 3.74 (s, 3H), 3.06-2.96 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 158.2, 158.0, 156.4, 132.4, 129.3, 120.8, 113.9, 55.2, 39.7, 33.8.

MS (70 eV, EI); m/z (%): 214 (M^+, 13), 121 (100), 108 (9), 91 (7), 77 (9), 52 (5), 39 (4), 28 (6).

Elemental Analysis calcd (%) for $C_{13}H_{14}N_2O$ (214.3): C 72.87, H 6.59, N 13.07; found: C 72.45, H 6.684, N 12.90.

2-[2-(4-Methoxyphenyl)ethyl]pyrazine (6e)



$[IrCl(cod)]_2$ (400 µL, 0.025 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (400 µL, 0.05 mmol, 0.125 M in THF), 2-methylpyrazine (275 µL, 3.0 mmol), 4-methoxybenzyl alcohol (118 µL, 1.0 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 48 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 3:1). Yield: 158 mg = 74%.

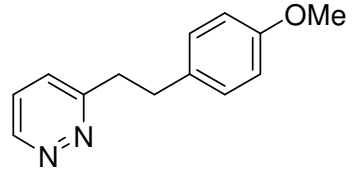
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (s, 1H), 8.38 (d, *J* = 2.2 Hz, 1H), 8.32 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 3H), 3.10-3.04 (m, 2H), 3.02-2.95 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 156.8, 144.7, 144.0, 142.2, 132.7, 129.3, 113.9, 55.2, 37.5, 34.5.

MS (70 eV, EI); m/z (%): 214 (M^+, 11), 121 (100), 91 (7), 78 (11), 65 (4).

Elemental Analysis calcd (%) for $C_{13}H_{14}N_2O$ (214.3): C 72.87, H 6.59, N 13.07; found: C 72.72, H 6.621, N 12.74.

3-[2-(4-Methoxyphenyl)ethyl]pyridazine (6f)



$[IrCl(cod)]_2$ (400 µL, 0.025 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (400 µL, 0.05 mmol, 0.125 M in THF), 3-methylpyridazin (274 µL, 3.0 mmol), 4-methoxybenzyl alcohol (118 µL, 1.0 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 48 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 1:3). Yield: 82 mg = 38%.

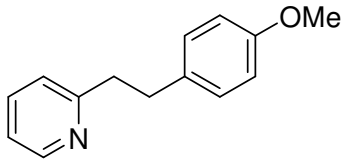
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (d, *J* = 4.0 Hz, 1H), 7.47 (dd, *J* = 8.5, 4.9 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 3H), 3.31 (t, *J* = 7.7 Hz, 2H), 3.06 (t, *J* = 7.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 158.1, 149.2, 132.1, 129.5, 128.3, 127.8, 113.9, 55.2, 37.8, 34.6.

MS (70 eV, EI); m/z (%): 214 (M^+, 28), 199 (8), 121 (100), 108 (10), 91 (13), 77 (20), 65 (11).

Elemental Analysis calcd (%) for $C_{13}H_{14}N_2O$ (214.3): C 72.87, H 6.59, N 13.07; found: C 73.01, H 6.784, N 12.94.

2-[2-(4-Methoxyphenyl)ethyl]pyridine (6g)



$[IrCl(cod)]_2$ (400 µL, 0.025 mmol, 0.0625 M in THF), $Py_2NP(i\text{-}Pr_2)$ (400 µL, 0.05 mmol, 0.125 M in THF), 2-picoline (296 µL, 3.0 mmol), 4-methoxybenzyl alcohol (118 µL, 1.0 mmol), diglyme (500 µL) and KO^{t}Bu (123 mg, 1.1 mmol), 48 h at 110°C. Purification by column chromatography (pentane/ethyl acetate, 6:1). Yield: 71 mg = 33%.

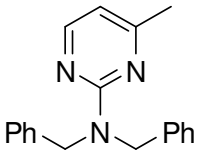
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 5.1 Hz, 1H), 7.56 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.13-7.04 (m, 4H), 6.81-6.76 (m, 2H), 3.75 (s, 3H), 3.09-3.02 (m, 2H), 3.02-2.94 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 157.9, 148.4, 137.1, 133.3, 129.4, 123.4, 121.4, 113.8, 55.2, 40.0, 35.0.

MS (70 eV, EI); m/z (%): 213 (M^+, 21), 121 (100), 108 (11), 91 (12), 78 (21), 65 (15), 51 (13), 39 (14).

Elemental Analysis calcd (%) for $C_{14}H_{15}NO$ (213.3): C 78.84, H 7.09, N 6.57; found: C 78.48, H 7.424, N 6.729.

Synthesis of *N,N*-dibenzyl-4-methylpyrimidin-2-amine



In a 50 mL round-bottom flask equipped with a magnetic stirrer, 2-amino-4-methylpyrimidine (0.654 g , 6.0 mmol) was dissolved in 15 mL dry THF. The reaction mixture was cooled to –30°C and *n*-BuLi (7.5 mL, 12.0 mmol, 1.6M in hexane) added dropwise. The mixture was allowed to warm to room temperature and stirred for 3h. After cooling to –30°C benzyl bromide (1.4 mL, 12.0 mmol) was added and the mixture stirred at rt for further 24h. The solution was concentrated, diethyl ether and water were added, the layers separated and the organic phase washed with diethyl ether (3 x 40 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The residue was further purified by column chromatography (pentane/diethyl ether; 40:1). Yield: 454 mg = 26%.

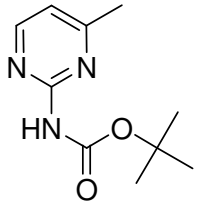
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 5.1 Hz, 1H), 7.32-7.26 (m, 4H), 7.26-7.22 (m, 6H), 6.41 (d, *J* = 4.8 Hz, 1H), 4.88 (s, 4H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 162.1, 157.2, 138.5, 128.4, 127.7, 126.9, 109.5, 48.7, 24.4.

MS (70 eV, EI); m/z (%): 289 (M^+, 4), 198 (100), 93 (15), 91 (52), 65 (26), 28 (11).

Elemental Analysis calcd (%) for $C_{19}H_{19}N_3$ (289.4): C 78.86, H 6.62, N 14.52; found: C 78.88, H 6.729, N 14.39.

(4-Methylpyrimidin-2-yl)-carbamic acid tert-butyl ester



In a 100 mL round-bottom flask equipped with a magnetic stirrer, 2-amino-4-methylpyrimidine (1.637 g , 15.0 mmol) was dissolved in 50 mL dry THF. Under stirring di-tert-butyl dicarbonate (5.2 mL, 22.5 mmol) was added and the reaction mixture stirred for 36h. Then methylene chloride and water were added, the layers separated and the organic phase washed with methylene chloride (3 x 40 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The residue was further purified by column chromatography (diethyl ether). Yield: 1.541 g = 74%.

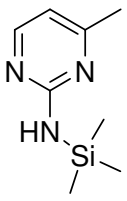
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 5.1 Hz, 1H), 7.98 (s_br, 1H), 6.79 (d, *J* = 5.1 Hz), 2.45 (s, 3H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 157.8, 157.3, 150.4, 115.3, 81.5, 28.2, 24.1.

MS (70 eV, EI); m/z (%): 209 (M^+, 3), 150 (6), 136 (19), 109 (100), 93 (8), 82 (12), 57 (73), 41 (33), 32 (24).

Elemental Analysis calcd (%) for $C_{10}H_{15}N_3O_2$ (209.2): C 57.40, H 7.23, N 20.08; found: C 57.29, H 7.262, N 20.06.

(4-Methylpyrimidin-2-yl)trimethylsilanylamine



In a flame-dried 100 mL round-bottom flask equipped with a magnetic stirrer, 2-amino-4-methylpyrimidine (1.09 g , 10.0 mmol) was dissolved in 50 mL dry diethyl ether and cooled to -50°C. Under vigorous stirring *n*-BuLi (6.3 mL, 10.0 mmol, 1.6 M in hexane) was added dropwise

and the reaction mixture stirred for 3h, allowing it to warm to room temperature. Then the reaction mixture was cooled to -30°C and trimethylchlorosilane (1.3 mL, 10.0 mmol) was added and stirred overnight at room temperature. The ether solution was filtered from the precipitate, the latter washed twice with diethyl ether (10 mL). The solvent were evaporated and the product dried in vacuo. Yield: 1.70 g = 93%,

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 5.1 Hz, 1H), 6.40 (d, *J* = 5.1 Hz, 1H), 4.68 (s_br, 1H), 2.26 (s, 3H), 0.24 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 164.2, 157.5, 110.6, 24.0, 0.5.

Elemental Analysis calcd (%) for $C_8H_{15}N_3Si$ (181.3): C 53.00, H 8.34, N 23.18; found: C 52.59, H 8.472, N 23.07.

[1] O. Kemal, C. B. Reese, *J. Chem. Soc., Perkin Trans. 1* **1981**, 1569-1573.

9. List of Publications

1) B. Blank, M. Colling-Hendelkens, C. Kollann, K. Radacki, D. Rais, K. Uttinger, G. R. Whittell, H. Braunschweig, *Chem. Eur. J.* **2007**, *13*, 4770-4778.
"Aminoborylene Complexes of Group 6 Elements and Iron: A Synthetic, Structural, and Quantum Chemical Study"

2) C. C. Kofink, B. Blank, S. Pagano, N. Götz, P. Knochel, *Chem. Commun.* **2007**, 1954-1956.
"Iron-Catalyzed Aryl–Aryl Cross-Coupling Reaction Tolerating Amides and Unprotected Quinolinones"

The following publications have been published, are submitted or are to be submitted during the work on this thesis:

3) B. Blank, M. Madalska, R. Kempe, *Adv. Synth. Catal.* **2008**, *350*, 749-758.
"An Efficient Method for the Selective Iridium-Catalyzed Monoalkylation of (Hetero)aromatic Amines with Primary Alcohols"

4) B. Blank, G. Glatz, R. Kempe, *Chem. Asian J.* **2009**, *4*, 321-327.
"Single and Double C–Cl-Activation of Methylene Chloride by P,N-ligand Coordinated Rhodium Complexes"

5) B. Blank, S. Michlik, R. Kempe, *Chem. Eur. J.* **2009**, *15,* 3790-3799.
"Selective Iridium-Catalyzed Alkylation of (Hetero)Aromatic Amines and Diamines with Alcohols under Mild Reaction Conditions"

6) B. Blank, S. Michlik, R. Kempe, *Adv. Synth. Catal.* accepted for publication.
"Synthesis of Selectively Mono-*N*-Arylated Aliphatic Diamines via Iridium-Catalyzed Amine Alkylation"

7) B. Blank, R. Kempe; *to be submitted*
"Catalytic Alkylation of Methyl-*N*-Heteroaromatics with Alcohols"

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Prof. Dr. Rhett Kempe

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11. Declaration/Erklärung

I hereby declare that I have written this work by myself and that no other sources than those mentioned in this work have been used.

This work has so far neither been submitted to the Faculty of Biology, Chemistry and Earth Sciences at the University of Bayreuth nor to any other scientific institution for the purpose of a doctoral thesis.

Hiermit versichere ich an Eides statt, dass ich die vorliegende Arbeit selbständig und nur unter Verwendung der angegebenen Hilfsmittel und Quellen angefertigt habe.

Diese Arbeit wurde bisher weder an der Fakultät für Biologie, Chemie und Geowissenschaften der Universität Bayreuth noch einer anderen wissenschaftlichen Einrichtung zum Zwecke der Promotion eingereicht.

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Benoît Blank