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

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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 of the iridium complex $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene) affords P,N ligand-coordinated 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.

Keywords: alkylation; amines; aminopyridines; iridium; P,N ligands; primary alcohols

Introduction

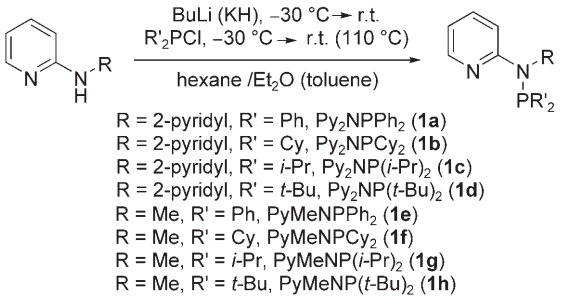
Nitrogen-containing molecules and especially amines are intermediates and products of enormous importance for chemical and life science applications. In the last decade, catalytic amine syntheses such as, for instance, Pd-catalyzed aminations of aryl halides,[1] hydroaminations[2] and hydroaminomethylations[3] 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*-alkylamines 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 coordinated iridium complexes and the use of these compounds as catalysts for the *N*-alkylation of (hetero)aromatic amines with primary alcohols.

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 centres. 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.



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 of $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene) in CH_2Cl_2 affords P,N ligand-coordinated iridium complexes in quantitative yields (Scheme 2).

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.

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 centres of the two olefinic cyclooctadiene bonds. We were surprised 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 phosphorus (mono- and bidentate), nitro-

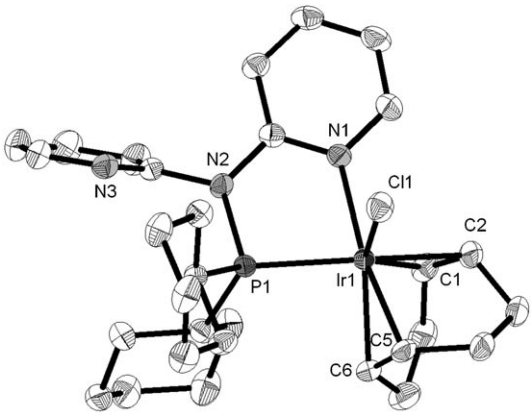
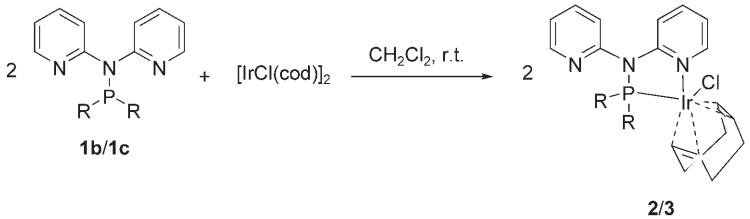


Figure 1. Molecular structure of monomeric $[(Py_2NPCy_2)Ir(cod)Cl]$ (**2**). Selected bond lengths [Å] and angles [°]: N1−Ir1 2.118(3), P1−Ir1 2.3024(11), Cl1−Ir1 2.5707(10), C1−Ir1 2.112(4), C2−Ir1 2.157(4), C5−Ir1 2.137(4), C6−Ir1 2.153(4), C1−C2 1.427(6), C5−C6 1.406(7), N1−Ir1−P1 80.57(10), P1−Ir1−Cl1 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).



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

gen, 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 behaviour of the isopropyl groups of **3** in solution and underline the crowded nature of the compound.

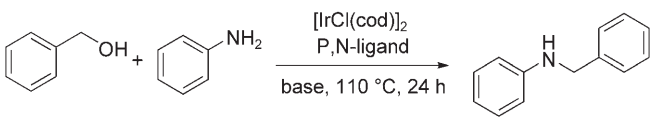
Catalytic Studies

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.

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 benzylphenylamine 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.



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

Table 1. Influence of substrate/base ratio.[a]

Entry	Base	Substrate:Base	Yield [%][b]
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

[a] *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.
[b] Yield determined by GC analysis with dodecane as internal standard.

Table 2. Solvent screening.[a]

Entry	Solvent	Temperature	Yield [%][b]
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[c]	110 °C	0
7	DME	110 °C	62
8	THF	70 °C	77
9	Et_3N[c]	110 °C	0

[a] *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.
[b] Yield determined by GC analysis with dodecane as internal standard.
[c] Reaction without KO-*t*-Bu.

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 triethylamine 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.

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

Table 3. Base screening.[a]

Entry	Base	Yield [%][b]
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	$N(i\text{-}Pr)_2Et$	0
14	KH	67

[a] *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.

[b] Yield determined by GC analysis with dodecane as internal standard.

were observed. KO-*t*-Bu was once again found to be the best base, leading to best conversions and highest yield of 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 $N(i\text{-}Pr)_2Et$ did not lead to any conversion of the reaction.

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 centre, 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 centre 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.

Having optimized important reaction parameters (solvent, ligand, and base), it was of interest to know

Table 4. Ligand screening.[a]

Entry	Ligand	Yield [%][b]
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

[a] *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-*t*-Bu, 1 mL diglyme, 110 °C, 24 h.

[b] Yield determined by GC analysis with dodecane as internal standard.

whether the amount of KO-*t*-Bu 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-*t*-Bu 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.[a]

Entry	Base	Substrate:Base	Yield [%][b]
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[c])

[a] *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.

[b] Yield determined by GC analysis with dodecane as internal standard.

[c] Isolated yield.

Table 6. Influence of amine/alcohol ratio.[a]

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

[a] *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.

[b] Yield determined by GC analysis with dodecane as internal standard.

Table 7. Influence of catalyst loading.[a]

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

[a] *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.

[b] 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.

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).

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.

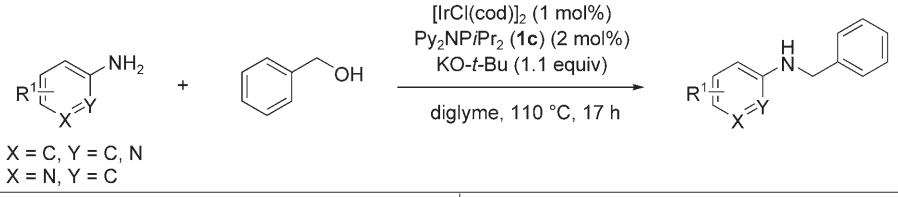
The *N*-alkylation reaction of 4-(trifluoromethyl)-aniline, carrying a usually very stable CF_3 group, surprisingly afforded many non-identifiable side-products and only led to moderate yields (34%) when reacted for 17 h. In order to avoid the decomposition of the product the reaction was also monitored 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).

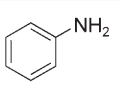
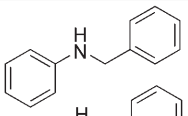
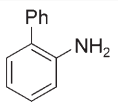
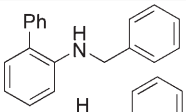
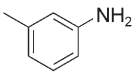
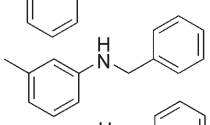
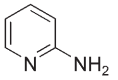
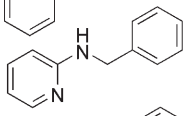
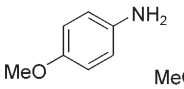
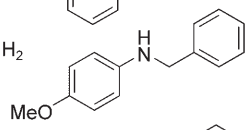
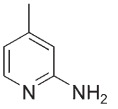
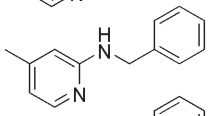
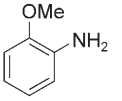
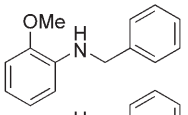
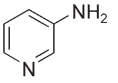
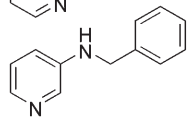
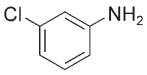
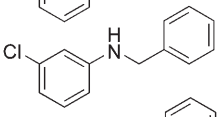
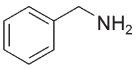
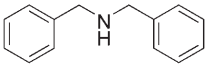
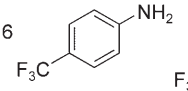
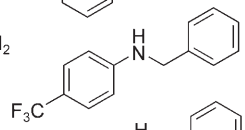
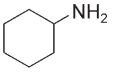
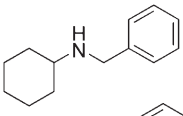
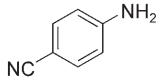
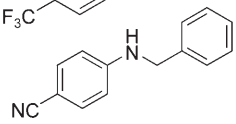
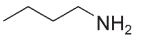
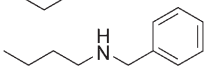
The *N*-alkylation of amines bearing nitro and ester groups was unsuccessful and did not afford the expected secondary amines. Instead, mainly the degradation products of the starting materials were observed. This degradation can be assigned to the use of stoichiometric amounts of the strong base KO-*t*-Bu, 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 comparison, 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.

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



Entry	Amine	Product	Yield [%][b]	Entry	Amine	Product	Yield [%][b]
1			92	8			92
2			92	9			93
3			97	10			94
4			79	11			97
5			96	12			3
6			67[c]	13			0
7			69[d]	14			0

[a] *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-*t*-Bu, 1 mL diglyme, 110 °C, 17 h (reaction times were not optimized).
[b] Isolated yield.
[c] Reaction time: 3 h.
[d] Reaction time: 20 min.

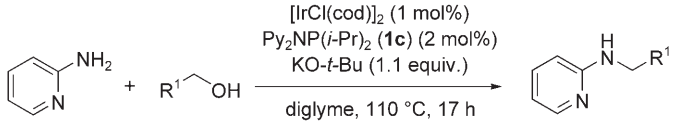
N-Alkylation of Aminopyridines with Primary Alcohols

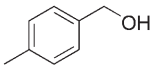
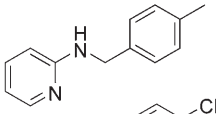
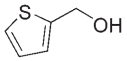
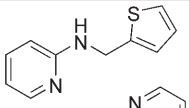
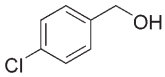
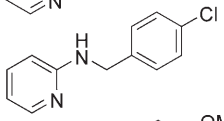
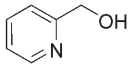
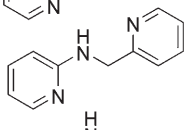
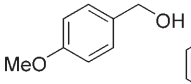
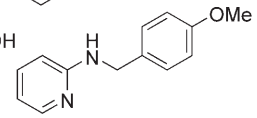
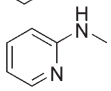
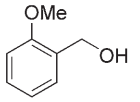
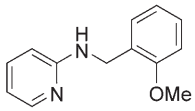
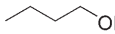
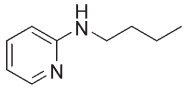
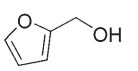
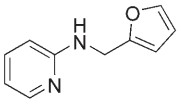
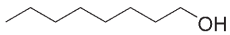
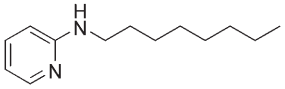
In order to show the general applicability of this method for the alkylation of aminopyridines, a broad scope of substituted benzyl alcohol derivatives as well as aliphatic alcohols and heteroaromatic alcohols were employed, selectively affording the monoalkylated compounds in good to excellent yields.

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*-positions 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 theses 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]

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



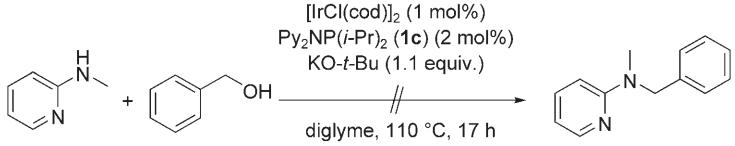
Entry	Alcohol	Product	Yield [%][b]	Entry	Alcohol	Product	Yield [%][b]
1			94	6			69
2			82[c]	7			44
3			97	8	CH_3OH		63[d]
4			95	9			75
5			71	10			72

[a] *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-*t*-Bu, 1 mL diglyme, 110 °C, 17 h (reaction times were not optimized).
[b] Isolated yield.
[c] Reaction time 4 h.
[d] 1.6 equiv of MeOH, Yield determined by GC analysis with dodecane as internal standard.

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]

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, espe-



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

cially the monomethylation, of aromatic amines is difficult to accomplish.

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.

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 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 under vacuum 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 under vacuum 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 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-*tert*-butylphosphine (2.3 mL, 12.0 mmol) was added dropwise with a syringe. The yellow solution 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 under vacuum and the resulting brown oil left to crystallize at −20 °C. The solid was dried under vacuum 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%).

$PyMeNP(i\text{-}Pr)_2$ (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%)..

$PyMeNP(t\text{-}Bu)_2$ (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 plase 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 $Py_2NP(i\text{-}Pr)_2$ (**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-*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 (3×20 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

The 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, °]: $a=9.5370(6)$, $b=10.9370(7)$, $c=15.2230(9)$, $\alpha=100.393(5)$, $\beta=96.344(5)$, $\gamma=94.013(5)$, V [Å^3]: 1545.66(17), crystal size [mm]: $0.35\times0.32\times0.15$, $\rho_{calcd.}$ [g cm^{-3}]: 1.694, μ [mm^{-1}] (Mo-K_α): 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.uk/data_request/cif (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

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

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