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ARTICLE TYPE

Room Temperature and Solvent-Free Iridium-Catalyzed Selective Alkylation of Anilines with Alcohols

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A bidentate iridium NHC/phosphine complex has been developed and applied to the N-monoalkylation of aromatic amines with a wide range of primary alcohols, and in the N-heterocyclization of amino alcohols. This reaction resulted in high isolated product yields, even at room temperature and under solvent-free conditions.

Amines are important compounds used as agrochemicals, additives and dyes in both the bulk and fine chemical industries, as well as in the pharmaceutical industry.¹ A typical method for preparing N-alkylamines is the nucleophilic substitution of an amine with an alkylating agent such as an alkyl halide.² However, the reaction is prone to overalkylation and many alkylating agents are toxic. Alternatively, reductive amination³ and catalytic alkylation of amines with alcohols⁴ have been received with significant interest. For the alkylation of amines with alcohols, water is the only byproduct, making it atom-economical. Also, the replacement of toxic alkylating agents by readily available alcohols makes this a greener route for amine synthesis.⁵ The overall transformation is based on a process called “borrowing hydrogen”⁶ or “hydrogen autotransfer”⁷ (Scheme 1).

Scheme 1 “Borrowing hydrogen” or “hydrogen autotransfer” in the alkylation of an amine with an alcohol.

The first use of homogeneous catalysts for the alkylation of amines with alcohols was described in 1981, and since then a number of metal-containing catalysts, including complexes of ruthenium, rhodium and iridium, have been evaluated in this transformation.⁴ Elegant results from the groups of Beller,⁸ Williams,⁹ Kempe,¹⁰ Fujita,¹¹ Martín-Matute,¹² Crabtree¹³ and Yus¹⁴ have made the alkylation of amines with alcohols an efficient method for the synthesis of a variety of amines. In the past few years, research in this field has focused mainly on iridium- and ruthenium-containing catalysts. In general, the iridium complexes are more reactive than the ruthenium complexes,^{12a} and since Fujita *et al.* first applied [Cp*IrCl₂]₂ (Cp* = pentamethylcyclopentadienyl) in the N-heterocyclization of amino alcohols in 2002,¹⁵ a number of iridium complexes have

been developed and applied in this transformation.¹⁶ Recent DFT calculations have provided a better understanding of the reaction pathways in some catalytic systems.¹⁷ Some catalysts have shown very high reactivities.^{10a, 12b, 18} However, this reaction typically requires high temperature (>100 °C) and there are only a few reported examples of the reaction at lower temperature.^{10, 12b} Moreover, we are not aware of any catalyst that allows the reaction to work at room temperature. Thus, more reactive catalysts are desirable.^{4d, 19}

N-Heterocyclic carbenes (NHCs) have found widespread applications as versatile ligands and experienced significant development in transition-metal catalysis in the past few years.²⁰ The high activity of the iridium catalysts in N-alkylation reactions, combined with the excellent performance of NHCs as ligands in homogeneous catalysis, inspired us to seek an easily accessible and highly active NHC-based iridium catalyst for N-alkylation with alcohols. Here, we report a highly reactive bidentate iridium NHC/phosphine complex that catalyzes the N-alkylation of aromatic amines with primary alcohols under mild conditions. Some reactions could even be carried out at room temperature and without solvent.

The three-step synthesis of the triphenylphosphine-functionalized imidazolium salt **1** was reported by Zhou and co-workers.²¹ Anion exchange with NaBARf·3H₂O (BARf = tetrakis(3,5-bis(trifluoromethyl)phenyl) borate) gave the corresponding BARf⁻ salt **2**. The iridium complex **3** was prepared by deprotonating **2** with KOtBu in the presence of [Ir(COD)Cl]₂ (COD = 1,5-cyclooctadiene). Rhodium complex **4** was obtained analogously (Scheme 2). Both complexes **3** and **4** were stable enough to be purified by silica gel column chromatography and stored in air for months without decomposition (as evaluated by both ¹H and ³¹P NMR spectroscopy). The structures of complexes **3** and complex **4** were confirmed by X-ray diffraction (Figure 1).

Scheme 2 Synthesis of iridium complex **3** and rhodium complex **4**.

The alkylation of aniline with benzyl alcohol was chosen for initial study. The best condition for the model reaction was: 1.0 equiv aniline, 1.1 equiv benzyl alcohol, 0.5 mol% **3**, 0.5 equiv KOtBu and 0.5 mL diglyme/1.0 mmol aniline at 50 °C, and

Fig. 1 Crystal structures of **3** and **4**. The hydrogen atoms and BARf^- are omitted; thermal ellipsoids are both shown at 50% probabilities.

therefore used in the further studies in this transformation (For detailed optimization studies, see ESI†).

Initially, we studied the reaction of aniline with different alcohols and the desired N-monoalkylated products were isolated in excellent yields (Table 1, entries 1–13). Benzyl alcohol derivatives bearing electron-donating substituents in the *meta* or *para* positions on the aromatic rings as well as 2-naphthylmethanol were well-tolerated (Entries 2, 3 and 5). More catalyst (1.0 mol%) was necessary to complete the reaction when (2-methylphenyl)methanol and 1-naphthylmethanol were used as substrates (Entries 4 and 6). Two heteroaromatic alcohols, furfuryl alcohol and 3-pyridinylmethanol, can also be used as alkylating reagents (Entries 7 and 8). An electron-deficient substrate, 4-bromobenzyl alcohol, was also successfully applied as a substrate, and no dehalogenation products were detected (Entry 9). When *para*- F_3C -substituted benzyl alcohol was used as the alkylating reagent, a low yield of the isolated product was obtained, along with multiple side products that could not be identified (Entry 10). Alkylation with aliphatic alcohols was less effective than that with the corresponding benzylic alcohols, 1.0 mol% catalyst had to be used to accelerate the reaction to completion in the reaction time used. Nevertheless, excellent yields were achieved (Entries 11–13). We also examined the alkylation of other aromatic amines with benzyl alcohol (Table 1, entries 14–21). Both electron-deficient and electron-rich substrates gave excellent yields (Entries 14–19). The alkylation of 3-pyridinamine was also successful, though 1.0 mol% catalyst loading was required to reach complete conversion (Entry 20). The 1-naphthalenamine was alkylated in an excellent yield of 96% (Entry 21). The alkylation of benzylamine with benzyl alcohol was attempted, however, no conversion was observed.

Having demonstrated the ability of complex **3** to catalyze the N-alkylation of aromatic amines with alcohols under very mild conditions (0.5–1.0 mol% catalyst loading at 50 °C), we attempted the transformation at room temperature. The reaction between aniline and benzyl alcohol indeed occurred at room temperature, although only 40% conversion was obtained in 24 h using 0.5 mol% catalyst. When performed using 1.0 mol% catalyst, the reaction proceeded to 72% conversion after 24 h and to completion after 48 h. Encouraged by this result, we examined several substrates that bore electron-donating and electron-withdrawing substituents on benzyl alcohols or anilines, and obtained excellent yields (Table 2, entries 1–8). Similarly to the reaction at 50 °C, aliphatic alcohols reacted more slowly than benzyl alcohol, 1.5 mol% catalyst was required to obtain complete alkylation within 48 h (Table 2, entries 9–11).

Solvent-free synthesis has received widespread attention due to the growing awareness of the pressing need for greener

Table 1 N-Alkylation of aromatic amines with various alcohols at 50 °C^a

$\text{R-OH} + \text{Ar-NH}_2 \xrightarrow[\text{diglyme, KOtBu, 50 °C, 24 h}]{\text{catalyst 3}} \text{R-NH-Ar}$					
Entry	Product	Yield (%) ^b	Entry	Product	Yield (%) ^b
1		97	12 ^c		95
2		94	13 ^c		97
3		94	14		96
4 ^c		96	15		93
5		95	16		95
6 ^c		91	17		94
7 ^c		94	18		95
8 ^c		95	19		96
9		94	20 ^c		92
10		71	21 ^c		96
11 ^c		94			

^a Reaction conditions: 0.5 mmol aniline, 0.55 mmol alcohol, 0.25 mmol KOtBu, 0.5 mol% catalyst, 0.25 mL diglyme, 50 °C, 24 h. ^b Isolated yield. ^c 1.0 mol% catalyst.

Table 2 N-Alkylation of aromatic amines with various alcohols at room temperature^a

$\text{R-OH} + \text{Ar-NH}_2 \xrightarrow[\text{diglyme, KOtBu, r.t., 48 h}]{\text{catalyst 3}} \text{R-NH-Ar}$					
Entry	Product	Yield (%) ^b	Entry	Product	Yield (%) ^b
1		96	7		90
2		92	8		93
3		93	9 ^c		90
4		89	10 ^c		93
5		93	11 ^c		96
6		83			

^a Reaction conditions: 0.5 mmol aniline, 0.55 mmol alcohol, 0.25 mmol KOtBu, 1.0 mol% catalyst, 0.25 mL diglyme, r.t., 48 h. ^b Isolated yield. ^c 1.5 mol% catalyst.

reactions.²² Therefore, we were interested in determining whether the reaction could be conducted without adding solvent. We were pleased to find a variety of secondary amines could be prepared in high isolated yields under solvent-free conditions (Table 3). Notably, the reaction of aniline with *para*- CF_3 -substituted benzyl alcohol was very clean under neat conditions and provided the corresponding monoalkylated product in an excellent isolated yield of 93% (Entry 5, 50 °C). We even carried out some reactions under solvent-free conditions at room temperature with 1.0 mol% catalyst after 48 h. A low yield in the reaction of 4-bromoaniline and benzyl alcohol was a consequence of incomplete conversion (Entry 3, r.t.). The solubility of the solid 4-bromoaniline was poor under these mild conditions, causing inefficient stirring in the resulting heterogeneous reaction. Interestingly, when aliphatic alcohols were employed as alkylating reagents at 50 °C or at room temperature under solvent-free conditions, a higher catalyst loading than that used

Table 3 N-Alkylation of aromatic amines with various alcohols under solvent-free conditions^a

$R-OH + Ar-NH_2 \xrightarrow[\text{neat, KOtBu}]{\text{catalyst 3}} R-NH-Ar$			
Entry	T	Product	Yield(%) ^b
1	50 °C/ r.t.		95/93
2	50 °C/ r.t.		90/92
3	50 °C/ r.t.		93/63
4	50 °C/ r.t.		94/91
5	50 °C/ r.t.		93/85
6	50 °C/ r.t.		90/92
7	50 °C/ r.t.		92/91
8	50 °C/ r.t.		93/90
9	50 °C/ r.t.		96/93

^a Reaction conditions: 1.0 mmol aniline, 1.1 mmol alcohol, 0.5 mmol KOtBu; 0.5 mol% catalyst, 50 °C, 24 h or 1.0 mol% catalyst, r.t., 48 h.

^b Isolated yield.

for benzyl alcohol was not needed because the high concentration of reactants lead to more favorable kinetics than in solution (Entries 7–9).²³

There are only a few reports on the preparation of N,N'-dialkylated diamines using this method, and long reaction time or high temperature was required in each of them.^{10b, 12a} We applied our approach to the alkylation of dapsone **5** and 1,3-benzenediamine **7** (Scheme 3). Excellent isolated yields were achieved. No mono-N-alkylated amines were observed under the reaction conditions used.

Scheme 3 N,N'-Dialkylation of dapsone and 1,3-benzenediamine.

Finally, intramolecular alkylation was attempted. With 2-(2-aminophenyl)ethanol **9** as the substrate, indoline would not be the expected product; rather, the isomerization of the intermediate **11** to indole **12** should be driven by aromatization (Scheme 4, left). When complex **3** was applied to 3-(2-aminophenyl)propanol **13**, the intermediate 3,4-dihydroquinoline **15** could not be dehydrogenated by the present catalytic system; thus 1,2,3,4-tetrahydroquinoline **16** was obtained as the only product (Scheme 4, right). These observations were consistent with the previous study of N-heterocyclization of amino alcohols by [Cp*IrCl₂]₂.¹⁵

Scheme 4 N-Heterocyclization of amino alcohols.

In conclusion, we have developed the iridium complex **3**, which bears a bidentate NHC/phosphine ligand and is an efficient catalyst for the N-alkylation of anilines with alcohols. A variety of aromatic amines were converted to the corresponding secondary amines with a range of alcohols in good to excellent yields. Cyclization of amino alcohols was also successful, producing indole and 1,2,3,4-tetrahydroquinoline. For the first time, this kind of transformation has been carried out at room temperature.

Notes and references

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