Amine Exchange

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Selective Amine Cross-Coupling Using Iridium-Catalyzed "Borrowing Hydrogen" Methodology**

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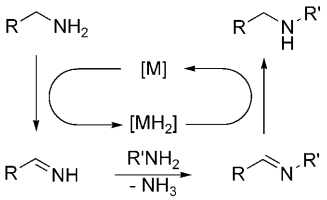
Amines have widespread importance with applications as pharmaceuticals, agrochemicals, dyes, and polymers.[1] In particular, the alkylation of amines has raised considerable attention, especially the control of monoalkylation.[2] Whilst alkyl halides are traditional alkylating agents for amines, they can be toxic and mutagenic. As an alternative, the alkylation of amines by alcohols has been achieved using various transition-metal catalysts.[3] Since the first examples of this reaction using homogeneous catalysts,[4] several groups,[5] including our own,[6] have reported transition-metal catalysts capable of achieving amine alkylation using alcohols; there is a report from Fujita, Yamaguchi, and co-workers on the use of $[\{Cp^*IrCl_2\}_2]$ (Cp^* = pentamethylcyclopentadienyl) for this alkylation reaction.[7]

The transition-metal-catalyzed alkylation of amines by amines has also been reported,[8] although the coupling of two amines, RNH_2 and $R'NH_2$, generally leads to a mixture of products including R_2NH, $RR'NH$, and R'_2NH. Recently, Beller and co-workers have demonstrated that the ruthenium-based Shvo catalyst can be used to effect selective amine coupling when one amine component is unable to undergo oxidation (i.e., anilines and *tert*-alkylamines).[9]

The coupling of amines can be considered to proceed by the "borrowing hydrogen" pathway outlined in Scheme 1.



Scheme 1. Borrowing hydrogen in the alkylation of an amine by another amine.

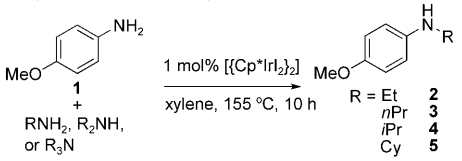
Temporary removal of hydrogen from an amine generates an imine, which can undergo addition of another amine and elimination of ammonia to form an *N*-alkyl imine. Return of the hydrogen from the catalyst provides a synthesis of the secondary amine product. The catalytic pathway may proceed via monohydride or dihydride complexes.

Herein we report the first examples of selective amine alkylation even when both of the amines are able to undergo oxidation. We have recently reported the use of the iridium complex $[\{Cp^*IrI_2\}_2]$ for hydrogen-transfer and dehydrogenation reactions leading to benzoxazoles.[10] Additionally, Blacker et al. have reported the use of this catalyst for the racemization of α-branched amines, which is believed to occur through the temporary removal of hydrogen.[11]

We chose the alkylation of 4-methoxyaniline (**1**) as a model reaction for the identification of amines that could act as good alkyl donors. The reaction of compound **1** with aliphatic amines led to the formation of the secondary amines **2**–**5** shown in Table 1. The reaction was found to be successful in the absence of an added base.

Ethyl transfer was achieved using diethylamine as the alkyl donor (Table 1, entry 1), but almost complete conversion was achieved when triethylamine was used (Table 1, entry 2), leading to the ethylated product in very good yield

Table 1: N-Alkylation of 4-methoxyaniline.



Entry	Amine donor	Product	Yield [%][a]
1	Et_2NH	**2**	35
2	Et_3N	**2**	95
3	$(nPr)_2NH$	**3**	50
4	$(nPr)_3N$	**3**	90
5	$iPrNH_2$	**4**	88
6	$(iPr)_2NH$	**4**	99
7	$(iPr)_2NH$	**4**[b]	95
8	$(iPr)_2NH$	**4**[c]	55
9	$(iPr)_2NH$	**4**[d]	16
10	(*i*Pr)EtNH	**2**/**4**	31/68
11	$(iPr)_2EtN$	**2**/**4**	5/94
12	$CyNH_2$	**5**	97

[a] Reaction conditions: aniline **1** (1 mmol), amine donor (3 mmol), $[Cp^*IrI_2]_2$ (1 mol%), xylene (2 mL), 155 °C, 10 h. Yield of isolated product after column chromatography is based on aniline **1**. [b] Reaction stopped after 5 h. [c] Toluene, 115 °C. [d] Using $[\{Cp^*IrCl_2\}_2]$ (1 mol%). Cy = cyclohexyl.

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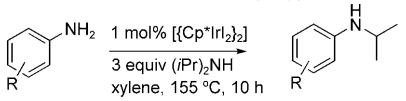
upon isolation. Similarly, transfer of *n*Pr was successful from di-*n*-propylamine (Table 1, entry 3), but was improved by using tri-*n*-propylamine (Table 1, entry 4). The transfer of an isopropyl group was found to be favorable, presumably because of the formation of a ketimine intermediate. Isopropylamine was effective (Table 1, entry 5), but diisopropylamine (Table 1, entry 6) gave complete conversion and an excellent yield of the *N*-isopropyl product **4**. Notably, after five hours the reaction was essentially complete (Table 1, entry 7), but the use of toluene as a solvent used a lower reaction temperature, thereby leading to a lower conversion of substrate into product. The use of $[\{Cp^*IrCl_2\}_2]$ as a catalyst (Table 1, entry 9) was significantly less effective than the corresponding iodide catalyst. When amine donors containing both ethyl and isopropyl groups were used (Table 1, entries 9 and 10), both groups were transferred but *N*-isopropylaniline (**4**) was the major product. Cyclohexylamine (Table 1, entry 12) was also successfully used as an alkylating agent, leading to N-alkylated product **5** in very good yield. In all cases, no over-alkylation to give the tertiary amine was detected.

We then investigated the transfer of the isopropyl group from diisopropylamine to a range of anilines, as identified in Table 2. In the majority of cases, the *N*-isopropylaniline was isolated in excellent yield. Even the electron-deficient 4-

Table 2: Conversion of anilines into *N*-isopropylanilines.



Entry	Aniline substrate	Yield [%][a]
1	$PhNH_2$	98
2	4-$MeC_6H_4NH_2$	99
3	4-(tBu)$C_6H_4NH_2$	99
4	4-$MeOC_6H_4NH_2$	99
5	3,4-$(OCH_2O)C_6H_3NH_2$	99
6	4-$(MeO_2C)C_6H_4NH_2$	97
7	4-$FC_6H_4NH_2$	95
8	3-$F_3CC_6H_4NH_2$	52
9	4-$O_2NC_6H_4NH_2$	26
10	3-$MeC_6H_4NH_2$	99
11	3-$ClC_6H_4NH_2$	97
12	2-$MeC_6H_4NH_2$	83
13	5-aminoindane	99

[a] Reaction conditions: aniline (1 mmol), $(iPr)_2NH$ (3 mmol), $[\{Cp^*IrI_2\}_2]$ (1 mol%), xylene (2 mL), 155 °C, 10 h. Yield of isolated product after column chromatography is based on aniline.

methoxycarbonyl- and 4-fluoroaniline (Table 2, entries 6 and 7) were successfully alkylated; for the 3-trifluoromethyl- and 4-nitroanilines (Table 2, entries 8 and 9) the low yields of the isolated products were a consequence of incomplete conversion under these reaction conditions. The reaction of the *ortho*-substituted aniline (Table 2, entry 12) also led to a lower yield of isolated product.

In the case of aniline alkylation, it is only the diisopropylamine which is able to undergo oxidation to the imine, and hence selectivity for the mixed product is expected to be favored. We therefore turned our attention to the alkylation of amines where the potential for oxidation to the imine exists. A range of benzylamines was alkylated successfully with remarkably high product yields (Table 3). The formation of alkylated amines using this approach represents an alternative to the more established Buchwald–Hartwig amination chemistry.[12]

Table 3: Conversion of benzylamines into *N*-isopropyl derivatives.

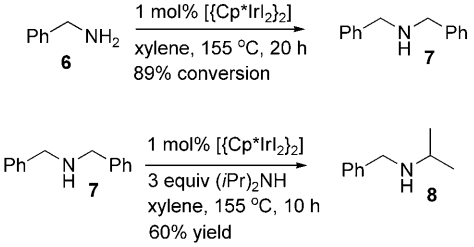
Entry	Benzylamine substrate	Yield [%][a]
1	$PhCH_2NH_2$	97
2	*p*-$MeC_6H_4CH_2NH_2$	99
3	*p*-$MeOC_6H_4CH_2NH_2$	98
4	*p*-$ClC_6H_4CH_2NH_2$	98
5	*p*-$F_3CC_6H_4CH_2NH_2$	99
6	3,4-$(OCH_2O)C_6H_3CH_2NH_2$	98
7	3,4-$(MeO)_2C_6H_3CH_2NH_2$	98
8	$PhCH(Me)NH_2$	98
9	Ph_2CHNH_2	98

[a] Reaction conditions: aniline (1 mmol), $(iPr)_2NH$ (3 mmol), $[\{Cp^*IrI_2\}_2]$ (1 mol%), xylene (2 mL), 155 °C, 10 h. Yield of isolated product after column chromatography is based on aniline.

When the reaction shown in entry 8 of Table 3 was repeated in the presence of (*S*)-binap (4 mol%; binap = 2,2′-bis(diphenylphosphanyl)-1,1'-binaphthyl), the product was formed with 6% *ee*. This result is consistent with the known ability of $[Cp^*IrI_2]$ to racemize amines.[11]

In all of the reactions identified in Table 3, the *N*-isopropyl-*N*-benzylamine product was obtained without any contamination from tertiary amines or dibenzylamines. The lack of formation of any dibenzylamine was particularly noteworthy, since oxidation of benzylamine into an imine would be expected to occur under these conditions. Indeed, a control reaction demonstrated that in the absence of diisopropylamine, benzylamine (**6**) underwent a self-coupling reaction to afford dibenzylamine (**7**). However, we also discovered that under the same reaction conditions, the reaction of dibenzylamine (**7**) with diisopropylamine led to the formation of *N*-isopropyl-*N*-benzylamine (**8**) in a reasonable yield (Scheme 2). This implies that if any dibenzylamine is formed in the reaction of benzylamine with diisopropylamine, then the reaction is self-correcting and leads to the observed *N*-isopropyl derivatives.

When dibenzylamine (**7**) was reacted under the same conditions with diethylamine or triethylamine, the mixed secondary amine, *N*-benzyl-*N*-ethylamine was formed but

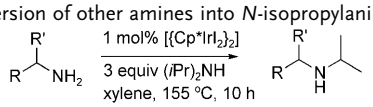


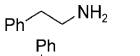
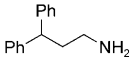
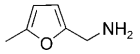
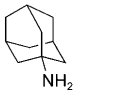
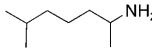
Scheme 2. Self-coupling of benzylamine and alkyl exchange of dibenzylamine.

also contained unreacted starting material and the tertiary amine *N*-benzyl-*N*,*N*-diethylamine.

Several other amines were also successfully alkylated, as shown in Table 4. Primary aliphatic amines (Table 4, entries 1 and 2) were converted into the *N*-isopropyl derivatives in excellent yields of isolated products. The furan-containing

Table 4: Conversion of other amines into *N*-isopropylanilines.



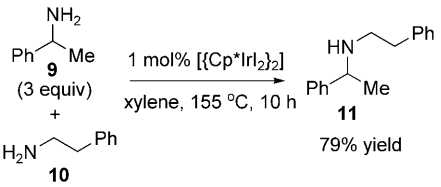
Entry	Amine substrate	Yield [%][a]
1		96
2		98
3		68
4		68
5		80

[a] Reaction conditions: aniline (1 mmol), $(iPr)_2NH$ (3 mmol), $[\{Cp^*IrI_2\}_2]$ (1 mol%), xylene (2 mL), 155 °C, 10 h. Yield of isolated product after column chromatography is based on aniline.

substrate (Table 4, entry 3) was successfully alkylated; however, some decomposition occurred during column chromatography, leading to a lower product yield. In the case of the alkylation of 1-adamantylamine, the lower product yield is a consequence of incomplete conversion, presumably for steric reasons. The *N*-isopropylated product obtained (Table 4, entry 5) has been used as an antihistamine (iproheptine).[13]

The $[\{Cp^*IrCl_2\}_2]$ complex was capable of alkylating aniline with ethyl, cyclohexyl, and isopropyl groups (Table 1), but we were also interested to see whether the reaction might be applicable to the coupling of other amine combinations. We therefore reacted the branched amine **9** with the unbranched amine **10**, and were pleased to find that we selectively formed the secondary amine **11** with a good yield of the isolated product (Scheme 3).

The observed reaction outcomes are consistent with a mechanism involving dehydrogenation of diisopropylamine to give an intermediate imine and subsequent transimination with the other amine component. The addition of hydrogen would then regenerate the mixed secondary amine. Crabtree, Eisenstein, and co-workers have suggested a mechanism for the catalyzed amination of alcohols which involves the carbonate anion.[14] However, in the amine coupling reaction



Scheme 3. Coupling of a branched amine with an unbranched amine.

catalyzed by $[\{Cp^*IrI_2\}_2]$, no carbonate, or any other additional base is added. Interestingly, they note that for alcohol amination, the amine inhibits the reaction by inhibiting alcohol complexation.

The ability to achieve the cross-coupling of two oxidizable amines appears to be favored by the formation of secondary amines containing one branched and one unbranched substituent, thereby relieving the known steric strain within amines containing more than one branched substituent.[15] The particular ease with which diisopropylamine and other branched amines can be transferred is also consistent with the greater stability (and therefore accessibility) of the assumed imine intermediates derived from them; imines arising from oxidation of a primary amine are generally less stable than those derived from a secondary amine, whilst aldimines arising from oxidation of an unbranched amine are generally less stable than ketimines derived from a branched amine.[16]

In summary, we have demonstrated for the first time that it is possible to couple two amines with excellent selectivity, even when both amine components are capable of undergoing oxidation to an imine. The simple catalytic system uses $[\{Cp^*IrI_2\}_2]$ in the absence of base.

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