Communications

Iron/Amino Acid Catalyzed Direct N-Alkylation of Amines with Alcohols**

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Higher amines are widely used in both the bulk and fine chemical industries as fundamental materials, additives, dyes, agrochemicals, etc.[1] Therefore, the development of a selective N-alkylation method that is cost effective, salt free, and environmentally benign is of considerable interest. However, the most common strategies to produce secondary or tertiary amines involve treating a primary amine with an alkylating reagent having a good leaving group (RX: X = halide, OTs, OTf, etc.). The main drawback of this conventional approach is the generation of a stoichiometric amount of wasteful (in)organic salts, as well as low secondary/tertiary amine product selectivity. In recent years, N-monoalkylation was demonstrated, wherein an alcohol[2] is used in place of RX and transition-metal catalysis involves Ru,[3] Ir,[4] Cu,[5] or Ag[6] catalyst precursors. These transition-metal-catalyzed N-alkylations are usually redox-type reactions involving "borrowing hydrogen"[2a,b] or "hydrogen autotransfer"[2c] mechanisms (alcohol oxidation/imine formation/imine hydrogenation). Although these reactions have found many applications using benzylic-type and saturated alcohols as the N-alkylating agents,[2] the supposedly generated metal hydride species are incompatible with some functional groups, including olefins. Herein we report a novel straightforward method of N-alkylation using alcohols and iron catalysis,[7] which involves a substitution (S_N) at the sp^3-carbon atom bearing the hydroxy group of the alcohol (Scheme 1). The development of a catalyst that is effective at near neutral pH was key to the successful N-alkylation.

Treatment of a 1,2,4-trimethylbenzene (1,2,4-TMB) solution of aniline **1a** (6 mmol) with benzyl alcohol **2a** (3 mmol) in the presence of FeBr₃ (3 mol%, based on the molar amount

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Scheme 1. General scheme of direct N-alkylation using an alcohol. Cp*H = 1,2,3,4,5-pentamethylcyclopenta-1,3-diene.

of **2a**), DL-pyroglutamic acid (**4a**; 6 mol%) at 160°C for 24 hours gave, after column chromatography on silica gel, the corresponding monoalkylated amine **3aa** in an yield of 71% upon isolation (Table 1, entry 1). Notably, the dialkylation reaction led to less than 5% of the tertiary amine as ascertained by GC/MS and ¹H NMR analyses. By using a smaller amount of **4a** (3 mol%) under otherwise identical reaction conditions, a slightly lower productivity was obtained

Table 1: N alkylation of **1a** with **2a** to give **3aa** using different reaction conditions.[a]

Entry	FeX₃	Ligand	Cp*H [mol%]	Conversion [%][b]
1	FeBr₃	4a	0	77 (71)
2	FeBr₃	4a	5	85 (82)
3[c]	FeBr₃	4a	5	99 (94)
4	FeCl₃	4a	5	59 (55)
5[c]	FeBr₃	none	0	43 (41)
6	FeBr₃	none	5	< 30
7	none	4a	0	< 1
8	FeBr₃	4b	0	45
9	FeBr₃	4c	0	58
10	FeBr₃	4d	5	46 (40)
11	FeBr₃	4e	5	52 (49)
12	FeBr₃	4f	5	44 (39)
13	FeBr₃	4g	5	68 (66)
14	FeBr₃	4h	5	60 (57)
15	FeBr₃	4i	5	60 (53)

[a] Unless otherwise specified, the reaction conditions were: **1a** (6 mmol), **2a** (3 mmol), FeBr₃ (3 mol%), **4a** (6 mol%), Cp*H (5 mol%) in 1,2,4-TMB (0.3 mL) at 160°C for 18 h. [b] Conversion was determined by GC analysis using biphenyl as internal standard. The values in parentheses are the yields of the isolated product **3aa**. [c] 24 h.

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(conversion of **2a**: 68%). Without **4a**, the yield of **3aa** decreased by almost half, even with a reaction time of 24 hours (entry 5). The use of other amino acids such as **4b–g** gave moderate yields (entries 8–13). The ester and amide derivatives **4h** and **4i** were also unable to give satisfactory results (entries 14 and 15, respectively). The combination of FeBr$_3$/**4a** with Cp*H (5 mol%) showed the highest catalytic activity, giving **3aa** in 82% yield (entry 2). The use of other diene additives, such as cycloocta-1,5-diene (cod) or 1,2,3,4,5-pentaphenylcyclopentadiene, gave results (**3aa**: ca. 70%) comparable to those obtained without using any diene additives (entry 1). By prolonging the reaction time to 24 hours the conversion of **2a** was maximized, thus giving a 94% yield of **3aa** upon isolation (entry 3). In the absence of **4a**, a combination of catalytic FeBr$_3$ (3 mol%) and Cp*H (5 mol%) gave a yield of **3aa** that was lower than that obtained with FeBr$_3$ alone (entry 5 vs. 6). FeCl$_3$ was less effective (**3aa**: 55%) than FeBr$_3$ (entry 4), and the reaction did not take place with **4a** alone (entry 7). When we used a 1:1:1 ratio of **1a**/**2a**/PhNMe$_2$ and **1a**/**2a**/iPr$_2$NEt under otherwise identical reaction conditions, **3aa** was obtained in 30% and <5%, respectively.

Encouraged by this discovery, we next examined a range of different substrates under the optimal reaction conditions (FeBr$_3$ (3 mol%), **4a** (6 mol%), Cp*H (6 mol%) in 1,2,4-TMB (Fe: 0.075 M), 160°C, 24 h). The results are summarized in Table 2. Coupling reactions between benzylic-type primary alcohols and anilines having different electronic properties mostly gave the expected products in high yields (entries 1–15). Even when the (halophenyl)methanols **2b–d** or 6-amino-2-bromopyridine (**1h**) were used, the results afforded the N-alkylation product in good yield and carbon–halogen bond cleavage did not occur (entries 1–3 and 13). There are a paucity of reports on direct coupling between anilines and allylic alcohols;[8] however, allylic alcohols and benzylic-type secondary alcohols can be classified as a family of compounds that readily generate carbocation equivalents and are far more reactive than the benzylic-type primary alcohols **2a–g**. In fact, under the reaction conditions for the Lewis acid catalyzed S$_N$-type N-alkylations,[9] in which carbocation species may favorably form from allylic alcohols, the N-alkylation using **2a** rarely proceeded. Additionally, under acidic conditions such as those employing FeCl$_3$,[10b] NbCl$_5$,[10c] and AuCl$_3$[11] as catalyst precursors, electron-rich aromatic substrates were prone to undergoing Friedel–Crafts-type alkylation[10] with alcohols. Fortunately, this undesirable alkylation, which should have occurred on the aromatic ring of the solvent (1,2,4-TMB) or aniline derivatives,[10b] was almost completely suppressed. The finding suggests that a more neutral pH environment was important.

The NH$_2$ of sulfonamides were readily alkylated with alcohols using several of the previously described methods,[2c,3h,i,5b,c,9] but this sulfonamide NH$_2$ remained untouched in the presence of the NH$_2$ group of aniline when using the present reaction (entry 12). The benzyl amines **1k–m** that have a nitrogen atom which is more basic than that of anilines, were also suitable substrates, albeit at a higher loading of FeBr$_3$ and an elevated reaction temperature (180°C; entries 16–18).

Table 2: Coupling between various amines **1** and alcohols **2**.[a]

Entry	Amine **1**	Alcohol **2**	Product **3**	Yield [%][b]
1	**1a** (X = H)	**2b** (Y = 4-Cl)	**3ab** (Y = 4-Cl)	91
2	**1a**	**2c** (Y = 3-Br)	**3ac** (Y = 3-Br)	94
3	**1a**	**2d** (Y = 2-I)	**3ad** (Y = 2-I)	88[e]
4[c]	**1a**	**2e** (Y = 4-CF$_3$)	**3ae** (Y = 4-CF$_3$)	92
5	**1a**	**2f** (Y = 3-Me)	**3af** (Y = 3-Me)	90
6	**1a**	**2g** (Y = 3-OMe)	**3ag** (Y = 3-OMe)	93
7	**1b** (X = 4-OMe)	**2a** (Y = H)	**3ba** (X = 4-OMe)	77[f]
8	**1c** (X = 2-OMe)	**2a**	**3ca** (X = 2-OMe)	78
9	**1d** (X = 2-F)	**2a**	**3da** (X = 2-F)	90
10	**1e** (X = 3-CF$_3$)	**2a**	**3ea** (X = 3-CF$_3$)	90[g]
11	**1f** (X = 3-CN)	**2a**	**3fa** (X = 3-CN)	64[g]
12	**1g** (X = 3-SO$_2$NH$_2$)	**2a**	**3ga**	78
13	**1h**	**2a**	**3ha**	83
14	**1i** (PhNHMe)	**2a**	**3ia** (PhN(Bn)Me)	87
15	**1j**	**2a**	**3ja**	89
16[c]	**1k**	**2a**	**3ka**	90
17[c]	**1l**	**2a**	**3la**	86
18[d]	**1m**	**2a**	**3ma**	83

[a] Reaction conditions: **1**/**2**/FeBr$_3$/**4a**/Cp*H = 200:100:3:6:6, in 1,2,4-TMB at 160°C for 24 h. [b] Yield of isolated, purified product based on **2**. Yield of the N-dialkylation product was consistently <5%. [c] **1**/**2**/FeBr$_3$/**4a**/Cp*H = 200:100:5:10:10 at 180°C for 36 h. [d] **1**/**2**/FeBr$_3$/**4a**/Cp*H = 200:100:10:20:20 at 200°C for 36 h. [e] 36 h. [f] 48 h. [g] 140°C.

The least reactive alcohols, such as fully saturated alcohols, were also tested (Table 3). By merely increasing the reaction temperature, the secondary amines derived from monoalkylation were obtained (entries 1–5). Even at a high temperature, the secondary alcohol **2k** and the interior olefin of **2l** were well tolerated (entries 4 and 5). The reaction pathway involving a carbocation (S$_N$1) is unlikely to occur with primary alcohols. The α/γ (>99%) and E/Z (or Z/E) (>99%) selectivities of the reaction with allylic alcohols

Table 3: Coupling between **1a** and various alcohols **2**.[a]

Entry	Alcohol 2	T [°C]	t [h]	Product 3	Yield [%][b]
1	**2h** Ph⌒⌒OH	200	36	**3ah** ⬡—NH⌒Ph	88
2	**2i** ⌒⌒(⌒)₅⌒OH	200	36	**3ai** ⬡—NH⌒(⌒)₆	85
3	**2j** ⌒⌒(⌒)₉⌒OH	200	36	**3aj** ⬡—NH⌒(⌒)₁₀	86
4	**2k** ⌒⌒(⌒)₆⌒OH	200	36	**3ak** ⬡—NH⌒(⌒)₈	70
5	**2l** ⌒⌒(⌒)₄⌒OH	200	36	**3al** ⬡—NH⌒(⌒)₄	85
6	**2m** (⌒)₄⌒⌒OH	140	24	**3am** ⬡—NH⌒(⌒)₄	83[c]
7	**2n**	100	36	**3an**	73[c]
8	**2o**	100	36	**3ao**	70[d]
9[e]	**2p** HO–⬡	100	24	**3ap** Ph–NH–⬡	80
10[e]	**2q** Ph⌒⌒Ph / OH	60	24	**3aq** Ph / HN–Ph	74

[a] Reaction conditions: **1**/**2**/FeBr₃/**4a**/Cp*H = 200:100:3:6:6, in 1,2,4-TMB. [b] Yield of isolated, purified products based on **2**. Yield of N-dialkylation product was consistently < 5%. [c] α/γ = > 99:1; E/Z = > 99:1. [d] α/γ = > 99:1; E/Z = 1: > 99. [e] Run in toluene instead of 1,2,4-TMB.

2m–o were excellent (entries 6–8), thus supporting the proposed S$_N$2 pathway. If the reaction mechanism involved either a borrowing hydrogen or an S$_N$1 pathway, the Z geometry of **2o** should have been lost.

So far, the mechanism of other transition-metal-catalyzed -alkylations of amines using simple saturated alcohols has been uniformly considered a borrowing hydrogen pathway.[1–6] In contrast, the present catalysis appears to involve a different mechanism. We performed a crossover experiment using different alcohols to check the likely mechanistic scenario (Scheme 2). (3-Methylphenyl)methanol (**2f**) was converted into **3af** in 94% yield, and was not labeled with
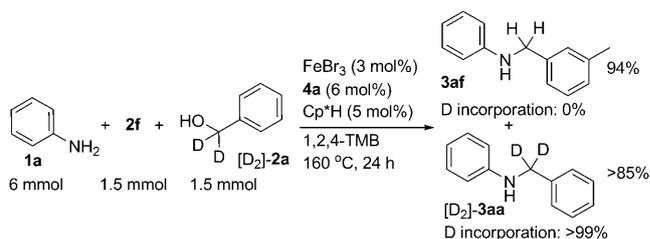
Scheme 2. Experiment using deuterium-labeled alcohol [D₂]-**2a**.

deuterium. In contrast, full incorporation (> 99%) of deuterium atoms into the benzylic position of product [D₂]-**3aa** was rigorously ascertained by ¹H NMR and HRMS methods. This result is in sharp contrast to the observation of D–H exchange in Ru-[3h,i] and Cu-mediated[5b] N-alkylation with alcohols.

Selective mono- or dimethylation of the aniline nitrogen atom is also possible by varying the ratio of aniline and CH₃OH used (Scheme 3). Three deuterium atoms of CD₃OH were preserved (deuterium incorporation into N,N-dimethylaniline: > 99%) at the same carbon atom.
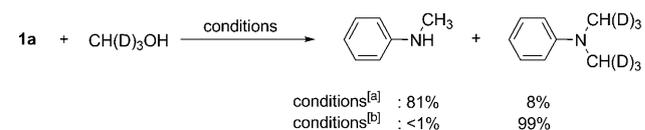
Scheme 3. N alkylation of **1a** using either CH₃OH or CD₃OH. Reaction conditions: [a] **1a**/CH₃OH/FeBr₃/**4a**/Cp*H = 250:100:5:10:10, in 1,2,4-TMB at 200°C for 36 h; [b] **1a**/CD₃OH/FeBr₃/**4a**/Cp*H = 100:266:5:10:10, in 1,2,4-TMB at 200°C for 36 h.

In summary, we have developed a highly selective and practical procedure for producing higher amines using acid-base cooperative catalysis[12] based on an iron(III)/amino acid combination that obviates the need for activated leaving groups. The broad substrate scope and functional group tolerance were highlighted with respect to each amine and alcohol component. These characteristic features provide a mechanistically distinct alternative to borrowing hydrogen strategies. The catalytic system enabled selective N-monoalkylation (over-alkylation < 5%) in most cases. Because of the inherent nature of more neutral pH conditions, elevated temperatures were required to obtain a good product yield. Nonetheless, prolonged heating at 160–200°C is acceptable for an industrial process because the extra heat energy recovered can be effectively reused for other purposes.

Experimental Section

Typical procedure: Iron(III) bromide (27 mg, 0.09 mmol), DL-pyroglutamic acid (**4a**; 23.5 mg, 0.18 mmol), 1,2,3,4,5-pentamethylcyclopenta-1,3-diene (Cp*H: 23.5 µL 0.15 mmol), benzyl alcohol (**2a**;

324.3 mg, 3.0 mmol), aniline (**1a**; 558.6 mg, 6.0 mmol), and 1,2,4-trimethylbenzene (0.3 mL) were added to a dry flask that was fitted with a Young's stopcock in an argon (Ar) atmosphere. The reaction mixture was stirred at 160 °C under Ar for 24 h and then cooled to room temperature and diluted with ethyl acetate (50 mL). The resulting mixture was washed with saturated aqueous NH_4Cl (2 × 20 mL) and then the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried over sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure using a rotary evaporator. The crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate 98:2) to give the *N*-phenylbenzylamine (**3aa**) as a white solid in 94 % yield (516 mg, 2.82 mmol).

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[12] Since our system comprises FeBr₃/**4a**·amine as a weak acid and amine as a weak base, both should be working cooperatively.