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Iron-catalyzed *N*-alkylation of aromatic amines via borrowing hydrogen strategy

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ABSTRACT

Earth-abundant transition metals could be used as a noble metal replacement in catalysis not only for different catalytic reactivity but environmentally benign methodology. We report here on the iron-catalyzed synthesis of *N*-alkylated amines via borrowing hydrogen strategy and differently functionalized aniline derivatives are alkylated in good yields.

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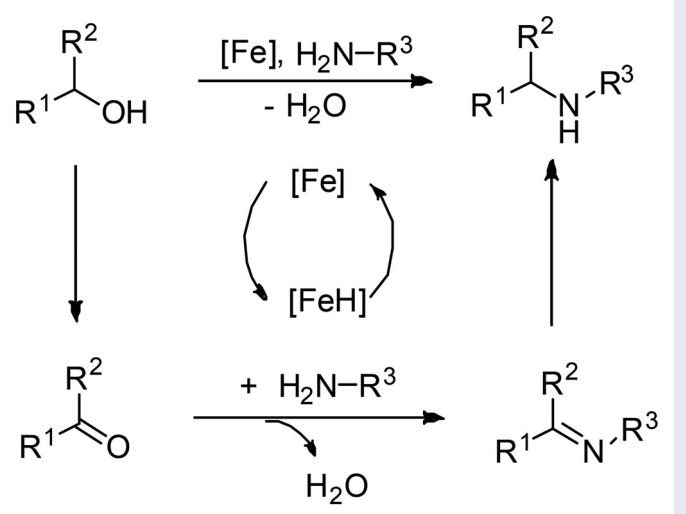
Iron; N-alkylation; borrowing hydrogen; aniline derivatives



1. Introduction

The efficient formation of carbon–nitrogen bonds is of importance for synthesis of a plethora of organic compounds, which could be applied in pharmaceuticals and fine chemicals [1, 2]. There are numbers of methods available for synthesis of amines due

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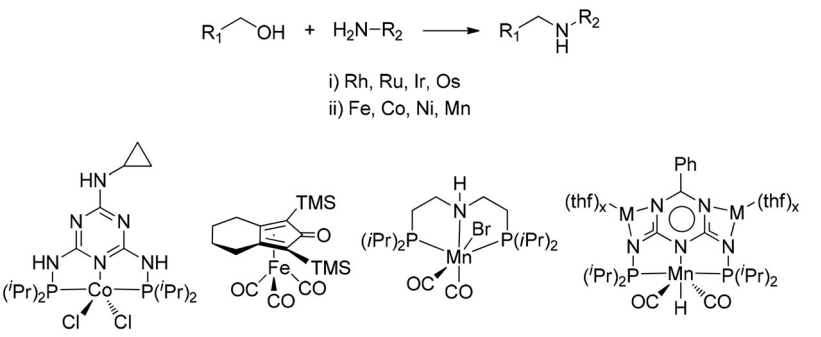


Scheme 1. Selected non-noble metal complex catalysts.

to their importance, such as hydroaminations, Ullmann reactions, Buchwald–Hartwig reaction, *etc.* [3–5]. Most of these methods require catalysts or additives with specific (noble metal) complexes. These methods proved their efficiency in numerous examples, but they often suffer from the co-production of considerable amounts of waste or side products. Sustainable, atom-economical and environmentally benign borrowing hydrogen methodologies have operational simplicity and generation of water as the only byproduct and have been widely used in C-C and C-N bond construction [6–8]. Through borrowing hydrogen strategy, alcohols and amines are directly reacted by acceptorless dehydrogenative coupling which is one of the most promising, green synthesis pathways for preparation of *N*-alkylated amines [9,10]. Alcohols are not only readily available by a variety of industrial processes but can be obtained renewably via catalytic conversion of lignocellulosic biomass or fermentation . Direct *N*-alkylation of amines with primary alcohols with ruthenium(II) [11, 12], rhodium(I) [13], iridium(III) [14, 15], and osmium(II) [16] has been documented through a borrowing hydrogen strategy. Due to the economic and ecological benefits as well as excellent reactivity, it is desired to apply non-noble metal catalysis in organic synthesis. In this regard, manganese(I), cobalt(II), and nickel(II) have achieved progress in *N*-alkylation of aromatic amines [17–23]. Recently, Hanson and co-workers reported a Co(II) catalyst bearing a bis(phosphino)-amine (PNP) ligand that could be used to catalyze *N*-alkylation of amines [24]. Kempe and co-workers introduced PN_5P ligand-stabilized Co(II) complexes for catalytic applications, highly active for alkylation of aromatic amines [25]. The mild reaction conditions allow synthesis of unsymmetrically alkylated diamines and the selective monoalkylation of (hetero)aromatic amines. The groups of Feringa and Barta, Zhao, and Wills reported *N*-alkylation of amines with primary and secondary alcohols to give substituted amines by utilizing Fe catalysts based on Knölker's complex featuring functionalized cyclopentadienone or hydroxycyclo-pentadienyl ligands [26–29]. They also reported a Mn-catalyzed *N*-alkylation. An air-stable $[Mn(I)(CO)_2Br]$ complex stabilized by a tridentate PNHP ligand and activated *in situ* by a base, catalyzed the *N*-alkylation of amines with alcohols very efficiently [30]. Kempe and co-workers introduced a Mn(I) pincer complex, active for dehydrogenative coupling of alcohols and amines to form imines selectively [18]. Intrigued by these recent discoveries, we describe herein the efficient coupling of alcohols and amines catalyzed by Fe(II) associate with an NNN ligand (Scheme 1).

2. Experimental

2.1. General considerations

Solvents were dried and distilled prior to use by literature methods. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker DRX-400 spectrometer and all chemical shift values refer to $\delta_{TMS} = 0.00$ ppm, $CDCl_3$ (δ (^{1}H), 7.26 ppm; δ (^{13}C), 77.16 ppm) and DMSO-d_6 (δ (^{1}H), 2.50 ppm; δ (^{13}C), 39.52 ppm). TLC analysis was performed by using glass plates coated with 0.2 mm silica gel. Flash column chromatography was performed on silica gel (200–300 meshes). All chemical reagents were purchased from commercial sources and used as received unless otherwise indicated: 2,6-dibromopyridine, benzene-1,2-diamine, 3,5-dimethyl-1*H*-pyrazole, 4,5-dimethylbenzene-1,2-diamine, *N*,*N*′-(4,5-diamino-1,2-phenylene)bis(4-methylbenzenesulfonamide), phenylmethanol, aniline, *p*-toluidine, 2-chloroaniline, 4-fluoroaniline, naphthalen-1-amine, (4-chlorophenyl)methanol, 2-phenylethanol, and heptan-1-ol.

2.2. General procedure for iron-catalyzed N-alkylation of aromatic amines (3)

Synthesis of N-benzylaniline (3a): Under a nitrogen atmosphere, a mixture of benzyl alcohol **1a** (216 mg, 2.0 mmol), aniline **2a** (186 mg, 2 mmol), *t*BuOK (168 mg, 1.5 mmol), $FeCl_2$ (5 mg, 0.04 mmol) and L1 (12 mg, 0.04 mmol) was stirred at 110 °C for 36 h. After cooling to ambient temperature, the mixture was filtered through a short pad of celite and rinsed with 10 mL CH_2Cl_2. The combined filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/ethyl acetate: 20:1, v/v) to afford **3a** as a white solid (340 mg, 93%) which was further analyzed by NMR.

N-benzylaniline (**3a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, $J = 2.7$ Hz, 4 H), 7.36-7.30 (m, 1 H), 7.24 (dd, $J = 10.8$, 4.5 Hz, 2 H), 6.80 (t, $J = 7.0$ Hz, 1 H), 6.67 (d, $J = 7.5$ Hz, 2 H), 4.33 (s, 2 H), 4.00 (s, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 148.2, 139.5, 129.3, 128.6, 127.5, 127.2, 117.5, 112.8, 48.2.

N-benzyl-4-methylaniline (**3 b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.35 (m, 4 H), 7.30 (t, $J = 14.8$ Hz, 1 H), 7.04 (d, $J = 7.9$ Hz, 2 H), 6.61 (d, $J = 8.2$ Hz, 2 H), 4.35 (s, 2 H), 3.93 (s, 1 H), 2.29 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 146.04, 139.8, 129.9, 128.7, 127.6, 127.3, 126.8, 113.10, 48.7, 20.5.

N-benzyl-2-chloroaniline (**3c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 4 H), 7.37-7.29 (m, 2 H), 7.16-7.10 (m, 1 H), 6.68 (t, $J = 7.4$ Hz, 2 H), 4.79 (s, 1 H), 4.44 (s, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 144.0, 138.9, 129.2, 128.8, 127.9, 127.5, 127.4, 119.2, 117.5, 111.6, 48.0.

N-benzyl-4-fluoroaniline (**3d**): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.39 (d, $J = 7.4$ Hz, 2 H), 7.31 (dd, $J = 9.8$, 4.9 Hz, 2 H), 7.23 (t, $J = 5.7$ Hz, 1 H), 6.86 (ddd, $J = 12.6$, 6.4, 2.9 Hz, 2 H), 6.63 (dt, $J = 8.6$, 4.2 Hz, 2 H), 5.40 (s, 1 H), 4.32 (s, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-d_6) δ 206.2, 157.3, 155.0, 146.4, 141.0, 129.2, 128.1, 127.6, 116.1, 115.9, 114.2, 114.2, 48.7.

N-benzylnaphthalen-1-amine (**3e**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, $J = 10.5$, 8.9 Hz, 2 H), 7.48-7.38 (m, 4 H), 7.35 (t, $J = 7.7$ Hz, 2 H), 7.32-7.20 (m, 3 H), 6.64 (d,

$J = 7.3$ Hz, 1 H), 4.48 (s, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.0, 139.0, 134.4, 128.9, 128.0, 127.6, 126.7, 125.9, 125.0, 123.6, 120.1, 118.1, 105.3, 48.9.

N-(4-chlorobenzyl)aniline (**3f**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4 H), 7.18 (t, $J = 7.9$ Hz, 2 H), 6.73 (t, $J = 7.3$ Hz, 1 H), 6.61 (d, $J = 8.0$ Hz, 2 H), 4.32 (s, 2 H), 4.06 (s, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.0, 138.1, 133.0, 129.4, 128.9, 128.8, 117.9, 113.0, 47.8.

N-phenethylaniline (**3 g**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, $J = 13.7$, 6.5 Hz, 2 H), 7.27 (dd, $J = 18.1$, 7.5 Hz, 5 H), 6.79 (t, $J = 7.2$ Hz, 1 H), 6.69 (d, $J = 7.9$ Hz, 2 H), 3.63 (s, 1 H), 3.46 (d, $J = 7.0$ Hz, 2 H), 2.97 (d, $J = 6.9$ Hz, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.1, 139.4, 129.4, 128.9, 128.7, 126.5, 117.6, 113.1, 45.1, 35.6.

N-heptylaniline (**3 h**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, $J = 7.7$ Hz, 2 H), 6.74 (t, $J = 7.3$ Hz, 1 H), 6.65 (d, $J = 8.2$ Hz, 2 H), 3.63 (s, 1 H), 3.14 (t, $J = 7.1$ Hz, 2 H), 1.69 − 1.64 (m, 2 H), 1.40-1.31 (m, 8 H), 0.95 (t, $J = 6.4$ Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.7, 129.3, 117.1, 112.8, 44.1, 31.9, 29.7, 29.3, 27.3, 22.7, 14.2.

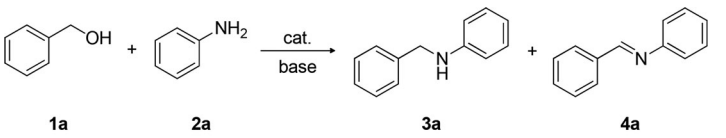
N-benzylideneaniline (**4a**): ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 7.96 (d, $J = 3.8$ Hz, 2 H), 7.51 (dd, $J = 3.8$, 0.7 Hz, 3 H), 7.37-7.47 (m, 2 H), 7.28 (td, $J = 7.3$, 1.7 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 152.1, 136.3, 131.4, 129.2, 128.9, 128.8, 126.0, 121.0.

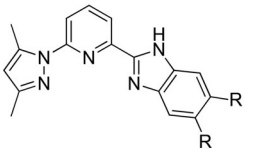
3. Results and discussion

First, FeX_2 and L1-L3 were screened for acceptorless dehydrogenative coupling of benzyl alcohol with aniline in toluene (2 mL) at 110 °C, and the results are summarized in Table 1. When $FeCl_2$, $FeBr_2$ and FeI_2 were used as pre-catalysts, an obvious catalyst effect was observed on the alkylation efficiency and selectivity with the order $FeCl_2 > FeBr_2 > FeI_2$ (entries 1-3); the size of the anion has a big influence on reaction efficiency, higher conversion with small Cl^-. The functional group on L1-L3 also has an influence on the alkylation reaction with $H > CH_3 >$ NHTs, indicating the electronic effect of ligand affects the reaction efficiency (entries 1, 4 and 5). The reaction efficiency was remarkably decreased with *t*BuONa and K_2CO_3 as the base, reaching 20% and 18% conversion for **2a** and poor selectivity for **3a**/**4a**. Using KOH, 99% conversion was achieved for **2** with a 74/26 selectivity for the target *N*-alkylation product **3a** and *N*-alkylation/dehydrogenation product **4a** (Table 1, entries 6-8). Reaction efficiency was improved by strong and bulky base. Under the closed system and high temperature conditions, the reaction could not efficiently occur (Table 1, entries 9 and 10). Lowering the base loading of *t*BuOK to 0.75 equiv., the *N*-alkylation has a comparable efficiency with that of 1 equiv., while not for 0.5 and 0.4 equiv. *t*BuOK which reduced the conversion of **2a** with deteriorated selectivities of **3a**/**4a**. Lowering the catalyst and ligand loading to 1.0 mol %, the reaction efficiency was decreased with 90% yield and 90/10 selectivity (entries 11-14).

Under optimal conditions, benzyl alcohol (**1a**) was employed to react with various anilines to prepare diverse secondary amines in Table 2. Benzyl alcohol (**1a**) reacted with *p*-toluidine (**2b**) to form *N*-benzyl-4-methylaniline **3b** in 90% yield, exhibiting lower reactivity than aniline (**2a**). 3-Chloroaniline (**2c**) also efficiently reacted with **1a**, producing the desired products in 88% yields. Both 4-fluoroaniline (**2d**) and

Table 1. Screening of reaction conditions.

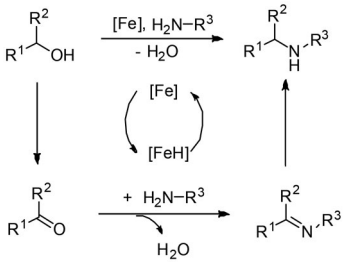




L1, R = H
L2, R = CH_3
L3, R = NHTs

Entry	Cat.	Base (equiv.)	Conv. (**2a**) (%)[a]	Yield (%)[a] (**3a**:**4a**)
1	$FeCl_2$+L1	1	>99	97:3
2	$FeBr_2$+L1	1	78	46:54
3	FeI_2+L1	1	57	67:33
4	$FeCl_2$+L2	1	67	82:18
5	$FeCl_2$+L3	1	56	73:27
6[b]	$FeCl_2$+L1	1	20	2:98
7[c]	$FeCl_2$+L1	1	18	3:97
8[d]	$FeCl_2$+L1	1	>99	74:26
9[e]	$FeCl_2$+L1	1	23	52:48
10[f]	$FeCl_2$+L1	1	65	77:23
11	**$FeCl_2$+L1**	**0.75**	**>99**	**97:3**
12	$FeCl_2$+L1	0.5	95	97:3
13	$FeCl_2$+L1	0.4	93	72:28
14[g]	$FeCl_2$+L1	0.75	90	90:10

Conditions: 2 mmol 1 and 2, tBuOK, 0.1 MPa N_2, toluene, reflux 36 h. 2 mol% FeX_2 [FeX_2:L (molar ratio) = 1:1].
[a]Determined by GC analysis.
[b]tBuONa.
[c]K_2CO_3.
[d]KOH.
[e]25-mL sealed tube.
[f]Xylene, reflux.
[g]1 mol% FeX_2 [FeX_2:L (molar ratio) = 1:1].

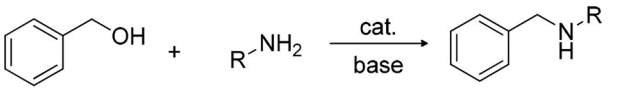


Scheme 2. Proposed mechanism.

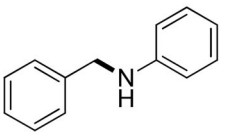
naphthalen-1-amine (**2e**) could effectively react with **1a** to form secondary amines **3d** (91%) and **3e** (93%), respectively.

Next, the protocol was extended to diverse alcohols in Table 3. 4-Chlorobenzyl alcohol (**1b**) worked well with aniline to afford the target product *N*-phenyl(4-

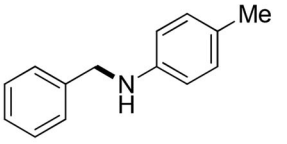
Table 2. Scope of anilines.



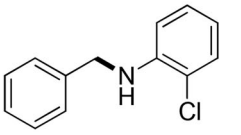
1a **2** **3**



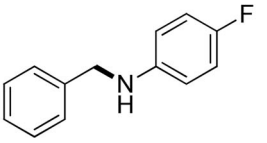
3a, 93%



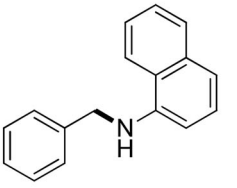
3b, 90%



3c, 88%



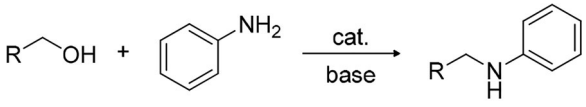
3d, 91%



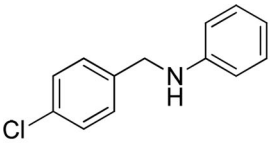
3e, 93%

Conditions: 2 mmol 1 and 2, 0.75 equiv. tBuOK, 0.1 MPa N_2, toluene, reflux 36 h. 2 mol% $FeCl_2$, 2 mol% L1.

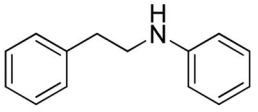
Table 3. Scope of primary alcohols.



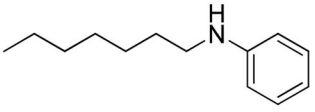
1 **2a** **3**



3f, 90%



3g, 82%



3h, 80%

Conditions: 2 mmol 1 and 2, 0.75 equiv. tBuOK, 2 mol% $FeCl_2$, 2 mol% L1, 0.1 MPa N_2, toluene, reflux 36 h.

chlorobenzyl)amine (**3f**) in 90% yield. Aliphatic secondary alcohols 2-phenylethanol (**1c**) and heptan-1-ol (**1d**) reacted with aniline (**2a**) less efficiently, giving **3g** and **3h** in 80-82% yields.

A simplified mechanism is proposed in Scheme 2. The $FeCl_2$(II) with **L1** promotes oxidation of the primary alcohols to the corresponding aldehyde by generation of an iron hydride species. Then, the base mediated condensation of the *in situ* formed

aldehyde and amine to form the imine intermediate. Subsequent transfer hydrogenation of the resultant imine with the iron hydride species yields the secondary amine.

4. Conclusion

Direct synthesis of secondary amines from *N*-alkylation of primary amines with alcohols occurs with $FeCl_2$ and **L1** through a borrowing hydrogen strategy. The catalyst system exhibited very high catalytic activity towards an array of amine and alcohol substrates. The present protocol provides a green method to access higher-order amines.

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Disclosure statement

The authors declare no competing financial interest.

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