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Amine Alkylation

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Cobalt-Catalyzed Alkylation of Aromatic Amines by Alcohols

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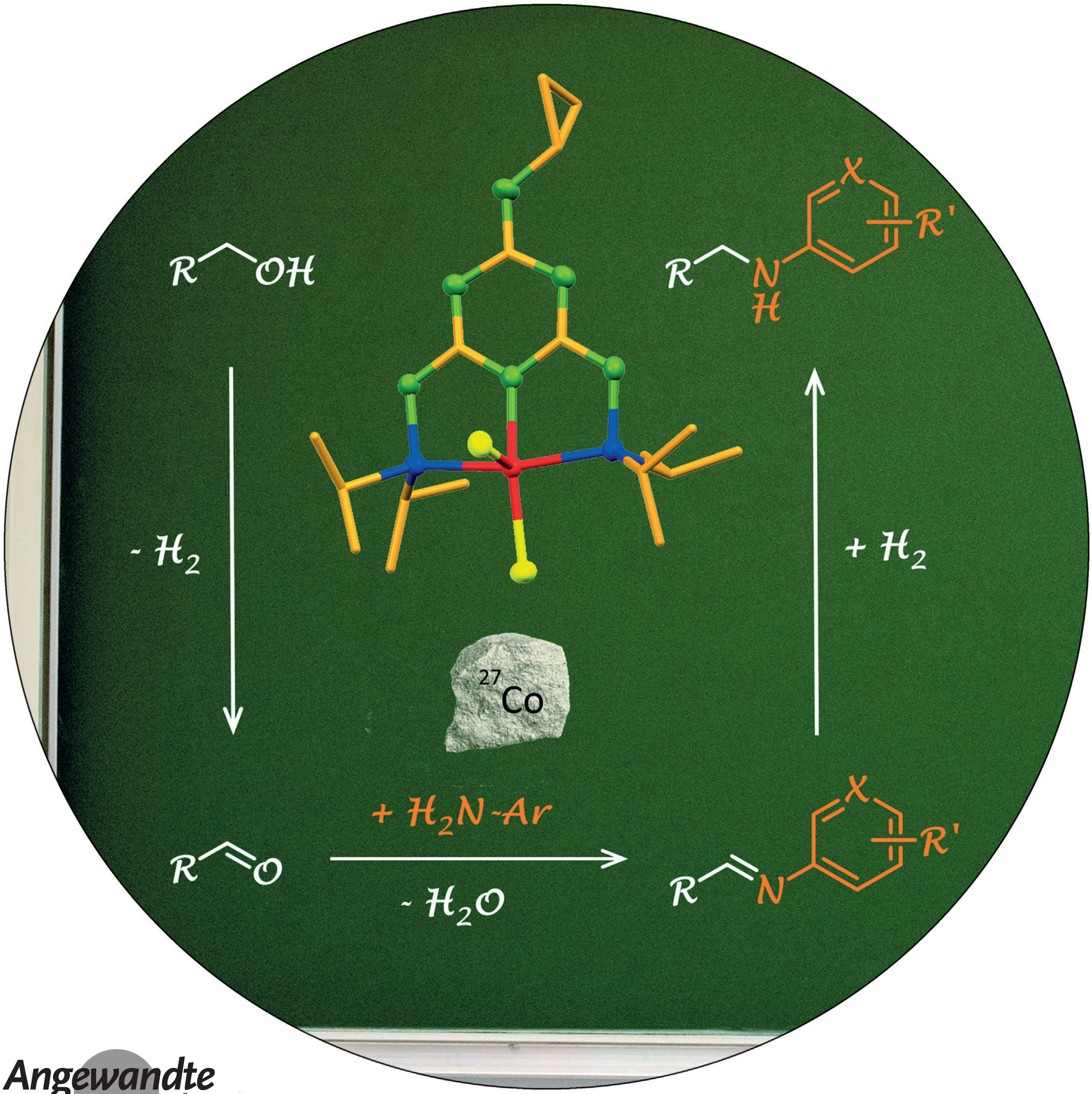
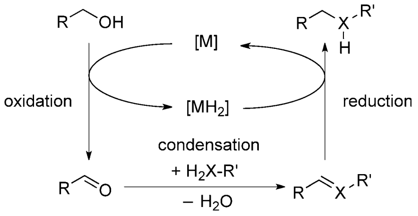


Angewandte International Edition Chemie

Abstract: *The implementation of inexpensive, Earth-abundant metals in typical noble-metal-mediated chemistry is a major goal in homogeneous catalysis. A sustainable or green reaction that has received a lot of attention in recent years and is preferentially catalyzed by Ir or Ru complexes is the alkylation of amines by alcohols. It is based on the borrowing hydrogen or hydrogen autotransfer concept. Herein, we report on the Co-catalyzed alkylation of aromatic amines by alcohols. The reaction proceeds under mild conditions, and selectively generates monoalkylated amines. The observed selectivity allows the synthesis of unsymmetrically substituted diamines. A novel Co complex stabilized by a* PN_5P *ligand catalyzes the reactions most efficiently.*

The borrowing hydrogen or hydrogen autotransfer (BH/HA) concept (Scheme 1) is an elegant method for the "green" or sustainable formation of C–C and C–N bonds.[1] In this concept, an alcohol is first oxidized by a transition-metal catalyst to the corresponding carbonyl compound. It can then undergo condensation reactions followed by a reduction step using the hydrogen equivalents obtained from the alcohol oxidation.[1,2] The first examples of the N-alkylation of amines by alcohols were reported by the groups of Watanabe[3] and Grigg.[4] In the last 10 years, this type of reaction has received a lot of attention, and elegant synthesis concepts have been developed.[1] Typically, noble transition metals such as ruthenium and iridium catalyze the alkylation of amines efficiently.[1] Our group has contributed to the development of such Ir catalysts.[5]



Scheme 1. Mechanism of BH/HA reactions. X = CH, N; [M] = transition-metal catalyst.

A key challenge in transition-metal-mediated catalysis is the substitution of expensive noble metals by Earth-abundant, inexpensive base metals. Homogeneous cobalt catalysts have been reported in reactions related to the key steps of BH/HA such as in hydrogenation (olefins,[6] ketones,[7] nitriles,[8] esters,[9] and CO_2[10]) as well as dehydrogenations.[11] However, the use of homogeneous cobalt catalysts in amine alkylation reactions by alcohols has not been reported to the best of our knowledge.

Herein we describe the efficient alkylation of aromatic amines by alcohols catalyzed by a cobalt complex stabilized by a PN_5P ligand. The catalyst operates under mild conditions and selective monoalkylation is observed. On the basis of this selectivity, the synthesis of unsymmetrically alkylated diamines becomes feasible.

We recently introduced $PN_{3-5}P$-Ir complexes as highly efficient homogeneous catalysts for the sustainable synthesis of N-heteroarenes, such as pyrroles and pyridines.[12] Very recently, we showed that Co complexes stabilized by a PN_5P ligand (triazine backbone) are highly active and selective catalysts for the hydrogenation of C=O bonds.[7a] The Co complexes are easy to synthesize and simple to activate. They can be synthesized quantitatively on a multigram scale and are air-stable as crystalline materials for a few months. The PN_3P ligand system (pyridine backbone) was introduced by Haupt and co-workers,[13] and the Kirchner group demonstrated the broad applicability of the ligand class.[14] Reports on Co complexes are rare.[7a,15]

The reaction of aniline with benzyl alcohol was investigated to identify an efficient Co-based catalyst for the alkylation of amines. To our delight, 5.0 mol% complex **1c** (which was the most active precatalyst in the hydrogenation of C=O bonds) already afforded *N*-benzylaniline (**3a**) in 84% yield under relatively mild reaction conditions (80 °C). A catalyst screening with 2.5 mol% of the complexes **1a–e** (Figure 1, Table 1) was next carried out. In addition to these already published Co complexes (**1a–c**),[7a] three new $CoCl_2$ complexes stabilized by a PN_5P ligand (**1d–f**) were synthesized, characterized, and applied (Figure 1, Table 1; see Table S2 in the Supporting Information). The cobalt precursor, $CoCl_2$, was also investigated, but afforded only 3% of the alkylated aniline (Table 1, entry 6). Complex **1d** was found to be the most active precatalyst in the test reaction. The molecular structure of **1d** was determined by X-ray crystal-structure analysis. The N2–C2 and the N3–C1 bonds (1.318(3) Å) of **1d** are shorter than the corresponding N–C bonds in **1a–c** (average 1.331 Å). This indicates a partial double-bond character for these N–C bonds in **1d** and, consequently, a more positively charged alkyl amine (N6) and a more

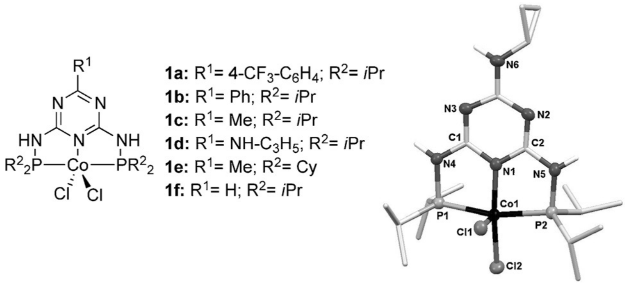


Figure 1. Synthesized Co complexes **1a–f** and molecular structure determined by X-ray crystal-structure analysis of **1d** with 50% probability of thermal ellipsoids. Hydrogen atoms (except NH) are omitted for clarity. Selected bond lengths [Å] and angles [°]: P1-Co1 2.202(1), P2-Co1 2.196(1), Co1-Cl1 2.464(1), Co1-Cl2 2.220(1), Co1-N1 1.926(2), C2-N2 1.318(3); P1-Co1-P2 164.36(3), N1-Co1-Cl1 90.34(7), N1-Co1-Cl2 162.43(7), N4-P1-Co1 99.18(8), N5-P2-Co1 99.97(8).

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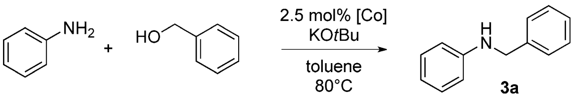
Table 1: Screening of cobalt complexes in the alkylation of aniline with benzyl alcohol.[a]



3a

Entry	Precatalyst	Yield[b] [%]
1	**1a**	42
2	**1b**	17
3	**1c**	35
4	***1d***	*62*
5	**1e**	35
6	$CoCl_2$	3

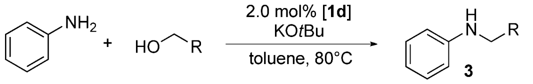
[a] Reaction conditions: 1.0 mmol aniline, 1.1 mmol benzyl alcohol, 1.0 mmol KO*t*Bu, 5 mL toluene, 80 °C, 20 h. [b] Determined by GC with dodecane as internal standard.

negatively charged coordinating N atom (N1). Interestingly, the Co complexes stabilized by a PN_3P ligand (pyridine backbone) resulted in significantly lower reaction rates than their PN_5P (triazine backbone) counterparts (see Table S2). The catalyst based on **1d** was used for the final optimizations of the reaction conditions. The use of a precatalyst at a loading of 2.0 mol% led to the formation of 93% *N*-benzylaniline (Table S7). An amine/alcohol ratio of 1.4:1 is beneficial.

With these optimized conditions in hand, aniline was alkylated with various alcohol derivatives (Table 2, **3a–l**). Substituted benzyl alcohols (**3a–h**) with several functional groups (halides, alkyl, thioether, methoxy) are applicable as well as aliphatic alcohols (**3i–l**). The resulting N-alkylated anilines were isolated in good to excellent yields, except for **3d** where debromination lowered the yield.

Next, substituted anilines were alkylated with benzyl alcohol to show the aniline variability (Table 3). Again, a notable functional group tolerance was observed. Halide (F, Cl, Br, and I) substituted *N*-benzylanilines (**4a–d**, **4g**) as well as 3,5-substituted *N*-benzylanilines (**4h,i**) were isolated in good to excellent yields, except for **4d** and **4g**, where partially dehalogenation again takes place. In addition, 3-aminopyridine was successfully alkylated with benzyl and aliphatic alcohols (Table 4).

Table 2: Alkylation of aniline with various primary alcohols.[a]



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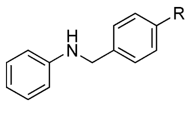
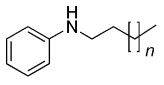
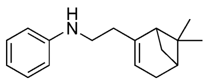
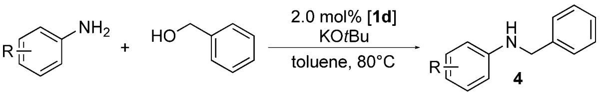
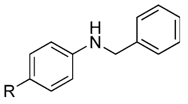
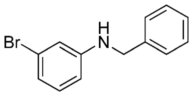
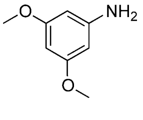
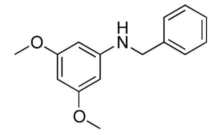
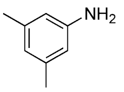
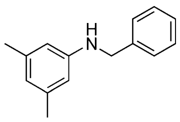
Entry	Alcohol	Product		Yield[b] [%]
1	R = C_6H_5	**3a**		90
2	R = 4-F(C_6H_4)	**3b**		84
3	R = 4-Cl(C_6H_4)	**3c**		72
4	R = 4-Br(C_6H_4)	**3d**		53
5	R = 4-Me(C_6H_4)	**3e**		94
6	R = 4-OMe(C_6H_4)	**3f**		88
7	R = 4-SMe(C_6H_4)	**3g**		71
8	R = 4-*tert*-butyl(C_6H_4)	**3h**		93
9	1-butanol	**3i**		90
10	1-hexanol	**3j**		82
11	$C_{22}H_{45}OH$	**3k**		86
12	(−)-Nopol	**3l**		96

[a] Reaction conditions: 1.4 mmol aniline, 1.0 mmol alcohol, 2.0 mol% precatalyst **1d**, 1.2 mmol KO*t*Bu, 3 mL toluene, 80 °C, 24 h. [b] Yield of isolated product.

Table 3: Alkylation of various aniline derivatives with benzyl alcohol.[a]



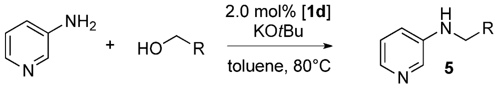
4

Entry	Amine	Product		Yield[b] [%]
1	R = 4-F	**4a**		86
2	R = 4-Cl	**4b**		69
3	R = 4-Br	**4c**		72
4	R = 4-I	**4d**		51
5	R = 4-Et	**4e**		76
6	R = 4-*i*Pr	**4f**		76
7	R = 3-Br	**4g**		57
8		**4h**		86
9		**4i**		63

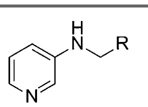
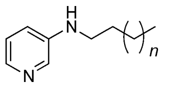
[a] Reaction conditions: 1.4 mmol aniline, 1.0 mmol alcohol, 2.0 mol% precatalyst **1d**, 1.2 mmol KO*t*Bu, 3 mL toluene, 80 °C, 24 h. [b] Yield of isolated product.

Finally, we were interested in the preferential selective alkylation of diamines with two different alcohols (Table 5). First, a monoalkylated diamine (**6a**) was synthesized in 91% yield. In a second step, **6a** was alkylated with benzylic and aliphatic alcohols to afford the corresponding unsymmetrically alkylated diamines (**7b–e**).

Table 4: Alkylation of 3-aminopyridine with various alcohols.[a]

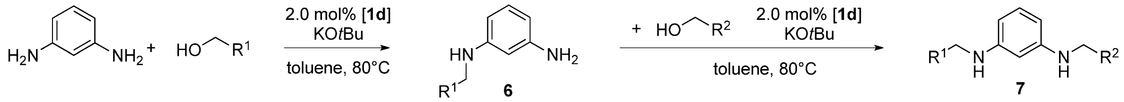


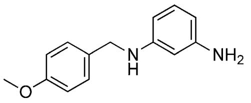
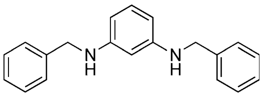
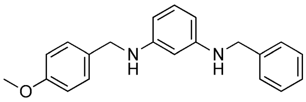
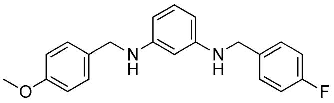
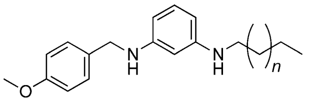
5

Entry	Alcohol	Product		Yield[b] [%]
1	R = C_6H_5	**5a**		89
2	R = 4-OMe(C_6H_4)	**5b**		61
3	R = 4-SMe(C_6H_4)	**5c**		76
4	R = 4-Me(C_6H_5)	**5d**		94
5	$C_{22}H_{45}OH$	**5e**		69
6	1-butanol	**5f**		76

[a] Reaction conditions: 1.4 mmol aminopyridine, 1.0 mmol alcohol, 2.0 mol% precatalyst **1d**, 1.2 mmol KO*t*Bu, 3 mL toluene, 80 °C, 24 h. [b] Yield of isolated product.

Table 5: Alkylation of diamines.



Entry	Alcohol R^1	Alcohol R^2		Product	Yield[d] [%]
1	R^1 = 4-OMe(C$_6$H$_4$)	–	**6a**[a]		91
2	R^1 = C$_6$H$_5$	R^2 = C$_6$H$_5$	**7a**[b]		73
3	R^1 = 4-OMe(C$_6$H$_4$)	R^2 = C$_6$H$_5$	**7b**[c]		71
4	R^1 = 4-OMe(C$_6$H$_4$)	R^2 = 4-F-(C$_6$H$_4$)	**7c**[c]		57
5	R^1 = 4-OMe(C$_6$H$_4$)	R^2 = propyl	**7d**[c]		76
6	R^1 = 4-OMe(C$_6$H$_4$)	R^2 = pentyl	**7e**[c]		79

[a] 3.0 mmol benzenediamine, 1.0 mmol alcohol, 2.0 mol% precatalyst **1d**, 1.2 mmol KO*t*Bu, 3 mL toluene, 80°C, 24 h. [b] 1.0 mmol benzenediamine, 2.0 mmol alcohol, 4.0 mol% precatalyst **1d**, 2.4 mmol KO*t*Bu, 3 mL toluene, 80°C, 24 h. [c] 1.0 mmol **6a**, 1.0 mmol alcohol, 2.0 mol% precatalyst **1d**, 1.2 mmol KO*t*Bu, 3 mL toluene, 80°C, 24 h. [d] Yield of isolated product.

In conclusion, we have reported on the first example of an alkylation of amines by alcohols catalyzed by a cobalt complex. A novel Co catalyst allows the reaction to be carried out under mild conditions (80°C) with a relatively low catalyst loading (2 mol%). The precatalyst is easily prepared from commercially available reagents in a two-step procedure and in almost quantitative yields. The mild reaction conditions allow the selective monoalkylation of aromatic amines and the synthesis of unsymmetrically alkylated diamines.

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Keywords: alcohols · amine alkylation · base metals · hydrogen-transfer catalysis · cobalt

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