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Alkylation

Chromium-Catalyzed Alkylation of Amines by Alcohols

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Dedicated to Marlies Schilling

Abstract: *The alkylation of amines by alcohols is a broadly applicable, sustainable, and selective method for the synthesis of alkyl amines, which are important bulk and fine chemicals, pharmaceuticals, and agrochemicals. We show that Cr complexes can catalyze this C–N bond formation reaction. We synthesized and isolated 35 examples of alkylated amines, including 13 previously undisclosed products, and the use of amino alcohols as alkylating agents was demonstrated. The catalyst tolerates numerous functional groups, including hydrogenation-sensitive examples. Compared to many other alcohol-based amine alkylation methods, where a stoichiometric amount of base is required, our Cr-based catalyst system gives yields higher than 90% for various alkyl amines with a catalytic amount of base. Our study indicates that Cr complexes can catalyze borrowing hydrogen or hydrogen autotransfer reactions and could thus be an alternative to Fe, Co, and Mn, or noble metals in (de)hydrogenation catalysis.*

The alkylation of amines by alcohols can proceed via a borrowing hydrogen or hydrogen autotransfer (BH/HA) mechanism (Figure 1, a). The alcohol is dehydrogenated by transferring a proton and a hydride to the catalyst, with the hydride binding to the metal and the proton being accepted by the ligand or support. The so-formed carbonyl compound can undergo a Schiff-base reaction[1] with an amine or ammonia, and the resulting imine is reduced through transfer of the hydride and the proton to it, thereby recycling the catalyst. This amine alkylation is a green or sustainable reaction since alcohols are employed[2] and it permits the selective alkylation of amines.[3] The reaction was discovered by Winans and Adkins[4] in 1932, and the groups of Grigg[5] and Watanabe[6] introduced the first homogeneous catalysts. The development of catalysts based on abundantly available metals to mediate chemical transformations typically associated with rare noble metals is a similarly important green or sustainable approach and may permit the observation of yet unknown selectivity patterns. We recently summarized the progress made in developing 3d metal catalysts for C–N and C–C bond formation reactions with alcohols using the BH/HA concept[7] and discovered that chromium catalysts have not been reported for these reactions to the best of our knowledge. Homogeneous catalysts of 3d metals for the alkylation of amines by alcohols through BH/HA have been discovered by the groups of Feringa and Barta (Fe),[8] our group (Co),[9] and Beller and co-workers (Mn).[10] Interestingly, these and related complexes have also been used to catalyze a variety of (de)hydrogenation reactions.[11]

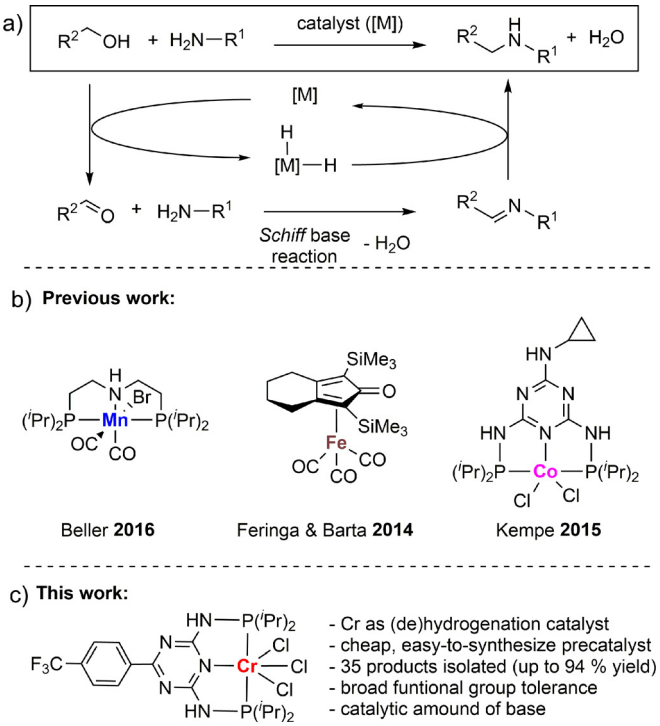

Figure 1. a) Alkylation of amines by alcohols via borrowing hydrogen or hydrogen autotransfer ([M] {transition} metal catalyst). b) Key developments of homogeneous 3d metal catalyst for the alkylation of amines by alcohols. c) Chromium based precatalyst used in this report.

Herein, we report that chromium complexes can catalyze the alkylation of amines by alcohols. We synthesized and isolated 35 examples of alkyl amines in yields up to 94%. Thirteen previously undisclosed products were obtained, and selective C–N bond formation by employing amino alcohols as the alkylating agent was demonstrated. Our catalyst tolerates numerous functional groups, among them hydrogenation-sensitive examples. We only use a catalytic amount

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of base, and a mechanism following the BH/HA concept is very likely.

Five Cr^{III} precatalysts **Cr-Ia–e** and the corresponding Cr^{II} precatalysts (**Cr-IIa–e**) were synthesized first (Figure 2, for the full synthetic procedure please see the Supporting Information). **Cr-If** and **Cr-IIf** were synthesized according to procedures reported by Kirchner and co-workers.[12] The molecular structure of **Cr-Id** (which turned out to be the precatalyst of the most active catalyst system, see below) was confirmed by X-ray diffraction (XRD) analysis. The magnetic susceptibility μ_{eff} was determined by SQUID measurements to be 3.9, which is fully consistent with a Cr^{III} center.

The reaction of aniline with benzyl alcohol was chosen as a model reaction and the different complexes were tested for their activity at a catalyst loading of 5 mol% (Table 1).

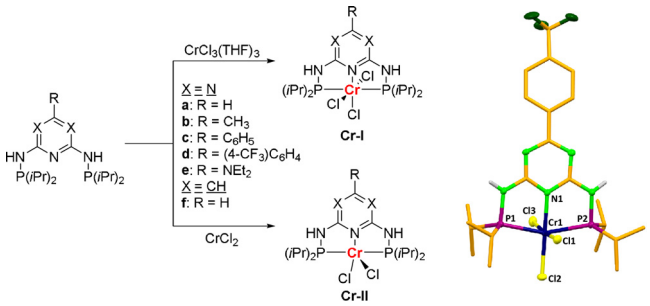
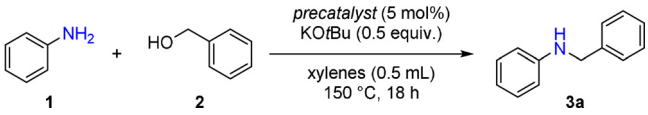


Figure 2. Synthesis of the complexes used in this study and molecular structure of **Cr-Id**. Thermal ellipsoids are shown at 50% probability, solvent molecules and C–H atoms omitted for clarity. Selected bond lengths [Å] and angles [°]: Cr1–N1 2.086(3), Cr1–P1 2.4492(11), Cr1–P2 2.4520(11), Cr1–Cl1 2.3085(11), Cr1–Cl2 2.2877(11), Cr1–Cl3 2.3055(11); P1-Cr1-P2 158.56(4), N1-Cr1-Cl2 179.29(9), Cl3-Cr1-Cl1 173.64(4).

Table 1: Catalyst system screening for the N-alkylation of aniline.[a]



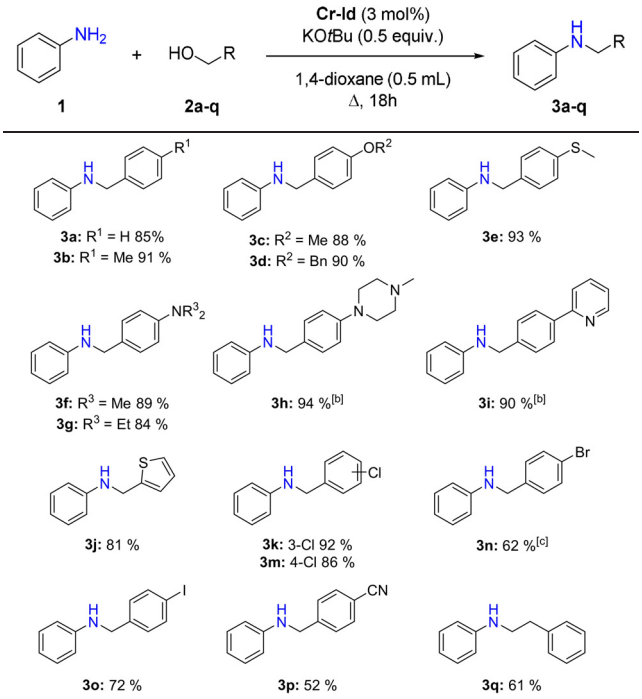
Entry	Precatalyst	Yield[b] [%]
1	**Cr-Ia**	21
2	**Cr-Ib**	24
3	**Cr-Ic**	29
4	**Cr-Id**	52 (97[c])
5	**Cr-Ie**	18
6	**Cr-If**	15
7	**Cr-IIa**	23
8	**Cr-IIb**	35
9	**Cr-IIc**	22
10	**Cr-IId**	58
11	**Cr-IIe**	31
12	**Cr-IIf**	1

[a] Reaction conditions: 5 mol% precatalyst (50 µmol), 0.5 equiv KO*t*Bu (0.5 mmol, 56 mg), 0.5 mL xylenes (mixture of isomers), 1 equiv benzyl alcohol (1 mmol, 104 µL) and 1 equiv aniline (1 mmol, 91 µL), 150 °C oil bath, 18 h. [b] Yield determined by GC-analysis using *n*-dodecane as internal standard. [c] 3 mol% **Cr-Id** (30 µmol), 0.5 equiv KO*t*Bu (0.5 mmol, 56 mg), 0.5 mL 1,4-dioxane, 1.2 equiv benzyl alcohol (1.2 mmol, 125 µL) and 1 equiv aniline (1 mmol, 91 µL), 150 °C oil bath, 18 h, bubble counter with backflow protection.

Electron-donating substituents at the triazine core do not significantly influence the outcome of the reaction (Table 1, entries 1–3 and 7–9), however, the electron-withdrawing substituent in **Cr-Id** and **Cr-IId** leads to a two-fold increase in product yield (Table 1, entries 4 and 10). Notably, switching from a triazine to a pyridine backbone decreases product formation, with the effect being more pronounced in Cr^{II} than Cr^{III} complexes (Table 1, entries 6 and 12). Despite giving the best yield so far (Table 1, entry 10), the result for **Cr-IId** could not be further increased, which is in contrast to the Cr^{III} analogue **Cr-Id** (Table 1, entry 4). When the reaction was run with a slight excess of benzyl alcohol (1.2 equiv) in 1,4-dioxane, the product **3a** was almost quantitatively obtained using only 3 mol% of **Cr-Id** (see the Supporting Information for screening reactions).

Having established optimal reaction conditions, the addressable substrate scope was evaluated using different primary alcohols (Table 2). The screening substrate **3a** was isolated in 85% yield. Substrates containing methyl (**3b**), methoxide (**3c**), and thiomethyl (**3e**) groups were synthesized in slightly better yields of 88–93%. The use of (4-benzyloxy)benzyl alcohol furnished product **3d** in 90% yield without any signs of cleavage of the benzyloxy group. Next, a series of electron rich, *N*,*N*-dialkyl-substituted *para*-aminobenzyl alcohols were tested and the resulting products **3f** and **3g** were isolated in 89 and 84% yield, respectively. The previously undisclosed product **3h**, which contains a piperazine moiety, was isolated almost quantitatively (94%). Heteroaromatic alcohols furnished the pyridine derivative **3i** and thiophene

Table 2: Substrate scope with respect to primary alcohols.[a]



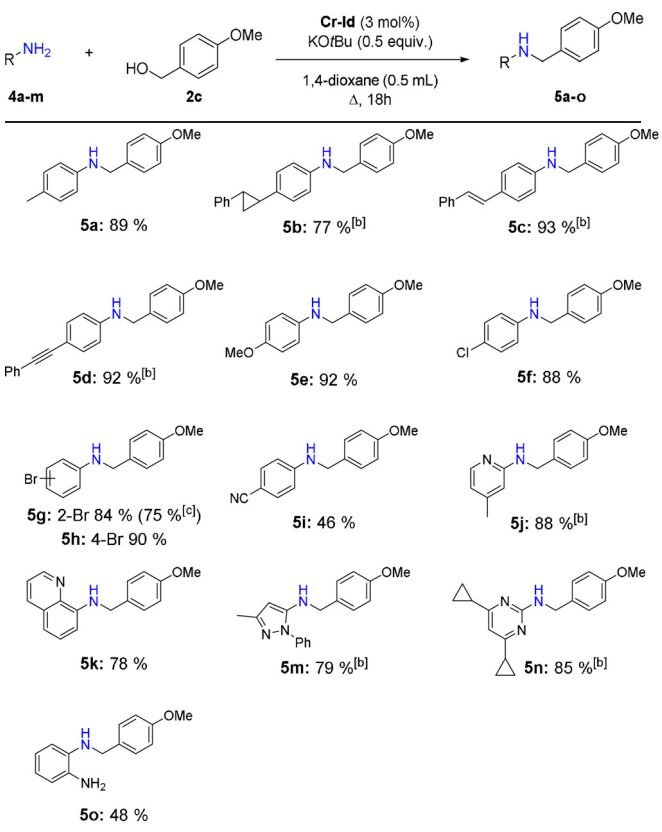
[a] 3 mol% **Cr-Id** (30 µmol), 0.5 equiv KO*t*Bu (0.5 mmol, 56 mg), 0.5 mL 1,4-dioxane, 1.2 equiv alcohol (1.2 mmol) and 1 equiv aniline (1 mmol, 91 µL), 150 °C oil bath, 18 h, bubble counter with backflow protection. Yields refer to isolated product. [b] New compound. [c] 5 mmol scale.

derivative **3j** in 90 and 81 % yield, respectively. Furthermore, halide-substituted benzyl alcohols reacted smoothly to give the products **3k–o** in 62–92 % yield. Notably, the strongly electron-withdrawing nitrile group was tolerated and the corresponding product **3p** was obtained in 52 % yield. Employing 2-phenylethanol instead of a benzylic alcohol resulted in a decrease in yield to 61 % (**3q**).

Next, the substrate scope with respect to the amine was evaluated (Table 3). For this purpose, a series of *para*-substituted anilines was tested. First, 4-methylaniline was reacted under standard conditions and furnished **5a** in 89 % yield. Next, radical-reaction and hydrogenation-sensitive substrates were tested. To our delight, cyclopropanes, double bonds, and triple bonds did not undergo undesired reactions, thus furnishing **5b–d** in very agreeable yields of 77–93 %. A substrate containing an electron-donating methoxide group was converted as efficiently as substrates containing electron-withdrawing groups like halides, leading to the isolation of **5e–h** in similar yields of 84–92 %. The synthesis of **5g** could be easily scaled up to 10 mmol scale, furnishing 2.20 grams (75 %) of product. Product **5i**, which contains the strongly electron-withdrawing nitrile group, was isolated in 46 % yield. Finally, a series of N-heterocyclic amines was subjected to catalytic N-alkylation. Aminopyridine **5j** and aminoquinoline **5k** were synthesized in respectable yields of 88 and 78 %, respectively. The five-membered heteroaromatic aminopyrazole reacted smoothly, affording **5m** in 79 % yield. Finally, 4,6-dicyclopropylpyrimidin-2-amine, which can easily be prepared from alcohols and guanidine by a one-pot procedure,[13] was reacted with *para*-methoxybenzyl alcohol and furnished product **5n** in a satisfying 85 % yield.

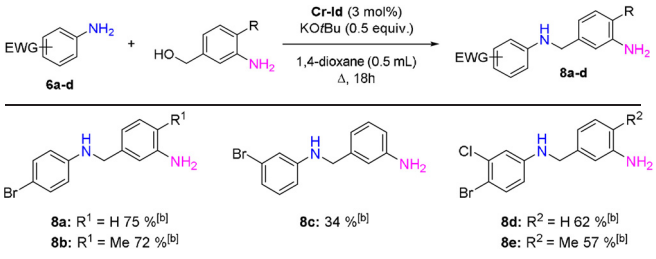
Based on a Hammett study (see the Supporting Information), electron-deficient anilines react faster with alcohols. Therefore, we hypothesized that a selective reaction with an unprotected amino benzyl alcohol should occur readily (Table 4). Indeed, the reaction between 4-bromoaniline with 3-aminobenzyl alcohol furnished **8a** in 75 % yield of isolated material. The yield is significantly affected by using 3-bromoaniline (Table 4; **8c**, 34 %), which is consistent with the findings from our Hammett study, since the position of the electron-withdrawing group in conjugation with the amine is pivotal. With an additional chlorine substituent in the *meta* position, **8d** can be obtained in a similar yield to **8a**. Amino alcohols containing an additional methyl group gave similar results, thus indicating that the selectivity arises from electronic factors rather than steric considerations.

Table 3: Substrate scope with respect to the amine.[a]



[a] 3 mol % **Cr-Id** (30 µmol), 0.5 equiv KO*t*Bu (0.5 mmol, 56 mg), 0.5 mL 1,4-dioxane, 1.2 equiv 4-methoxybenzyl alcohol (1.2 mmol, 149 µL) and 1 equiv amine (1 mmol), 150 °C oil bath, 18 h, bubble counter with backflow protection. Yields refer to isolated product. [b] New compound. [c] 10 mmol scale.

Table 4: Alkylation of anilines using 3-aminobenzyl alcohols.[a]



[a] 3 mol % **Cr-Id** (30 µmol), 0.5 equiv KO*t*Bu (0.5 mmol, 56 mg), 0.5 mL 1,4-dioxane, 1.2 equiv aminobenzyl alcohol (1.2 mmol) and 1 equiv amine (1 mmol), 150 °C oil bath, 18 h, bubble counter with backflow protection. Yields refer to isolated product. [b] new compound. EWG = electron withdrawing group.

Finally, preliminary mechanistic experiments were conducted (Figure 3). A mercury-drop test showed no influence of mercury on the yield of the model reaction (65 % without mercury, 69 % at 225 mol % Hg loading), thus indicating that the active catalyst is likely to be homogeneous in nature. This is further supported by the partial inhibition of the reaction by the phosphine oxide $OPPh_3$ (0.3 mol % $OPPh_3$: 56 % of **3a**). The activation of **Cr-Id** was then examined upon addition of KO*t*Bu to the complex by using IR spectroscopy. The complex exhibits a broad NH resonance at 3214 cm^{-1}, which gradually disappears upon the addition of base. We concluded that a doubly deprotonated species could act as the active catalyst, which is similar to our recent findings with a Mn catalyst.[14] Then, the dehydrogenation and hydrogenation step of the proposed BH/HA cycle were examined. 18 % alcohol was consumed in a closed flask and 27 % was consumed when the same reaction was run using a bubble counter with backflow protection for pressure equalization. Afterwards, the ability

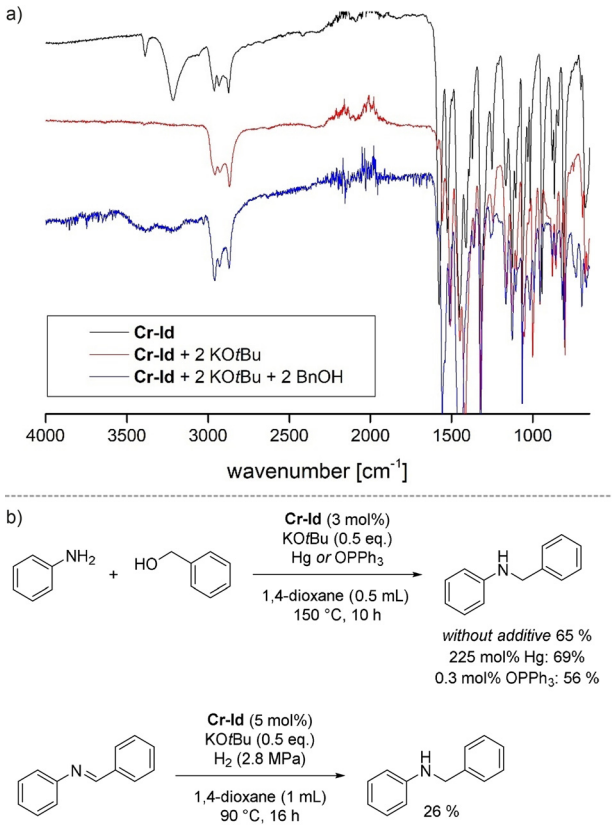


Figure 3. a) IR spectroscopy of **Cr-Id** after activation with 2 equivalents of KO*t*Bu and reaction with benzyl alcohol (normalized). b) Poisoning and hydrogenation experiments.

of the catalyst to hydrogenate the intermediate imine was probed. When employing 5 mol% **Cr-Id** and 50 mol% KO*t*Bu, 26% amine product **3a** was observed. To gain insight into the nature of the rate-determining step, a Hammett study was conducted.[15] It could be observed that electron-donating groups at the anilines like Me and OMe lead to a decreased reaction rate. On the other hand, increased reaction rates are obtained for anilines with electron-withdrawing groups like Cl, Br, and styrene. This leads to the assumption that the rate-determining step is likely hydride transfer to the imine, since electron-withdrawing groups at the aniline can cushion the build-up of negative charge during hydride transfer.

In summary, we have established that Cr complexes can mediate (de)hydrogenation catalysis. The catalytic N-alkylation of amines by alcohols was explored since it is an important and green or sustainable C–N bond-formation reaction. The chromium complexes we use as precatalysts are inexpensive and easy to synthesize. Our catalyst system mediates the alkylation of amines under conditions comparable to other homogeneous 3d metal catalysts with the noteworthy exception that only sub-stoichiometric quantities of base are required. In total, 35 amines (13 of which have not been reported so far) were synthesized and isolated in yields up to 94%. The catalyst system tolerates functional groups such as aryl iodide, CN, and other hydrogenation-sensitive groups like benzyl ether, alkene, and alkyne groups, and unprotected amino benzyl alcohols are efficiently converted. The active catalyst is likely to be homogeneous in nature, as indicated by poisoning experiments. The results of a Hammett study indicate that the rate-determining step is most likely hydride transfer to the imine. Furthermore, a borrowing hydrogen or hydrogen autotransfer mechanism is very likely.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alcohols · alkylation · borrowing-hydrogen reactions · chromium · hydrogen autotransfer

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