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Chromium Catalyzed Alkylation of Amines by Alcohols

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Dedicated to Marlies Schilling

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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, or agrochemicals. Here we report that Cr complexes can catalyze this C-N bond formation reaction. We synthesized and isolated 35 examples of alkylated amines. Thirteen previously undisclosed products could be obtained, and the use of amino alcohols as alkylating agents could be demonstrated. The catalyst tolerates numerous functional groups, among them hydrogenation sensitive examples. In comparison to many other alcohol-based amine alkylation protocols where a stoichiometric amount of base is required, our Cr based catalyst system permits product isolation with yields higher than 90 % for various alkyl amines with a catalytic amount of base only. Our study indicates that Cr complexes can catalyze borrowing hydrogen or hydrogen auto-transfer reactions and, thus, could be an alternative to Fe, Co and Mn or noble metals in (de)hydrogenation catalysis.

The alkylation of amines by alcohols can proceed via the borrowing hydrogen or hydrogen auto-transfer (BH/HA) mechanism (Figure 1, top). The alcohol is dehydrogenated by transferring a proton and a hydride to the catalyst with the hydride binding to the metal and the proton becoming 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 becomes reduced by transferring the hydride and the proton to it and 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 of abundantly available metals to mediate chemical transformation 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 to the best of our knowledge. Homogeneous catalysts of 3d metals for the alkylation of amines by alcohols via BH/HA have been discovered by the groups of Feringa and Barta (Fe),[8] our group (Co),[9] and Beller and coworkers (Mn).[10] Interestingly, these and related complexes have also been used to catalyze a variety of dehydrogenation reactions.[11]

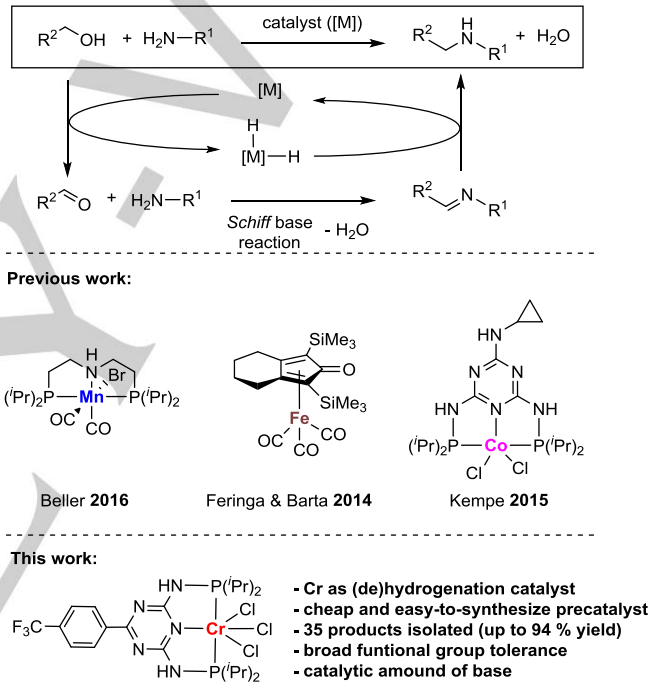


Figure 1. *Top: Alkylation of amines by alcohols via borrowing hydrogen or hydrogen auto-transfer ([M] {transition} metal catalyst). Middle: Key development of homogeneous 3d metal catalyst for the alkylation of amines by alcohols. Bottom: Chromium based precatalyst used in this report.*

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 could be obtained and the selective C-N bond formation employing amino alcohols as the alkylating agent could be demonstrated. Our catalyst tolerates numerous functional groups, among them hydrogenation sensitive examples. We only use a catalytic amount 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 supporting information [SI]). **Cr-If** and **Cr-IIf** were synthesized according to literature procedures by Kirchner and coworkers.[12] The molecular structure of **Cr-Id** (which turned out to be the precatalyst of the

most active catalyst system, *vide infra*) was confirmed by X-ray crystal structure analysis (XRD). The magnetic susceptibility μ_{eff} was determined by SQUID measurements to be 3.9 which is fully consistent with a Cr(III) center.

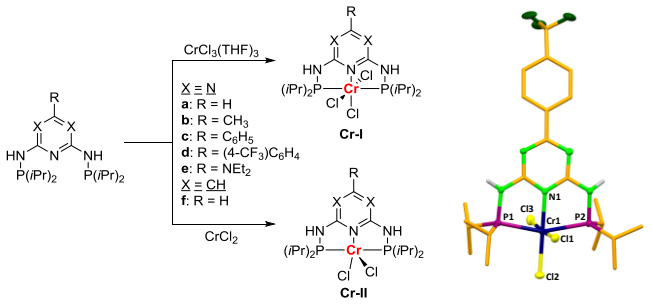
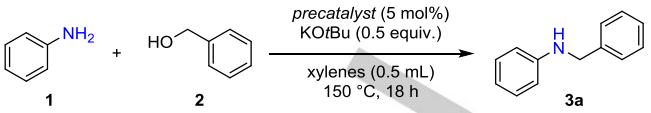


Figure 2. Synthesis of the complexes used in this study and molecular structure of **Cr-Id**. Thermal ellipsoids at 50 % probability, solvent molecules and C-H atoms omitted for clarity. Selected bond lengths [Å] and angles [°]: Cr1-N1 2.086(3), Cr1-P1 2.4492(11), Cr1-P2 2.4520(11), Cr1-Cl1 2.3085(11),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

The reaction of aniline with benzyl alcohol was chosen as a model reaction and the different complexes tested for their activity at a catalyst loading of 5 mol% (Table 1). 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; 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). If the reaction was run with a slight excess of benzyl alcohol (1.2 equivalents) in 1,4-dioxane under ambient pressure, the product **3a** was almost quantitatively obtained using only 3 mol% of **Cr-Id** (see **SI** for screening reactions).

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



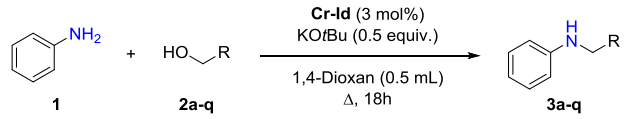
1 2 3a

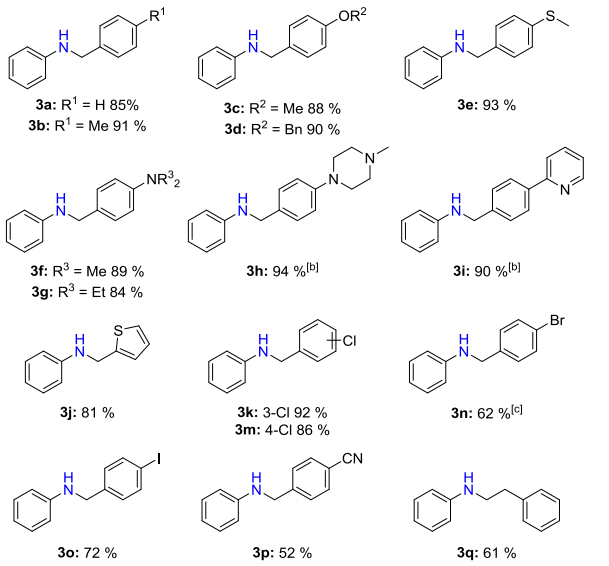
Entry	Precatalyst	Yield[b] [%]
1	**Cr-Ia**	21
2	**Cr-Ib**	24
3	**Cr-Ic**	29
4	**Cr-Id**	52 (97[c])
5	**Cr-Ie**	18
6	**Cr-If**	15
7	**Cr-IIa**	23
8	**Cr-IIb**	35
9	**Cr-IIc**	22
10	**Cr-IId**	58
11	**Cr-IIe**	31
12	**Cr-IIf**	1

[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.

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 to 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**, containing a piperazine moiety could be isolated almost quantitatively (94 %). Heteroaromatic alcohols furnished the pyridine derivative **3i** and thiophene derivative **3j** in 90 and 81 % yield, respectively. Furthermore, halide-substituted benzyl alcohols reacted smoothly giving the products **3k-o** in 62 to 92 % yield. Notably, the strong 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**).

Table 2. Substrate scope regarding primary alcohols[a]

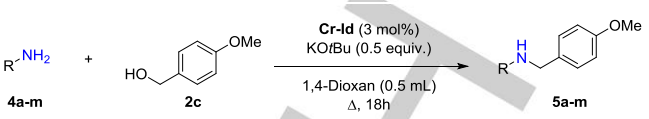


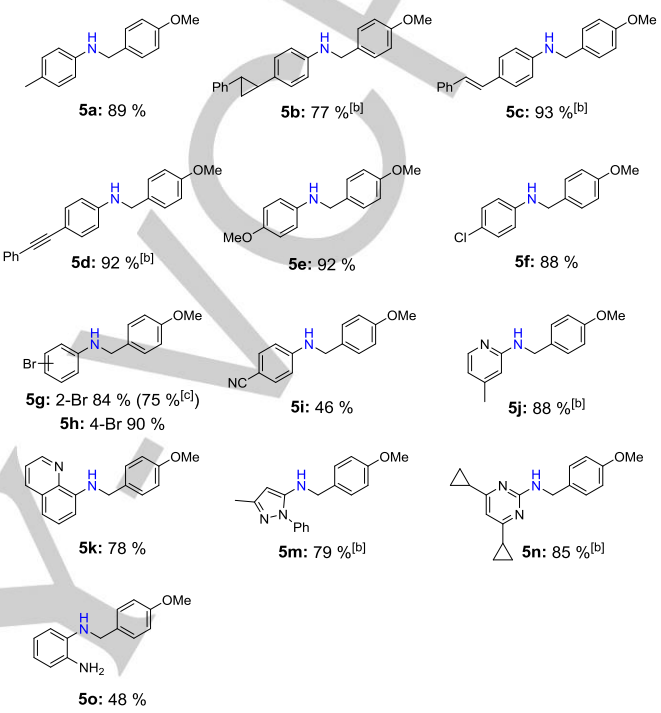


[a] 3 mol% **Cr-Id** (30 µmol), 0.5 equiv. KO*t*Bu (0.5 mmol, 56 mg), 0.5 mL 1,4-dioxane, 1.2 equiv alcohol (1.2 mmol) and 1 equiv aniline (1 mmol, 91 µL), 150 °C oil bath, 18 h, bubble counter with backflow protection. Yields refer to isolated product; [b]: new compound; [c]: 5 mmol scale.

Next, the substrate scope regarding 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, and triple bonds did not undergo undesired reactions, therefore furnishing **5b-d** in very agreeable yields of 77 to 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 to 92 %. The synthesis of **5g** could be easily scaled up to 10 mmol scale, furnishing 2.20 grams (75 %) of product. Product **5i**, containing the strongly electron withdrawing nitrile group could be isolated in 46 % yield. Lastly, 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. Lastly, 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.

Table 3. Substrate scope regarding the amine[a].

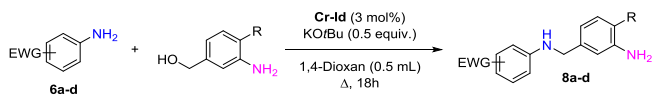


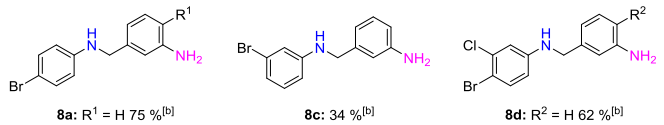


[a] 3 mol% **Cr-Id** (30 µmol), 0.5 equiv. KO*t*Bu (0.5 mmol, 56 mg), 0.5 mL 1,4-dioxane, 1.2 equiv 4-methoxybenzyl alcohol (1.2 mmol, 149 µL) and 1 equiv amine (1 mmol), 150 °C oil bath, 18 h, bubble counter with backflow protection. Yields refer to isolated product; [b]: new compound; [c]: 10 mmol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

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

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. The mercury drop test shows no influence of mercury on the yield of the model reaction (65 % without mercury, 69 % at 225 mol% Hg-loading) 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 by addition of KO*t*Bu to the complex 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 were consumed in a closed flask and 27 % were consumed when the same reaction was run using a bubble counter with backflow protection for pressure equalization. Afterwards, the ability of the catalyst to hydrogenate the intermediate imine was probed. 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. It could be observed that electron donating groups 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 could likely be the hydride transfer to the imine, since electron withdrawing groups at the aniline can cushion the build-up of negative charge during hydride transfer.

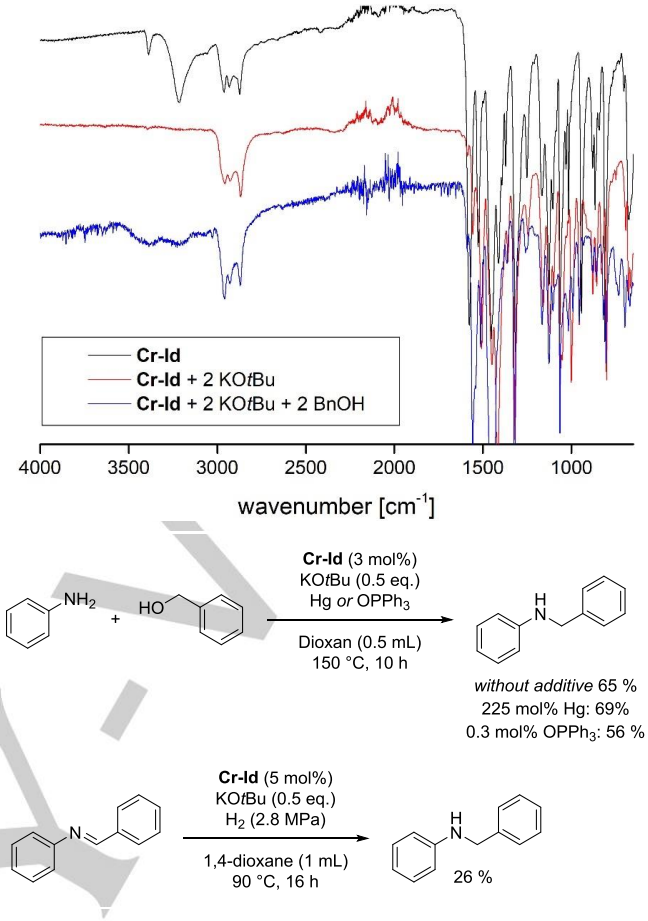


Figure 3. Top: IR spectroscopy of **Cr-Id** after activation with 2 equivalents of KO*t*Bu and reaction with benzyl alcohol (normalized); Bottom: Poisoning and hydrogenation experiments.

In summary we established evidence 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 described in literature so far) have been synthesized and isolated in yields up to 94 %. The catalyst system tolerates functional groups such as Aryl-I, CN and other hydrogenation sensitive groups like benzyl ether, alkene and alkyne and converts unprotected amino benzyl alcohols efficiently. The active catalyst is likely to be of homogeneous nature as indicated by poisoning experiments. The Hammett study indicates that the rate determining step is most likely the hydride transfer to the imine. Furthermore, a borrowing hydrogen or hydrogen autotransfer mechanism is very likely.

Acknowledgements

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Keywords: alcohols • amine alkylation • borrowing hydrogen chromium • hydrogen autotransfer

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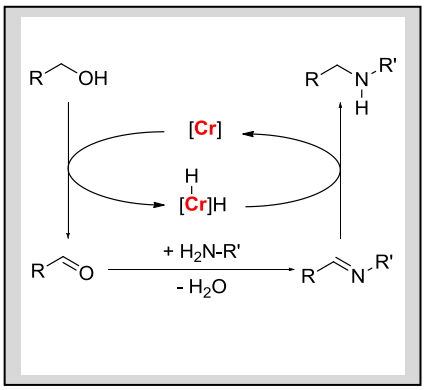

Easily accessible Cr complex catalyse the alkylation of amines by alcohols, a sustainable or green C-N formation reaction following the borrowing hydrogen or hydrogen autotransfer concept. The work indicates that Cr complexes can mediate (de)hydrogenation catalysis.

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