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 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 and it permits the selective alkylation of amines. The reaction was discovered by Winans and Adkins in 1932, and the groups of Grigg and Watanabe 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 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), our group (Co), and Beller and co-workers (Mn). Interestingly, these and related complexes have also been used to catalyze a variety of (de)hydrogenation reactions.

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 of base.

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

Five CrIII precatalysts Cr-Ia–e and the corresponding CrII precatalysts (Cr-IIa–e) were synthesized first (Figure 2, for the full synthetic procedure please see the Supporting Information). Cr-II and Cr-III were synthesized according to procedures reported by Kirchner and co-workers. The molecular structure of Cr-IId (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 $\mu_{eff}$ was determined by SQUID measurements to be 3.9, which is fully consistent with a CrIII 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).

**Table 1:** Catalyst system screening for the N-alkylation of aniline.

| Entry | Precatalyst | Yield [%] |
|-------|-------------|-----------|
| 1     | Cr-Ia       | 21        |
| 2     | Cr-Ib       | 24        |
| 3     | Cr-Ic       | 29        |
| 4     | Cr-IId      | 52 (90%)  |
| 5     | Cr-Ie       | 18        |
| 6     | Cr-Iff      | 15        |
| 7     | Cr-IIa      | 23        |
| 8     | Cr-IIb      | 35        |
| 9     | Cr-IIc      | 22        |
| 10    | Cr-IIId     | 58        |
| 11    | Cr-IIe      | 31        |
| 12    | Cr-IIff     | 1         |

[a] Reaction conditions: 5 mol% precatalyst (50 μmol), 0.5 equiv KOtBu (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-IId (30 μmol), 0.5 equiv KOtBu (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.

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-IId and Cr-IIId 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 CrIII than CrII complexes (Table 1, entries 6 and 12). Despite giving the best yield so far (Table 1, entry 10), the result for Cr-IIId could not be further increased, which is in contrast to the CrIII analogue Cr-IId (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-IId (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 (3e), 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.

| R          | Yield [%] |
|------------|-----------|
| R=Me       | 85%       |
| R=MMe      | 91%       |
| R=MeO      | 88%       |
| R=MMeO     | 90%       |
| R=Et       | 84%       |
| R=EtO      | 90%       |
| R=Me      | 89%       |
| R=Et      | 84%       |
| R=Me-CN   | 92%       |
| R=Et-CN   | 86%       |
| R=Me-Br   | 82%       |
| R=Et-Br   | 87%       |
| R=Me-CN   | 81%       |
| R=Et-CN   | 81%       |
| R=Me-CN   | 72%       |
| R=Et-CN   | 52%       |
| R=Me-CN   | 91%       |

[a] 3 mol% Cr-IId (30 μmol), 0.5 equiv KOtBu (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.
Table 3: Substrate scope with respect to the amine.\textsuperscript{[a]}

| Substrate | Reaction Conditions | Yield (%)
|-----------|--------------------|----------
| 4a-m      | 1,4-dioxane, 0.5 mL, 18 h | 89%
| 5a        | 1,4-dioxane, 0.5 mL, 18 h | 77%
| 5b        | 1,4-dioxane, 0.5 mL, 18 h | 90%
| 5c        | 1,4-dioxane, 0.5 mL, 18 h | 92%
| 5d        | 1,4-dioxane, 0.5 mL, 18 h | 62%
| 5e        | 1,4-dioxane, 0.5 mL, 18 h | 92%
| 5f        | 1,4-dioxane, 0.5 mL, 18 h | 88%
| 5g        | 1,4-dioxane, 0.5 mL, 18 h | 64%
| 5h        | 1,4-dioxane, 0.5 mL, 18 h | 46%
| 5i        | 1,4-dioxane, 0.5 mL, 18 h | 88%
| 5j        | 1,4-dioxane, 0.5 mL, 18 h | 79%
| 5k        | 1,4-dioxane, 0.5 mL, 18 h | 70%
| 5l        | 1,4-dioxane, 0.5 mL, 18 h | 58%
| 5m        | 1,4-dioxane, 0.5 mL, 18 h | 79%
| 5n        | 1,4-dioxane, 0.5 mL, 18 h | 85%
| 5o        | 1,4-dioxane, 0.5 mL, 18 h | 48%

[a] 3 mol% Cr-Id (30 µmol), 0.5 equiv KOtBu (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.

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\textsubscript{3} (0.3 mol% OPPh\textsubscript{3}; 56% of 3a). The activation of Cr-Id was then examined upon addition of KOtBu to the complex by using IR spectroscopy. The complex exhibits a broad NH resonance at 3214 cm\textsuperscript{-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.\textsuperscript{[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
of the catalyst to hydrogenate the intermediate imine was probed. When employing 5 mol% Cr-Id and 50 mol% KOtBu, 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 benzyl ether, alkene, and alkyne groups, and hydrogenation-sensitive groups like aryl iodide, CN, and other hydrogenation-sensitive groups at the anilines like Me and OMe lead to a decreased reaction rate. On the other hand, increased reaction rates are 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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