Synthetic Methods

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Chemoselective Catalytic Conjugate Addition of Alcohols over Amines**

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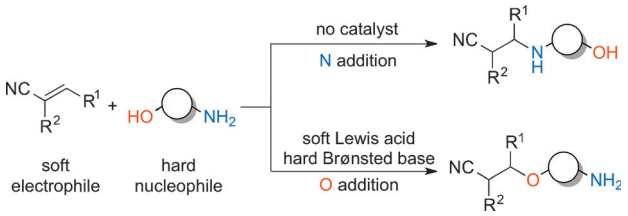
Abstract: *A highly chemoselective conjugate addition of alcohols in the presence of amines is described. The cooperative nature of the catalyst enabled chemoselective activation of alcohols over amines, allowing the conjugate addition to soft Lewis basic α,β-unsaturated nitriles. Divergent transformation of the nitrile functionality highlights the utility of the present catalysis.*

Catalyst-controlled chemoselective reactions offer new opportunities for minimal reliance on protecting groups,[1] even in the presence of innately more reactive functionalities.[2] Despite the prospects for contributions to both atom and step economy[3] of catalyst-controlled chemoselective reactions, progress in this area, especially the reversal of the innate reactivity of amines and alcohols, has been limited relative to catalyst-controlled stereo- or regioselective reactions. Some examples of catalyst-controlled chemoselective reactions of hydroxy groups in the presence of an amino group were recently reported,[4,5] including our O-selective acylation.[4e,j] The reaction patterns were, however, highly limited and remain unexplored. Moreover, the reported reactions include the inevitable formation of stoichiometric amounts of unneeded co-products, such as inorganic salts and alcohols, thus reducing the reaction efficiency. Herein, we report the first example of a catalyst-controlled chemoselective conjugate addition of a hydroxy group in the presence of an amino group. Conjugate addition of the hydroxy group was performed under proton-transfer conditions and is applicable to natural product synthesis.[6]

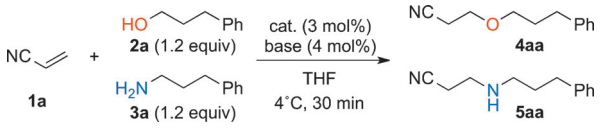
We envisioned that soft Lewis acidic transition metals would activate soft Lewis basic electrophiles, even in the presence of hard hydroxy and amino groups. While a simple Lewis acid catalyst would activate electrophiles to facilitate subsequent coupling of innately more nucleophilic amines,[7] a cooperative catalyst comprising soft Lewis acids and hard Brønsted bases would enable the simultaneous activation of both soft Lewis basic electrophiles and hard hydroxy groups through selective deprotonation of the hydroxy group over the amino group as a result of the difference in acidity, allowing chemoselective coupling (Scheme 1).[8] Thus, we selected commercially available acrylonitrile (**1a**) as a representative soft electrophile.[9] Divergent transformation of a nitrile, which is a masked carboxylic acid functionality, is beneficial for further elaboration of the product.[10]

The initial study examined the use of a 1:1 mixture of alcohol **2a** and amine **3a** (Table 1).[11] Without the catalyst, the N adduct **5aa** was obtained exclusively in 17% yield at room temperature in 3 h (Table 1, entry 1). The use of 4 mol% of strong base (*n*BuLi or LiHMDS) to generate the more nucleophilic metal alkoxide afforded O adduct **4aa**,



Scheme 1. Strategy for reversing innate reactivity.

Table 1: Optimization of reaction conditions.[a]



Entry	Cat.	Base	Ratio O/N[b]	Yield of **4aa** [%][b]
1[c]	–	–	<1/99	(17)
2	–	*n*BuLi	1.6/1	6
3	–	LiHMDS	1.5/1	9
4	CuOAc, dppe	*n*BuLi	>20/1	83
5	Cu(MeSal), dppe	*n*BuLi	>20/1	84
6	Cu(MeSal), dppe	LiHMDS	>20/1	88
7	Cu(MeSal), dppe	–	0.6/1	3
8	mesitylcopper, dppe	–	>20/1	83[d]

[a] Conditions: **1a** (1.2 mmol), **2a** (1.44 mmol), **3a** (1.44 mmol), THF (1.2 mL). [b] Determined by GC analysis using nonadecane as an internal standard. Yield of **5aa** is shown in parenthesis. [c] At room temperature for 3 h. [d] Determined by ^{1}H NMR analysis using durene as an internal standard. dppe = 1,2-bis(diphenylphosphino)ethane, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, MeSal = 3-methylsalicylate.

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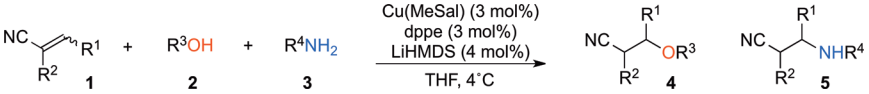
albeit in low yield and low selectivity (Table 1, entries 2 and 3).[12] We next examined the combined use of a transition metal and Brønsted base. Screening of various metals showed that poorly soluble copper(I) acetate afforded **4aa** in 83% yield (Table 1, entry 4).[13,14] Commercially available copper(I) 3-methylsalicylate, which showed higher solubility, delivered **4aa** in high yield with high chemoselectivity (Table 1, entry 5). The less basic LiHMDS also promoted the conjugate addition of alcohol with the same efficiency (Table 1, entry 6). Omission of a Brønsted base gave poor results, suggesting that the combined use of copper(I) complex with Brønsted base was essential for obtaining both high yield and high chemoselectivity (Table 1, entry 7). Using mesitylcopper with a dppe ligand resulted in efficient catalytic performance, indicating that copper(I) alkoxide is the actual catalytic species (Table 1, entry 8).[15,16]

With the optimized conditions in hand, we explored the substrate scope of the catalytic chemoselective conjugate addition of alcohols (Table 2). Reactions of mixtures of structurally similar amines **3a–3d** and alcohols **2a–2d**, respectively ($R^3 = R^4$), gave O adducts **4aa–4ad** in high yield. Furthermore, the N-Boc-protected substrate **2e** afforded product **4ae** in high yield. Products **4bb** and **4db** were obtained in acceptable yields, when crotononitrile and methacrylonitrile were employed. The pharmaceutically active compounds **2f** and **2g**, cholesterol (**2h**), and cinchonidine (**2i**) were successfully converted into conjugate adducts **4af–4ai**.

Table 2: Chemoselective conjugate addition of alcohols (**2**) over amines (**3**).[a]

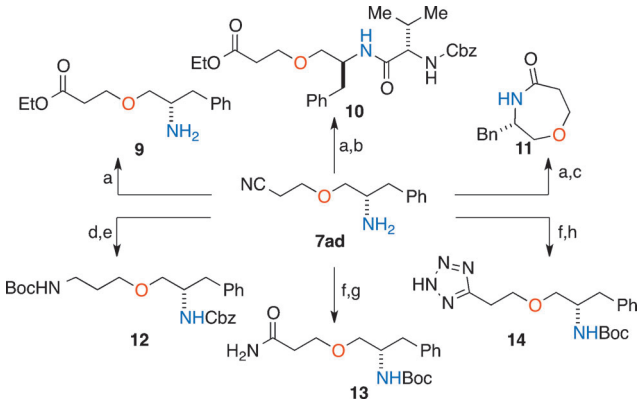


Entry	1	2	3	4 (yield [%])
1	**1a**	**2a**	**3a**	**4aa** (86)
2	**1a**	**2b**	**3b**	**4ab** (87)
3	**1a**	**2c**	**3c**	**4ac** (86)
4	**1a**	**2d**	**3d**	**4ad** (76)
5	**1a**	**2c**	**3e**	**4ac** (88)
6[b]	**1a**	**2e**	**3b**	**4ae** (83)
7[b,c,d]	**1b**	**2b**	**3b**	**4bb** (63)
8[b,d,e]	**1c**	**2b**	**3b**	**4cb** (78)
9[b,d,e]	**1d**	**2b**	**3b**	**4db** (61)
10[b,f]	**1a**	**2f**	**3b**	**4af** (80)
11[b,f]	**1a**	**2g**	**3b**	**4ag** (84)
12[b]	**1a**	**2h**	**3b**	**4ah** (54)
13[b,c,f]	**1a**	**2i**	**3b**	**4ai** (79)

[a] Conditions: **1** (1.0 equiv), **2** (1.2 equiv), **3** (1.2 equiv), THF (1.0 M). Yields of isolated products are given. In all cases, the O/N ratio (measured by ^{1}H NMR analysis of the crude reaction mixture) was >20/1. [b] *n*BuLi was used instead of LiHMDS. [c] 2 equivalents of **1** were used. [d] Reaction was performed at room temperature. [e] 5 equivalents of **1** were used. [f] DMF was used as solvent.[10] "O" = O adduct, "N" = N adduct.

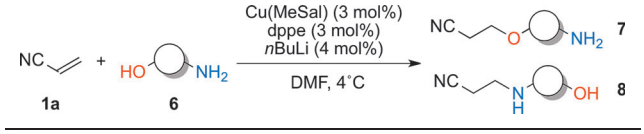
We next performed the reaction using amino alcohols **6** (Table 3). A survey showed that DMF was an optimal solvent for amino alcohols, and O adducts **7** were obtained with high selectivity. The length of the alkyl chain did not affect the chemoselectivity (**7aa**, **7ab**). In preceding chemoselective catalytic reactions, β-amino alcohols could not be used as substrates.[4] In contrast, exclusive O-selective addition of L-phenylalaninol (**6d**) was observed with 0.5 mol% catalyst. An aniline NH group did not affect either the yield or chemoselectivity (**7af**, **7ag**).[17] In the presence of a primary amine in α position, secondary alcohols selectively reacted with **1a** to afford the O adduct (**7ah**). The process could be applied to amino alcohols with a primary alcohol and a highly nucleophilic secondary amine, although the chemoselectivity decreased slightly (**7ai**). The pharmaceutically active compounds **6j** and **6k**) proved to be good substrates. High chemoselectivities were observed using compounds **6l** and **6m**, but the yields were low as a result of poor solubility. Chemoselective conjugate addition was also possible with substrates containing amide functionalities with acidic NH protons without loss of the stereoinformation at the α position of the amide, based on ^{1}H NMR analysis (**7ao**, **7ap**). The tolerance of esters was demonstrated in a highly chemoselective conversion of H-Ser-Phe-O*t*Bu (**7aq**).

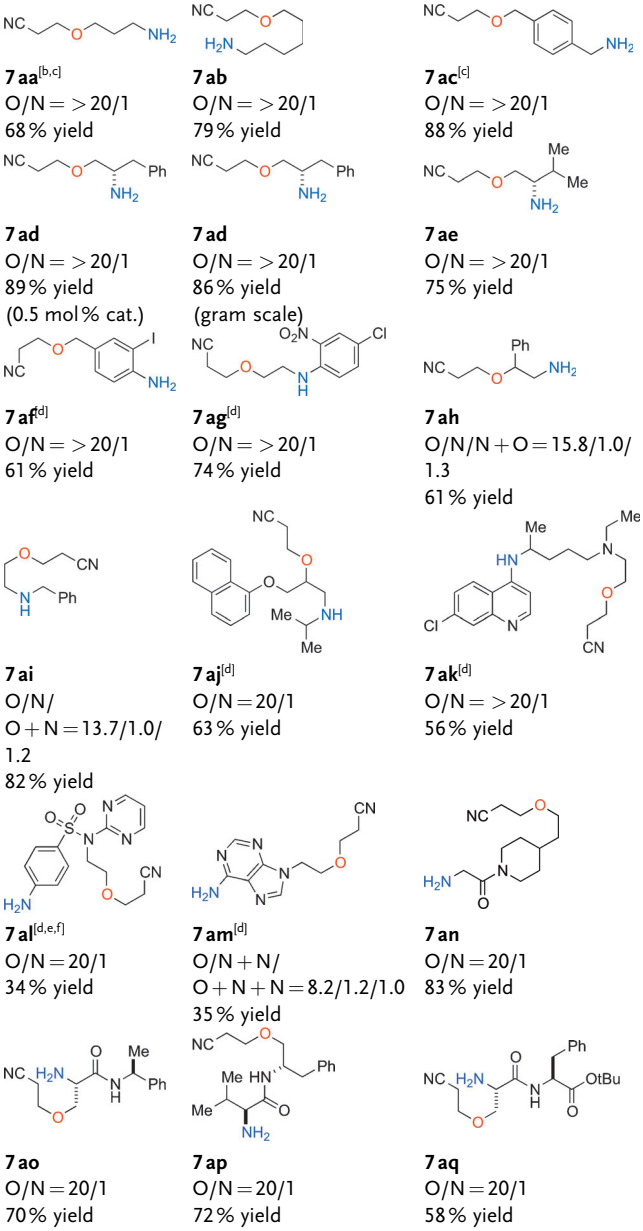
The usefulness of the present chemoselective catalysis was demonstrated by further elaboration of the nitrile functionality (Scheme 2). Product **7ad**, derived from a chiral amino alcohol, was transformed into ethyl ester **9** under Pinner reaction conditions. This ester was converted into amide **10** by coupling with Z-Val-OH with no stereochemical erosion, based on ^{1}H NMR analysis, and seven-membered lactam **11** through intramolecular amidation. The nitrile functionality of **7ad** could be readily reduced with $NiCl_2/NaBH_4$, providing diamine **12**.[18] The hydration of the nitrile functionality was possible using Wilkinson's catalyst and acetoaldoxime affording primary amide **13**.[19] Employment of sodium azide produced tetrazole **14**.[20]



Scheme 2. Transformation of the product. Reagents and conditions: a) TMSCl, EtOH, 50 °C, 13 h, 72%; b) Z-Val-OH, EDC, HOBt, NMM, DMF, RT, 24 h, 92%, d.r. = >20/1; c) 1. 1 N NaOH, MeOH, RT, 2 h; 2. EDC, HOBt, NMM, DMF, RT, 12 h, 65% over two steps; d) CbzCl, Et_3N, CH_2Cl_2, RT, 1 h, 87%; e) $NiCl_2$ (cat.), $NaBH_4$, MeOH, 0 °C→RT, Boc_2O, 73%; f) Boc_2O, Et_3N, CH_2Cl_2, RT, 0.5 h, 86%; g) $[RhCl(PPh_3)_3]$ (cat.), $CH_3CH{=}NOH$, toluene, reflux, 1.5 h, 97%; h) NaN_3, Et_3NHCl, DMF, 120 °C, 24 h, 86%. Boc = *tert*-butyloxycarbonyl, HOBt = 1-hydroxybenzotriazole, EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, NMM = *N*-methylmorpholine, TMS = trimethylsilyl.

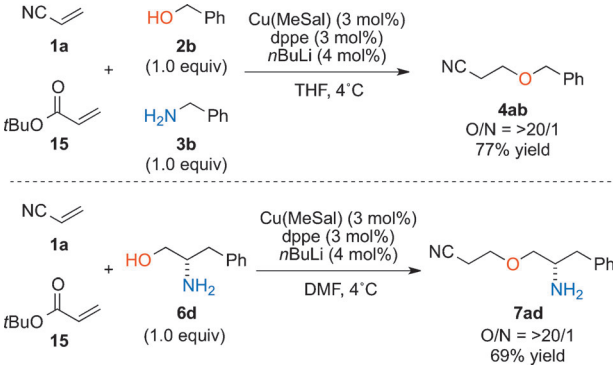
Table 3: Substrate scope of amino alcohols (**6**).[a]





[a] Conditions: **1a** (1.0 equiv), **6** (1.2 equiv), DMF (1.0 M). Yields of isolated products are given. O/N ratios were measured by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated as the N-Boc-protected product. Yield over two steps is given. [c] LiHMDS was used instead of *n*BuLi. [d] Reaction was performed at room temperature. [e] A mixture of DMF/DMSO = 1/1 was used as a solvent. [f] 2 equivalents of **1a** were used. DMF = *N*,*N*-dimethylformamide, "N + N" = N,N-dialkylated product, "O + N" = O,N-dialkylated product, "O + N + N" = O,N,N-trialkylated product.[11]

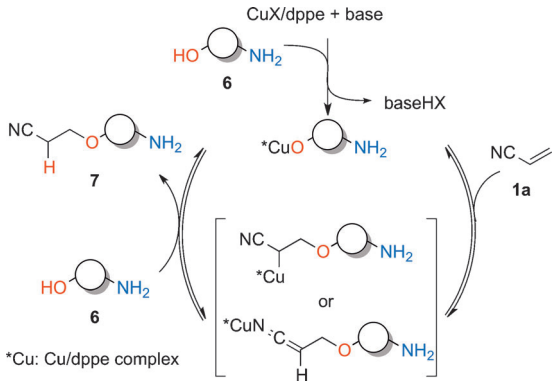
The present catalysis turned out to be highly chemoselective, not only for nucleophiles, but also for electrophiles. In the presence of relatively hard electrophile *tert*-butyl acrylate (**15**) as an additional electrophile, selective conjugate addition of alcohol to soft acrylonitrile was achieved over the three other possible reaction pathways, while a mixture of N adducts derived from both **1a** and **15** were obtained without catalyst (Scheme 3).[11] In a similar way, amino alcohol **6d** selectively reacted with **1a** over **15** to give **7ad**.



Scheme 3. Competitive conjugate addition of amino alcohol to acrylonitrile.

A series of control experiments were conducted to gain preliminary mechanistic insight.[11] Although O adducts **4** underwent retro-reaction, N adducts **5** were almost completely recovered under the present catalysis, suggesting that the N adduct did not undergo retro-reaction and the kinetically favorable O adduct was obtained under optimal conditions. The plausible catalytic cycle is depicted in Scheme 4. The combined use of copper(I) complex with Brønsted base generated the actual catalytic species copper(I) alkoxide (Table 1, entry 8).[11] The nucleophilic addition of copper alkoxide to acrylonitrile (**1a**) then proceeded to afford the C- or N-bound copper intermediate.[21–23] Subsequent protonation occurred with the OH proton to give amino ether **7** with the concomitant generation of copper(I) alkoxide.

In conclusion, we developed a highly chemoselective catalytic conjugate addition of alcohols in the presence of innately more nucleophilic amines. It is particularly noteworthy that a variety of β-amino alcohols, including pharmaceutically active compounds and peptides, are applicable to the present catalysis. Further studies to elucidate the precise reaction mechanism and the application of this unique catalytic chemoselective activation of functionalities with innately low reactivity in other reactions are in progress.



Scheme 4. Plausible catalytic cycle.

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