**Current Topics**

Reversal or Control of the Innate Reactivity of Functional Groups

**Communication to the Editor**

Catalytic Chemoselective Conjugate Addition of Amino Alcohols to α,β-Unsaturated Ester: Hydroxy Group over Amino Group and Conjugate Addition over Transesterification

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A highly chemoselective conjugate addition of amino alcohols to α,β-unsaturated esters using a soft Lewis acid/hard Brønsted base cooperative catalyst was developed. This catalysis achieved chemoselective addition of a hydroxy group over an amino group. Moreover, soft metal alkoxide generation enabled chemoselective soft conjugate addition over hard transesterification. Various amino alcohols, including unprecedented cyclic β-amino alcohol, were applicable to the present catalysis.

Key words chemoselective catalysis; amino alcohol; α,β-unsaturated ester; cooperative catalyst; soft metal alkoxide

Conjugate addition of alcohols to electron-deficient olefins, the oxa-Michael reaction, is a highly atom-economical transformation for the construction of carbon–oxygen bonds under proton transfer conditions.1–3) In particular, conjugate addition of alcohols to α,β-unsaturated carboxylate derivatives is an efficient and straightforward methodology for concise access to synthetically useful β-hydroxy carboxylic acid derivatives. Although the use of α,β-unsaturated ester as an electrophile for catalytic conjugate addition of alcohols is more advantageous for further transformation, examples are highly limited due to difficulties in controlling the chemoselectivity between conjugate addition (1,4-addition) and transesterification (1,2-addition). Conjugate addition reactions of simple alcohols to α,β-unsaturated esters were recently reported,4–6) but transesterification or hydrolysis of esters concomitantly proceeded to afford the corresponding undesired transesterification products or carboxylic acids. Moreover, only simple primary alkyl alcohols were utilized in the previous reports.4–6) To date, catalytic chemoselective conjugate addition of alcohols to α,β-unsaturated esters has remained unexplored.7)

Chemoselective reactions could contribute to the atom- and step-economical synthesis of the molecules while bypassing the tedious protection-deprotection process.8,9) Although chemoselective reactions have been extensively investigated, examples of catalyst-controlled reversal of the innate reactivity are quite limited, as represented by the chemoselective reaction of hydroxy groups over more nucleophilic amino groups.10–13) We recently developed a catalytic chemoselective conjugate addition of amino alcohols to α,β-unsaturated nitriles through simultaneous activation of both soft Lewis basic electrophiles and hard hydroxy groups.14,15) Based on previous studies, we hypothesized that our cooperative catalyst system comprising a soft Lewis acid/hard Brønsted base should chemoselectively generate enhanced nucleophilic soft metal alkoxide due to the difference in acidity, and thereby soft conjugate addition of alkoxide would be preferred over undesired hard transesterification, as exemplified by soft copper catalyzed conjugate addition.16,17) Commercially available bulky tert-butyl acrylate (1a) was selected as an electrophile to suppress the further undesired transesterification reaction. We first focused on the combined use of a soft Lewis acid/hard Brønsted base as shown in Table 1. We selected the polar N,N-dimethylformamide (DMF) as a solvent to dissolve the polar amino alcohols. Exclusive formation of N-adduct 4aa was observed in the absence of the catalyst, indicating that the amino group is innately more nucleophilic than the hydroxy group (entry 1). In sharp contrast, previously optimized conditions of the soft Lewis acid/hard Brønsted base cooperative catalyst chemoselectively delivered O-adduct 3aa as a major product, without formation of the undesired transesterification product (entry 2). Copper(I) acetate provided O-adduct 3aa in superior yield (entry 3). Screening of various metal acetates revealed that silver(I) acetate afforded slightly better selectivity than copper salts (entry 4). Chemoselectivity was further improved by performing the reaction at −20°C to suppress the formation of undesired N-adduct 4aa (entry 5).

A control experiment, we examined hard Brønsted base catalysts. Lithium bis(trimethylsilyl)amide (LiHMDS) as a catalyst did not promote conjugate addition of the hydroxy group (entry 6). As expected, catalytic amounts of NaHMDS and KHMDS provided undesired transesterification product 5aa, although O-adduct 3aa was observed chemoselectively (entries 7, 8).18) Other hard Brønsted base catalysts, such as alkaline earth metals and rare earth metal alkoxides, did not afford the O-adduct 3aa (data not shown). We also investigated the reaction

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with methyl acrylate as an electrophile, but only a complex mixture was afforded, even under optimized conditions.

Having determined the optimal conditions for chemoselective catalytic conjugate addition to \( \alpha,\beta \)-unsaturated ester (Table 1, entry 5), we next investigated the scope of applicable amino alcohols (Table 2). The alkyl chain length of the amino alcohols did not affect the yield or chemoselectivity (2a–d).

Benzyl type amino alcohol (2e) was determined to be good substrate. \( \beta \)-Amino alcohols derived from chiral \( \alpha \)-amino acids were also applicable to the present chemoselective catalysis (2f, g). It is noteworthy that previously inapplicable cyclic \( \beta \)-amino alcohol (2h) gave the corresponding O-adduct in 65% yield after a prolonged reaction time. 14) O-Selective conjugate addition also proceeded, even in the presence of an enhanced nucleophilic secondary amino group, although the chemoselectivity was decreased (2i).

We next directed our attention to the use of less electrophilic acrylamide (Chart 2). \( \alpha,\beta \)-Unsaturated Weinreb amide (1b) was successfully converted into the corresponding O-adducts 3bf and 3bg in high yield with high chemoselectivity.

The wide functional group compatibility of the present chemoselective conjugate addition was demonstrated using functionalized amino alcohols (Chart 3). High chemoselectivity was observed using amino alcohol 2j containing amide functionalities with acidic NH protons and corresponding product 3aj was isolated in high yield. The pharmaceutical agent hydroxychloroquine (2k), which has highly coordinative quinoline and aryl amine functionalities, was chemoselectively transformed into O-adduct 3ak in 33% yield.

In summary, we developed a highly chemoselective con-
jugate addition of amino alcohols to $\alpha,\beta$-unsaturated ester, achieving chemoselective addition of a hydroxy group over an amino group and chemoselective conjugate addition over transesterification, using a soft Lewis acid/hard Brønsted base cooperative catalyst. Soft metal alkoxide generation enabled chemoselective soft conjugate addition over hard transesterification. Various amino alcohols, including unprecedented cyclic $\beta$-amino alcohol, were applicable to the present catalysis. Further studies to expand the substrate generality and extend the application to the synthesis of biologically active molecules are underway.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

References and Notes
1) Nising C. F., Bräse S., Chem. Soc. Rev., 37, 1218–1228 (2008).
2) Hintermann L., Top. Organomet. Chem., 3, 123–155 (2010).
3) Nising C. F., Bräse S., Chem. Soc. Rev., 41, 988–999 (2012).
4) Kisanga P. B., Ilankumaran P., Fetterly B. M., Verkade J. G., J. Org. Chem., 67, 3555–3560 (2002).
5) Munro-Leight C. D., Delp S. A., Blue E. D., Gunnoc T. B., Organometalics, 26, 1483–1493 (2007).
6) Copper catalyzed conjugate addition of alcohols using stoichiometric amount of base, see: Wang F., Yang H., Fu H., Pei Z., Chem. Commun., 49, 517–519 (2013).
7) Recent example of catalytic enantioselective intramolecular conjugate addition of hydroxylamines or phenols to $\alpha,\beta$-unsaturated ester derivatives, see: Kobayashi Y., Taniguchi Y., Hayama N., Inokuma T., Takemoto Y., Angew. Chem. Int. Ed., 52, 11114–11118 (2013).
8) For a review on atom- and step-economy, see: Trost B. M., Science, 254, 1471–1477 (1991).
9) For a review on atom- and step-economy, see: Wender P. A., Verma V. A., Paxton T. J., Pillow T. H., Acc. Chem. Res., 41, 40–49 (2008).
10) For a review on chemoselective reaction, see: Trost B. M., Science, 219, 245–250 (1983).
11) For a review on chemoselective reaction, see: Shenvi R. A., O’Malley D. P., Baran P. S., Acc. Chem. Res., 42, 550–541 (2009).
12) For a review on chemoselective reaction, see: Afagh N. A., Yudin A. K., Angew. Chem. Int. Ed., 49, 262–310 (2010).
13) For a review on chemoselective reaction, see: Mahaththananchai J., Dumas A. M., Bode J. W., Angew. Chem. Int. Ed., 51, 10954–10990 (2012).
14) Uesugi S., Li Z., Yazaki R., Ohshima T., Angew. Chem. Int. Ed., 53, 1611–1615 (2014).
15) Li Z., Yazaki R., Ohshima, T., Org. Lett., 18, 3350–3353 (2016).
16) Shibasaki M., Yoshikawa N., Chem. Rev., 102, 2187–2210 (2002).
17) For a review on Lewis acid/Bronsted base cooperative catalysis, see: Kumagai N., Shibasaki M., Angew. Chem. Int. Ed., 50, 4760–4772 (2011).
18) NaHMDS or KHMDS catalysis under lower temperature decreased the chemical yield of 3aa and undesired product 5aa was also detected based on $^1$H-NMR analysis of the crude reaction mixture.
19) Nahm S., Weinreb S. M., Tetrahedron Lett., 22, 3815–3818 (1981).
20) Balasubramaniam S., Aidhen I. S., Synthesis, 23, 3707–3738 (2008).