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Catalytic Asymmetric Iterative/Domino Aldehyde Cross-Aldol Reactions for the Rapid and Flexible Synthesis of 1,3-Polyols

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Supporting Information

ABSTRACT: We report here catalytic asymmetric iterative and domino cross-aldol reactions between aldehydes, endowed with a high level of robustness, flexibility, and generality. A Cu(I)-DTBM-SEGPHOS complex catalyzes an asymmetric cross-aldol reaction between acceptor aldehydes and boron enolates derived from donor aldehydes, which are generated through Ir-catalyzed isomerization of allyloxyboronates. The unit process can be repeated using the aldol products in turn as acceptor substrates for the subsequent asymmetric aldol reaction. The donor aldehydes and stereoselectivity can be flexibly switched in a stepwise manner for the double-aldol reaction. Furthermore, asymmetric triple- and quadruple-aldol reactions are possible in one-pot using the appropriate amounts of donors and amine additives, rapidly elongating the carbon skeleton with controlling up to eight stereocenters. The method should be useful for straightforward synthesis of enantiomerically and diastereomerically enriched 1,3-polyols.

1,3-Polyols are ubiquitous and privileged structural motifs in polyketide natural products and drugs.[1] Polyketides are estimated to be five times more likely to possess drug activity than other natural product families,[2a] and polyketide-derived pharmaceuticals comprise 20% of the top-selling small molecule drugs.[2b] For the synthesis of the 1,3-polyol motifs,[3] a catalytic asymmetric aldol reaction would be a powerful unit process. Despite marked progress, however, the development of catalytic asymmetric aldol reactions has focused mainly on the use of ketones and carboxylic acid derivatives as donors.[4] Thus, the installation of a second 1,3-diol unit through iterative use of aldol reactions requires nonproductive steps; i.e., protection of the β-hydroxy group, followed by reduction and/or oxidation of the terminal carbonyl group to the corresponding aldehyde. An ideal unit reaction for 1,3-polyol synthesis is the catalytic asymmetric cross-aldol reaction between two different aldehydes,[5] directly providing an aldehyde moiety for subsequent iterative aldol reactions (Figure 1A, upper row). Here we disclose catalytic asymmetric iterative/domino aldehyde cross-aldol reactions for the straightforward synthesis of enantiomerically and diastereomerically enriched 1,3-polyols.

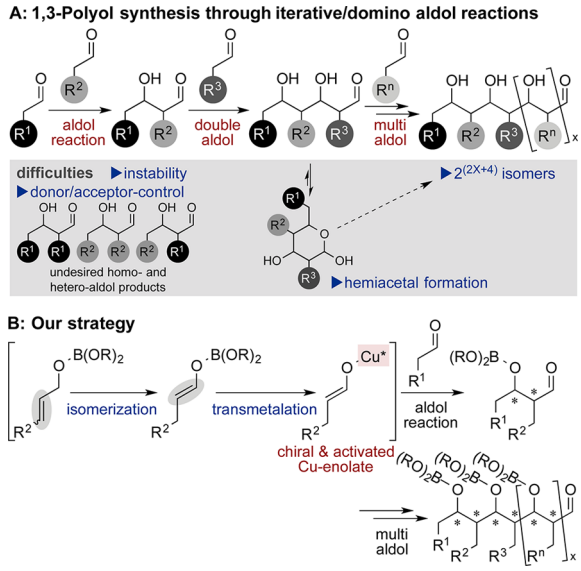

Figure 1. (A) Ideal approach to 1,3-polyols through iterative/domino aldehyde cross-aldol reactions (upper row) and its potential difficulties (bottom row). (B) Our strategy for the catalytic asymmetric iterative/domino aldehyde cross-aldol reactions.

Although the idea of iterative asymmetric aldehyde cross-aldol reactions is conceptually simple, it is extremely challenging for the following reasons (Figure 1A, bottom row). First, two aldehydes must be differentiated as either a donor or an acceptor. Otherwise, undesired homo- and hetero-aldol products will be randomly produced. A few organocatalyzed asymmetric cross-aldol reactions of aldehydes[6] were reported previously; however, the donor/acceptor-control was based on the inherent steric and/or electronic characteristics of the substrates. Thus, Mukaiyama-type aldol reactions[7] using preactivated donor aldehyde enolates are a reliable way.[8] Second, the intermediate β-hydroxy aldehydes are generally unstable. Acidic, basic, and high temperature conditions can cause undesired side reactions, such as a retro-aldol reaction, dehydration, hemiacetal formation, and polymerization. Third, the number of possible stereoisomers increases exponentially as the iteration proceeds. High fidelity in

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both enantio- and diastereoselectivity for a unit aldol reaction is essential to avoid the formation of multiple stereoisomers. Finally, the products of more than double-aldol reactions exist as cyclized hemiacetal forms lacking a reactive aldehyde functional group. To prevent the formation of the unreactive hemiacetals, hydroxy groups of the intermediates need to be protected in more than double-aldol reactions. Precedent examples for iterative aldehyde cross-aldol reactions are limited to the proline-catalyzed asymmetric aldol reaction, followed by a diastereoselective Mukaiyama aldol reaction,[9a,b] the proline-catalyzed asymmetric double-aldol reaction with switching of the catalyst chirality to avoid microscopic reversibility,[9c] the engineered enzyme-catalyzed asymmetric double-aldol reaction,[9d] a catalytic diastereoselective (racemic) one-pot triple-aldol reaction,[5,10a−d] and an enzyme-catalyzed asymmetric triple-aldol reaction.[10e] There is much room left for improvement in these pioneering examples especially with regard to the substrate generality and practicality.

We envisioned that a copper(I) alkoxide-catalyzed asymmetric aldol reaction between aldehydes and aldehyde-derived boron enolates would fulfill the requirements discussed above (Figure 1B). Carreira's group[11] and our group[12] independently reported that the reactivity of silicon enolates is markedly enhanced by copper(I) catalysis through the formation of copper enolates from silicon enolates and that catalytic asymmetric aldol reactions are possible under mild conditions by introducing chiral ligands to copper catalysts. Based on the similar characteristics of silicon and boron atoms, we hypothesized that a catalytic asymmetric aldol reaction between aldehydes and aldehyde-derived boron enolates is possible by copper(I) catalysis through the generation of highly reactive aldehyde-derived chiral copper(I) enolates. After the aldol reaction, copper aldolate intermediates are trapped by the boron atom, generating *O*-protected aldol products and thus preventing the formation of unreactive hemiacetal in more than double-aldol reactions. Aldehyde-derived boron enolates[13] should be generated without formation of any wastes through transition metal-catalyzed C═C double bond isomerization of allyloxyboronates, based on our previous findings.[14]

We began our study by optimizing the single-aldol reaction between 3-phenylpropanal (**1a**) and boron enolate **3a** (R^2, R^3 = H), which was generated from **2a** in a different vessel prior to the aldol reaction. Both the isomerization conditions from **2a** to **3a** and copper sources as well as chiral ligands significantly affected the result of the aldol reaction.[15] We identified the optimized conditions as isomerization of **2a** to **3a** using 0.5 mol % $[Ir(cod)(PPh_2Me)_2]PF_6$ complex preactivated under H_2 atmosphere as a catalyst[16] in acetone at 0 °C, followed by an asymmetric aldol reaction with **1a** using 5 mol % mesitylcopper (MesCu)-(*R*)-DTBM-SEGPHOS catalyst in the presence of 1 equiv of isopropanol in THF at −60 °C, which afforded product **4a**′ after reduction in 80% yield, 97:3 dr, and 95% ee.

Under the optimized conditions, a variety of aliphatic, aryl, and heteroaryl aldehydes all afforded the cross-aldol products in moderate to excellent yields with high diastereo- and enantioselectivity (Figure 2A). The cross-aldol products were obtained from the combination of sterically less-hindered propanal as an acceptor and sterically more demanding aldehydes as donors (**4e** and **4f**). The enamine catalysis[17] did not produce aldol products from this donor/acceptor combination. As donors, not only methyl, but also ethyl, butyl, and dimethyl groups could be introduced at the α-position of the product (**4b**−**4f**, **4m**).

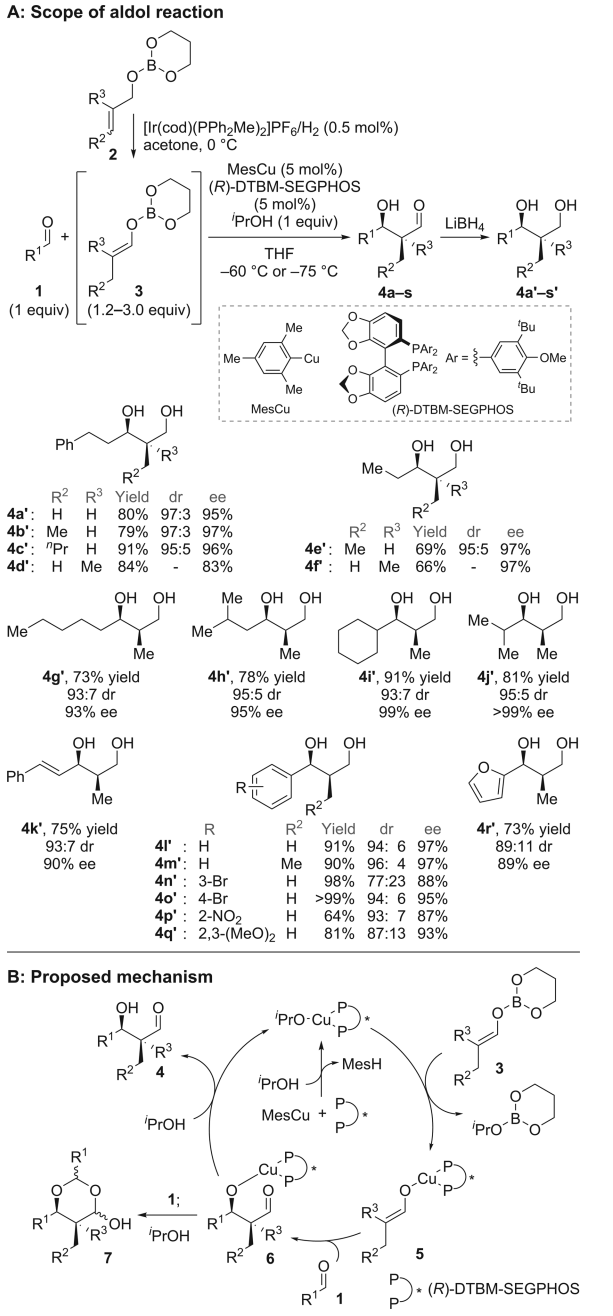

Figure 2. (A) Scope of the catalytic asymmetric cross-aldol reaction between aldehydes. Yield and selectivity were determined after reduction due to the instability of β-hydroxy aldehydes under analytical conditions. See the SI for detailed reaction conditions. (B) Plausible catalytic cycle.

A plausible catalytic cycle is depicted in Figure 2B. By mixing MesCu, (*R*)-DTBM-SEGPHOS, and isopropanol, chiral CuO^{i}Pr was generated with the extrusion of mesitylene. Transmetalation between the copper alkoxide and **3** afforded chiral copper enolate **5**, which reacted with **1** to form copper aldolate **6**. Facile protonation of **6** with isopropanol was key to promoting the catalytic cycle because the copper aldolate could otherwise irreversibly consume aldehyde **1** via nucleophilic attack to produce undesired cyclic hemiacetal **7**.

We then turned our attention to the double-aldol reaction. Although the copper catalysis realized the single-aldol reaction, the reactivity was not sufficient for the double-aldol reaction. To

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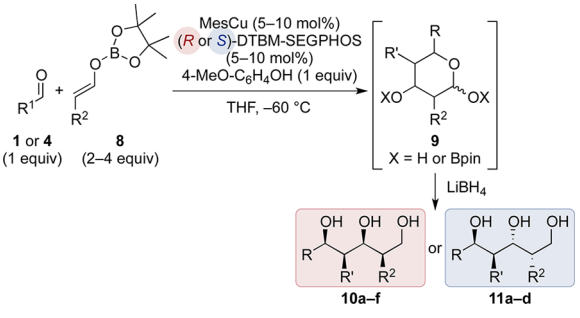
increase the reactivity, the diol moiety of boron enolates was changed to pinacol, anticipating that the increased electron density would facilitate the transmetalation step.[15] The double-aldol reaction smoothly proceeded in one-pot from aldehyde **1** and boron enolate **8** in the presence of 1 equiv of 4-methoxyphenol, instead of isopropanol,[15] to produce the corresponding cyclized hemiacetals **9** in the reaction mixture. After reduction with $LiBH_4$, the desired triol **10** was obtained in good yield and stereoselectivity (Table 1, entries 1−4). Stepwise introduction of different donors at the first and second steps was also possible using monoaldol products **4a** and **4b**, which were synthesized by the method in Figure 2, as acceptor aldehydes (Table 1, entries 5 and 6). Furthermore, switching the chirality of the catalyst in the first and second aldol reactions provided stereodivergent access to triols (Table 1, entries 7−10). Both the enantioselectivity and diastereoselectivity were predominantly controlled by the catalyst, not by the substrates. Two distinct enolates were introduced in a stepwise manner with switching the stereoselectivity as well (Table 1, entries 9 and 10).

We extended this approach to more than double-aldol reactions. An additional difficulty with this reaction stage comprised the facile formation of unreactive hemiacetals **9** at the double-aldol stage, if hydroxy groups of the aldol products were not protected. We hypothesized that hemiacetal formation would be prevented by trapping the copper aldolate intermediate **6** as non-nucleophilic boronate **12** through a reaction with boron enolate **8** in the catalyst turnover step (Figure 3A), which would require aprotic conditions. Based on this hypothesis, we examined the reactions between **1a** and **8a** (4.5 equiv) under various conditions without protic additives; however, the desired triple aldol product was produced at most in only trace amounts (<3%). Instead, the diboronate of hemiacetal **13** was obtained as a major product (~50%). This unexpected result is likely due to intramolecular boron/copper migration in copper aldolate **14** generated after double-aldol reaction, producing **15**, which instantly cyclizes to a hemiacetal.

To prevent the formation of hemiacetal **13** and/or facilitate the desired reaction pathways, we investigated additive effects to find that the addition of 2 equiv of triethylamine was effective, generating triple-aldol product **17a** in 71% yield, 90:10 dr (**17a**/other isomers), and >99% ee after reduction (Figure 3B). The conditions were also applicable to α,β-unsaturated aldehyde **1k** and aromatic aldehyde **1l**. Furthermore, the use of *N*,*N*,*N*′,*N*′-tetramethyl-1,4-butanediamine instead of triethylamine realized the first catalytic asymmetric one-pot quadruple-aldol reaction, generating one of 256 possible isomers in high diastereo- and enantioselectivity (Figure 3C). Elucidation of the origins of amine additive effects awaits future detailed mechanistic studies. For the moment, we confirmed that addition of triethylamine increased the concentration of reactive aldehyde form **16a** (R^1 = $Ph(CH_2)_2$, R^2 = Me) of the double-aldol intermediate, based on NMR studies of the reaction mixture.[15]

In conclusion, we developed copper(I)-catalyzed asymmetric iterative/domino cross-aldol reactions between aldehydes and aldehyde-derived boron enolates, which are generated from allyloxyboronates via iridium-catalyzed double bond isomerization. This method leads to the rapid production of a range of enantiomerically and diastereomerically enriched 1,3-polyols. Two novel findings in this study are (1) flexible and stepwise switching of the donors and the stereoselectivity in the first and second steps of the iterative double-aldol reaction; and (2) robust and one-pot double, triple, and quadruple catalytic asymmetric domino aldol reactions using the appropriate amounts of donors and amine additives. These findings demonstrate that the Cu(I)-catalyzed asymmetric iterative cross-aldol reactions of aldehydes could serve as an ideal method for rapid 1,3-polyol synthesis.

Table 1. Copper-Catalyzed Asymmetric Double-Aldol Reaction[a]



entry	Acceptor	Donor	Product	Yield (%) dr[a] ee (%)
<with (*R*)-DTBM-SEGPHOS>				
1	**1a**	**8a**	**10a**	86% yield 96:1:3 dr >99% ee
2	**1a**	**8b**	**10b**	85% yield 98:0:2 dr >99% ee
3	**1k**	**8a**	**10c**	89% yield 86:14 dr >99% ee
4[c]	**1l**	**8b**	**10d**	58% yield 94:6 dr >99% ee
5	**4a**	**8b**	**10e**	72% yield 92:4:4 dr >99% ee
6	**4b**	**8a**	**10f**	93% yield 92:1:7 dr >99% ee
<with (*S*)-DTBM-SEGPHOS>				
7	**4a**	**8a**	**11a**	61% yield 4:92:4 dr >99% ee
8	**4b**	**8b**	**11b**	63% yield 2:95:3 dr >99% ee
9	**4a**	**8b**	**11c**	64% yield 4:94:2 dr >99% ee
10	**4b**	**8a**	**11d**	71% yield 6:80:14 dr >99% ee

[a]Yield refers to the combined yield of all diastereomers. Diastereomeric ratio (dr) refers to the ratio of **10**/**11**/other isomers. [b]Two equivalents of triethylamine was added. See the SI for experimental details.

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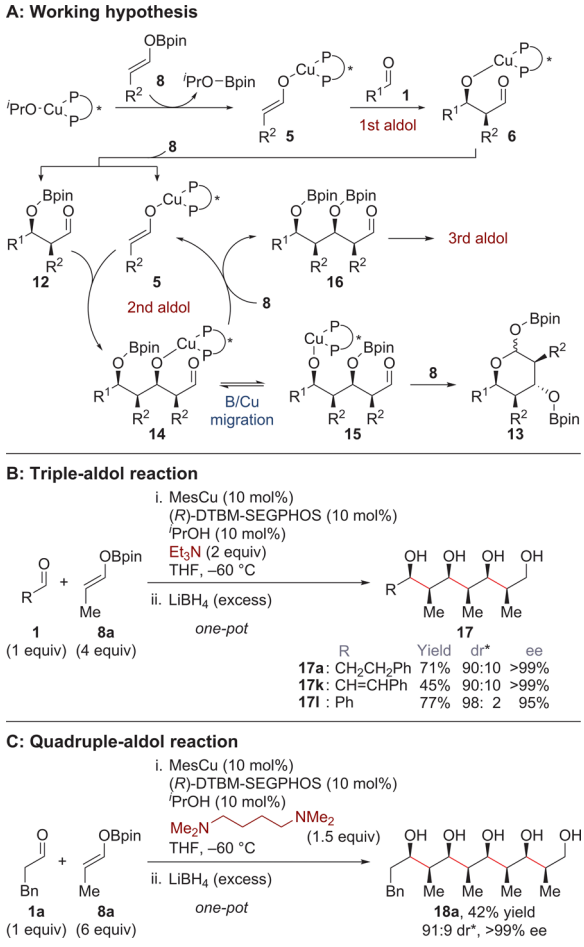

Figure 3. Copper-catalyzed asymmetric triple- and quadruple-aldol reactions. (A) Working hypothesis for the reaction progress to the triple-aldol reaction. (B,C) Catalytic asymmetric triple- and quadruple-domino aldol reactions. *Diastereoselectivity refers to the ratio of the major diastereomer to minor diastereomers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11192.

Experimental details and characterization data (PDF)
X-ray crystallographic data for **10a** (CIF)
X-ray crystallographic data for ***ent*-17a** (CIF)

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Notes

The authors declare no competing financial interest.

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