

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

Luqing Lin,^{†,‡,||} Kumiko Yamamoto,^{†,||} Harunobu Mitsunuma,[†] Yamato Kanzaki,[†] Shigeki Matsunaga,^{*,†,§,⊥} and Motomu Kanai^{*,†,‡}

[†]Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan [‡]ERATO, Japan Science and Technology Agency, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan [§]ACT-C. Japan Science and Technology Agency, Tokyo 113-0033, Japan

Supporting Information

ABSTRACT: We report here catalytic asymmetric iterative and domino cross-aldol reactions between aldehvdes, 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 Ircatalyzed 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 quadruplealdol 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 crossaldol reactions of aldehydes⁶ 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 reactions⁷ 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 Mukaivama aldol reaction.^{9a,b} the prolinecatalyzed asymmetric double-aldol reaction with switching of the catalyst chirality to avoid microscopic reversibility,9 the engineered enzyme-catalyzed asymmetric double-aldol reaction,^{9d} a catalytic diastereoselective (racemic) one-pot triplealdol 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 group¹¹ and our group¹² 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 aldehydederived 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 enolates¹³ 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 (\mathbb{R}^2 , $\mathbb{R}^3 =$ 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) (PPh₂Me)₂]PF₆ complex preactivated under H₂ atmosphere as a catalyst¹⁶ 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 catalysis¹⁷ 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 CuOⁱPr 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 doublealdol reaction smoothly proceeded in one-pot from aldehyde 1 and boron enolate 8 in the presence of 1 equiv of 4methoxyphenol, instead of isopropanol,¹⁵ to produce the corresponding cyclized hemiacetals 9 in the reaction mixture. After reduction with LiBH₄, 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 (\sim 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 11. Furthermore, the use of $N_1N_1N_2N_2$ 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



Table 1. Copper-Catalyzed Asymmetric Double-Aldol Reaction $\!\!\!\!\!^a$

"Yield refers to the combined yield of all diastereomers. Diastereomeric ratio (dr) refers to the ratio of 10/11/other isomers. ^bTwo equivalents of triethylamine was added. See the SI for experimental details.

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.

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C: Quadruple-aldol reaction

(4 equiv)

(1 equiv)



 17a: CH₂CH₂Ph 71%
 90:10
 >99%

 17k: CH=CHPh
 45%
 90:10
 >99%

 17l: Ph
 77%
 98: 2
 95%

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

S 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)

AUTHOR INFORMATION

Corresponding Authors

*smatsuna@pharm.hokudai.ac.jp

*kanai@mol.f.u-tokyo.ac.jp

Present Address

[⊥]Faculty of Pharmaceutical Sciences, Hokkaido University, Kitaku, Sapporo 060-0812, Japan.

Author Contributions

^{II}These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Rychnovsky, S. D. Chem. Rev. 1995, 95, 2021.

(2) (a) Rohr, J. Angew. Chem., Int. Ed. 2000, 39, 2847. (b) Weissman, K. J.; Leadlay, P. F. Nat. Rev. Microbiol. 2005, 3, 925.

(3) (a) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 2006, 557. (b) Li, J.; Menche, D. *Synthesis* **2009**, 2009, 2293. (c) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, 31, 504. (d) Harrison, T. J.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, 133, 7308.

(4) (a) Schetter, B.; Mahrwald, R. Angew. Chem., Int. Ed. 2006, 45, 7506. (b) Modern Aldol Reactions; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (c) Gröger, H.; Vogl, E. M.; Shibasaki, M. Chem. - Eur. J. 1998, 4, 1137. (d) Trost, B. M.; Brindle, C. S. Chem. Soc. Rev. 2010, 39, 1600.

(5) Brady, P. B.; Yamamoto, H. In *Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2013; p 269.

(6) (a) Northrup, A. B.; MacMillan, D. W. C. J. Am. Chem. Soc. 2002, 124, 6798.
(b) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. Angew. Chem., Int. Ed. 2004, 43, 6722.
(c) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. Angew. Chem., Int. Ed. 2007, 46, 1738.
(d) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. Angew. Chem., Int. Ed. 2008, 47, 2082.
(e) Markert, M.; Scheffler, U.; Mahrwald, R. J. Am. Chem. Soc. 2009, 131, 16642.
(f) Kano, T.; Sugimoto, H.; Maruoka, K. J. Am. Chem. Soc. 2011, 133, 18130.

(7) Mukaiyama, T.; Narasaka, K.; Banno, K. Chem. Lett. 1973, 1011.
(8) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. J. Am. Chem. Soc. 1974, 96, 7503. (b) Denmark, S. E.; Ghosh, S. K. Angew. Chem., Int. Ed. 2001, 40, 4759. (c) Boxer, M. B.; Yamamoto, H. J. Am. Chem. Soc. 2006, 128, 48.

(9) (a) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. Angew. Chem., Int. Ed. 2004, 43, 2152. (b) Northrup, A. B.; MacMillan, D. W. C. Science 2004, 305, 1752. (c) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. Angew. Chem., Int. Ed. 2005, 44, 1343. (d) Szekrenyi, A.; Garrabou, X.; Parella, T.; Joglar, J.; Bujons, J.; Clapés, P. Nat. Chem. 2015, 7, 724.

(10) (a) Albert, B. J.; Yamamoto, H. Angew. Chem., Int. Ed. 2010, 49, 2747. (b) Albert, B. J.; Yamaoka, Y.; Yamamoto, H. Angew. Chem., Int. Ed. 2011, 50, 2610. (c) Brady, P. B.; Yamamoto, H. Angew. Chem., Int. Ed. 2012, 51, 1942. (d) Brady, P. B.; Albert, B. J.; Akakura, M.; Yamamoto, H. Chem. Sci. 2013, 4, 3223. (e) Gijsen, H. J. M.; Wong, C.-H. J. Am. Chem. Soc. 1995, 117, 7585.

(11) (a) Krüger, J.; Carreira, E. M. J. Am. Chem. Soc. 1998, 120, 837.
(b) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. Angew. Chem., Int. Ed. 1998, 37, 3124.

(12) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2006, 128, 7164.

(13) (a) Wulff, G.; Hansen, A. Angew. Chem., Int. Ed. Engl. 1986, 25, 560. (b) Hoffmann, R. W.; Ditrich, K.; Fröch, S. Liebigs Ann. Chem. 1987, 1987, 977.

(14) (a) Lin, L.; Yamamoto, K.; Matsunaga, S.; Kanai, M. Angew. Chem., Int. Ed. 2012, 51, 10275. (b) Lin, L.; Yamamoto, K.; Matsunaga, S.; Kanai, M. Chem. - Asian J. 2013, 8, 2974.

(15) For full details, see Supporting Information.

(16) Ohmura, T.; Yamamoto, Y.; Miyaura, N. Organometallics 1999, 18, 413.

(17) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* 2007, 107, 5471.