博士論文（要約）

論文題目　Catalytic Asymmetric Iterative Aldol Reaction

for the Rapid Synthesis of 1,3-Polyols

(触媒的不斉多連続アルドール反応によるポリオール合成)

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CATALYTIC ASYMMETRIC ITERATIVE ALDOL REACTION FOR THE RAPID SYNTHESIS OF 1,3-POLYOLS

A Dissertation Presented

by

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Abstract

1,3-Polyols are ubiquitous structural motifs in biologically active polyketide natural products. To access these units, 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. 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, directly providing an aldehyde moiety for the subsequent iterative aldol reactions. The research described in this thesis involves the study of catalytic asymmetric iterative aldehyde cross-aldol reactions for the straightforward synthesis of enantiomerically and diastereomerically enriched 1,3-polyols.

Chapter 1 describes the chiral copper(I) alkoxide catalyzed asymmetric iterative cross-aldol reactions. Detailed study was conducted on a Cu(I)–DTBM-SEGPHOS complex catalyzed asymmetric *syn*-selective cross-aldol reaction between acceptor aldehydes and boron enolates generated through Ir-catalyzed isomerization of allyloxyboronates. This unit process was repeated using the aldol products in turn as an

acceptor aldehyde for the second asymmetric aldol reaction, whose stereochemistry was controlled by the chirality of the catalyst. Furthermore, substrate generality and reaction mechanism were considered for the asymmetric triple-aldol reaction. These findings demonstrate that the Cu(I)-catalyzed asymmetric iterative cross-aldol reactions of aldehydes could serve as an ideal method for the rapid 1,3-polyol synthesis.

Chapter 2 describes xxx.

Table of Contents

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List of Abbreviations

Ac: acetyl
acac: acetylacetonate
aq.: aqueous
Ar: aryl
9-BBN: 9-borabicyclo[3.3.1]nonane
BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn: benzyl
Bu: butyl
Bz: benzoyl
c-Pen: cyclopentyl
cat.: catalyst
COD: 1,5-cyclooctadiene
Cy: cyclohexyl
DIPPF: 1,1'-bis(di-*iso*-propylphosphino)ferrocene
DMF: *N*,*N*-dimethylformamide
DMSO: dimethylsulfoxide
dr: diastereomeric ratio
DTBM: 3,5-di-*tert*-butyl-4-methoxyphenyl
E-: *entgegen*
ee: enantiomeric excess
equiv: equivalent
ESI: electrospray ionization
Et: ethyl
h: hour
HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol
HMPA: hexamethylphosphoric triamide
HRMS: high resolution mass spectrometry
^{i}Bu: *iso*-butyl
Ipc: isopinocampheyl
^{i}Pr: *iso*-propyl
IR: infrared spectroscopy
J: coupling constant, NMR spectroscopy
KHMDS: potassium bis(trimethylsilyl)amide
L: neutral ligand, general
LC/MS: liquid chromatography–mass spectrometry
LDA: lithium diisopropylamide
LHMDS: lithium hexamethyldisilazide
M: metal, general
Me: methyl
Mes: mesityl, 1,3,5-trimethylphenyl
min: minute
MOM: methoxymethyl

MS: molecular sieves
NMP: *N*-methylpyrrolidone
NMR: nuclear magnetic resonance
Np: naphthyl
Nu: nucleophile
PG: protective group
Ph: phenyl
pin: pinacol
PMB: *para*-methoxybenzyl
PMP: *para*-methoxyphenyl
ppm: parts per million
R: alkyl, general
rac: racemic
R_f: retention factor (TLC)
rt: room temperature
sat.: saturated
TBS: *tert*-butyldimethylsilyl
^{t}Bu: *tert*-butyl
TES: triethylsilyl
Tf: trifluoromethanesulfonyl
TFA: trifluoroacetic acid
THF: tetrahydrofuran
TIPS: triisopropylsilyl
TLC: thin-layer chromatography
TMEDA: *N,N,N',N'*-tetramethylethylenediamine
TMS: trimethylsilyl
Tol: tolyl
Ts: *para*-toluenesulfonyl
U: enzyme unit
X: anionic group or ligand, general
Z-: *zusammen*

Note

Portions of this dissertation have been taken, with permission, from the following publication:

Lin, L.*; Yamamoto, K.*; Mitsunuma, H.; Kanzaki, Y.; Matsunaga, S.; Kanai, M. Catalytic Asymmetric Iterative/Domino Aldehyde Cross-Aldol Reactions for the Rapid and Flexible Synthesis of 1,3-Polyols. *J. Am. Chem. Soc.* **2015**, *137*, 15418-15421.

*denotes equal contribution

Additional work performed during my Ph.D. studies, not included in this dissertation, has been published in:

Yamamoto, K.; Garber, J. A. O.; Rolfes, J. D.; Borghes, J.; Boursalian, G. B.; Ritter, T. Direct Palladium-Catalyzed Aryl C−H Fluorination. *In Preparation.*

INTRODUCTION

1. Importance of 1,3-Polyol Synthesis

Polyketides are a large class of natural products, whose structures can be explained as being derived from poly-β-keto chains.[1] Included in such compounds are polyphenols, macrolides, polyenes, polyethers, and enediynes.[2] Polyketides are estimated to be five times more likely to possess drug activity than other natural product families,[3] and polyketide-derived pharmaceuticals comprise 20% of the top-selling small molecule drugs.[4]

One of the most ubiquitous structural motifs in these biologically active polyketides is the 1,3-polyols, containing multiple stereocenters with 1,3-oriented hydroxy groups. Despite enormous strides, however, concise access to such complex structures by current synthetic methods remains extremely challenging. Indeed, nearly all the commercial polyketides, such as erythromycin A[5], amphotericin B[6], and rifamycin SV[7] (Figure 1), are prepared through fermentation or semi-synthesis. The *de novo* chemical synthesis would offer entry to the rapid and flexible access not only to the polyketides but also to the otherwise inaccessible functional analogues.

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[1] *Medicinal Natural Products*; Dewick, R. M.; John Wiley & Sons: West Sussex, England, 2002.
[2] Hertweck, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4688.
[3] Rohr, J. *Angew. Chem., Int. Ed.* **2000,** *39*, 2847.
[4] Weissman, K. J.; Leadlay, P. F. *Nat. Rev. Microbiol.* **2005,** *3*, 925.
[5] Isolation of erythromycin A: McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother.* **1952**, *2*, 281. Synthesis and antibacterial activity of clarithromycin: Morimoto, S.; Takahashi, Y.; Watanabe, Y.; Omura, S. *J. Antibiot.* **1984**, *37*, 187.
[6] Isolation of amphotericin B: Stiller, E. T.; Vandeputte, J.; Wachtel, J. L. *Antibiot. Annu.* **1955-1956**, *3*, 587.
[7] Isolation of rifamycin B: Sensi, P.; Margalith, P.; Timbal, M. T. *Farmaco, Ed. Sci.* **1959**, *14*, 146. Synthesis and antibacterial activity of rifamycin SV: Sensi, P.; Timbal, M. T.; Maffii, G. *Experientia* **1960**, *16*, 412. Synthesis and antibacterial activity of rifaximin: Marchi, E.; Montecchi, L.; Venturini, A. P.; Mascellani, G.; Brufani, M.; Cellai, L. *J. Med. Chem.* **1985**, *28*, 960.

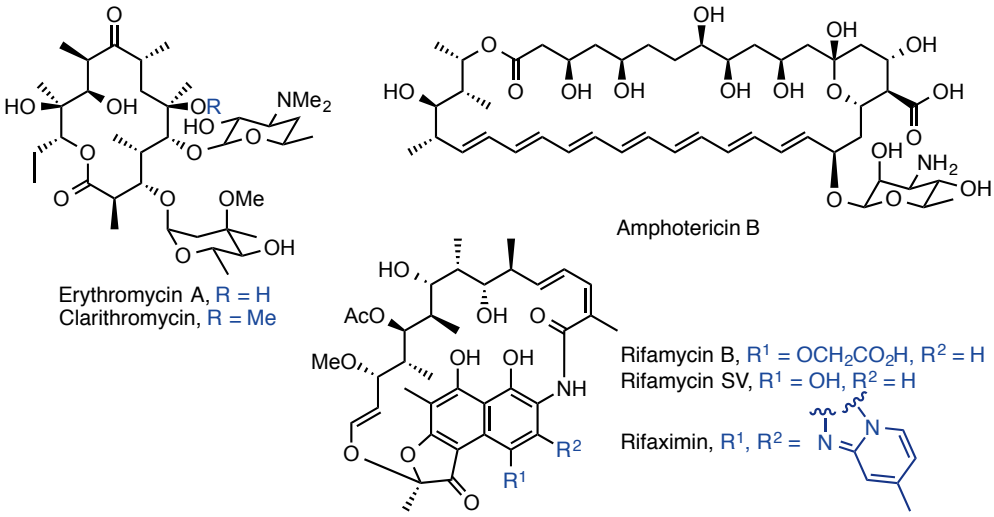

Figure 1 Representative polyketide natural products and their derivatives used in human medicine.

2. Stereoselective Synthesis of 1,3-Diols

Due to the importance and diversity, polyketide natural products inspired the development of many strategies toward the synthesis of 1,3-polyols.[8,9] With regard to many criteria, aldol reactions,[10] allylations/crotylations,[11] and epoxide-opening reactions[12] have been common approaches based on the stereocontrol in acyclic system.[13] In this section, introduction of aldol reaction is provided. A separate section

[8] For reviews on 1,3-diol synthesis, see: (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635. (b) Schneider, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 1375. (c) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, *4*, 557. (d) Li, J.; Menche, D. *Synthesis* **2009**, *14*, 2293.

[9] For reviews on 1,3-polyol synthesis in the context of polyketide syntheses, see: (a) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (c) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (d) Yeung. K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237. (e) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, *19*, 413.

[10] For selected reviews on aldol reaction, see: (a) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (b) *Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2013. (c) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352. (d) Schetter, B.; Mahrwald, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 7506.

[11] For selected reviews on allylation and crotylation, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. For the current state-of-the-art methods, see: (c) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504.

[12] (a) Sections 2.1.2 and 2.2.1 in Oishi, T.; Nakata, T. *Synthesis* **1990**, 635. (b) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511. (c) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365.

[13] For selected examples of other notable contributions, see: alkylation of cyanohydrin followed by reductive decyanation; (a)Rychnovsky, S. D.; Hoye, R. *J. Am. Chem. Soc.* **1994**, *116*, 1753. Silylformylation−allylsilylation; (b) Harrison, T.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 7308. Oxy-Michael reaction (c) Evans, D. A.; Gauchet-Pruent, J. A. *J. Org. Chem.* **1993**, *58*, 2446. For selected examples of other promising contributions, see: acyl halide−aldehyde cyclocondensation (d) Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 7438. Oxy-alkenylation; (e) Holt, D.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 7857. C−H functionalization; (f) Chen. K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.*

is created for the cross-aldol reaction of aldehydes, which is the major subject of this dissertation.

2.1 Traditional Aldol Reaction

The aldol reaction is a carbon−carbon bond forming reaction between an enolizable carbonyl compound and either an aldehyde or a ketone to generate a β-hydroxy carbonyl compound with up to two new stereocenters. The aldol reaction continues to serve as the strategically important, reliable transformation because of its selectivity, scope, and predictability.

Figure 2 summarizes the brief timeline of aldol reaction. Following the first example of aldol condensation of acetone reported by Kane in 1838 (Figure 3a),[14]

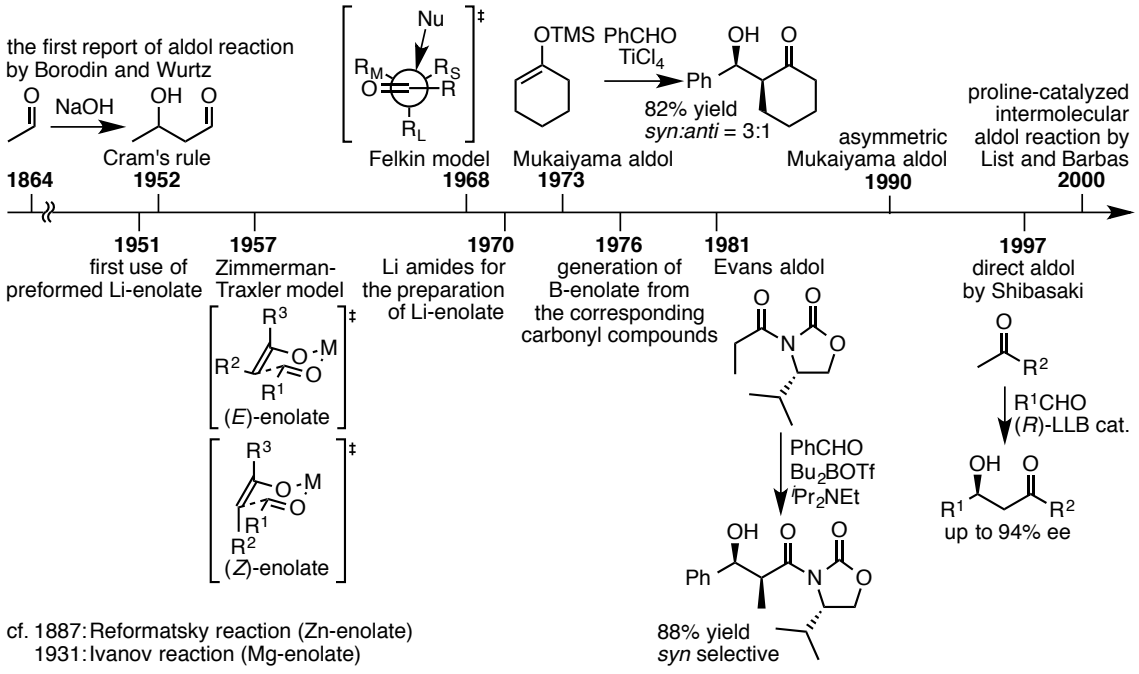

Figure 2[15] Brief timeline of aldol reaction.

2008, *130*, 7247. (g) Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 6586.

[14] (a) Kane, R. *Ann. Phys.* **1838**, *120*, 473. (b) Kane, R. *J. Prakt. Chem.* **1838**, *15*, 129.

[15] This timeline was drawn by modifying the group meeting handout of the David W. C. MacMillan group at Princeton University, presented by A. B. Northrup in 2002.

Borodin and Wurtz independently recognized the aldol reaction of acetaldehyde in 1864 and 1872, respectively (Figure 3b).[16]

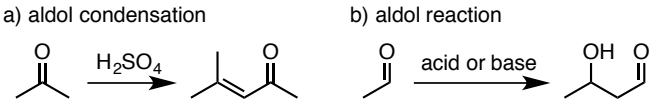

Figure 3 The original aldol reactions. (a) Aldol condensation reported by Kane. (b) Aldol reaction reported by Borodin and Wurtz.

In the era of traditional aldol reaction, reactions were run in protic solvents and mediated either by acid or base. Under these conditions, the reaction is reversible (Figure 4a) and mixed aldol reaction between two different enolizable aldehydes and/or ketones leads to the formation of mixture, because each component can serve as both nucleophile and electrophile (Figure 4b).

One of the most efficient methods reported during this era is the intramolecular aldol condensation, which is known as Robinson annulation (Figure 5).[17] The utility of this reaction can be seen, with its subsequent modifications, in the synthesis of natural products and other organic compounds.[18] The traditional aldol reaction, however, suffers from the general lack of chemo- and stereoselectivity, limiting the use in carbon backbone construction.

[16] (a) Borodin, A. *J. Prakt. Chem.* **1864**, *93*, 413. (b) Wurtz, A. *Ber. Dtsch. Chem. Ges.* **1872**, *5*, 326. (c) Wurtz, A. *J. Prakt. Chem.* **1872**, *5*, 457.
[17] Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285.
[18] The Wieland−Miescher keton is a versatile synthon, which has been employed in the total synthesis of terpenoids and steroids.

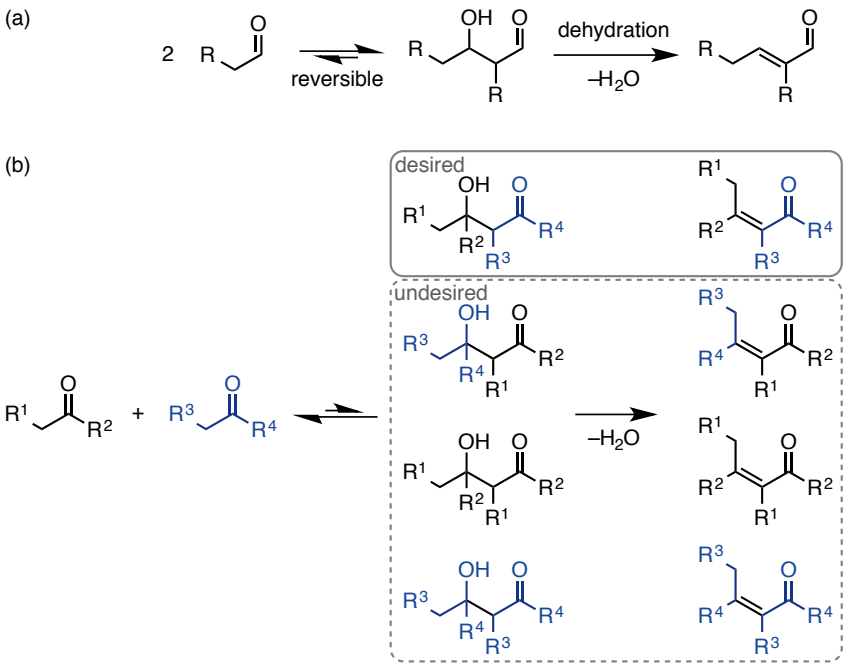

Figure 4 Problematic points of traditional aldol reaction. (a) In general, the equilibrium is located on the product side for aldol reaction between aldehydes and on the starting material side for ketones. This equilibrium can be shifted by a subsequent dehydration step, however, two stereocenters and hydroxy group is also eliminated. (b) In cross-aldol reaction, undesired self- and cross-aldol products are generated in addition to the desired product.

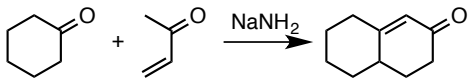

Figure 5 The original Robinson annulation. The reaction proceeds via Michael addition followed by aldol condensation.

2.2 Aldol Reaction of Preformed Enolates

The chemistry of preformed enolates has made a great impact on this situation. Although Hauser reported the first use of preformed lithium enolate in 1951 (Figure

6a),[19] extensive study has been started since 1970 when lithium amide bases, especially LDA,[20] were used for the formation of enolates in aprotic solvents. In contrast with the traditional aldol reaction, this approach enables the chemo- and diastereoselective aldol reaction. First, the metal enolate is generated irreversibly from the donor carbonyl compounds. Second, region-defined enolates are obtained through either kinetic or thermodynamic control (Figure 7). Finally, selective generation of either (*E*)- or (*Z*)-enolate is possible by changing the substituent group of carbonyl compound, base, and solvent (Figure 8). This is particularly important because the diastereoselectivity of

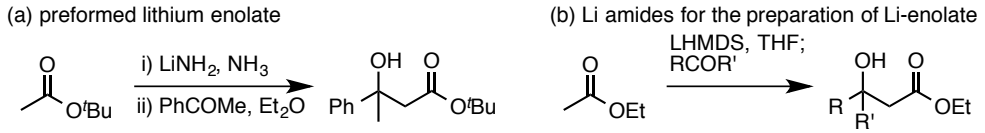

Figure 6 (a) The original example of preformed lithium enolate for aldol reaction. (b) The original example of the use of lithium amide for the formation of lithium enolate in the context of aldol reaction.[21]

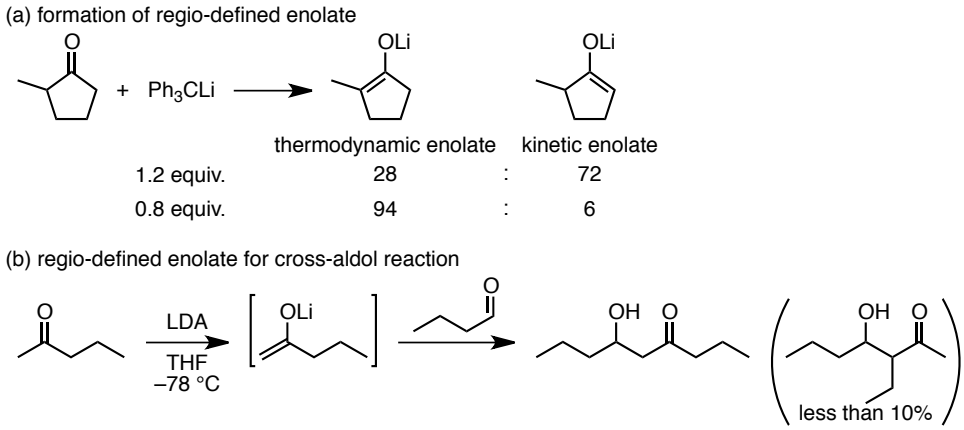

Figure 7 (a) The original report of the preparation of lithium enolate from an unsymmetrical ketone through either kinetic or thermodynamic control.[22] (b) The first use of regio-defined enolates in cross-aldol reaction.[23]

[19] Hauser, C. R.; Puterbaugh, W. H. *J. Am. Chem. Soc.* **1951**, *73*, 2972.
[20] LDA, soluble, strong , and non-nucleophilic base, was first used in 1950 for Claisen condensation: Hamell, M.; Levine, R. *J. Org. Chem.* **1950**, *15*, 162.
[21] Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.
[22] House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341.
[23] Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459.

aldol reaction is correlated to the configuration of the enolates;[24] (*E*)-enolates furnish mainly *anti*-aldols whereas (*Z*)-enolates generate predominantly *syn*-aldols.

The Zimmerman−Traxler model[25] is the most widely accepted transition state when explaining the simple diastereoselectivity (Figure 9).[26] The aldehyde and metal enolate reacts via a six-membered transition state having a chair conformation.[27]

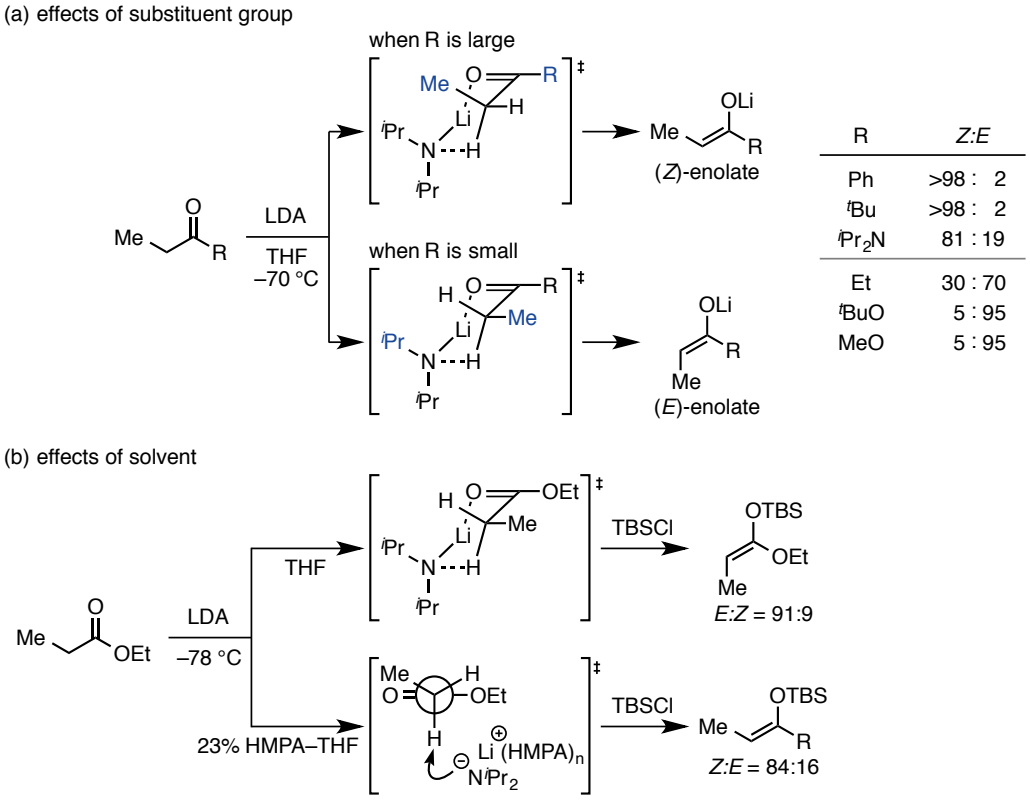

Figure 8 Selective formation of (*E*)- or (*Z*)-enolate. (a) With LDA, the amount of (*Z*)-enolate increases as the size of R increases. The amide base can also have a substantial effect on the *E*/*Z* ratio.[28] (b) HMPA effects the degree of solvation of the lithium cation and changes the transition state to generate (*Z*)-enolate.[29]

[24] Most aldol reactions with preformed enolates generate kinetically controlled products.
[25] Zimmerman and Traxler originally proposed the six-membered chair-like transition state for the Ivanoff reaction; Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920. For the original Ivanoff reaction, see: Ivanoff, D.; Spassoff, A. *Bull. Soc. Chim. France* **1931**, *49*, 371.
[26] In practice, the diastereoselectivity can be highly metal dependent and only a few metals, such as boron, reliably generate the indicated product.
[27] An important modification of the Zimmerman-Traxler model is a boat/twist-boat conformation to explain the (*Z*)−*anti* correlation, see: (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975. (b) Hoffmann, R. W.; Ditrich, K.; Froech, S. *Tetrahedron* **1985**, *41*, 5517.
[28] Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
[29] During the study on Claisen Rearrangement, Ireland found that solvent polarity effects the ratio of enolates: Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

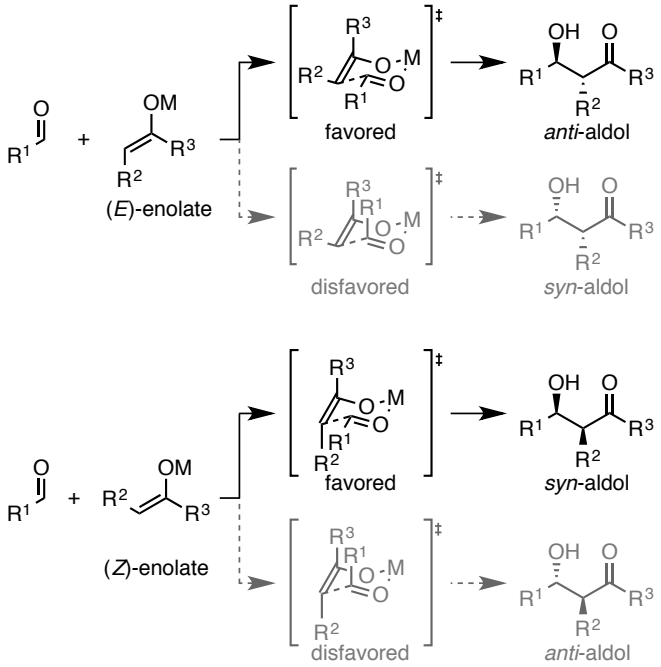

Figure 9 The Zimmerman−Traxler model.

Another rationale for the diastereoselectivity relies on open transition state without coordination of the aldehyde to the enolate.[30] It involves an *anti*-periplanar orientation of enolate and carbonyl group, giving predominantly *syn*-aldols independent of enolate geometry (Figure 10). This outcome has been observed in Mukaiyama aldol reaction (*vide infra*)[31] as well as in aldol reaction of metal and "naked" enolates.[32] The question whether the transition state is closed or open, and whether it is chair, half-chair, twist-boat, or others cannot be answered by simple "either−or". There exist strong preferences, however, substitution pattern, counter-ion, and reaction conditions affect the favored transition state.

[30] Early discussions of open transition states for aldol reaction were made by Yamamoto and Noyori, see: (a) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, *21*, 4607. (b) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.

[31] For the investigations into transition state geometry in the Mukaiyama aldol reaction, see: Denmark, S. E.; Lee, W. *Chem. Asian J.* **2008**, *3*, 327.

[32] Early reports described in the context of open transition state, see: Sn-enolate; (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Chem. Soc. Chem. Commun.* **1981**, 162. "Naked" enolate; (b) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106.

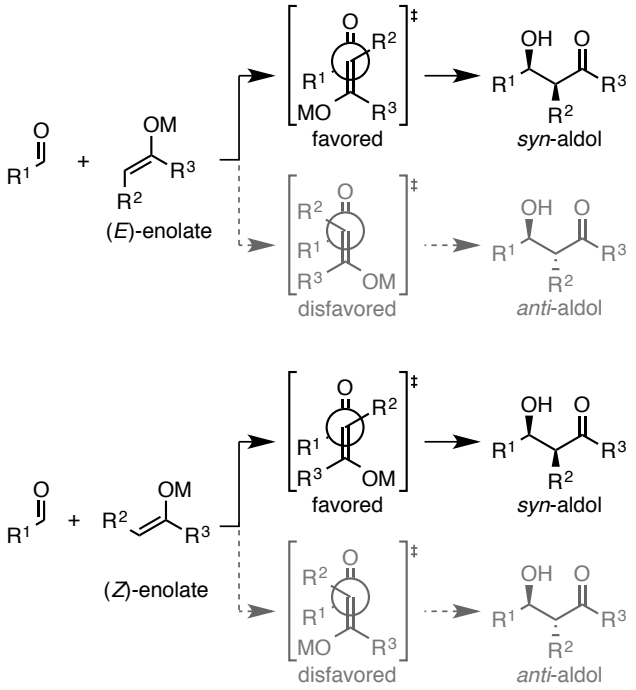

Figure 10 Open transition state model.

2.2.1 Group I and II Enolates

Generation of different metal enolates and their use in aldol reaction has been extensively studied for the stereoselective aldol reaction under milder conditions. Group I and II enolates,[33] such as Li, Na, K, and Mg, are formed by stoichiometric deprotonation of carbonyl compounds, transmetalation from the corresponding silyl enol ethers, conjugate addition to α,β-unsaturated carbonyl compounds, or reduction of α-halogenated carbonyl compounds (Figure 11). These metal enolates react with aldehydes with a very low activation barrier. For example, the reactions between aldehydes and lithium enolates are often conducted at low temperatures (typically at −78 °C) and quenched within seconds.

The utility of group I and II enolates, especially lithium enolates, can be seen in the

[33] For selected reviews on aldol addition of group I and II enolates, see: (a) Braun, M. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; p 1. (b) Heathcock, C. H. In *Comprehensive Organic Synthesis II, Volume 2*; Knochel, P.; Molander, G. A., Ed.; Elsevier: Oxford, UK, 2014; p 340.

total syntheses of natural products. In the Woodward's first total synthesis of erythromycin A,[34] the introduction of the C1−C2 unit was accomplished by coupling of the chiral aldehyde and the lithium enolate of *tert*-butyl thiopropionate (Figure 12). The following kinetic protonation furnished the intermediate possessing all the carbon

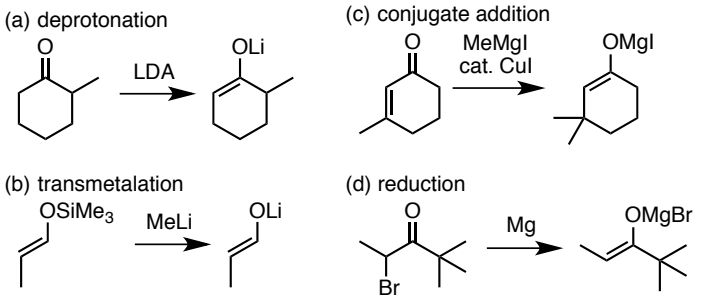

Figure 11 Generation of group I and II enolates. (a) Deprotonation by stoichiometric amount of metal bases. (b) Transmetalation from the corresponding silyl enol ethers. (c) Conjugate addition to α,β-unsaturated carbonyl compounds. (d) Reduction of α-halogenated carbonyl compounds.

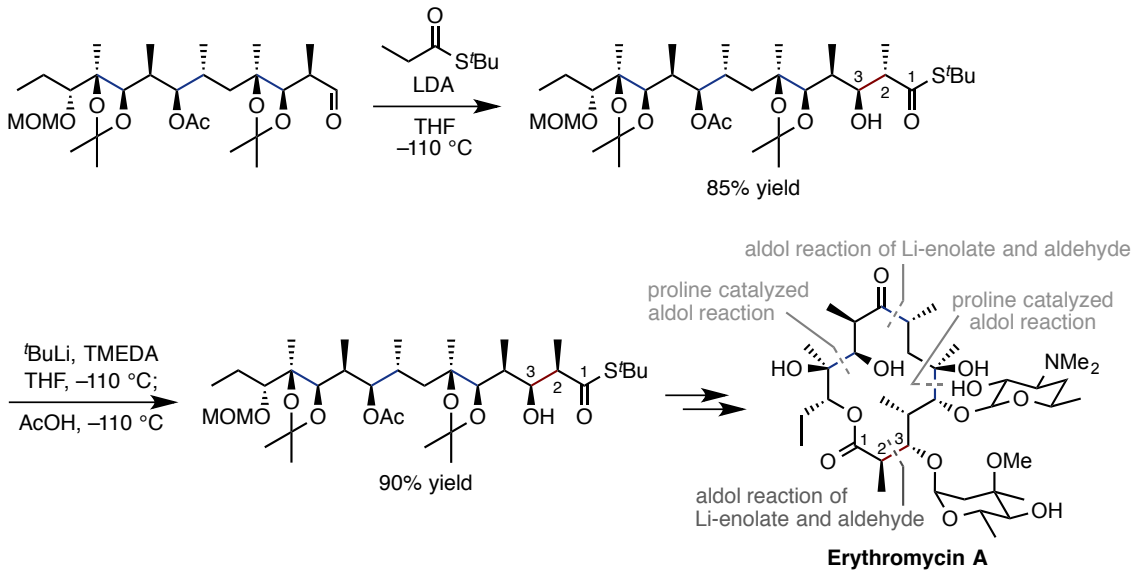

Figure 12 The lithium enolate in Woodward's total synthesis of erythromycin A.

[34] The total synthesis of erythromycin A was Woodward's last major scientific accomplishment: (a) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210. (b) *Ibid.* **1981**, *103*, 3213. (c) *Ibid.* **1981**, *103*, 3215.

skeleton and stereocenters of erythronolide A seco acid. The stereoselectivity of aldol reaction at C3 can be explained by Cram's rule (Figure 13)[35] and Felkin−Anh model (Figure 14).[36]

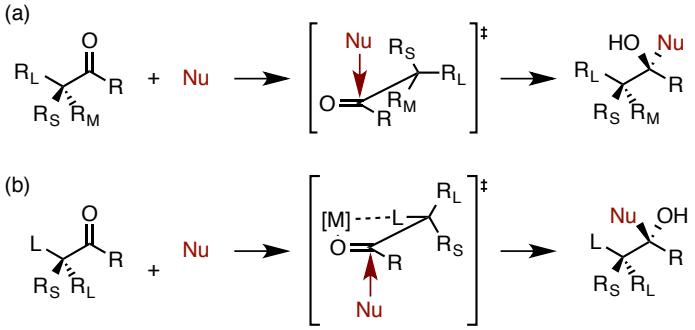

Figure 13 Cram's rule. (a) When nucleophiles react with α-chiral carbonyl compounds, they attack the carbonyl groups form the least hindered side. α-Chiral carbonyls involve an *anti*-periplanar orientation of the large substituent R_L and carbonyl group. (b) When chelation between the carbonyl group and substituents of the α-stereocenter L can occur, the substrate is locked by the bidentate chelation effect. Nucleophiles attack the carbonyl groups from the least hindered side to give *anti*-Cram products.

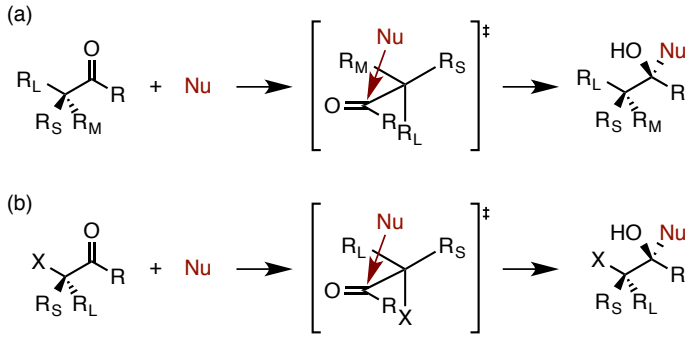

Figure 14 Felkin−Anh model. (a) The large substituent R_L is placed orthogonal to the carbonyl group. Nucleophilic attacks occur in not 90° but in a Bürgi−Dunitz angle, favoring approach closer to the smaller substituents R_S. (b) When substituents of the α-stereocenter X have an electron withdrawing effect, X is placed orthogonal to the carbonyl group so that $\sigma^*_{C\text{-}X}$ orbital is aligned parallel to the π* orbital of the carbonyl group.

[35] (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1952**, *81*, 2748.

[36] (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199. (b) Anh, N. T.; Lefour, E. J-M.; Dâu, M-E. T. H. *J. Am. Chem. Soc.* **1973**, *95*, 6146. (c) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, *17*, 155.

2.2.2 Boron Enolate

In terms of both preparation and selectivity, boron enolate serves as one of the most widely used enolate for aldol reaction.[37] Although several methods had been known,[38] Mukaiyama reported the first generation of boron enolates from the corresponding carbonyl compounds and their use in cross-aldol reaction (Figure 15).[39] Coordination of the carbonyl group to the Lewis acidic boron triflate increases the acidity of the α-proton, allowing the use of weaker base such as tertiary amine for the preparation of boron enolates. Regio-defined enolates are obtained through either kinetic[39] or thermodynamic control (Figure 16).[40]

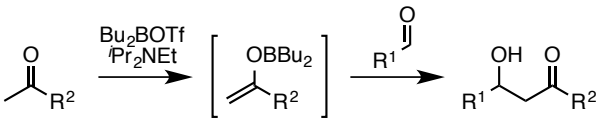

Figure 15 The original report of the preparation of boron enolates from the corresponding ketones using dibutylboron triflate and tertiary amine, followed by aldol reaction.

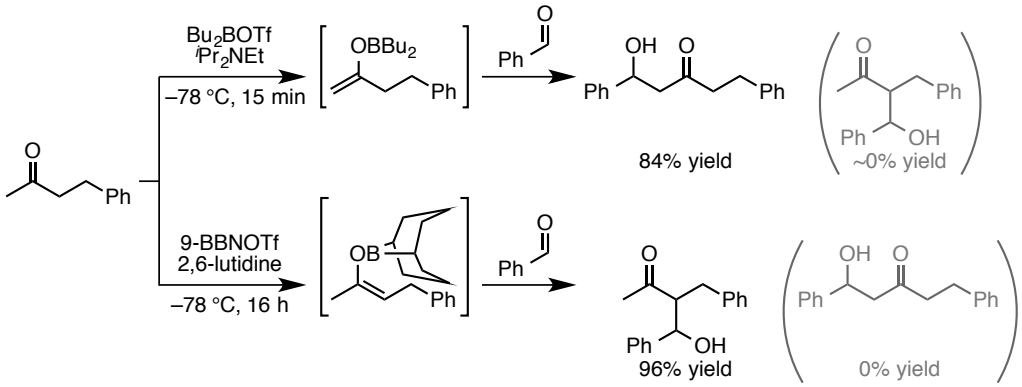

Figure 16 Formation of regio-defined boron enolates.

[37] For selected reviews on aldol addition of boron enolate, see: (a) Mukaiyama, T.; Matsuo, J. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; p 127. (b) Koskinen, A. M. P. *Chem. Rec.* **2014**, *14*, 52.

[38] (a) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936. (b) Pasto, D. J.; Wojtkowski, P. W. *Tetrahedron Lett.* **1970**, *3*, 215. (c) Mukaiyama, T.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3215.

[39] Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559.

[40] (a) Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Chem. Lett.* **1977**, 153. (b) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

The diastereoselectivity of boron enolate-mediated aldol reaction reliably follow the pathway indicated by the Zimmerman−Traxler model. Due to the shorter bond length between boron and oxygen, 1,3-diaxial interactions in the transition state is maximized and thus furnish aldol adducts stereoselectively (Figure 17).[41]

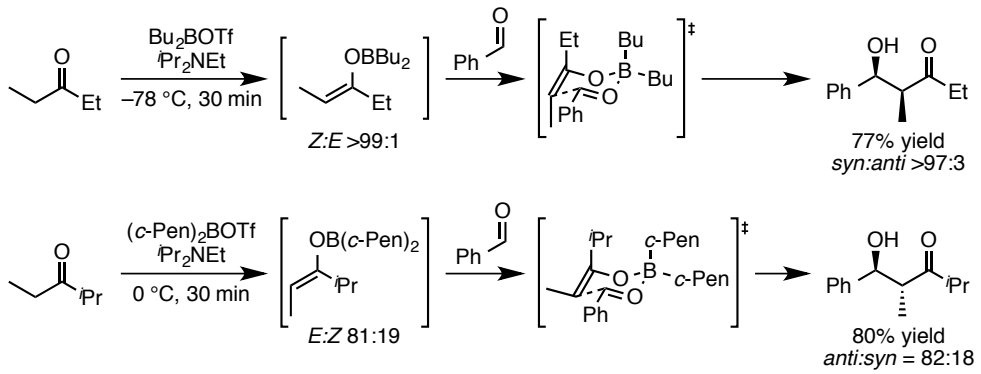

Figure 17 Stereoselective generation of (*Z*)- and (*E*)-boron enolates and their use for aldol reaction.

Introduction of chiral auxiliaries into donor carbonyl compounds proved to be a very dependable method for the enantio- and diastereoselective synthesis of polyketide natural products. Evans reported the first aldol reaction involving boron enolates substituted by a chiral oxazolidinone auxiliary in 1981 (Figure 18).[42] A chiral boron enolate reacts with aldehydes to afford the corresponding *syn* aldol products in good yields with excellent level of chiral induction.

[41] (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (b) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, *20*, 2225.

[42] (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans' lecture note for Chemistry 206 Advanced Organic Chemistry; The Aldol Reaction−1; http://isites.harvard.edu/fs/docs/icb.topic93502.files/Lectures_and_Handouts/27-Aldol-1.pdf

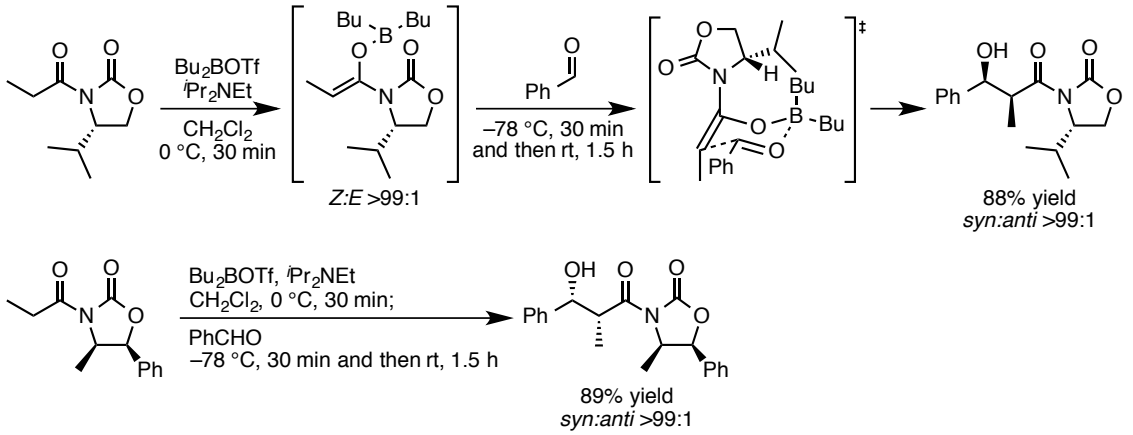

Figure 18 The original report of Evans' asymmetric boron aldol reaction.

The utility of asymmetric boron-mediated aldol reactions was demonstrated by the Novartis process chemistry group in their synthesis of discodermolide,[43] a marine sponge-derived anticancer drug candidate (Figure 19).[44] The hybridized Novartis−Smith[45]−Paterson[46] synthetic route produced more than 60 g of the structurally complex polyketide. In their synthesis, Evans' *syn*-selective aldol reaction and Paterson's Ipc aldol method[47] were employed to control 9 of 13 stereocenters in the final product.

[43] Isolation of discodermolide: Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912, Correction *J. Org. Chem.* **1991**, *56*, 1346.

[44] (a) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Daeffler, R.; Osmani, A.; Schreiner, K.; Seeger-Weibel, M.; Bérod, B.; Schaer, K.; Gamboni, R.; Chen, S.; Chen, W.; Jagoe, C. T.; Kinder, F. R., Jr.; Loo, M.; Prasad, K.; Repič, O.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xu, D. D.; Xue, S. *Org. Process Res. Dev.* **2004**, *8*, 92. (b) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Grimler, D.; Koch, G.; Daeffler, R.; Osmani, A.; Hirni, A.; Schaer, K.; Gamboni, R.; Bach, A.; Chaudhary, A.; Chen, S.; Chen, W.; Hu, B.; Jagoe, C. T.; Kim, H.-Y.; Kinder, F. R., Jr.; Liu, Y.; Lu, Y.; McKenna, J.; Prashad, M.; Ramsey, T. M.; Repič, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L. *Org. Process Res. Dev.* **2004**, *8*, 101. (c) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Koch, G.; Kuesters, E.; Daeffler, R.; Osmani, A.; Seeger-Weibel, M.; Schmid, E.; Hirni, A.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, S.; Chen, W.; Geng, P.; Jagoe, C. T.; Kinder, F. R., Jr.; Lee, G. T.; McKenna, J.; Ramsey, T. M.; Repič, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L. *Org. Process Res. Dev.* **2004**, *8*, 107. (d) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Seger, M.; Schreiner, K.; Daeffler, R.; Osmani, A.; Bixel, D.; Loiseleur, O.; Cercus, J.; Stettler, H.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, G.-P.; Chen, W.; Geng, P.; Lee, G. T.; Loeser, E.; McKenna, J.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Reel, N.; Repič, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xue, S. *Org. Process Res. Dev.* **2004**, *8*, 113. (e) Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Repič, O.; Wang, R.-M. *Org. Process Res. Dev.* **2004**, *8*, 122.

[45] (a) Smith III, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654. (b) Smith III, A. B.; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823. For their first generation synthesis, see: (c) Smith III, A. B.; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011.

[46] (a) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem. Int. Ed.* **2000**, *39*, 377. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereining, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

[47] Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787.

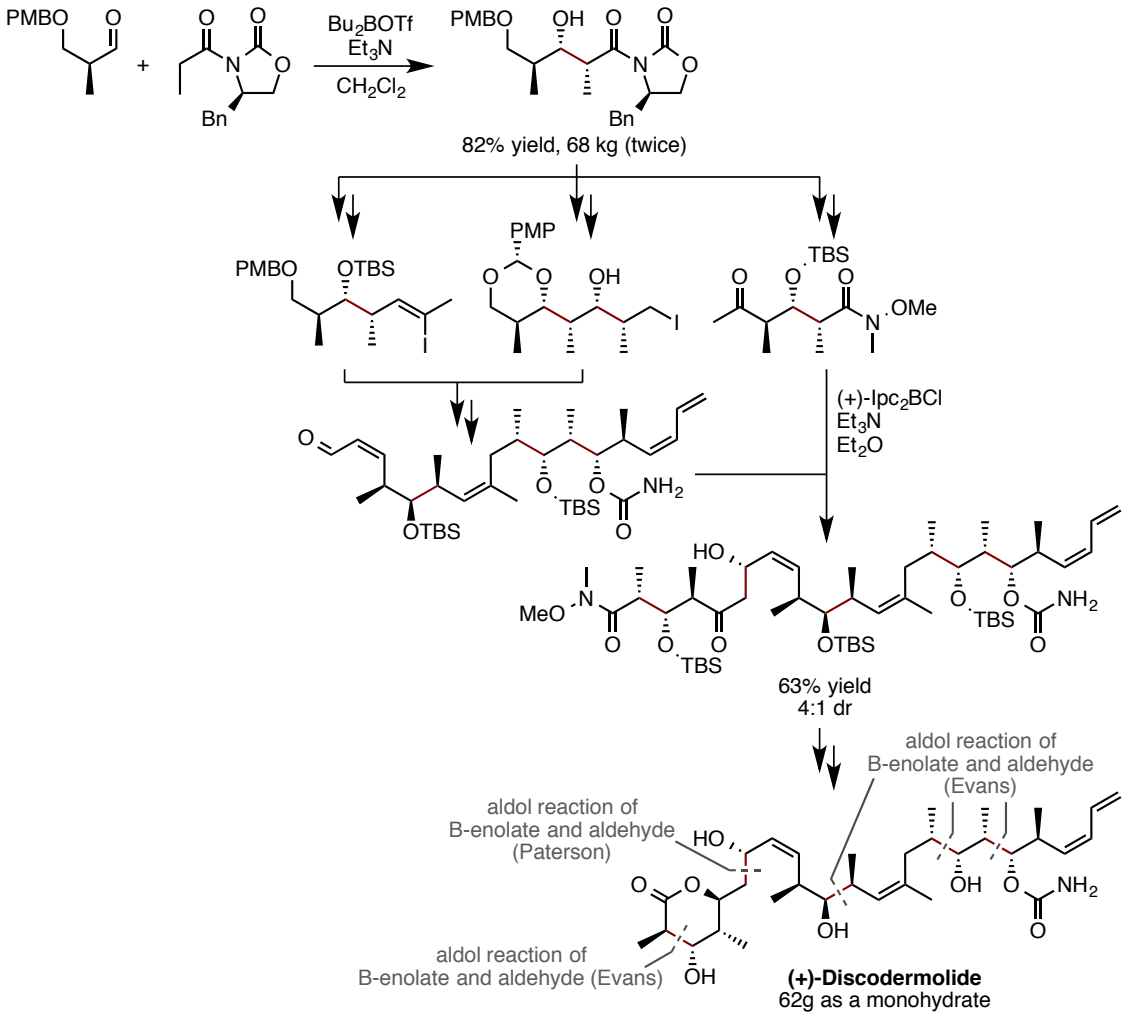

Figure 19 The boron enolates in large-scale synthesis of discodermolide by Novartis.

2.2.3 Silicon Enolate

Among group IV enolates, silicon enolates serve as the most useful enolates in modern organic chemistry.[48] Two unique features of silicon enolates are that most of them are isolable and storable, and that the reaction proceeds under acidic conditions.

Although the preparation of silicon enolate had been known,[49] Mukaiyama

[48] For selected reviews on aldol addition of silicon enolate, see: (a) Ref 37a. (b) Kobayashi, S.; Yamashita, Y.; Yoo, W.-J.; Kitanosono, T.; Soulé, J.-F. In *Comprehensive Organic Synthesis II, Volume 2*; Knochel, P.; Molander, G. A., Ed.; Elsevier: Oxford, UK, 2014; p 396. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (d) Kan, S. B. J.; Ng, K. K.-H.; Paterson, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 9097.

[49] For the first report of the preparation of silicon enolate, see: Gilman, H.; Clark, R. *J. Am. Chem. Soc.* **1947**, *69*, 967.

reported an aldol reaction of silicon enolates[50] and aldehydes in the presence of titanium tetrachloride, so called "Mukaiyama aldol reaction" in 1973 (Figure 20).[51,52] In general, the stereochemical outcome is explained by the open transition state model because the silicon atom is not sufficiently Lewis acidic to bind and activate the aldehyde (*vide supra*).

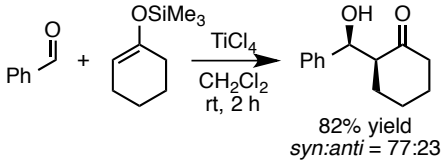

Figure 20 Lewis acid-mediated aldol reaction of silicon enolates.

The Mukaiyama aldol reaction triggered the development of chiral Lewis acids for the catalytic asymmetric reactions. The pioneering work[53] was reported by Mukaiyama, utilizing a chiral diamine/tin(II) triflate complex as a catalyst (Figure 21).[54] The following works demonstrated excellent enantioselectivity with titanium, boron, tin, palladium, copper, rare earth, and other Lewis acid catalysts.[48]

In their total synthesis of Taxol, Mukaiyama employed *anti*-selective aldol reaction of silyl ketene acetal and aldehyde using stoichiometric amounts of chiral diamine, tin(II) triflate, and dibutyltin diacetate (Figure 22).[55] By utilizing three Mukaiyama

[50] Silicon enolate is often called as "silyl enol ether" since it appeared in the report in 1968, see: (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462. (b) *Ibid.* **1968**, *90*, 4464.

[51] (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

[52] At high temperature, silyl enol ethers react with aldehyde without catalyst, see: Birkofer, L.; Ritter, A.; Vernaleken, H. *Chem. Ber.* **1966**, *99*, 2518.

[53] The first catalytic asymmetric Mukaiyama aldol reaction was reported by Reetz. However, the enantioselectivity was not enough for general applications, see: (a) Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. *Chem. Ind.* **1986**, 824. (b) Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721.

[54] (a) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett.* **1990**, 129. (b) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455.

[55] (a) Mukaiyama, T.; Shiina, I.; Sakata, K.; Emura, T.; Seto, K.; Saitoh, M. *Chem. Lett.* **1995**, 179. (b) Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K.; Mukaiyama, T. *Chem. Lett.* **1997**, 1139. (c) Shiina, I.; Iwadare, H.; Sakoh, H.; Hasegawa, M.; Tani, Y.; Mukaiyama, T. *Chem. Lett.* **1998**, 1. (d) Shiina, I.; Saitoh, K.; Fréchard-Ortuno, I.; Mukaiyama, T. *Chem. Lett.* **1998**, 3. (e) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121.

aldol reactions, they achieved the 6th successful total synthesis of Taxol.

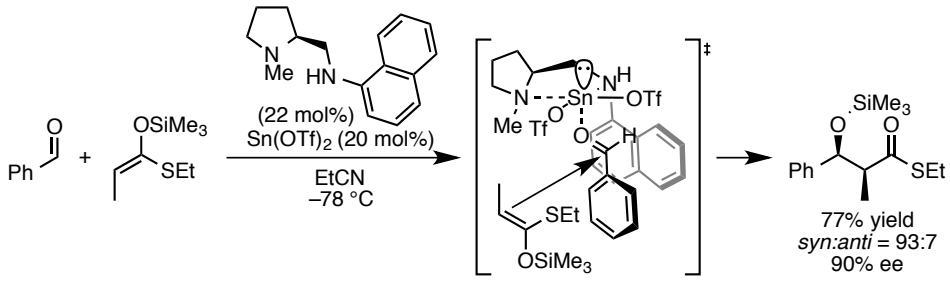

Figure 21 The catalytic enantioselective Mukaiyama aldol reaction.

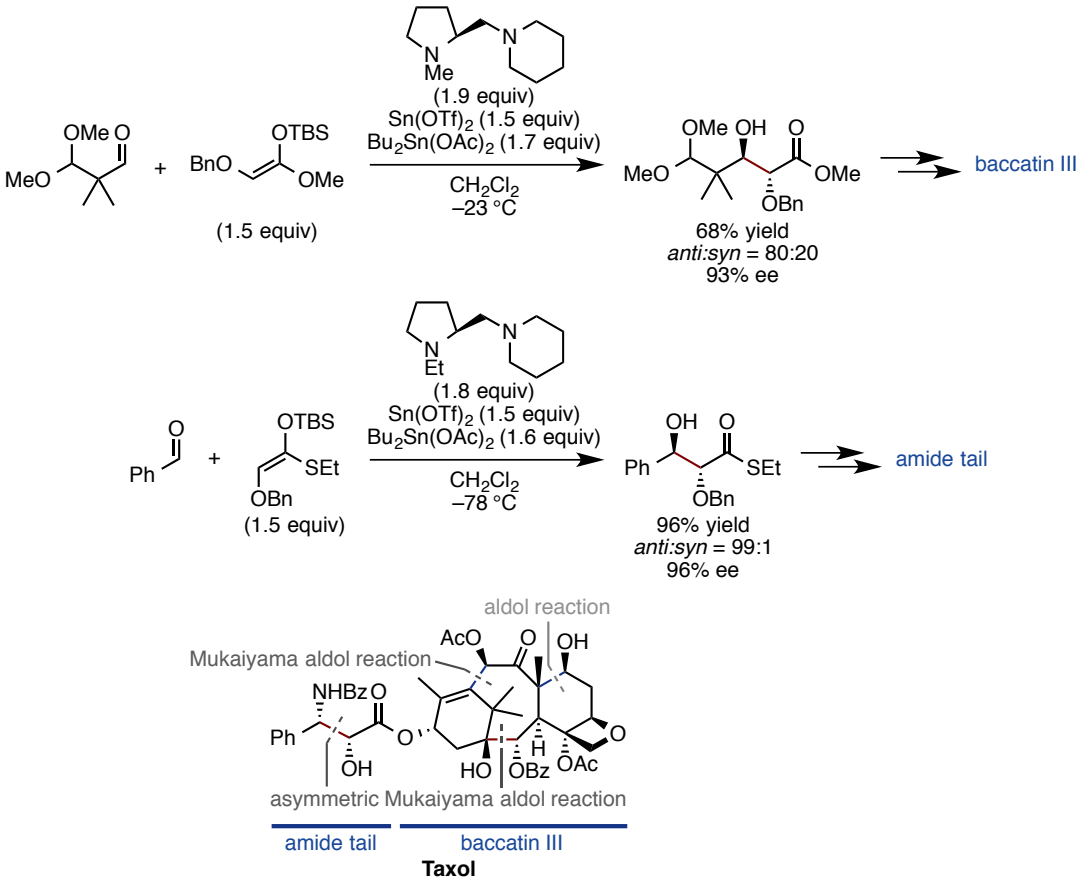

Figure 22 The silicon enolates in Mukaiyama's total synthesis of Taxol.

2.3 Direct Aldol Reaction

Although aldol reaction of preformed enolates allowed this reaction to emerge as a strategy-level reaction in natural product synthesis, it requires stoichiometric amounts of reagents, which result in waste. Development of catalytic asymmetric direct aldol reaction,[56] in which the pre-activation of enolates is not necessary, provides an atom economical[57] alternative for this transformation. Inspired by enzymes,[58] the small molecule catalysts, which realize both high efficiency and broad substrate generality, i.e. which mimic and exceed nature, have been developed.

In 1997, Shibasaki reported the first intermolecular direct catalytic asymmetric aldol reaction of simple ketones and aldehydes using a lanthanum−lithium−BINOL complex, LLB (Figure 23a).[59] Acceleration of the reaction was achieved using LLB−KOH catalyst prepared from LLB, KHMDS, and H_2O (Figure 23b).[60] Several mechanistic studies indicated that KOH functions as a Brønsted base and lanthanum ion acts as a Lewis acid. The rate determining enolate generation step is promoted by KOH and the following aldol addition step proceeds through activation of aldehyde by Lewis acidic lanthanum ion (Figure 23c). Protonation of the generated aldolate furnishes the product and regenerates the catalyst.

[56] For selected reviews on catalytic asymmetric aldol reaction, see: (a) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600. (b) Masakatsu, S.; Matsunaga, S.; Kumagai, N. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; p 197.

[57] (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259.

[58] For selected reviews on enzyme-catalyzed aldol reaction, see: (a) Ref 10c. (b) Clapés, P.; Joglar, J. In *Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2013; p 475.

[59] Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1871.

[60] Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.

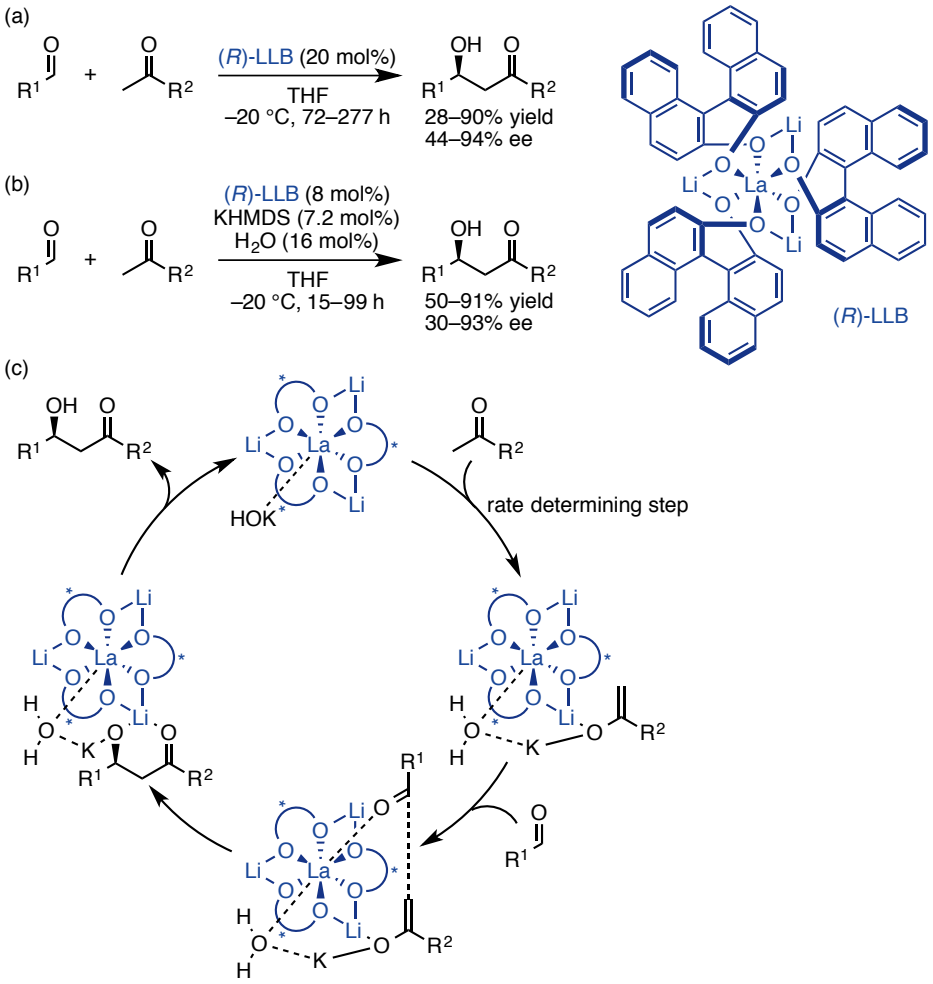

Figure 23 (a) The original report of intermolecular direct catalytic asymmetric reaction of simple ketones and aldehydes. (b) The improved catalysis using (*R*)-LLB−KOH prepared from (*R*)-LLB, KHMDS, and H_2O. (c) The working model of the aldol reaction promoted by (*R*)-LLB−KOH catalyst.

In 2000, List and Barbas shed light on proline's remarkable ability as a catalyst.[61,62] A catalytic amount of proline promotes the intermolecular aldol reaction between acetone and aldehydes (Figure 24a).[63] Based on both theory and experiment, the plausible catalytic cycle is depicted in Figure 24b.[62] The nucleophilic enamine intermediate **III** would be generated through the formation of carbinolamine **I** and

[61] For the roots of aminocatalysis, see: List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730.
[62] For selected reviews on organocatalyzed aldol reaction, see: (a) List, B. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; p 161. (b) Mase, N.; Hayashi, Y. In *Comprehensive Organic Synthesis II, Volume 2*; Knochel, P.; Molander, G. A., Ed.; Elsevier: Oxford, UK, 2014; p 273. For the selected review on asymmetric enamine catalysis, see: (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
[63] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

iminium ion **II**. The carbon−carbon bond formation proceeds via transition state **IV** in which protonation of the acceptor carbonyl group occurs by the carboxylic acid. The generated iminium ion **V** is hydrolyzed to release the product and regenerate the catalyst. This landmark report invoked the explosive growth in the field of asymmetric organocatalysis.[64]

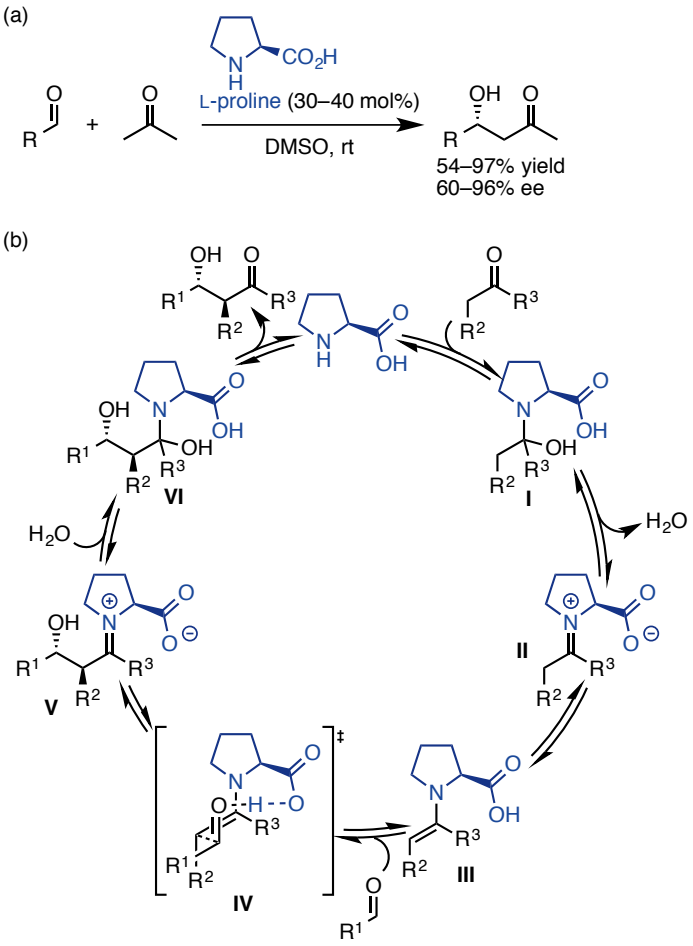

Figure 24 (a) The original report of proline-catalyzed intermolecular aldol reaction. (b) The proposed catalytic cycle for the proline-catalyzed intermolecular aldol reaction.

[64] MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

3. Cross-Aldol Reaction of Aldehydes

As mentioned in the previous section, a catalytic asymmetric aldol reaction is a highly valuable synthetic method for constructing the 1,3-polyol motifs. Despite marked progress, however, the development of catalytic asymmetric aldol reactions has focused mainly on the use of ketones, esters, thioesters, and other carboxylic acid derivatives as donors (Figure 25a). Thus, to install a second 1,3-diol unit in an iterative approach requires protection of the β-hydroxy group, followed by reduction or oxidation of the terminal carbonyl group to the corresponding aldehyde function. As a result, each elongation step requires additional protecting group manipulations and redox treatments, as well as isolation and purification of the intermediates. Therefore, an ideal unit reaction for 1,3-polyol synthesis is the catalytic asymmetric cross-aldol reaction between two different aldehydes, providing an aldehyde moiety for subsequent iterative aldol reactions (Figure 25b).

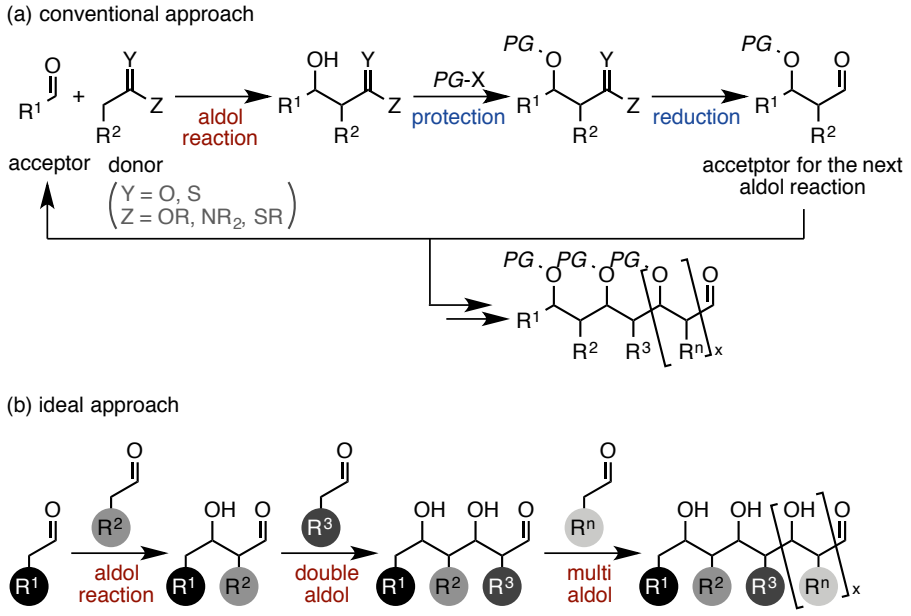

Figure 25 (a) A conventional aldol approach to 1,3-polyols through aldol reaction. (b) An ideal aldol approach through iterative cross-aldol reactions between aldehydes.

Although this idea is conceptually simple, catalytic asymmetric iterative cross-aldol reactions between two aldehydes are extremely challenging for the following reasons. First, even for a single aldol reaction, two aldehydes must be differentiated as either a donor or an acceptor (Figure 26a). Otherwise, undesired homo- and hetero-aldol products will be randomly produced.[65] Generation of preformed active metal enolates is often difficult by simple deprotonation/metallation of the corresponding aldehydes because of self-condensation (Figure 26b). Second, the intermediate β-hydroxy

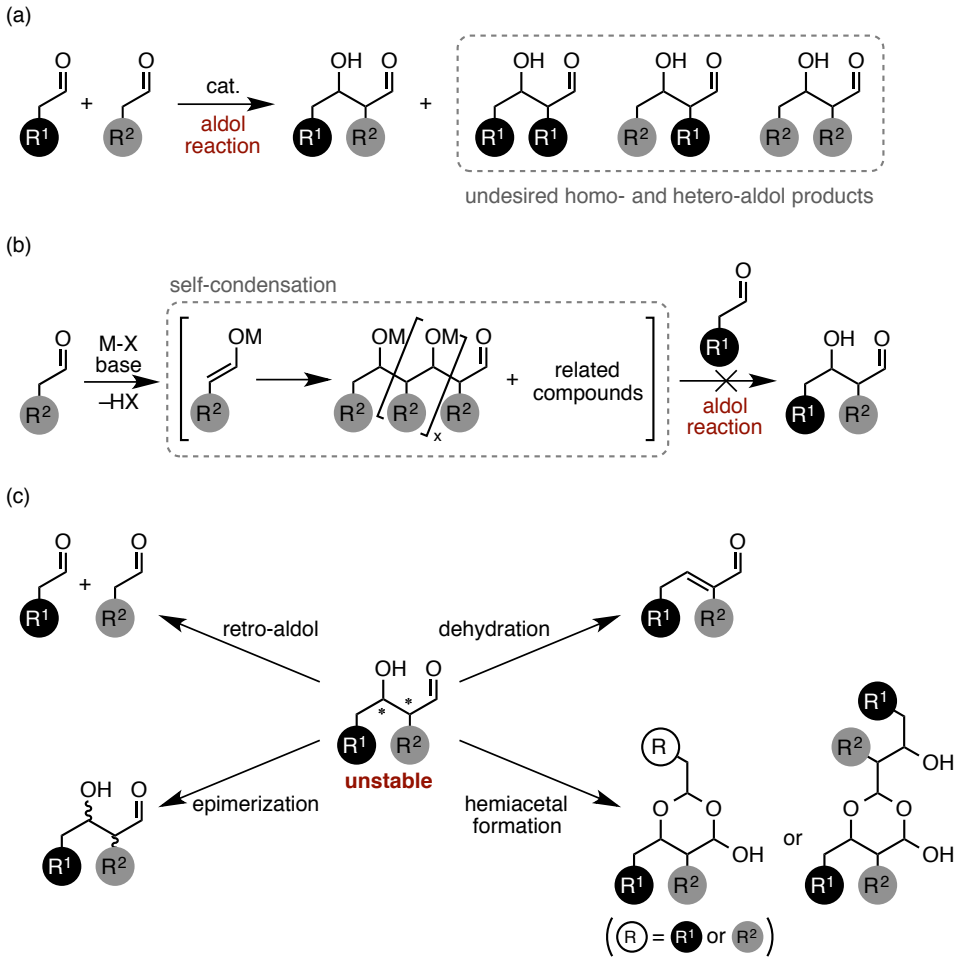

Figure 26 The difficult points of catalytic asymmetric aldol reaction of aldehydes. (a) Donor/Acceptor control. (b) Self-condensation of preformed active metal enolates. (c) Instability of the product.

[65] Tishchenko-type reaction is also problematic.

aldehydes are generally unstable (Figure 26c). Acidic, basic, and high temperature conditions can cause undesired side reactions, such as a retro-aldol reaction, epimerization, dehydration, hemiacetal formation, and polymerization. Thus, it is necessary to perform the reaction under mild conditions at a neutral pH and low temperature. Third, the number of possible stereoisomers increases exponentially as the iteration of the aldol reaction proceeds (Figure 27). High fidelity in both enantio- and diastereoselectivity for a unit aldol reaction is essential to avoid complication due to the formation of multiple stereoisomers. Finally, the products of double- and more than double-aldol reactions exist as cyclized hemiacetal forms lacking a reactive aldehyde functional group. To avoid generating the unreactive cyclic hemiacetals, hydroxy groups of the intermediate aldol products need to be protected in more than double-aldol reactions.

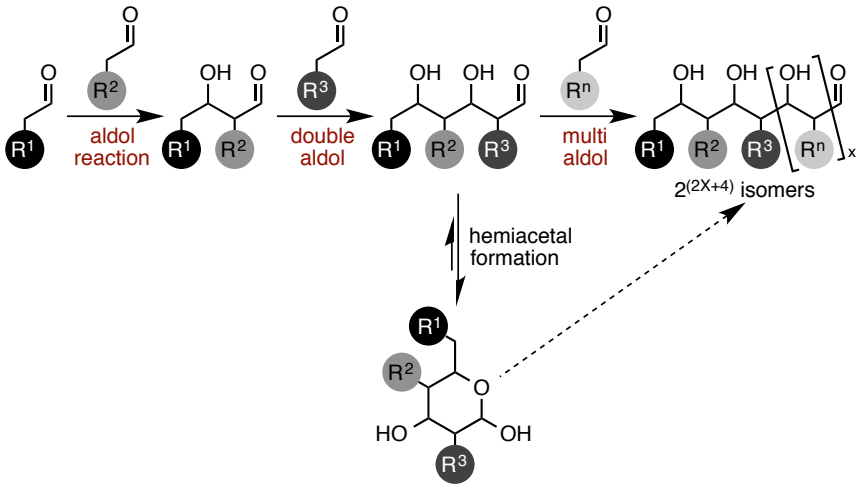

Figure 27 Potential difficulties of multi-aldol reactions.

3.1 Single-Aldol Reaction

A number of notable advances have been reported for cross-aldol reaction of aldehydes. Mukaiyama reported that the silyl enol ether, prepared from isobutyraldehyde, reacted with aldehydes in the presence of titanium tetrachloride in good yields (Figure 28).[51b]

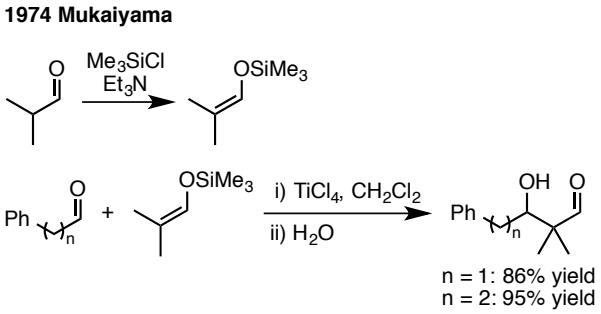

Figure 28 The original report of aldehyde-derived silyl enol ether for cross-aldol reaction of aldehydes.

In 1980, Heathcock prepared the (*E*)- and (*Z*)-lithium enolates of propanal from the corresponding silyl enol ethers and demonstrated the aldol addition to benzaldehyde in low diastereoselectivity (Figure 29).[28] It was mentioned that aldol addition to enolizable aldehydes was unsuccessful with lithium enolate.

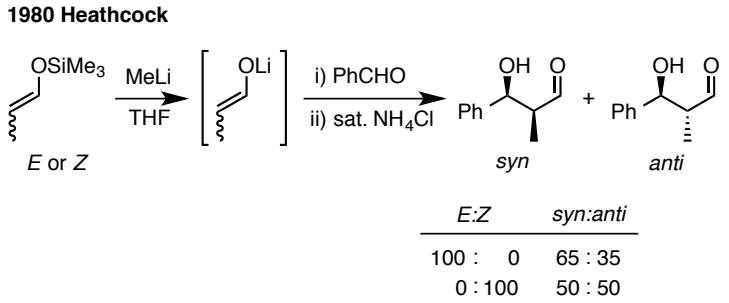

Figure 29 The original report of lithium enolate for the cross-aldol reaction of aldehydes.

Tin(II) enolate showed a bit better substrate generality. Both Aryl and enolizable alkyl aldehydes reacted with tin enolate, which was generated from 2-bromo-2-methylpropanal and metallic tin prepared from tin chloride and potassium (Figure 30).[66]

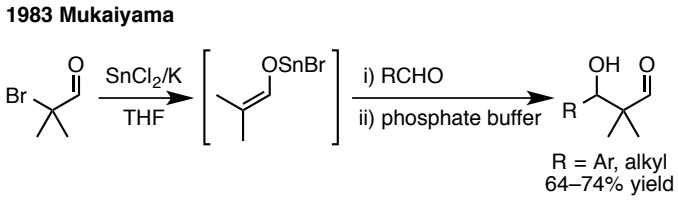

Figure 30 The original report of tin enolate for the cross-aldol reaction of aldehydes.

In 1987, Hoffmann demonstrated the aldol addition of aldehyde-derived boron enolate (Figure 31).[67,68] Although enol borate itself has a high tendency towards polymerization, the reaction stopped at the single-aldol stage because of the 1,3,2-dioxaborinane formation by an intramolecular addition of the boron−oxygen bond to the aldehyde.

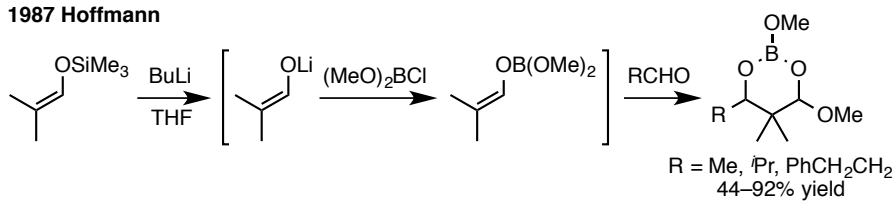

Figure 31 The example of boron enolate for the cross-aldol reaction of aldehydes.

As for the diastereoselective reaction, titanium enolates realized the *syn*-selective addition to appropriately chosen aldehydes (Figure 32).[69] The products can be

[66] Kato, J.; Mukaiyama, T. *Chem. Lett.* **1983**, 1727.
[67] Hoffmann, R. W.; Ditrich, K. Fröch, S. *Liebigs Ann. Chem.* **1987**, 977.
[68] Prior to the Hoffmann's report, aldol reaction of aldehyde-derived boron enolate was reported by Wulff: (a) Wulff, G.; Hansen, A. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 560. (b) Wulff, G.; Birnbrich, P.; Hansen, A. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1158.
[69] (a) Mahrwald, R.; Costisella, B.; Gündogan, B. *Tetrahedron Lett.* **1997**, *38*, 4543. (b) Mahrwald, R.; Costisella, B.; Gündogan, B.

isomerized to the more stable *anti* products with the catalytic amount of $Ti(O^iPr)_4$ in the presence of TMEDA. The trichlorotitanium enolates are also generated by reduction[70] or conjugate addition,[71] furnishing *syn*-aldols in moderate to excellent diastereoselectivity. On the other hand, aldol addition of a titanium enolate derived from titanium alkoxide and either (*Z*)- or (*E*)-silyl enolate showed low to moderate diastereoselectivity with weak dependence on enolate geometry (Figure 32).[72] However, it is quite notable that this system realizes the aldol reaction of aldehyde enolates with ketones, not aldehydes,[73] because of the formation of cyclic titanate after the aldol

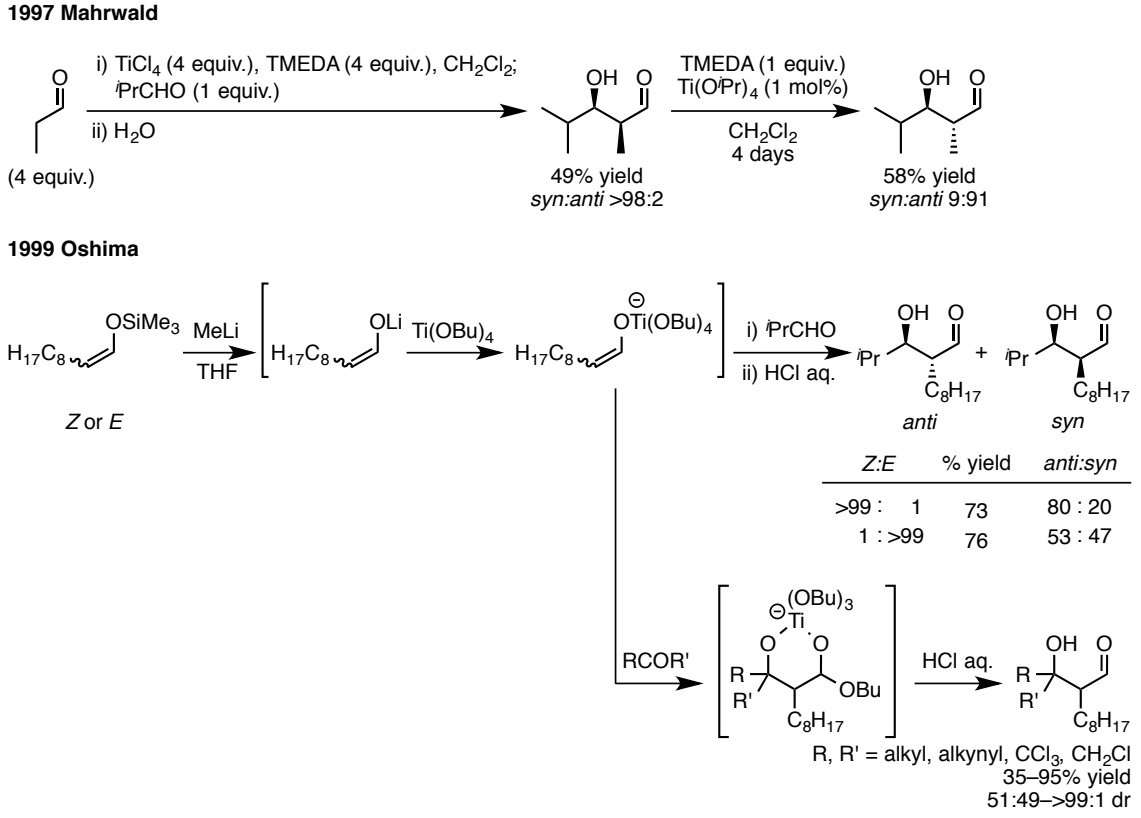

Figure 32 The notable examples of titanium enolate for the cross-aldol reaction of aldehydes.

Synthesis **1998**, 262.

[70] Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 4558.

[71] Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1383.

[72] Yachi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **1999**, *121*, 9465.

[73] This is the only example, which realized the aldol reaction between acceptor ketones and donor aldehydes. The major challenges are that: (1) the reaction is a thermodynamically very unfavorable process in comparison with the reaction of acceptor aldehydes and donor ketones, (2) aldehyde enolates deprotonate α-hydrogen of ketones to generate the ketone enolates, (3) the β-hydroxy aldehydes, the aldol adducts, are more reactive as acceptors than the starting ketones.

addition.

In 2001, Denmark reported the first catalytic, diastereoselective, and enantioselective cross-aldol reactions of aldehydes (Figure 33).[74, 75] The enoxytrichlorosilane was selected as a donor because it has a poor nucleophilicity and relatively Lewis-acidic silicon atom owing to the strongly electron-withdrawing trichloro moiety. When the Lewis base catalyst (*R,R*)-**1**, alkyl linked bis-phosphoramides, is employed, two phosphine oxide groups bind to the silicon atom to generate the cationic trigonal bipyramidal species followed by the coordination of aldehyde to provide a cationic octahedral silicon complex. The subsequent carbon−carbon bond formation takes place through a chair-like transition state to form the *in situ* protected product, α-chloro silyl ether, which hampers the oligomerization processes. After the conversion to the corresponding dimethyl acetals, products were obtained in excellent diastereoselectivity, moderate to good yields, and low to moderate enantioselectivity.

Further investigations reveal that the aldol addition of acetaldehyde-derived silyl enol ether is also possible by the Lewis base catalyst (*R,R*)-**1** (Figure 34).[76,77] Although the catalyst is the same, it binds to $SiCl_4$ to form a chiral siliconium ion, which acts as a Lewis acid to activate acceptor aldehydes. The following carbon−carbon bond formation proceeds through open transition structure to furnish six-membered chlorohydrin as well.

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[74] Denmark, S. E.; Ghosh, S. K. *Angew. Chem. Int. Ed.* **2001**, *40*, 4759.

[75] For review on Lewis base catalysis of the Mukaiyama aldol reaction, see: Beutner, G. L.; Denmark, S. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 9086.

[76] Denmark, S. E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10190.

[77] The aldol addition of acetaldehyde had not been described in any broad sense before 2005. For example, Paterson utilized the TBS enol ether of acetaldehyde in his total synthesis of Swinholide A. The electrophile was, however, a highly electrophilic oxonium ion: Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. The enzyme, 2-deoxyribose-5-phosphate aldolase (DERA), also catalyzes acetaldehyde aldol reaction: Barbas III, C. F.; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1990**, *112*, 2013.

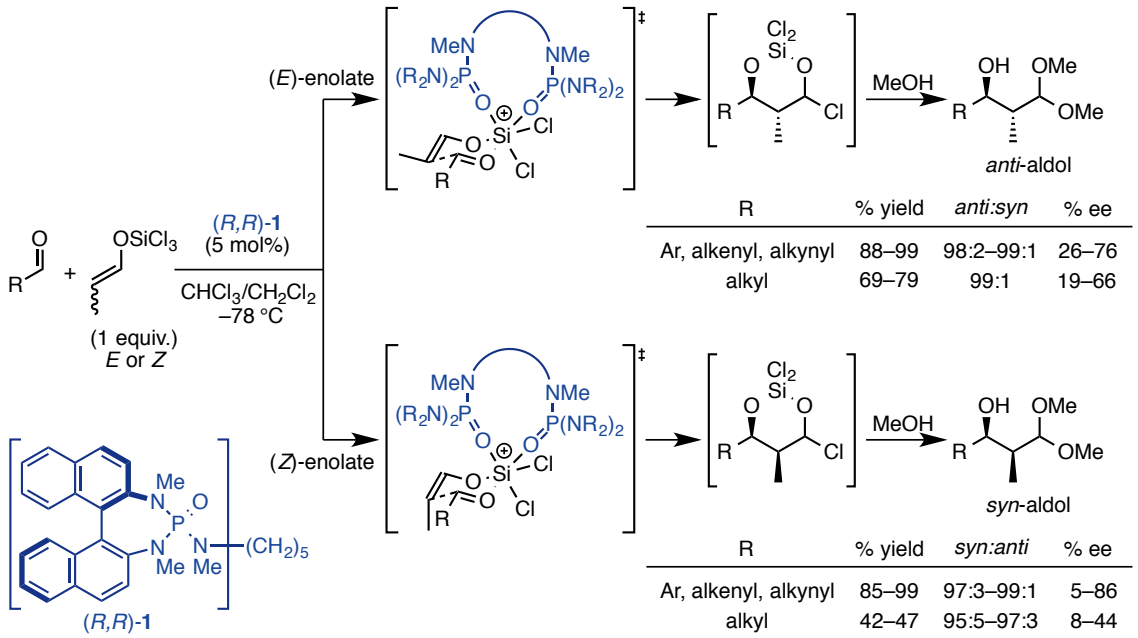


Figure 33 The first catalytic, diastereoselective, and enantioselective cross-aldol reactions of aldehydes.

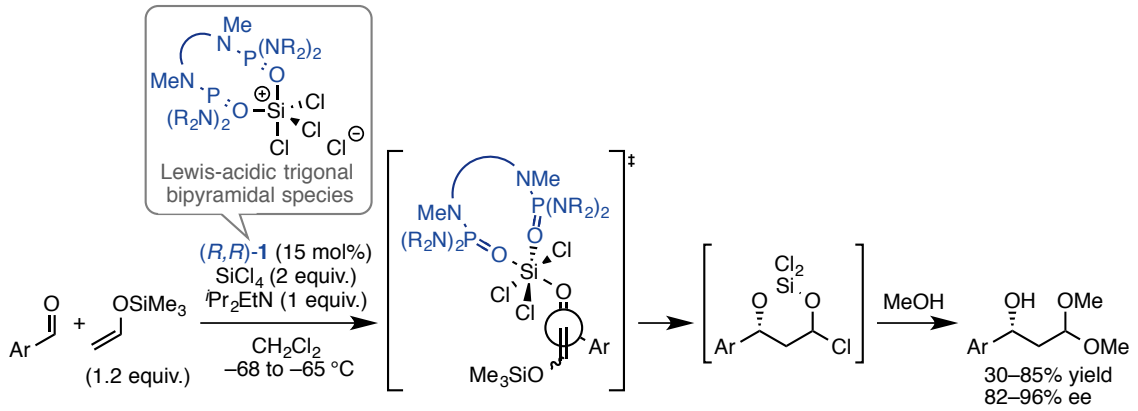


Figure 34 Lewis base catalyzed enantioselective aldol addition of acetaldehyde-derived silyl enol ether.

In 2002, MacMillan reported the first catalytic asymmetric direct aldol reaction of aldehydes (Figure 35a).[78] The proline catalysis realized the *anti*-selective cross-aldol reaction between nonequivalent aldehydes in good yields and high enantioselectivity. Although syringe pump addition of donor aldehydes was required to suppress the

[78] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.

homodimerization of donors, enamine activation has emerged as a powerful strategy for the aldehyde cross-aldol reaction. The following reports improved the substrate generality and diastereoselectivity by modifying proline or utilizing other amino acids,[79] however, *syn*-selective reaction had not been achieved before 2007.

In 2007, Maruoka utilized an axially chiral amino sulfonamide (*S*)-**2**, which was designed for asymmetric Mannich reaction reported by the same group,[80] for cross-aldol reaction of aldehydes (Figure 35b). In analogy with the Mannich reaction, they expected that the acceptor aldehyde would be activated by the distal acidic proton of the triflamide, and that the reaction would proceed through s-*cis*-enamine

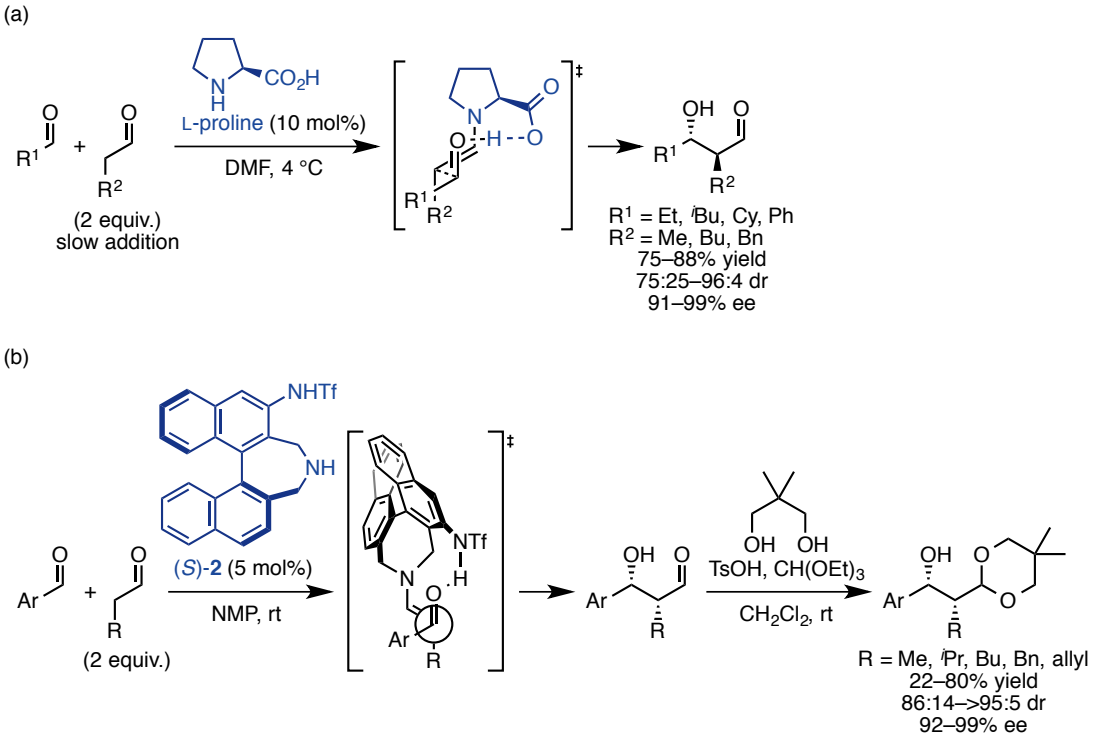


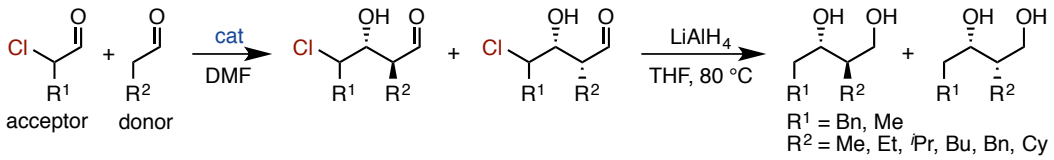
Figure 35 Direct aldol reaction of aldehydes catalyzed by organocatalyst. (a) The original report by MacMillan. (b) The *syn*-selective reaction by enamine catalysis.

[79] For selected examples, see: (a) Mase, N.; Tanaka, F.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 2420. (b) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722. (c) Wang, W.; Li, H.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 5077. (d) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T., Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5527. (e) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2082. (f) Markert, M.; Scheffler, U.; Mahrwald, R. *J. Am. Chem. Soc.* **2009**, *131*, 16642.

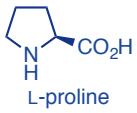
[80] Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408.

intermediate to generate *syn*-aldols. Although the generality of acceptor aldehydes are limited to relatively electrophilic aryl aldehydes, a highly *syn*-selective and enantioselective direct cross-aldol reaction was achieved.

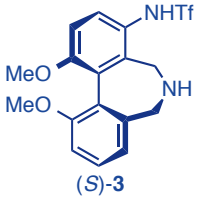
The current state-of-the-art cross-aldol reaction of aldehydes was also reported by Maruoka in 2011 (Figure 36).[81] They solved the long-standing problem of donor/acceptor control by introducing α-halo group to acceptor aldehydes. The formation of enamine intermediates from sterically hindered α-haloaldehydes is suppressed and desired donor aldehyde-derived enamine intermediates are predominantly formed. Moreover, the generated enamine intermediate reacts with more electrophilic α-haloaldehydes over the other donor aldehydes. By utilizing proline or an axially chiral amino sulfonamide (*S*)-**3** as a catalyst, highly enantioselective cross-aldol reaction between aliphatic aldehydes proceeded to generate *anti*- or *syn*-aldols, respectively. The halogen group on the product can be removed under reductive conditions with the reduction of the aldehyde moiety.



acceptor	donor	cat	% yield	*anti:syn*	% ee
1 equiv.	8 equiv.	L-proline (30 mol%), 0 °C	55–91	77:23 – >95: 5	94–98
2 equiv.	1 equiv.	(*S*)-**3** (5 mol%), rt	73–90	25:75 – 5:>95	96–99



L-proline



(*S*)-**3**

Figure 36 The current state-of-the-art cross-aldol reaction of aldehydes.

[81] Kano, T.; Sugimoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 18130.

A method to generate aldehyde-derived enolates from non-carbonyl precursors via an orthogonal activation mode[82] would provide an alternative and complementary approach to obtain aldehyde-aldehyde cross-aldol products. In 2012, our group reported the first one-pot isomerization/aldehyde-cross-aldol sequence (Figure 37a).[83] A Rh/dippf catalyst promoted the isomerization of primary allylic alcohol borates[84] at ambient temperature under neutral conditions to chemoselectively afford aldehyde-derived enolates *in situ* (Figure 37b). The isomerization/aldol sequence proceeded in one-pot, giving cross-aldol adducts in moderate to good *syn*-selectivity. Even readily enolizable aldehydes, such as propanal, were used as acceptors in these reaction conditions, which cannot be achieved by enamine catalysis. Further investigations toward the enantioselective variants, however, were all failed by using

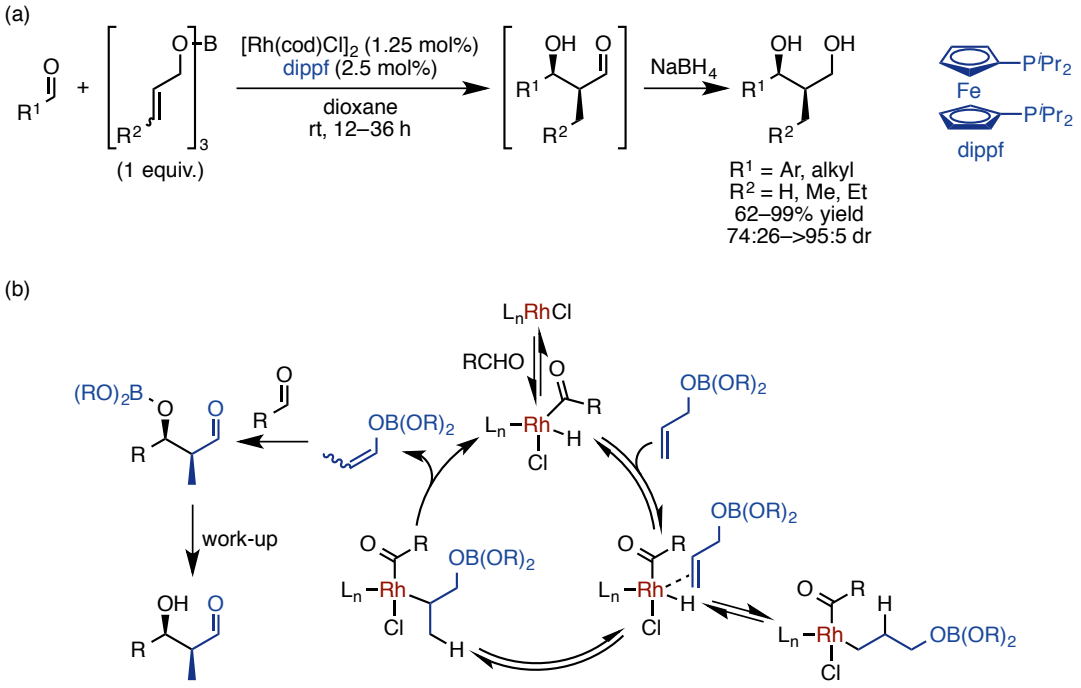


Figure 37 Rh-catalyzed cross-aldol reaction. (a) Substrate scope. (b) Plausible catalytic cycle.

[82] Sheppard, T. D. *Synlett* **2011**, *10*, 1340.
[83] Lin, L.; Yamamoto, K.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 10275.
[84] Although isomerization of the triallyloxyborane into an enol borane was reported by ruthenium catalyst, its reactivity toward aldol reaction was disclosed by our group; Krompiec, S.; Suwiński, J.; Gibas, M.; Grobelny, J. *Polish J. Chem.* **1996**, *70*, 133.

either chiral rhodium catalysts or chiral alkoxyboranes.

3.2 Double-Aldol Reaction

Double-aldol reaction, the sequence of two aldol reactions; i.e., the first aldol addition of an aldehyde to an acceptor aldehyde followed by the second aldol addition of an aldehyde to the generated β-hydroxy aldehyde,[85] was described by enzyme catalysis in 1994. Wong reported that the enzyme, 2-deoxyribose-5-phosphate aldolase (DERA), catalyzes stereospecific addition of acetaldehyde to α-substituted acetaldehydes to form β-hydroxy aldehydes, which react subsequently with another acetaldehyde to form 2,4-dideoxyhexose derivatives in a stereospecific manner (Figure 38a).[86] DERA also accepts propanal as a donor substrate by increasing the amounts of DERA and reaction time (Figure 38b).[87]

The current progress of enzyme catalysis on aldol reaction is the utilization of engineered D-fructose-6-phosphate aldolase (FSA). A set of FSA variants with

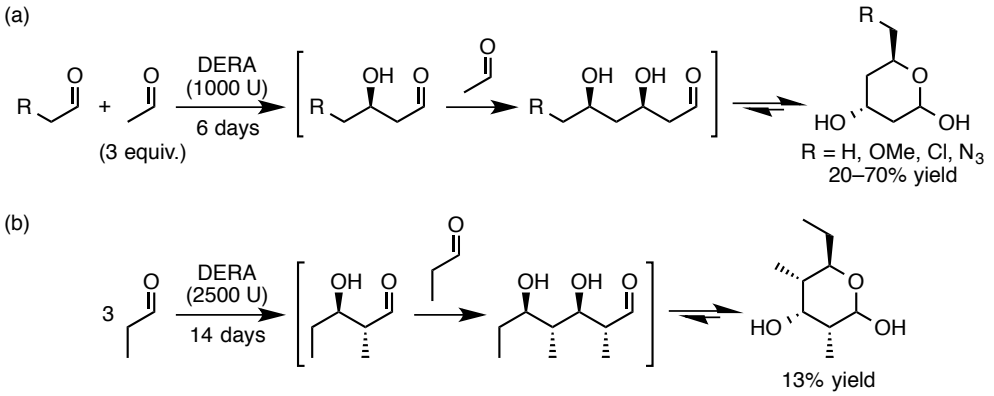


Figure 38 Asymmetric double-aldol reaction catalyzed by DERA. (a) Acetaldehyde was used as a donor. (b) Trimerization of propanal.

[85] In this section, only the aldehyde-double-aldol reaction is described. For the examples of ketone-double-aldol reactions, see: (a) Yun, S.-S.; Suh, I.-H.; Choi, S.-S.; Lee, S. *Chem. Lett.* **1998**, 985. (b) Schmittel, M.; Ghorai, M. K. *Synlett* **2001**, *12*, 1992. (c) Haeuseler, A.; Henn, W.; Achmittel, M. *Synthesis* **2003**, *16*, 2576. (d) Wang, X.; Meng, Q.; Perl, N. R.; Xu, Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12806. (e) Cinar, M. E., Schmittel, M. *J. Org. Chem.* **2015**, *80*, 8175. Our group reported the aldehyde-ketone aldol sequence; (f) Lin, L.; Yamamoto, K.; Matsunaga, S.; Kanai, M. *Chem. Asian J.* **2013**, *8*, 2974.

[86] Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 8422.

[87] Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 7585.

enhanced activity and selectivity does catalyze the formation of a variety of D-idose derivatives in low to moderate yields (Figure 39a).[88] Furthermore, the pertinent combination of differentially engineered FSAs realizes the synthesis of L-glucose derivatives by alternating the stereochemical course of the first addition (Figure 39b).

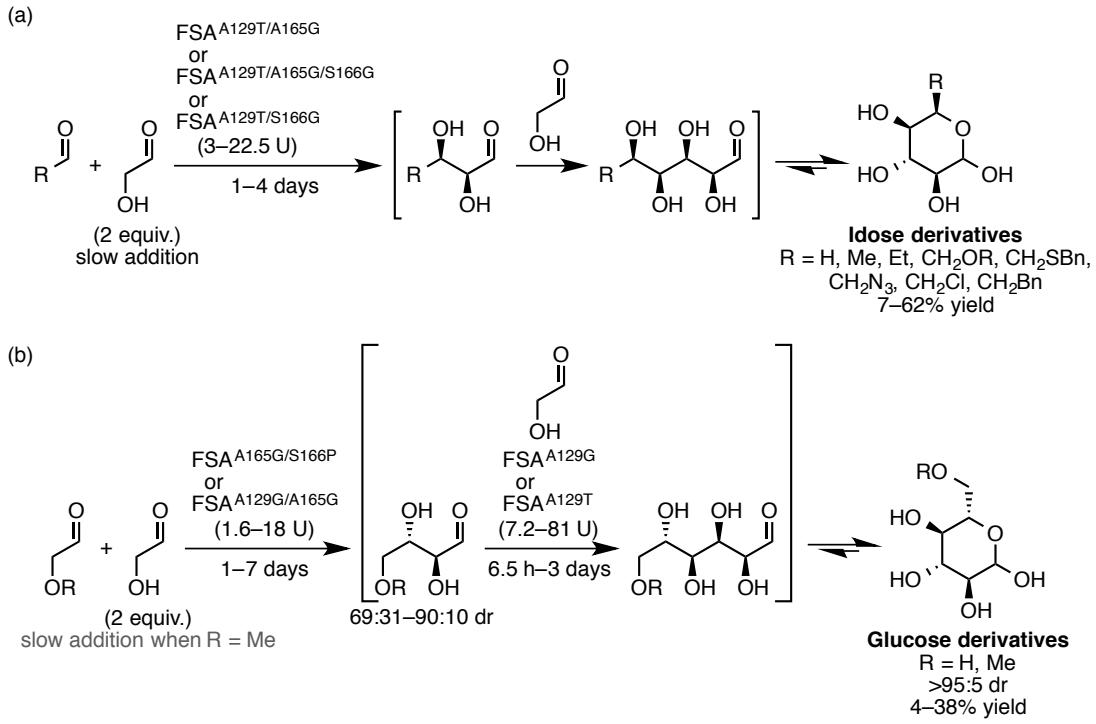


Figure 39 Engineered enzyme catalyzed asymmetric double-aldol reaction. (a) Synthesis of D-idose derivatives. (b) Synthesis of L-glucose derivatives.

Inspired by the Wong's enzyme catalyzed assembly, Barbas and Córdova investigated the proline catalysis for the enzyme-like asymmetric double-aldol reaction. In 2002, just before the MacMillan's first report of proline catalyzed asymmetric direct aldol reaction of aldehydes,[78] they studied the trimerization of acetaldehyde to find that the product was not the hexose-like cyclized trimer, which was obtained by DERA, but 5-hydroxy-(2*E*)- hexenal (Figure 40a).[89] In contrast to acetaldehyde, however, propanal

[88] Szekrenyi, A.; Garrabou, X.; Parella, T.; Joglar, J.; Bujons, J., Clapés, P. *Nat. Chem.* **2015,** *7,* 724.
[89] Córdova, A.; Notz, W.; Barbas III, C. F. *J. Org. Chem.* **2002**, *67*, 301.

and proline provided the cyclic trimer as a major product (Figure 40b).[90] The yield and enantioselectivity vary depending on the solvent, reaction time, temperature, and procedure.[90d] Judging from the product's absolute configuration, the reaction suffered from the mismatch between L-proline-derived enamine and single-aldol product at the second aldol addition stage. Indeed, when L- and D-proline was used at the first and second step, respectively, excellent enantioselectivity and wider substrate generality were obtained (Figure 40c).[91]

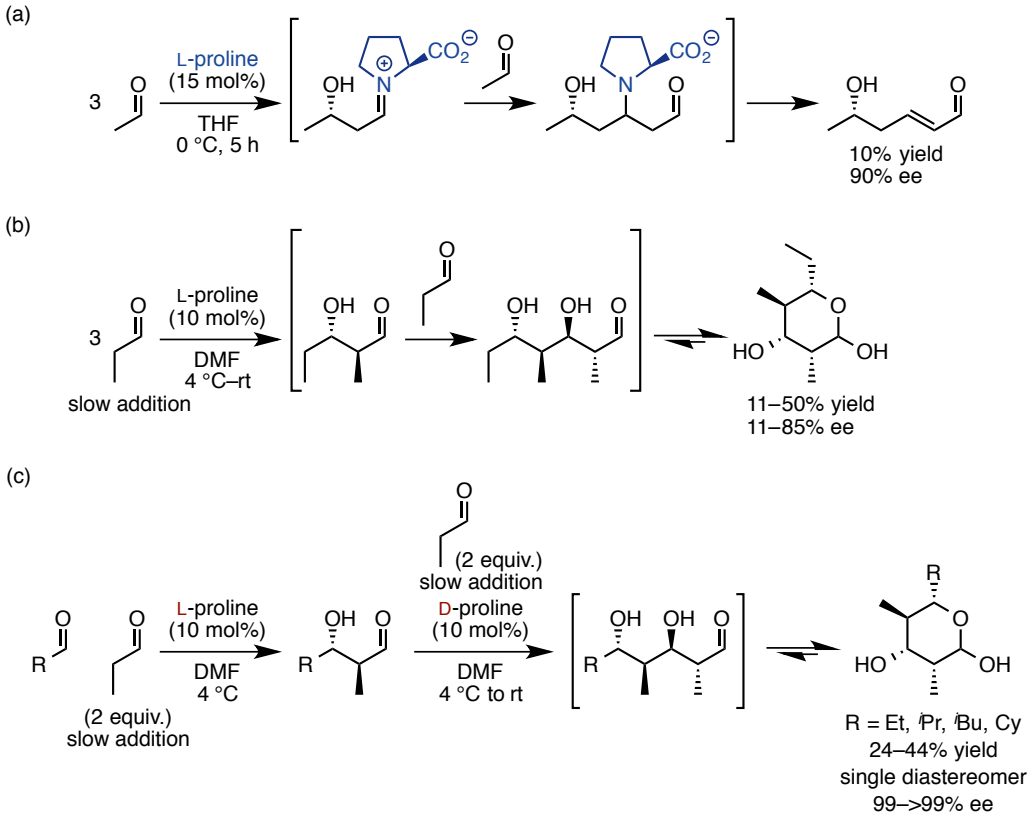


Figure 40 Proline catalyzed asymmetric double-aldol reaction. (a) Self-aldolization of acetaldehyde. (b) Self-aldolization of propanal.[92] (c) The sequential L- and D-proline catalyzed asymmetric double-aldol reaction.

[90] (a) Chowdari, N. S.; Ramachary, D. B.; Córdova, A.; Barbas III, C. F. *Tetrahedron Lett.* **2002**, *43*, 9591. (b) Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res.* **2004**, *37*, 580. (c) Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 3949. (d) Córdova, A.; Ibrahem, I.; Casas, J.; Sundén, H.; Engqvist, M.; Reyes, E. *Chem. Eur. J.* **2005**, *11*, 4772.

[91] Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1343.

[92] The absolute and relative configurations of the products were miss assigned in ref 90 (a)-(c). The chemical shifts reported in those papers are completely matched with those reported in ref 91, where the configurations were assigned based on the X-ray crystallographic analysis.

In 2004, MacMillan expanded the substrate scope of proline catalysis to enantioselective direct aldol reaction of α-oxyaldehydes.[93] Exposure of α-siloxy-acetaldehyde to L-proline does provide dimerized product, α,γ-oxy-protected L-erythrose. To this enantioenriched aldehyde, the diastereoselective Mukaiyama aldol reaction of α-oxy-enolsilane proceeded to generate differentially protected glucose, mannose, or allose just by changing Lewis acid and solvent (Figure 41).[94] They further demonstrated the utility of this methodology by applying the reaction sequence to the preparation of $^{13}C_6$-labeled hexoses.

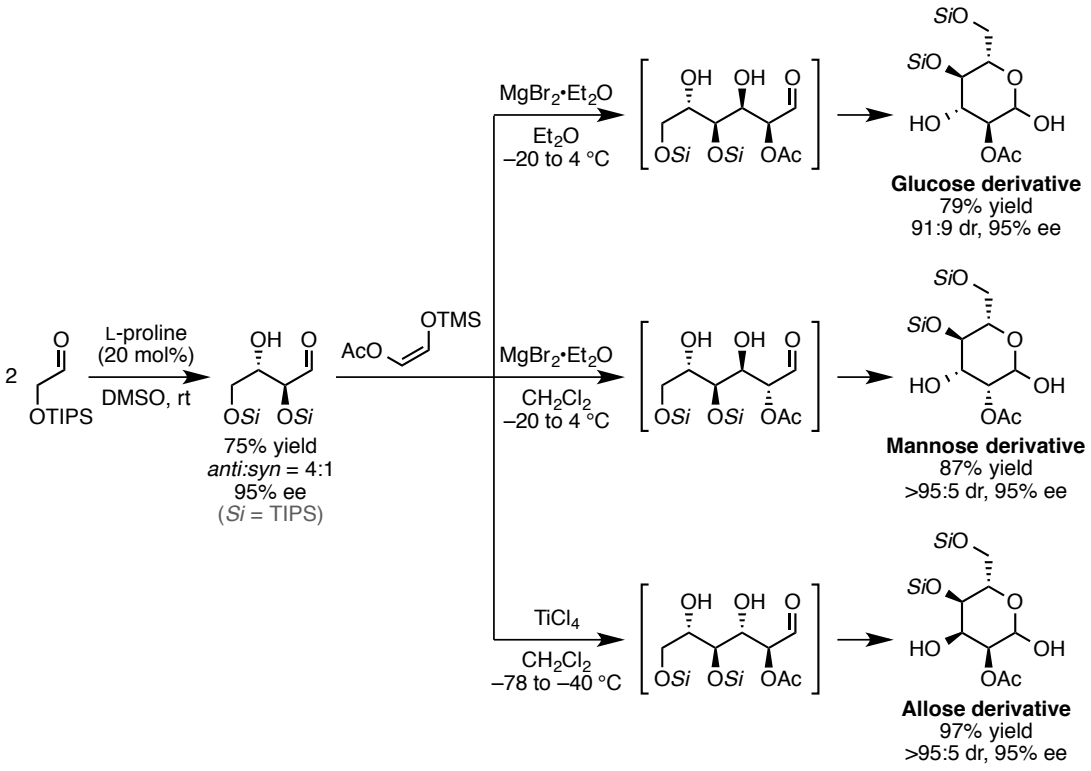


Figure 41 Two-step synthesis of differentially protected sugars by proline catalyzed dimerization of α-oxyaldehyde[95] followed by Mukaiyama aldol reaction.

[93] Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.
[94] Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752.
[95] Although the yield and catalyst amount are reported to be 92% and 10 mol%, respectively, for the proline catalyzed dimerization of α-oxyaldehyde in ref 93 and 94, it seems to be more appropriate to correct those numbers to be 75% yield and 20 mol%, respectively, judging from the supporting information of ref 93.

3.3 More than Double-Aldol Reactions

There is one big difference between double-aldol reaction and more than double-aldol reaction. The products of double- and more than double-aldol reactions exist as cyclized hemiacetal forms lacking a reactive aldehyde functional group. To realize more than double-aldol reactions, either of the two strategies have to be taken; shift the equilibrium to aldehyde forms or protect the generated hydroxy groups to avoid hemiacetal formation.

The first triple-aldol reaction was reported by Wong in 1995.[87] The DERA-catalyzed sequential aldol reaction was applied for the tetramerization of acetaldehyde (Figure 42a). A very large amount of DERA and long period of time (14 days) did furnish the triple-aldol product in 6% yield along with 64% yield of double-aldol product. Combination of DERA and *N*-acetylneuraminic acid aldolase

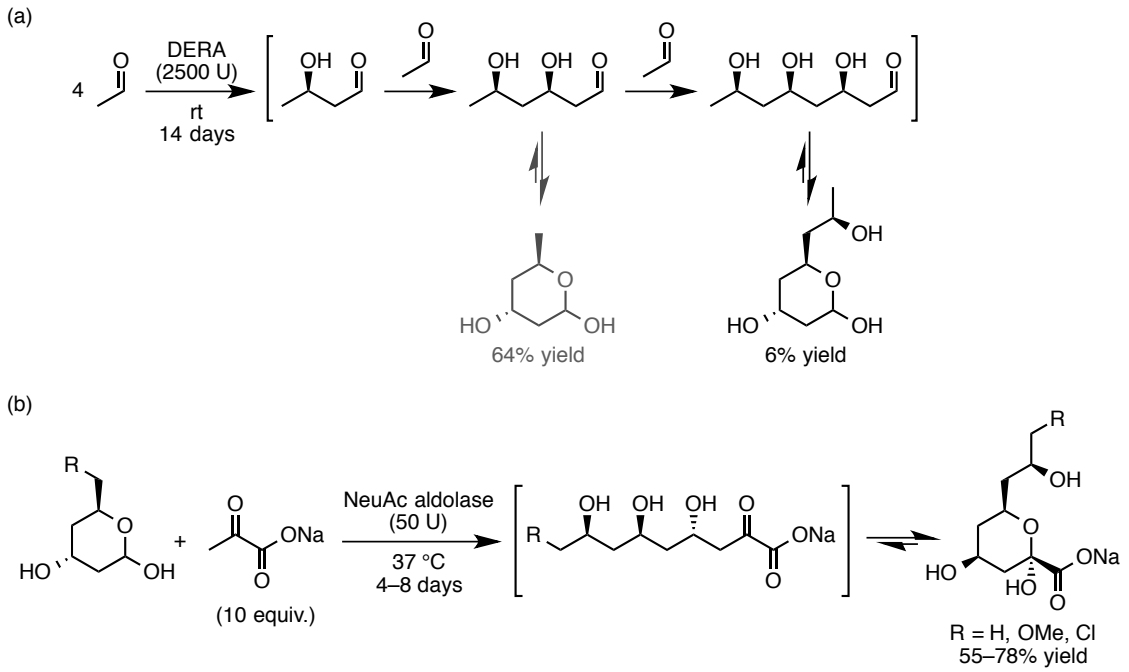


Figure 42 Enzyme catalyzed asymmetric triple-aldol reactions. (a) DERA-catalyzed tetramerization of acetaldehyde. (b) NeuAc aldolase catalyzed asymmetric triple-aldol reaction.

(NeuAc aldolase) gave sialic acid derivatives in 55−78% yields (Figure 42b). NeuAc aldolase only accepts pyruvate as a donor substrate but is more flexible for acceptor substrates. When the enzyme and pyruvate are added to the double-aldol product described in Figure 38a, nine-carbon sugar derivatives were obtained without isolation of the double-aldol intermediate.

The current state-of-the-art multi-aldol reaction of aldehydes has been reported by Yamamoto.[96] This methodology employs catalytic, sequential, one-pot Mukaiyama aldol reactions of tris(trimethylsilyl)silyl ("super-silyl") enol ether. High steric shielding provided by the super-silyl group and its unique properties allowed to tame the reactivity of enolates and diastereoselection in aldol additions.

Acetaldehyde derived super-silyl enol ether readily undergoes aldol addition to aldehydes promoted by 0.05 mol% triflimide precatalyst (Figure 43a, the first line).[97] The active catalyst is the silylium Lewis acid, $[(TMS)_3Si]^+[Tf_2N]^-$, generated by protodesilylation of the super-silyl enol ether (Figure 43b, upper row). Propanal derived (*Z*)- or (*E*)-enolate predominantly generates *syn*- or *anti*-aldol, respectively (Figure 43a, second and third line).[98] This unique correlation is not usually observed in classical Mukaiyama aldol reaction. Introduction of either halogen atom or oxygen functionality at the α-position of β-siloxy aldehyde was also possible by enhancing the Lewis acidity of the active catalyst. Pentafluorophenylbis(triflyl)methane ($C_6F_5CHTf_2$), instead of triflimide, generates a stronger Lewis acid $[(TMS)_3Si]^+[C_6F_5CTf_2]^-$ [99] *in situ* to catalyze addition of halogenated super-silyl enol ethers to aromatic and aliphatic aldehydes, producing *anti*-β-siloxy α-fluoro-, chloro-, or bromo-aldehydes (Figure 43a,

[96] Brady, P. B.; Yamamoto, H. In *Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2013; p 269.
[97] Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48.
[98] Brady, P. B.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1942.
[99] Hasegawa, A.; Ishihara, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5731.

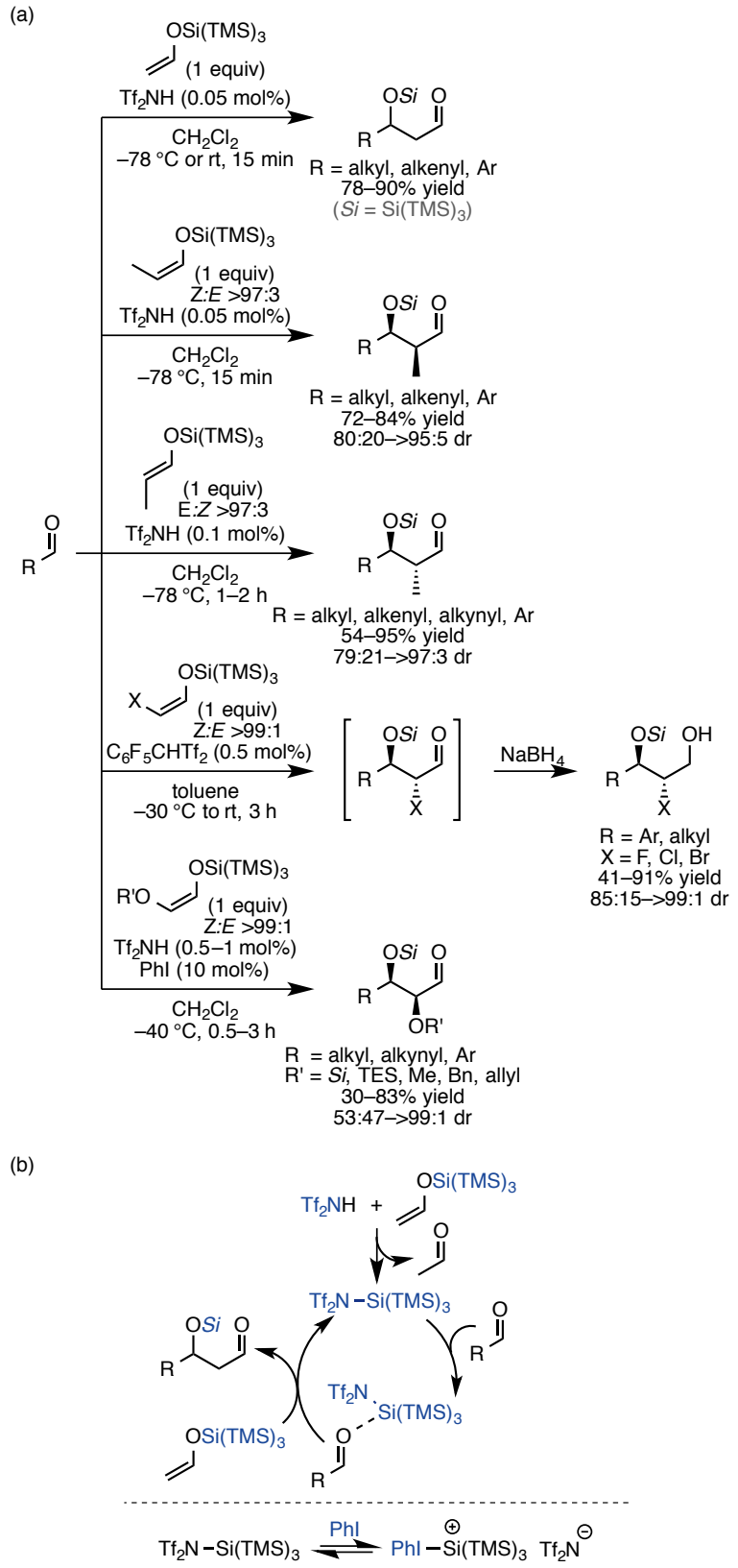


Figure 43 Mukaiyama aldol reactions of "super-silyl" enol ether. (a) Scope of super-silyl enol ethers. (b) Plausible catalytic cycle.

fourth line).[100] Addition of iodobenzene also enhances the Lewis acidity of silylium by stabilizing the silylenium cation (Figure 43b, bottom row). This cationic $[PhI{-}Si(TMS)_3]^+$ catalyzes the aldol addition of oxygenated super-silyl enol ethers to provide *syn*-α,β-dioxyaldehydes (Figure 43a, last line).[101]

The super-silyl chemistry can be applied to the first cascade Mukaiyama aldol reaction. Just by increasing the amount of super-silyl enolate, single-aldol products undergo a second aldol addition with another equivalent of enolate, resulting in 3,5-*syn*-bis-siloxy aldehydes (Figure 44a).[97] This stereochemical outcome is due to the bulky super-siloxy group, restricting the conformational freedom, as well as the β-C−O and C=O dipole-dipole interactions. Sequential aldol−aldol reaction using two different super-silyl enol ethers are also possible (Figure 44b).[98]

As the sequential aldol reaction proceeds, the rate of the next aldol addition becomes slow because of the generated bulky super-siloxy groups. However, addition

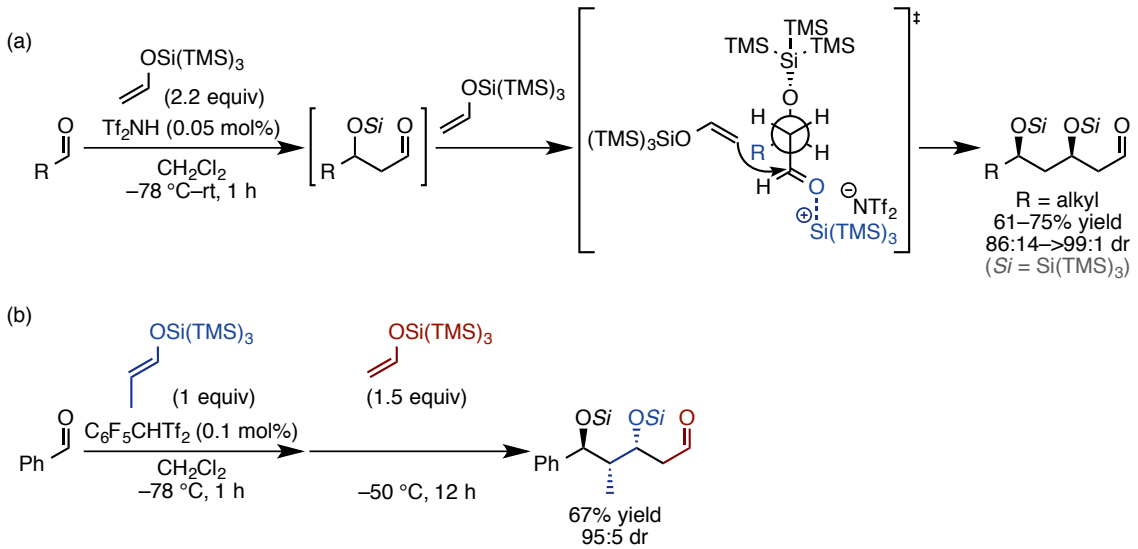


Figure 44 Double-aldol reactions mediated by super-silyl enol ethers. (a) Acetaldehyde double-aldol reactions. (b) Mixed double-aldol reaction.

[100] Saadi, J.; Akakura, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 14248.
[101] Gati, W.; Yamamoto, H. *Chem. Sci.* **2016**, *7*, 394.

of organoiodide (*vide supra*) realizes the triple-aldol reactions. Five equivalents of acetaldehyde derived super-silyl enol ether undergo aldol addition for three times to provide 3,5,7-trisiloxy aldehydes having 3,5,7-*syn*–*syn* stereochemistry (Figure 45a).[102] Mixed-triple aldol reaction again worked well, involving different donors at each step of the aldol addition (Figure 45b and c).[98,103]

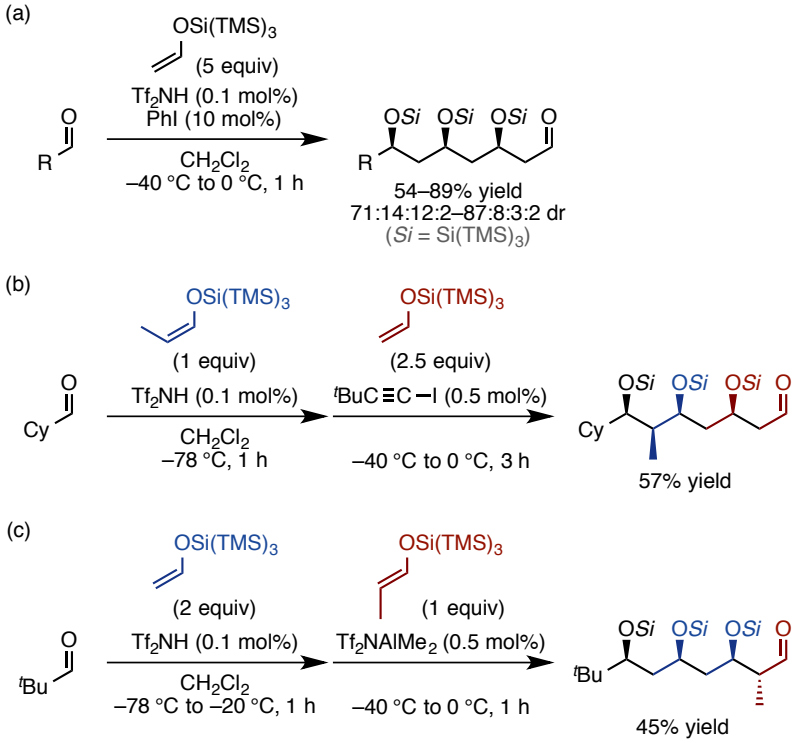


Figure 45 Triple-aldol reactions mediated by super-silyl enol ethers. (a) Acetaldehyde triple-aldol reactions. (b and c) Mixed triple-aldol reactions.

The utility of these catalytic diastereoselective (racemic) one-pot Mukaiyama aldol reactions of super-silyl enol ethers can be seen in the concise total syntheses. For example, EBC-23, which was identified as a new anticancer agent,[104] was synthesized

[102] Albert, B. J.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 2747.
[103] For detailed discussion on stereoselectivity, see: Brady, P. B.; Albert, B. J.; Akakura, M.; Yamamoto, H. *Chem. Sci.* **2013**, *4*, 3223.
[104] EBC-23 was isolated from the fruit of *Cinnamomum laubatii*; Reddell, P. W.; Gordon, V. A. WO 2007070984A1 20070628 PCT Int. Appl. 2007.

in 7 steps (5 steps for the longest linear sequence in 17% overall yield),[105] while Williams took 15 steps (11 steps for the longest linear sequence in 6% overall yield) (Figure 46a).[106] The method was also applied for the spiroketal synthesis, affording known synthetic intermediate of avermectin A_{1a} (Figure 46b)[107] along with other 10 functional analogs.[108]

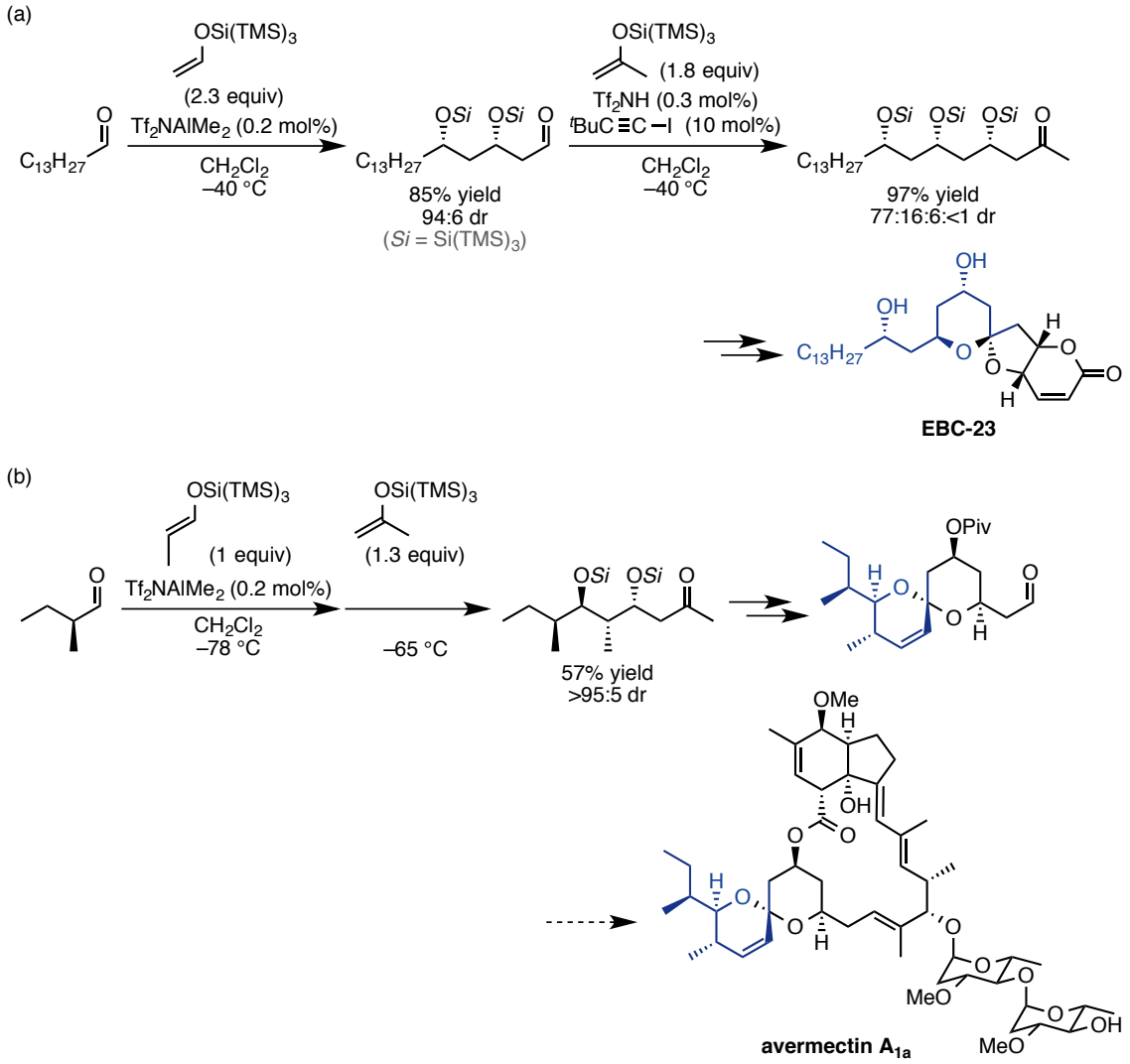


Figure 46 Super-silyl chemistry in the total synthesis. Parts of the molecules constructed by this method are shown in blue. (a) Total synthesis of EBC-23. (b) The formal total synthesis of avermectin A_{1a}.

[105] Albert, B. J.; Yamaoka, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 2610.
[106] Dong, L.; Gordon, V. A.; Grange, R. L.; Johns, J.; Parsons, P. G.; Porzelle, A.; Reddell, P.; Schill, H.; Williams, C. M. *J. Am. Chem. Soc.* **2008**, *130*, 15262.
[107] Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967.
[108] Brady, P. B.; Oda, S.; Yamamoto, H. *Org. Lett.* **2014**, *16*, 3864.

3.4 Aldol Polymerization

From the viewpoint of polymer chemistry, aldol reaction of aldehydes has been investigated for more than 60 years. Besides polymerization of vinyl acetates, aldol polymerizations serve as alternative synthetic methods for the preparation of poly(vinyl alcohol), PVA.

The first aldol polymerization of acetaldehyde was reported by Degering in 1951 (Figure 47).[109] Although the structure of the product had been unclear, further study revealed that the polymer was generated through multiple aldol reactions and partial dehydrations because it contained double bonds, hydroxy groups, and aldehydes.[110]

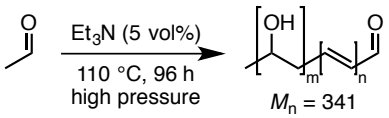


Figure 47 The original report of aldol polymerization of acetaldehyde.

Silyl vinyl ethers are also used for polymerization. In 1965, before the Mukaiyama's report of aldol reaction of silyl enol ether,[52] Murahashi studied the polymerization of vinyl trimethylsilyl ether under tin(IV) or aluminum Lewis acids to obtain poly(vinyl trimethylsilyl ether), which was easily converted to PVA (Figure 48).[111]

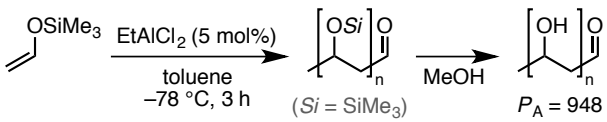


Figure 48 The original report of polymerization of silyl vinyl ether.

[109] Degering, ED. F.; Stoudt, T. *J. Polym. Sci.* **1951**, *7*, 653.
[110] Imoto, T.; Oota, T.; Kanabara, G. *Nippon Kagaku Zasshi* **1961**, *82*, 492.
[111] Murahashi, S.; Nozakura, S.; Sumi, M. *J. Polym. Sci., Part B* **1965**, *3*, 245.

In principle, direct aldol polymerization would furnish PVA with perfect atom economy by controlling stereochemistry of the main chain. Despite enormous strides, however, it remains extremely challenging by current methodologies.[112]

[112] For the recent report in this area, see: Kusumoto, S.; Ito, S.; Nozaki, K. *Asian J. Org. Chem.* **2013**, *2*, 977.

RESULTS AND DISCUSSION

Chapter 1: Copper(I) Alkoxide Catalyzed Asymmetric Iterative Cross-Aldol Reactions

In 2011, we launched a research program for the development of *de novo* chemical synthesis of 1,3-polyols by asymmetric iterative cross-aldol reactions of aldehydes. As a first approach, diastereoselective cross-aldol reaction was investigated based on the hypothesis that chemoselective activation of donor aldehyde would be possible by generating aldehyde-derived boron enolates from non-carbonyl precursor (Figure 1.1a). The simultaneous sequence of isomerization of allyl alcohol derivatives and *syn*-selective aldol addition proceeded under rhodium catalysis (see section 3.1),[1,2] but this reaction system was not suitable as a unit reaction for iterative aldol reactions due

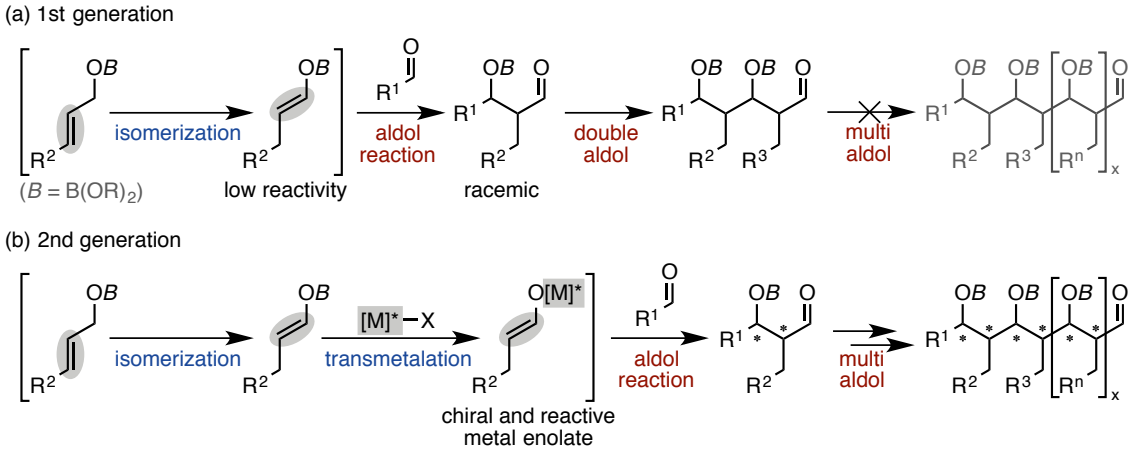


Figure 1.1 Our strategies for the catalytic iterative aldehyde cross-aldol reaction. (a) An initial approach; chemoselective activation of donor enolate through isomerization of allyl alcohol derivatives. (b) A revised approach throughout this chapter; generation of chiral and reactive metal enolate.

[1] The initial idea of generating aldehyde-derived donor enolate through isomerization of allyl alcohol derivatives belongs to Prof. Shigeki Matsunaga. The initial discovery of a Rh-catalyzed isomerization/aldol reaction sequence was made by Dr. Luqing Lin, a former graduate student in the Kanai group.

[2] (a) Lin, L. Ph.D. Thesis, The University of Tokyo, 2013. (b) Lin, L.; Yamamoto, K.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 10275. (c) Lin, L.; Yamamoto, K.; Matsunaga, S.; Kanai, M. *Chem. Asian J.* **2013**, *8*, 2974.

to its moderate reactivity and diastereoselectivity.[3]

We then envisioned that generation of highly reactive and chiral metal enolate through transmetalation would realize asymmetric multi-aldol reactions (Figure 1.1b). As a metal source, we selected Cu(I) based on the previous findings from Carreira's group and our group. Carreira reported the first chiral Cu(I) fluoride catalyzed aldol reaction of ester-derived silicon dienolate and aldehydes (Figure 1.2a).[4] They showed spectroscopic and chemical evidence for the existence of copper enolate as a reactive species, and thus the reaction mechanism is different from that of well-established Lewis acid promoted aldol reaction.[5] This finding was extended to a general aldol reaction between *ketones* and ester-derived silicon enolates by our group (Figure 1.2b).[6] Based on the similar characteristics of silicon and boron elements, we hypothesized that the reactive aldehyde-derived chiral copper(I) enolate would be generated from the

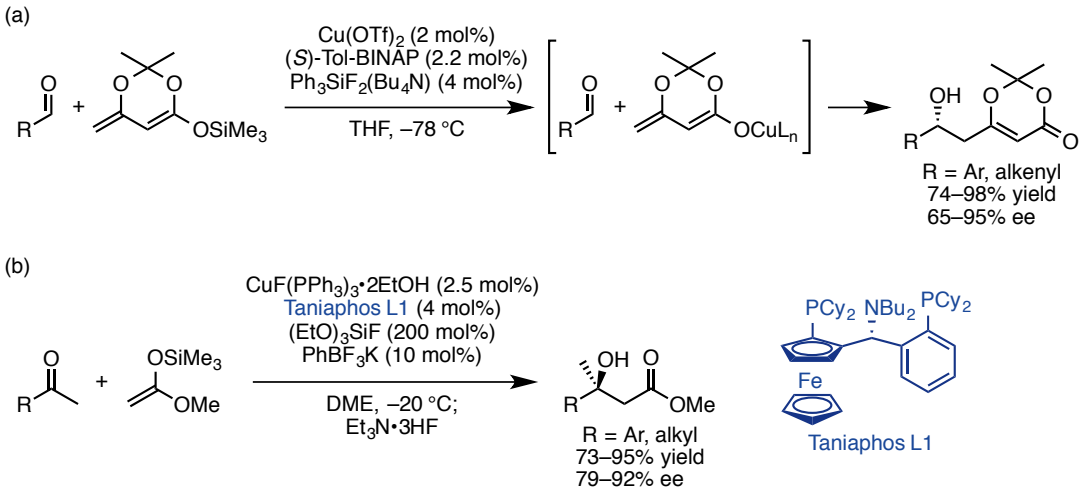


Figure 1.2 Chiral Cu(I)-catalyzed aldol reactions. (a) The original report of chiral Cu(I)-catalyzed aldol reaction reported by Carreira. (b) Catalytic asymmetric aldol addition to ketones reported by our group.

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[3] The application of Rh-catalyzed isomerization/aldol reaction sequence to double-aldol reaction was part of my M.S. study, see: Yamamoto, K. M.S. Thesis, The University of Tokyo, 2013.
[4] Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.
[5] Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 3124.
[6] (a) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644. (b) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164.

corresponding boron enolate.[7] After the aldol reaction, metal-aldolate intermediates are trapped by the boron atom, generating *O*-protected aldol products and thus preventing unreactive hemiacetal formation in more than double-aldol reactions.

1. Single-Aldol Reaction[8]

We began our study with optimization of cross-aldol reaction between 3-phenylpropanal **1a** and boron enolate **3a**. As an initial study, **3a** was generated from 2-allyloxy1,3,2-dioxaborinane **2a** in a different vessel prior to the aldol reaction referring Ir-catalyzed isomerization of silyl ethers reported by Miyaura.[9] As is often the case with Cu(I)-catalyzed asymmetric reactions,[10] copper(I) fluoride, copper(I) acetate, and copper(I) alkoxides promoted the desired cross-aldol reaction and furnished *syn*-aldol **4a** as a major product (Table 1.1, entries 1, 12-17, 19-28). In most cases, yields are moderate due to the formation of undesired hemiacetal **5a** (Scheme 1.1). However, increasing the amount of 2-propanol from 5 mol% to an equivalent improved the result to generate **4a'** in 80% yield, 97:3 dr, and 95% ee (Table 1.1, entry 28, *vide infra*). Neither other copper(I) halides nor other copper(I) salts catalyzed the reaction

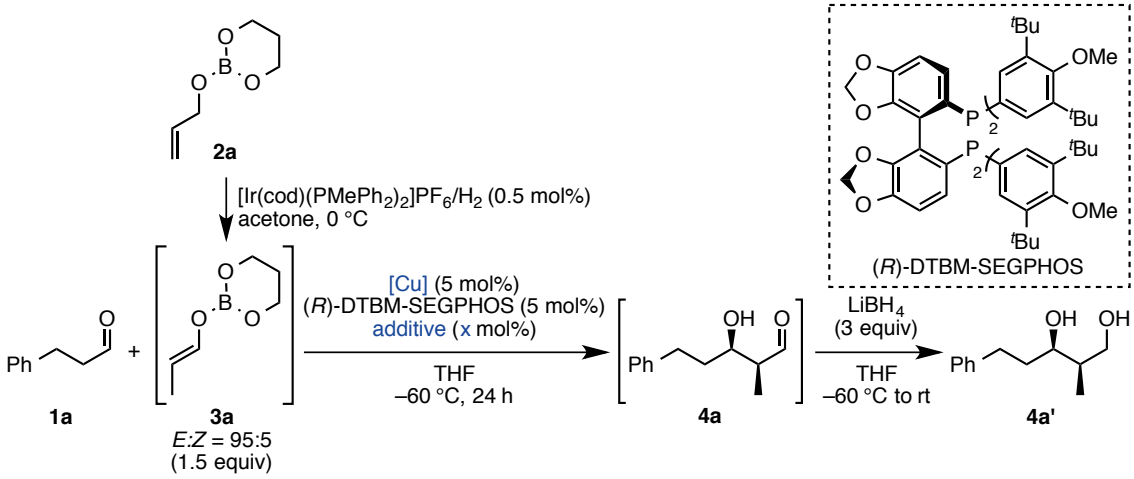
[7] The initial idea of generating chiral Cu-enolate belongs to Prof. Motomu Kanai. The initial discovery of a chiral Cu-catalyzed asymmetric aldehyde-cross-aldol reaction was made by Luqing. I thank Luqing for his contributions to the work described in this chapter, on the preparation of boron enolate and studies on single-aldol reaction.

[8] Much of the credit for the work described in this section belongs to Luqing. Luqing was the first to identify the catalyst system and substrate generality. I performed all the experiments described in this section except Table 1.4 and Figure 1.3. Yamato Kanzaki, a current graduate student in the Kanai group, performed the substrate scope in Figure 1.3 as well as control experiment in Table 1.4.

[9] (a) Ohmura, T.; Shirai, Y.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **1998**, 1337. (b) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413.

[10] For selected examples of Cu(I) catalyzed reactions reported by our group, see: allylation; (a) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. (b) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (c) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687. (d) Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M. *J. Am. Chem. Soc.* **2012**, *132*, 6638. (e) Kawai, J.; Chikkade, P. K.; Shimizu, Y.; Kanai, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7177. Alkenylation and arylation; (f) Tomita, D.; Wada, R.; Kanai, M. Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138. (g) Tomita, D.; Kanai, M. Shibasaki, M. *Chem. Asian J.* **2006**, *1-2*, 161. Alkynylation; (h) Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2997. Aldol reaction; (i) Ref 6. (j) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147. (k) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757. (l) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440. (m) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 7439. (n) Shi, S.-L.; Kanai, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3932. Mannich reaction; (o) Suto Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500. (p) Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146. (q) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610. Hetero-Diels−Alder reaction; (r) Chen, I-H.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 5151. Borylation; (s) Chen, I-H.; Itano, W.; Kanai, M. Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664. Aldol condensation−aza-Michael reaction; (t) Shi, S.-L.; Wei, X.-F.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2012**, *134*, 17019.

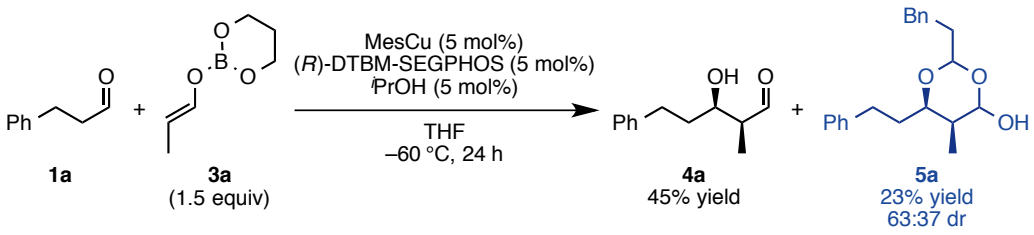
Table 1.1 Evaluation of Copper Precatalysts[a]



entry	[Cu]	additive (x mol%)	% yield[b]	*syn:anti*	% ee
1	$CuF•3PPh_3$		45	90:10	90
2	CuCl		<5	ND	ND
3	CuBr		<5	ND	ND
4	CuI		<5	ND	ND
5	CuCN		<5	ND	ND
6	CuSCN		12	93:7	0
7	CuSPh		<5	ND	ND
8	$CuOP(=O)Ph_2$		<5	ND	ND
9	CuTC		<5	ND	ND
10	CuMeSal		<5	ND	ND
11	$Cu(cod)(F_6\text{-acac})$		<5	ND	ND
12	CuOAc	none	58	97:3	96
13		LiO^{t}Bu (5)	72	97:3	95
14		NaO^{t}Bu (5)	65	97:3	95
15		KO^{t}Bu (5)	9	89:11	63
16		LiOMe (5)	60	98:2	95
17		LiO^{i}Pr (5)	50	97:3	95
18	$Cu(OAc)_2$		<5	ND	ND
19	CuOTf•1/2toluene	LiO^{t}Bu (5)	46	95:5	83
20		NaO^{t}Bu (5)	56	94:6	79
21		KO^{t}Bu (5)	22	92:8	83
22		LiOMe (5)	8	93:7	5
23		LiO^{i}Pr (5)	51	95:5	93
24	MesCu	$Et_3N•3HF$ (1.7)	64	97:3	95
25		MeOH (5)	48	97:3	95
26		^{i}PrOH (5)	50	97:3	95
27		^{t}BuOH (5)	43	97:3	95
28		^{i}PrOH (100)	80	97:3	95
29	$Cu(OMe)_2$		29	65:35	1

[a]Yield and selectivity were determined after reduction due to the instability of β-hydroxy aldehyde **4a** under analytical conditions. [b]Yield refers to either isolated yield after purification by column chromatography on silica gel or calculated yield determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. ND = not determined. TC = thiophene-2-carboxylate. MeSal = 3-methylsalicylate. F_6-acac = hexafluoroacetylacetonate.

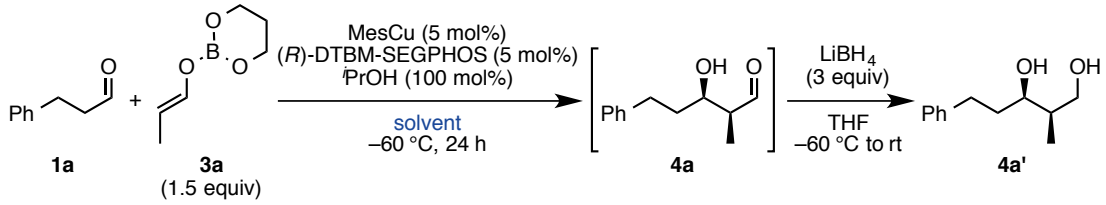
Scheme 1.1



except CuSCN, which generated **4a'** in 12% yield but in racemic form (Table 1.1, entries 2-11). Lewis acidic Cu(II) acetate and Cu(II) methoxide showed low reactivity with no stereoselectivity, supporting that this reaction proceeds via chiral copper(I) enolate addition to aldehyde (Table 1.1, entries 18 and 29).

Aprotic solvents were evaluated using conditions in Table 1.1, entry 28 (Table 1.2). Regardless of the polarity, reaction proceeded to generate **4a'** in high *syn*-selectivity, whereas yields and enantioselectivity were varied (Table 1.2, entries 1-5). When hexane was used as a solvent, **4a'** was not obtained due to the low solubility of the catalyst (Table 1.2, entry 6).

Table 1.2 Evaluation of Solvents[a]

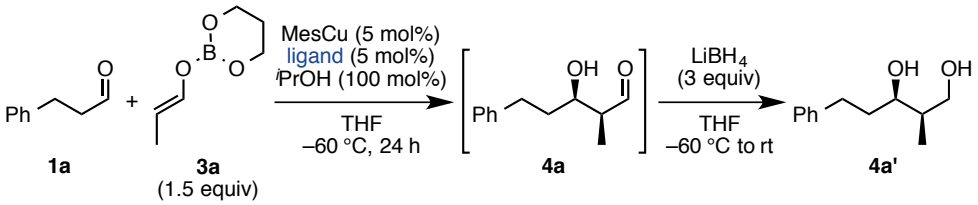


entry	solvent	% yield[b]	*syn:anti*	% ee
1	THF	80	97:3	95
2	Et_2O	60	94:6	90
3	EtOAc	41	93:7	87
4	CH_2Cl_2	57	92:8	41
5	toluene	92	95:5	76
6	hexane	<5	ND	ND

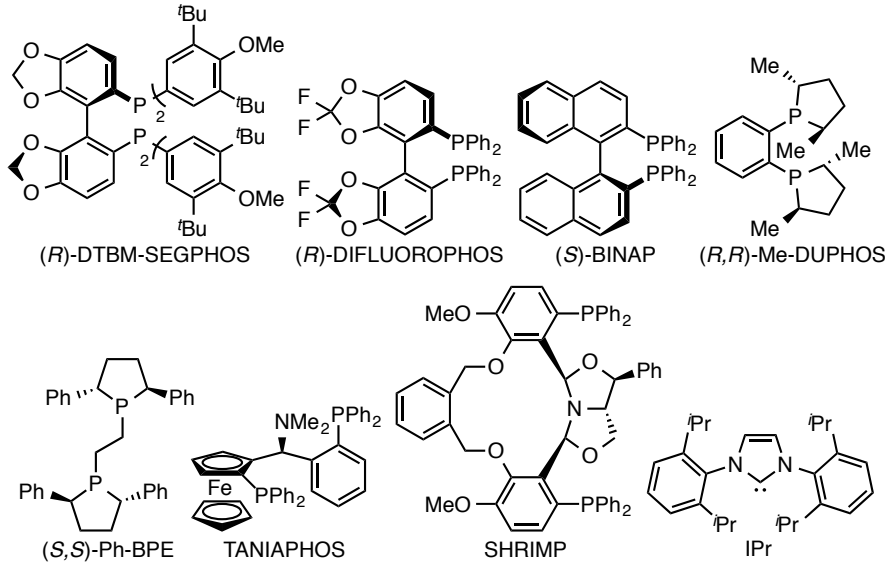
[a]Yield and selectivity were determined after reduction due to the instability of β-hydroxy aldehyde **4a** under analytical conditions. [b]Yield refers to either isolated yield after purification by column chromatography on silica gel or calculated yield determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. ND = not determined.

Next, ligands were evaluated using previously reported, "typical" bidentate chiral phosphines for Cu(I) catalysis (Table 1.3, entries 1-7). Yields, diastereo-, and enantioselectivity were varied depending on the structure and electronic properties of the ligands, indicating that the transition state and reactivity of the copper(I) enolate can be controlled by appropriate ligand on Cu(I). IPr ligand showed low reactivity against

Table 1.3 Evaluation of Ligands[a]



entry	ligand	% yield[b]	*syn:anti*	% ee
1	(*R*)-DTBM-SEGPHOS	80	97: 3	95
2	(*R*)-DIFLUOROPHOS	60	92: 8	44
3	(*S*)-BINAP	79	88:12	40
4	(*R,R*)-DUPHOS	79	80:20	2
5	(*S,S*)-Ph-BPE	51	85:15	6
6	TANIAPHOS	69	92: 8	23
7	SHRIMP	90	81:19	36
8	IPr	65	87:13	ND
9	IPr[c]	27	87:13	ND
10	IPr[d]	<5	ND	ND

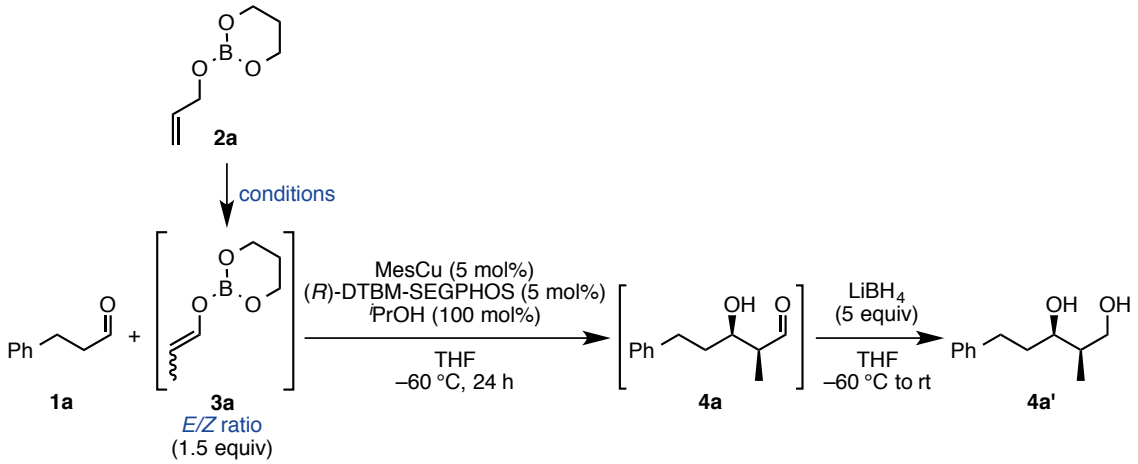


[a]Yield and selectivity were determined after reduction due to the instability of β-hydroxy aldehyde **4a** under analytical conditions. [b]Yield refers to either isolated yield after purification by column chromatography on silica gel or calculated yield determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. [c]IPr 10 mol% was used. [d]IPr 15 mol% was used. ND = not determined.

the expectation that electron rich carbene would enhance the nucleophilicity of the copper(I) enolate (Table 1.3, entries 8-10).

The *E/Z* ratio of enolate also affected the diastereo- and enantioselectivity (Table 1.4). As the ratio of (*Z*)-enolate increases,[11] the ratio of *anti*-**4a'** increased, indicating that the reaction does not proceed via simple open transition state. *E/Z* geometry of the enolate, however, showed influence on the enantioselectivity of **4a'**, implying that aldol addition does not go through simple six-membered closed transition state. Elucidation of the transition state and its application to *anti*-selective reaction are future tasks.[12]

Table 1.4 The Effects of *E/Z* Ratio of Enolate[a]



entry	conditions	*E/Z* ratio[b]	% yield[c]	*syn:anti*	% ee (*syn*)	% ee (*anti*)
1	$[Ir(cod)(PMePh_2)_2]PF_6/H_2$ (0.5 mol%) acetone, 30 min, 0 °C	*E:Z* = 95: 5	80	97: 3	95	46
2	$[Ir(cod)(PMePh_2)_2]PF_6/H_2$ (0.5 mol%) acetone (50 mol%) CH_2Cl_2, 1 h, 0 °C	*E:Z* = 76:24	71	94: 6	90	71
3	$RuHCl(CO)(PPh_3)_3$ (0.5 mol%) THF, 12 h, 120 °C	*E:Z* = 19:81	70	58:42	21	95

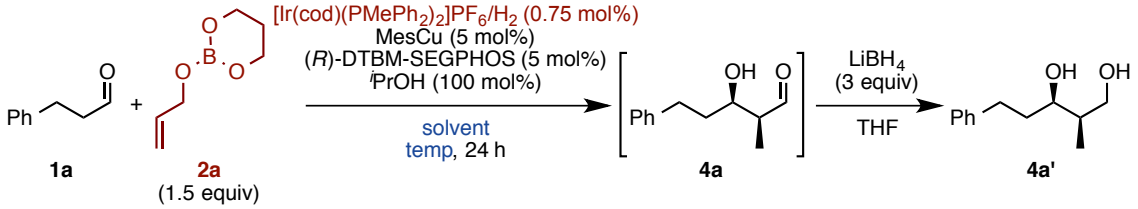
[a]Yield and selectivity were determined after reduction due to the instability of β-hydroxy aldehyde **4a** under analytical conditions. [b]The *E/Z* ratio was determined by ^1H NMR spectroscopy. [c]Yield refers to isolated yield after purification by column chromatography on silica gel.

[11] Boron enolate **3a** was prepared by modifying the reported procedure, see: Ir-catalyzed isomerization; (a) Ref 9. Ru-catalyzed isomerization; (b) Sasson, Y.; Rempel, G. L. *Tetrahedron Lett.* **1974**, *15*, 4133.

[12] One possible explanation for the relationship between *E/Z* ratio and stereoselectivity is the formation of multimetallic $[Cu(I)\text{-enolate}]_n$ species. Generation of highly (*Z*)-selective boron enolate and investigations of Lewis base additive effects on *anti*-selective reaction are ongoing.

Last, simultaneous isomerization/aldol sequence was tested (Table 1.5). Both yields and selectivity were not satisfactory compared with the prior generation of boron enolate. Ir-catalyzed isomerization well proceeds at 0 ˚C, at which aldol reaction does not due to the high reactivity of copper(I) enolate and Cu(I) alkoxides. Lowering temperature ended up in no boron-enolate generation.

Table 1.5 Simultaneous Isomerization/Aldol Reaction

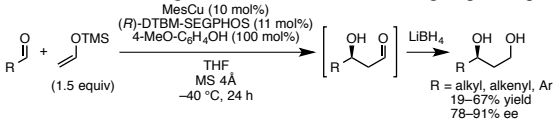


entry	solvent	temp	% yield[b]	*syn*:*anti*	% ee (*syn*)	% ee (*anti*)
1	THF	0 °C	9	83:17	82	60
2		–20 °C	11	85:15	82	70
3		–40 °C	4	88:12	82	75
4		–60 °C	<5	ND	ND	ND
5[c]	acetone	0 °C	64	88:12	83	55
6		–20 °C	46	87:13	85	71
7		–40 °C	<5	ND	ND	ND
8		–60 °C	<5	ND	ND	ND

[a]Yield and selectivity were determined after reduction due to the instability of β-hydroxy aldehyde **4a** under analytical conditions. [b]Yield refers to either isolated yield after purification by column chromatography on silica gel or calculated yield determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. [c]Reaction time was 5 h. ND = not determined.

Under the thus-optimized conditions,[13] 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 1.3, **4a**-**4s**). It is noteworthy that the desired cross-aldol products were obtained from the combination of sterically less hindered propanal as an acceptor and sterically more demanding aldehydes as donors (Figure 1.3,

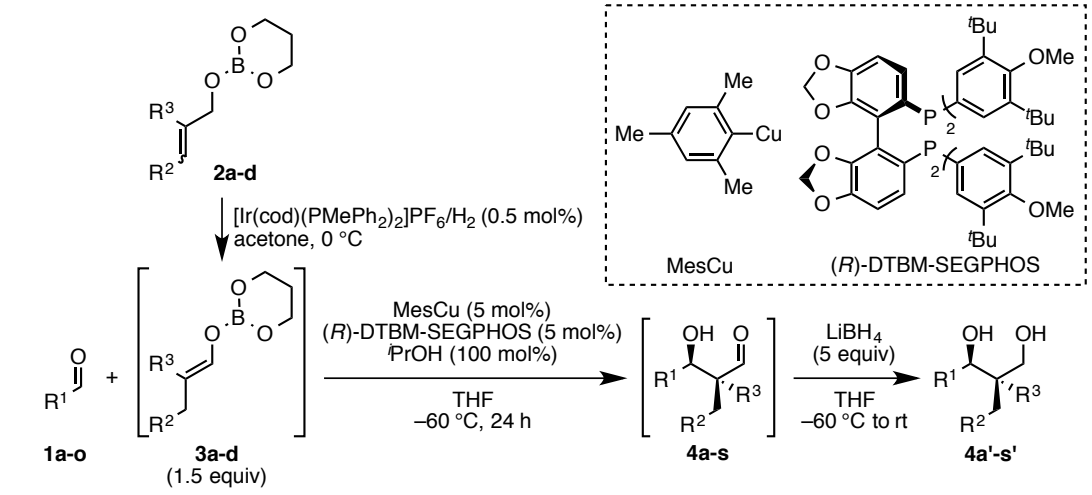
[13] *Acetaldehyde*-derived *silicon* enolate can be applied to the Cu(I)-mediated aldol reaction by modifying the reaction conditions. Investigations were done by Takashi Ida, a current graduate student in the Kanai group, as a part of his M.S. study.

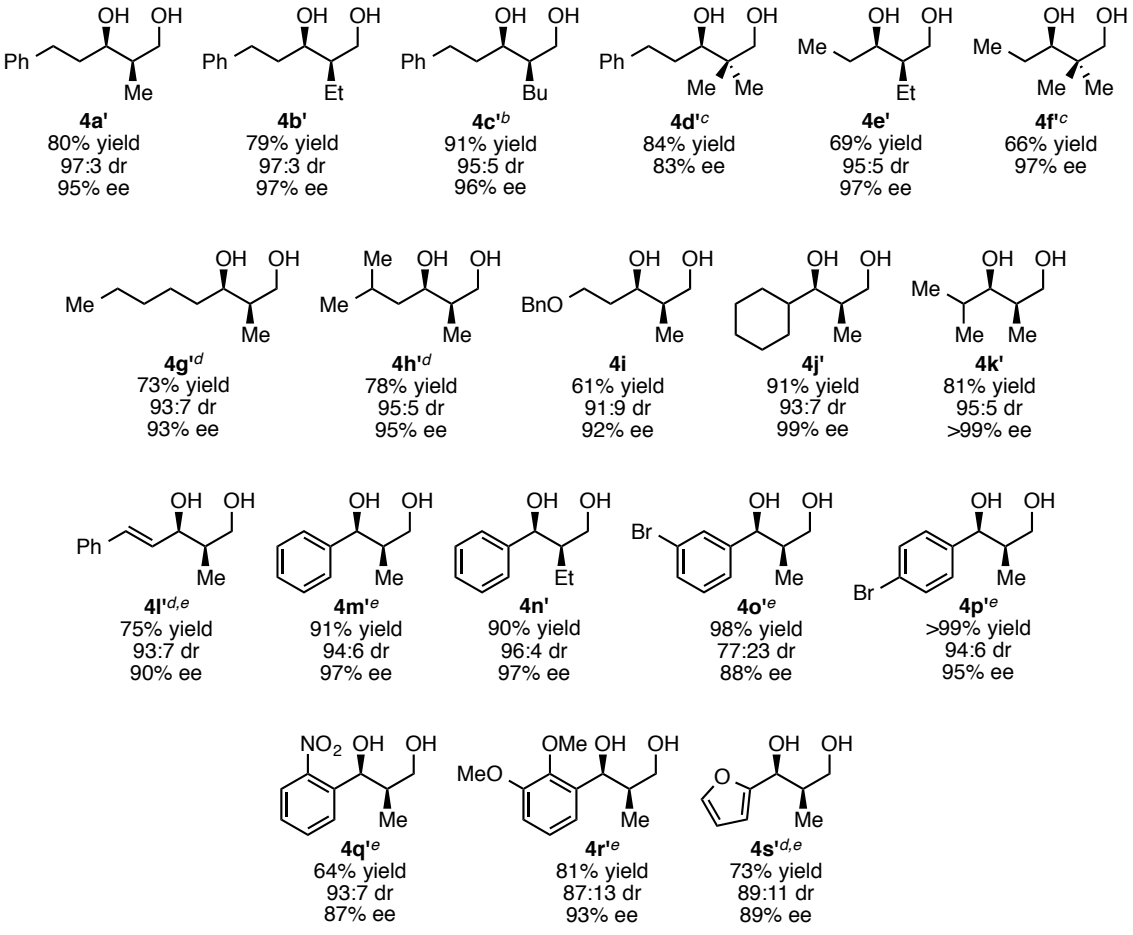


4e and **4f**). The enamine catalysis cannot produce aldol products from this donor/acceptor combination. As donors, not only methyl, but also ethyl, butyl, and dimethyl groups were introduced at the α-position of the product (Figure 1.3, **4b**-**4f** and **4n**).

A plausible catalytic cycle is depicted in Figure 1.4. By mixing MesCu, (*R*)-DTBM-SEGPHOS, and 2-propanol, chiral CuO^{i}Pr is generated with the extrusion of mesitylene.[14] Transmetalation between the copper alkoxide and boron enolate **3** affords chiral copper(I) enolate **6** with retention of the enolate geometry.[15] The generated enolate **6** reacts with aldehyde **1** to form copper aldolate **7**. Although the exact transition state is unclear, one possibility is the six-membered boat-like transition state (Figure 1.5). Facile protonation of **7** with 2-propanol was key to promoting the catalytic cycle, because the copper aldolate could irreversibly consume aldehyde **1** via nucleophilic attack to produce undesired cyclic hemiacetal **5**. Notably, the C−C bond-forming aldol reaction was the predominant pathway from copper enolate **6**, compared to protonation, even in the presence of a stoichiometric amount of 2-propanol.[16]

[14] Tsuda, T.; Watanabe, K.; Miyata, K.; Yamamoto, H.; Saegusa, T. *Inorg. Chem.* **1981**, *20*, 2728.
[15] Trapping experiment of copper enolate **6** with TMSCl revealed that the transmetalation proceeds without isomerization of the enolate. See SI for details.
[16] It may be due to the soft character of Cu(I)-enolate compared with the hard proton source.





[a]Yield and selectivity were determined after reduction due to the instability of b-hydroxy aldehyde **4** under analytical conditions. Yield refers to isolated yield after purification by column chromatography on silica gel. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the major diastereomer was determined by HPLC. [b]Enolate 3 equiv was used. [c]Enolate 2 equiv was used. [d]Enolate 1.2 equiv was used. [e]Reaction temperature was –75 °C.

Figure 1.3 Scope of aldol reaction.

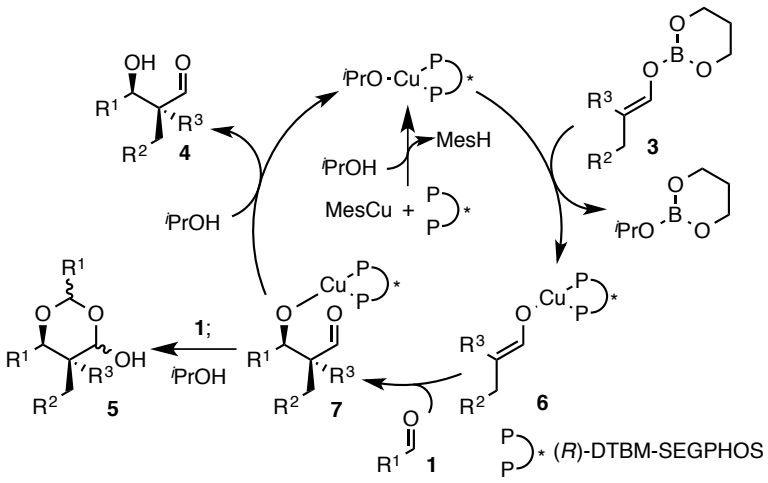


Figure 1.4 Plausible catalytic cycle.

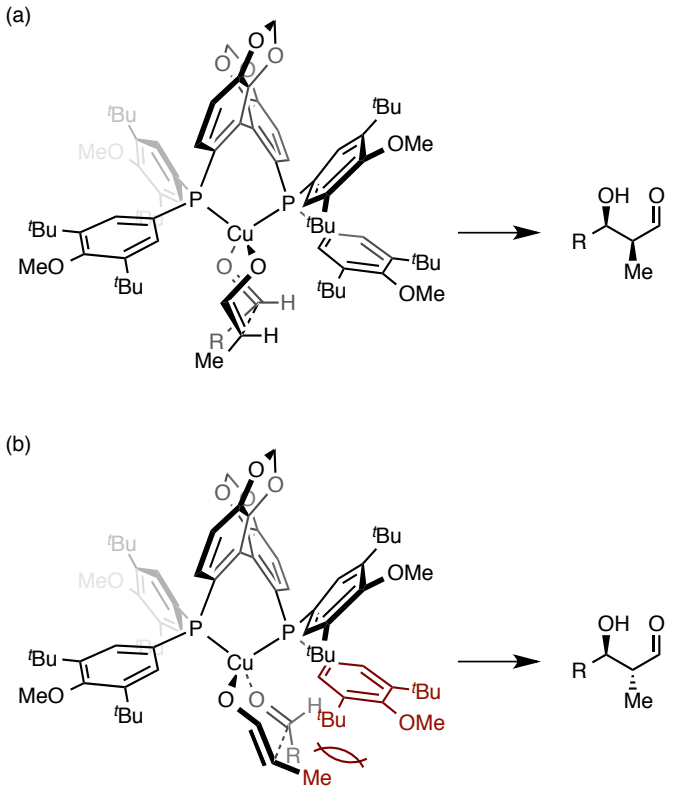


Figure 1.5 (a) One possible six-membered boat-like transition state, which affords *syn*-aldols. (b) Disfavored six-membered chair-like transition state, which generates *anti*-aldols.

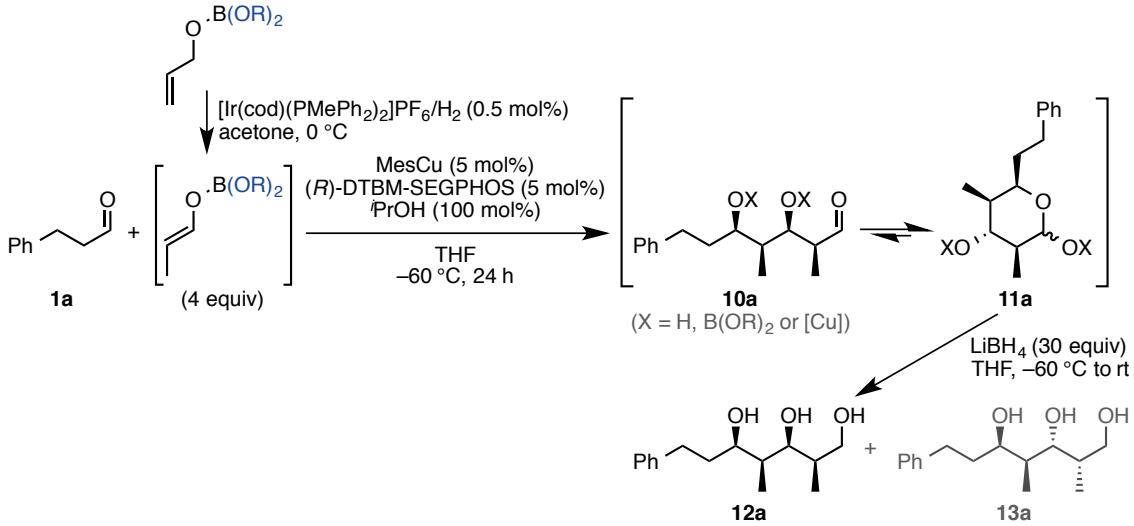
2. Double-Aldol Reaction

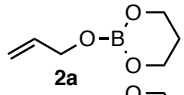
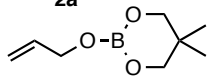
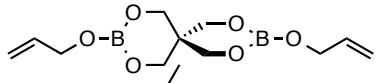
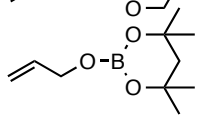
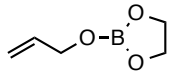
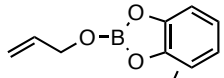
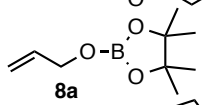
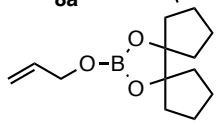
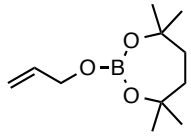
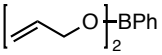
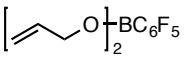
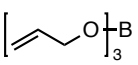
Although the copper catalysis realized the single-aldol reaction, the reactivity was not sufficient for the double-aldol reaction (Table 1.6, entry 1). To increase the reactivity, the diol moiety of boron enolate was evaluated, anticipating that both the increased electron density and the Thorpe-Ingold effect[17] would enhance the efficiency of the transmetalation step (Table 1.6, entries 2-12). Because double-aldol product **10a** rapidly underwent cyclization to form the hemiacetal **11a**, selectivity was evaluated after reduction with $LiBH_4$. As expected, pinacol containing boron enolate **9a** enhanced the reactivity to generate double-aldol product as a major product in high diastereoselectivity (Table 1.6, entry 7). Introduction of two enolizable parts in one molecule, however, turned out to be not effective (Table 1.6, entry 3).[18]

To further increase the efficiency by facilitating the protonation of the copper aldolate intermediate **7**, relatively acidic protic additives were evaluated based on the hypothetical catalytic cycle (Figure 1.6). Transmetalation between pinacol containing boron enolate **9** and a chiral copper alkoxide would smoothly form copper enolate **6**, which reacts with **1** to produce copper aldolate **7**. The concentration of **7** can be increased due to the enhanced efficiency of the transmetalation step. Protonation of **7** by acidic proton source would promote the formation of **4** rather than reacting with aldehyde to form undesired hemiacetal **5**. The generated single-aldol product **4** goes into the next catalytic cycle. After the double-aldol addition and cyclization, hemiacetal **11'** would be formed, which then reacts with borate **14** to close the catalytic cycle. Indeed, when an equivalent of 4-methoxyphenol was employed, the ratio of single-aldol product/double-aldol product/triple-aldol product was improved to be 1:97:2 and

[17] Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.
[18] I appreciate Prof. Hisashi Yamamoto for his advice of introducing more than two enolates in one molecule.

Table 1.6 Evaluation of Diol moieties of Boron Enolates[a]



entry	enolate precursor	single:double:triple[b]	dr (**12a**:**13a**:other isomers)[c]
1	 **2a**	80 : 17 : 4	79 : 6 : 15
2		88 : 10 : 2	100 : 0 : 0
3[d]		78 : 16 : 6	80 : 8 : 12
4		100 : 0 : 0	ND
5		99 : 1 : 0	ND
6		0 : 0 : 0	ND
7	 **8a**	36 : 62 : 0	96 : 2 : 2
8		100 : 0 : 0	ND
9		100 : 0 : 0	ND
10[e]		100 : 0 : 0	ND
11[e]		100 : 0 : 0	ND
12[f]		100 : 0 : 0	ND

[a]Selectivity was determined based on the area% of LC/MS chart of the crude reaction mixture. [b]The selectivity refers to the ratio of single-aldol products/double-aldol products/triple-aldol products. [c]Diastereomeric ratio of double-aldol products. [d]Enolate precursor 2 equiv was used. [e][Ir(cod)(PMePh$_2$)$_2$]PF$_6$/H$_2$ 1 mol% was used. [f][Ir(cod)(PMePh$_2$)$_2$]PF$_6$/H$_2$ 1.5 mol% was used.

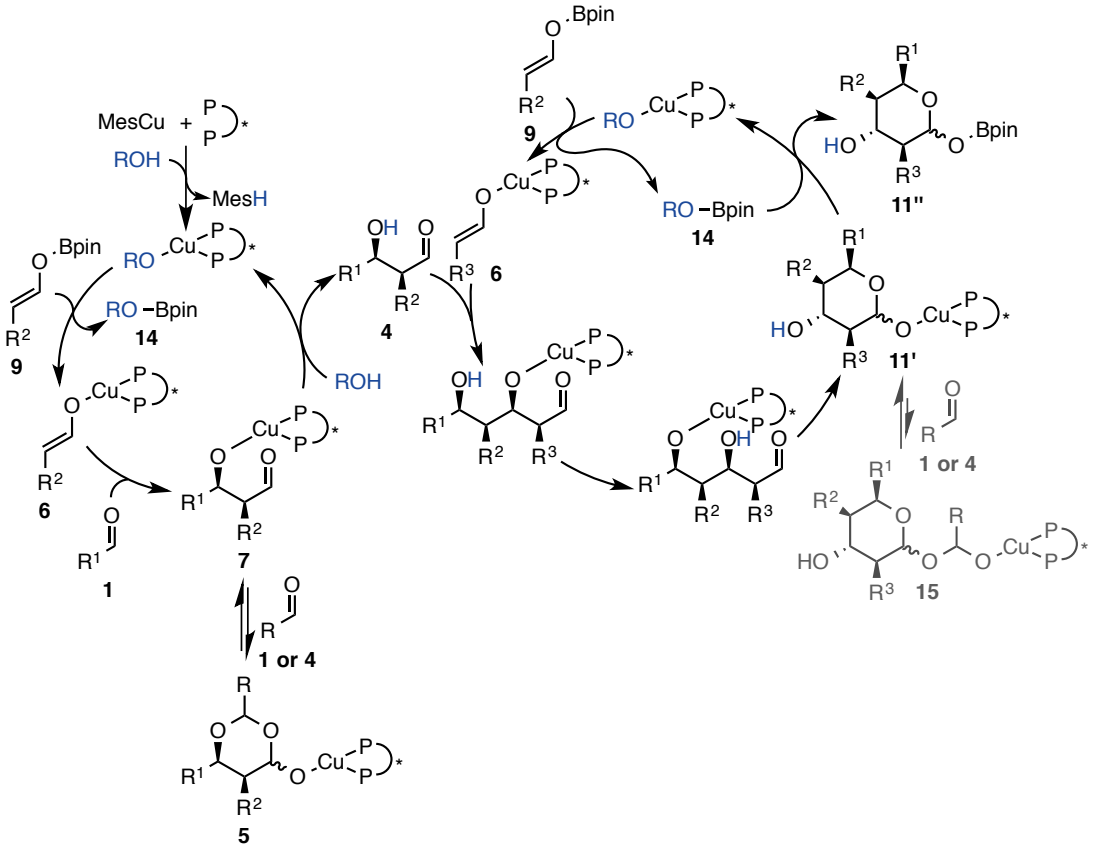
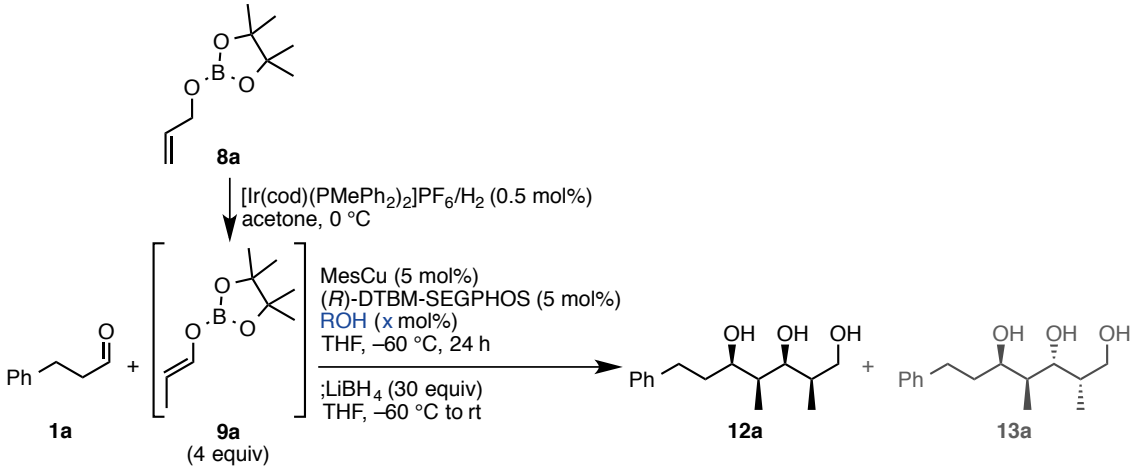


Figure 1.6 Plausible catalytic cycle for double-aldol reaction.

Table 1.7 Evaluation of Protic Additives[a]



entry	ROH (x mol%)	single:double:triple[b]	dr (**12a**:**13a**:other isomers)[c]
1	^{i}PrOH (5)	26:71:3	92:4:4
2	^{i}PrOH (100)	38:62:0	96:2:2
3	4-MeO-C_6H_4OH (5)	75:24:1	93:4:3
4	4-MeO-C_6H_4OH (100)	1:97:2	96:1:3

[a]Selectivity was determined based on the area% of LC/MS chart of the crude reaction mixture. [b]The selectivity refers to the ratio of single-aldol products/double-aldol products/triple-aldol products. [c]Diastereomeric ratio of double-aldol products.

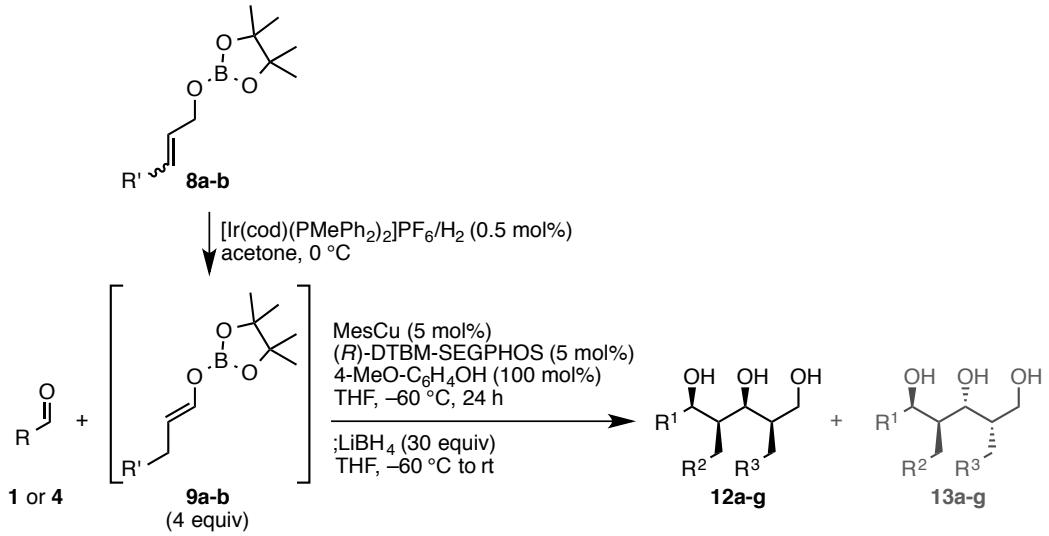
diastereoselectivity was 96:1:3 (Table1.7, entry 4).

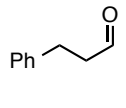
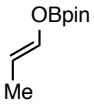
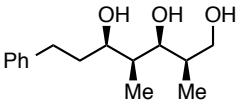
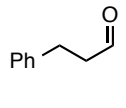
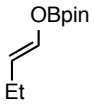
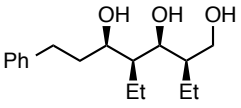
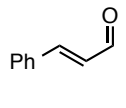
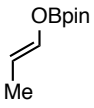
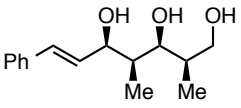
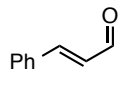
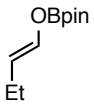
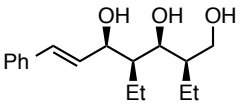
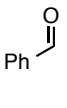
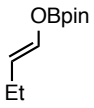
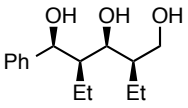
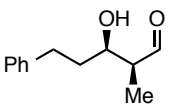
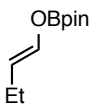
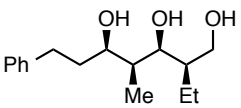
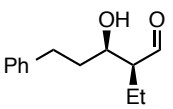
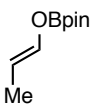
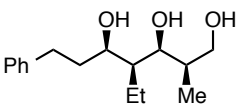
With the optimized conditions in hand, the scope of double-aldol reaction was evaluated (Table 1.8). The reaction smoothly proceeded in one-pot from aldehyde **1a** and four equivalents of boron enolates **9a** or **9b** in the presence of an equivalent of 4-methoxyphenol, to produce the corresponding cyclized hemiacetals **11** in the reaction mixture. After reduction with $LiBH_4$, the desired triols **12a** and **12b** were obtained in 86% yield, 96:1:3 dr, and >99% ee, and in 85% yield, 98:0:2 dr, and >99% ee, respectively (Table 1.8, entries 1 and 2). As acceptors, not only aliphatic, but also α,β-unsaturated and aryl aldehydes were utilized (Table 1.8, entries 3-5). Stepwise introduction of different donors at the first and second steps was also possible using mono-aldol products **4a** and **4b** generated by the method in Figure 1.3, as acceptor aldehydes (Table 1, entries 6 and 7).

Next, we turned our attention to switching the stereoselectivity of double-aldol reaction. Because the single-aldol products are chiral, there should be match/mismatch effects between chiral substrates and chiral catalysts in double-aldol processes. The stereoselectivity of triols **12** having 2,3,4,5-*syn*−*syn*−*syn* stereochemistry can be explained by Felkin-Anh model. If the catalysis is robust enough to overcome match/mismatch effects, however, switching the chirality of the catalysts in the first and second aldol reactions would provide triols **13** having 2,3,4,5-*syn*−*anti*−*syn* stereochemistry as a major isomer.

With this in mind, double-aldol reaction was investigated using single-aldol product **4b** and (*S*)-DTBM-SEGPHOS as a chiral ligand. When hydrogen of the β-hydroxy group of **4b** was used both as an alkoxide source and as a proton source, the ratio of single-aldol product/double-aldol product/triple-aldol product was 14:85:1 and

Table 1.8 Scope of Double-Aldol Reaction

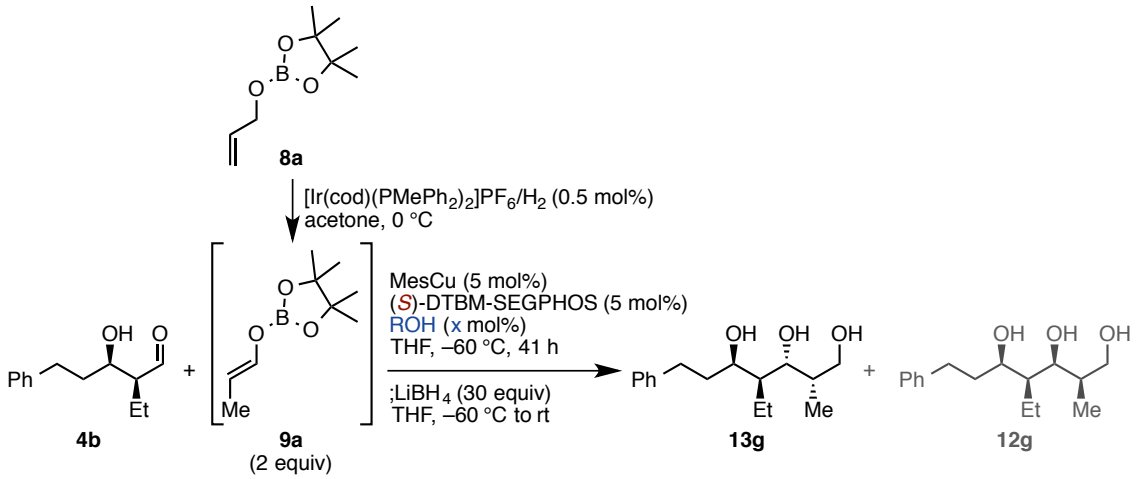


entry	acceptor	donor	product	% yield[a]	dr (**12**:**13**:other isomers)[b]	% ee
1	 **1a**	 **9a**	 **12a**	86	96:1:3	>99
2	 **1a**	 **9b**	 **12b**	85	98:0:2	>99
3[c]	 **1l**	 **9a**	 **12c**	89	86:14	>99
4[c,d]	 **1l**	 **9b**	 **12d**	91	92:8	>99
5[c,d]	 **1m**	 **9b**	 **12e**	58	94:6	>99
6[e]	 **4a**	 **9b**	 **12f**	72	92:4:4	>99
7[e]	 **4b**	 **9a**	 **12g**	93	92:1:7	>99

[a]Yield refers to the combined yield of all diastereomers. [b]Diastereomeric ratio of double-aldol products was determined based on the area% of LC/MS chart of the crude reaction mixture. [c]Diastereomeric ratio refers to the ratio of **12**:other isomers. [d]4-MeO-C_6H_4OH 5 mol% and Et_3N 2 equiv were used. [e]MesCu 10 mol% and (*R*)-DTBM-SEGPHOS 10 mol% were used. Reaction time was 48 h.

diastereoselectivity of the double-aldol product was 62:26:12 (Table 1.9, entry 1). The addition of catalytic amount of appropriately acidic alcohols turned out to be effective (Table 1.9, entries 2-6), and an equivalent of 4-methoxyphenol with 10 mol% catalyst showed the best diastereoselectivity (Table 1.9, entry 8).[19] The improved diastereoselectivity can be explained by the plausible catalytic cycle depicted in Figure 1.7. The key should be protonation of copper aldolate **15g'** because aldol addition of copper(I) enolate **6a** to **4b** can be reversible and thus can cause epimerization of double-aldol product.

Table 1.9 Evaluation of Protic Additives for Switching the Stereoselectivity of Double-Aldol Reaction[a]



entry	ROH (x mol%)	pK_a H_2O (DMSO)	single:double:triple[b]	dr (**13g**:**12g**:other isomers)[c]	% ee
1	none		14:85:1	62:26:12	>99
2	^{i}PrOH (5)	16.5 (29.3)	15:84:1	63:25:12	>99
3	CF_3CH_2OH (5)	12.5 (23.5)	14:85:1	72:16:12	>99
4	4-MeO-C_6H_4OH (5)	10.2 (19.1)	14:85:1	66:23:11	>99
5	HFIP (5)	9.3 (18.2)	17:82:1	65:24:11	>99
6	C_6F_5OH (5)	5.5	98: 2:0	ND	ND
7	4-MeO-C_6H_4OH (100)		36:64:0	75:14:11	>99
8[d]	4-MeO-C_6H_4OH (100)		30:70:0	81:10: 9	>99

[a]Selectivity was determined based on the area% of LC/MS chart of the crude reaction mixture. [b]The selectivity refers to the ratio of single-aldol products (i.e., reduced form of **4b** and other minor isomers)/double-aldol products (i.e., **13g**, **12g**, and other isomers)/triple-aldol products. [c]Diastereomeric ratio of double-aldol products. [d]MesCu 10 mol% and (*S*)-DTBM-SEGPHOS 10 mol% were used.

[19] Although it has not been tested, there is a room to improve the diastereoselectivity by using an equivalent of 2,2,2-trifluoroethanol instead of 4-methoxyphenol.

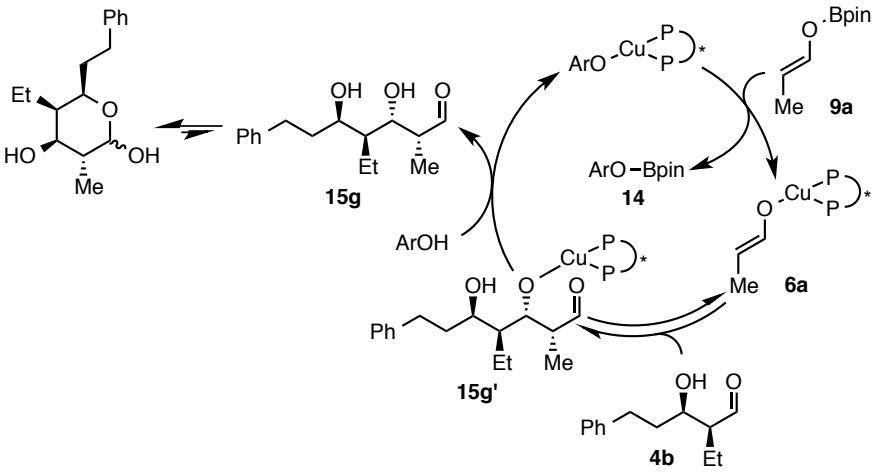
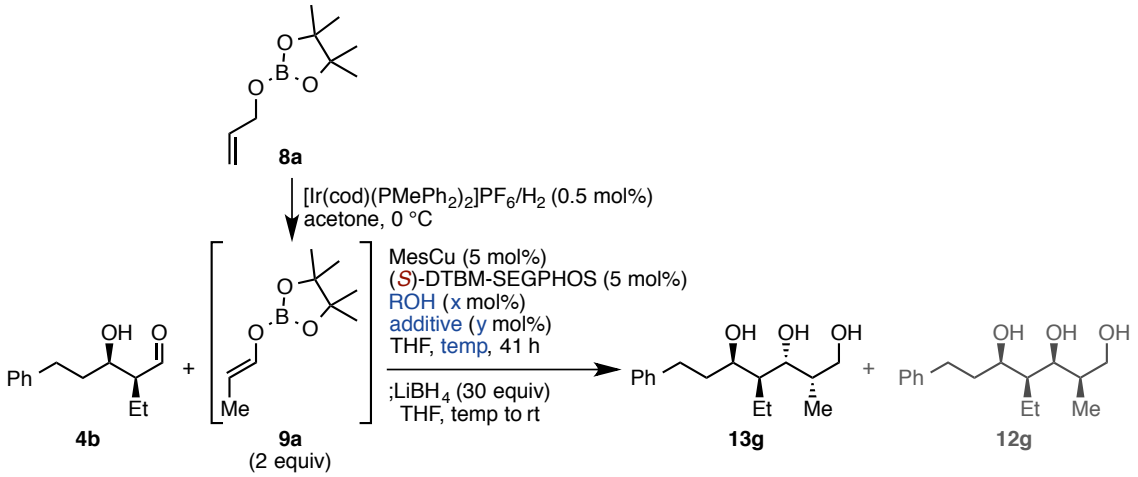


Figure 1.7 Plausible catalytic cycle for double-aldol reaction with switching the stereoselectivity in the double-aldol addition.

Other parameters were also investigated for switching the diastereoselectivity of double-aldol reaction. To improve the yield of double-aldol product, the amount of enolate **9a** was increased to four equivalents (Table 1.10, entry 3). However, it ended up in decreased yield and diastereoselectivity. Neither increasing reaction temperature nor decreasing temperature was effective for yields of double-aldol product, although diastereoselectivity was improved as increasing the temperature possibly due to the effective protonation of **15g'** (Table 1.10, entries 4-6). An amine additive, which enabled a triple-aldol reaction (*vide infra*), did not improve yields and stereoselectivity when started with single-aldol product **4b**, having proton source in the molecule (Table 1.10, entries 7 and 8).[20]

[20] An amine additive would increase the nucleophilicity of Cu(I)-enolate by coordinating to the metal center (see the next section for detailed discussion). When there are proton sources, however, it would also facilitate the protonation of the enolate.

Table 1.10 Effects of Other Parameters for Switching the Stereoselectivity of Double-Aldol Reaction[a]

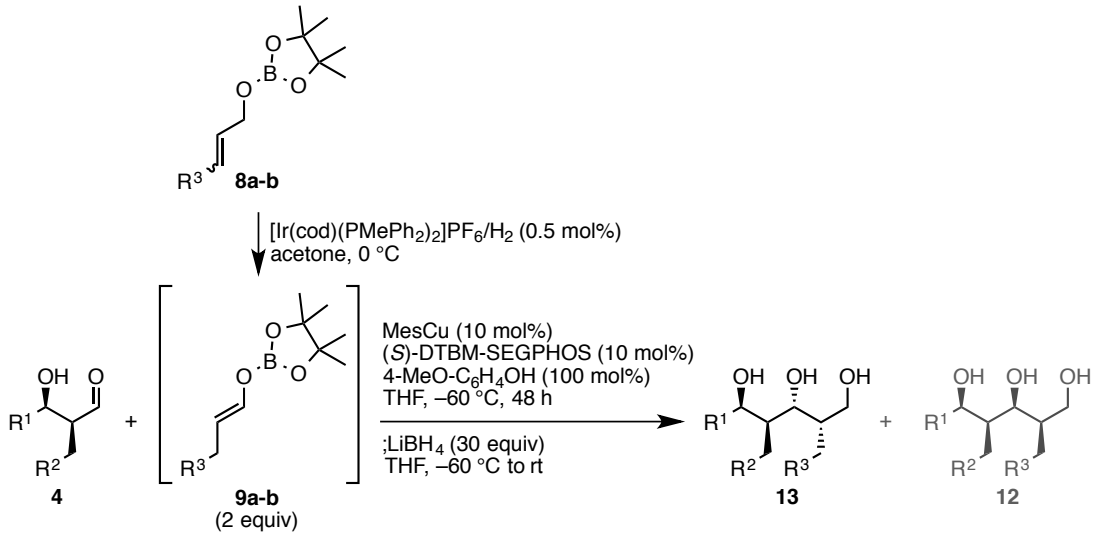


entry	ROH (x mol%)	additive (y mol%)	temp	single:double:triple[b]	dr (**13g**:**12g**:other isomers)[c]	% ee
1	4-MeO-C_6H_4OH (100)	none	–60 °C	36:64:0	75:14:11	>99
2[d]	4-MeO-C_6H_4OH (100)	none	–60 °C	30:70:0	81:10: 9	>99
3[e]	4-MeO-C_6H_4OH (100)	none	–60 °C	45:55:0	41:47:12	>99
4	4-MeO-C_6H_4OH (100)	none	–80 °C	49:51:0	49:41:10	>99
5	4-MeO-C_6H_4OH (100)	none	–40 °C	65:35:0	84: 5:11	>99
6	4-MeO-C_6H_4OH (100)	none	–20 °C	50:50:0	87: 3:10	>99
7	^{i}PrOH (5)	Et_3N (100)	–60 °C	73:26:1	38:30:32	98
8	4-MeO-C_6H_4OH (5)	Et_3N (100)	–60 °C	73:26:1	34:35:31	98

[a]Selectivity was determined based on the area% of LC/MS chart of the crude reaction mixture. [b]The selectivity refers to the ratio of single-aldol products (i.e., reduced form of **4b** and other minor isomers)/double-aldol products (i.e., **13g**, **12g**, and other isomers)/triple-aldol products. [c]Diastereomeric ratio of double-aldol products. [d]MesCu 10 mol% and (*S*)-DTBM-SEGPHOS 10 mol% were used. [e]Enolate **9a** 4 equiv was used.

By using reaction conditions in Table 1.9, entry 8, substrate generality was investigated (Table 1.11). Just by changing the chirality of the ligand, stereodivergent access to triols **13** was realized. Both the enantioselectivity and diastereoselectivity were predominantly controlled by the catalyst, and not by the substrates. Two distinct enolates were introduced in a stepwise manner with switching the stereoselectivity as well (Table 1.11, entries 3 and 4). The catalytic asymmetric double-aldol reaction is endowed with a high level of robustness, flexibility, and generality.

Table 1.11 Scope of Double-Aldol Reaction for Stereodivergent Access to triols 13



entry	acceptor	donor	product	% yield[a]	dr (**13**:**12**:other isomers)[b]	% ee
1	**4a**	**9a**	**13a**	61	92:4:4	>99
2	**4b**	**9b**	**13b**	63	95:2:3	>99
3	**4a**	**9b**	**13f**	64	94:4:2	>99
4	**4b**	**9a**	**13g**	71	80:6:14	>99

[a]Yield refers to the combined yield of all diastereomers. [b]Diastereomeric ratio of double-aldol products was determined based on the area% of LC/MS chart of the crude reaction mixture.

3. Triple-Aldol Reaction[21]

We extended this approach to more-than-double iterative aldol reactions. An additional difficulty with this reaction comprised the facile formation of unreactive hemiacetals **11** at the double-aldol stage, if hydroxy groups of the double-aldol products were not protected. We hypothesized that hemiacetal formation would be prevented by trapping the copper aldolate intermediate **7** as non-nucleophilic borate **4'** through a reaction with boron enolate **9** in the catalyst turnover step (Figure 1.8), which would require aprotic conditions. We examined the reaction between hydrocinnamaldehyde **1a** and four equivalents of boron enolate **9a** without protic additives, however, the ratio of single-aldol product/double-aldol product/triple-aldol product/quadruple-aldol product

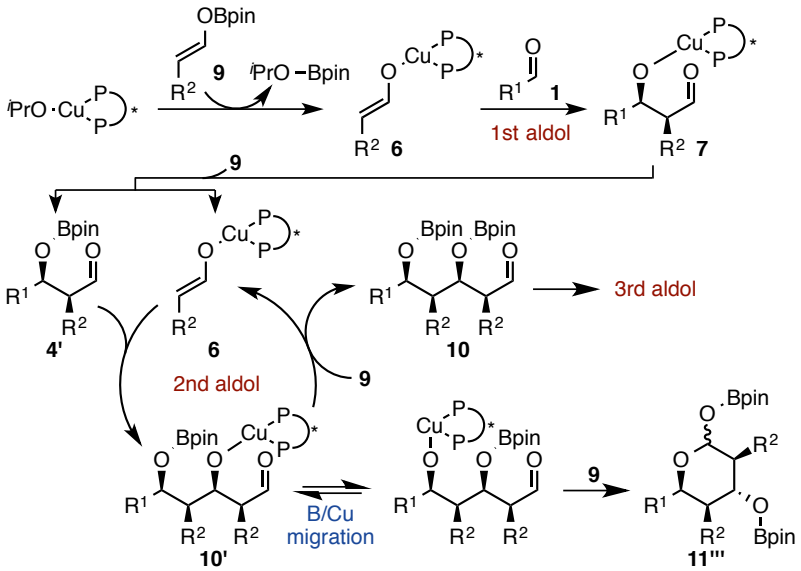
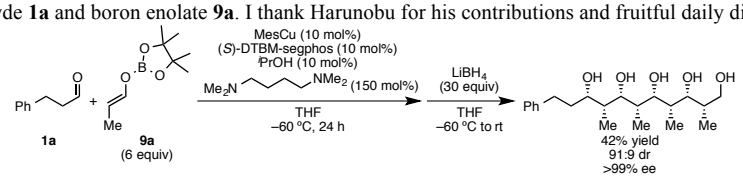


Figure 1.8 Working hypothesis for triple-aldol reaction.

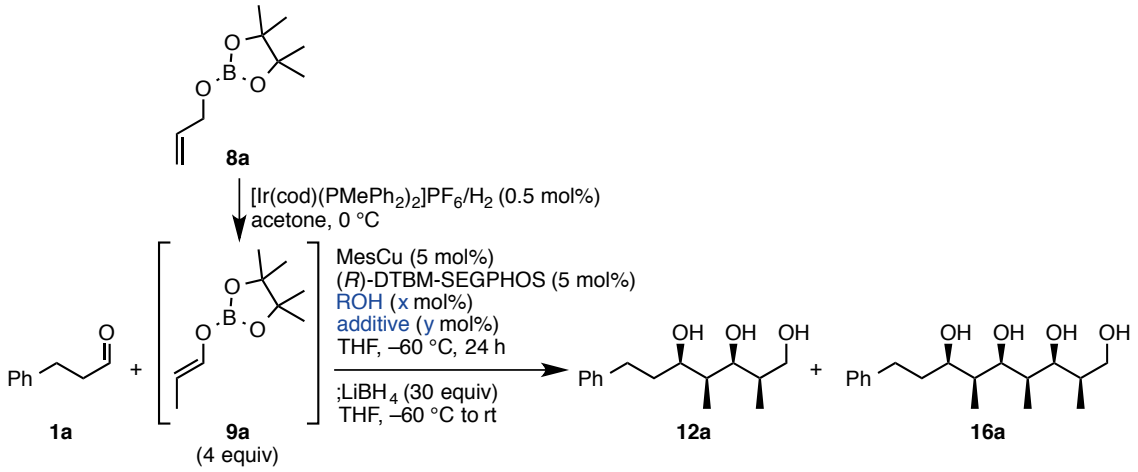
[21] Much of the credit for the work described in this section belongs to Dr. Harunobu Mitsunuma, a former graduate student in the Kanai group. Harunobu was the first to identify the amine additive effects for more than double-aldol reactions, see: Mitsunuma, H. Ph.D. Thesis, The University of Tokyo, 2015. I performed all the experiments described in this section except the isolation of **16a** and ^{1}H NMR study of Figure S2, which were done by Harunobu. He also achieved a quadruple-aldol reaction with hydrocinnamaldehyde **1a** and boron enolate **9a**. I thank Harunobu for his contributions and fruitful daily discussions.



was 26:70:3:1 (Table 1.12, entry 1). Instead, the hemiacetals **5** and **11'''** seemed to be the major products. This unexpected formation of **11'''** is likely due to intramolecular boron/copper migration in copper aldolate **10'** generated after double-aldol reaction.

During investigations aiming at preventing the hemiacetal formations and/or facilitating the desired reaction pathways, we stumbled across an effect of amine additive. When catalytic amount of triethylamine was added, the ratio of triple-aldol product became 28% (Table 1.12, entry 3). Further increasing the amount to 200 mol% improved the ratio to 83% (Table 1.12, entry 4). When an equivalent of proton source was added to this reaction conditions, however, the ratio decreased to 47% (Table 1.12,

Table 1.12 Optimization of the Reaction Conditions for Triple-Aldol Reaction[a]



entry	ROH (x mol%)	additive (y mol%)	single:double:triple:quadruple[b]	dr of double-aldol[c] (**12a**:**13a**:other isomers)	dr of triple-aldol[d] (**16a**:other isomers)
1	^{i}PrOH (5)	none	26:70: 3:1	92: 4: 4	ND
2	^{i}PrOH (100)	none	38:62: 0:0	96: 2: 2	ND
3	^{i}PrOH (5)	Et_3N (5)	1:67:28:4	96: 2: 2	90:10
4	^{i}PrOH (5)	Et_3N (200)	6: 8:83:3	65:14:21	92: 8
5	^{i}PrOH (100)	Et_3N (200)	2:49:47:2	94: 2: 4	93: 7
6	4-MeO-C_6H_4OH (5)	none	75:24: 1:0	93: 4: 3	ND
7	4-MeO-C_6H_4OH (100)	none	1:97: 2:0	96: 1: 3	ND
8	4-MeO-C_6H_4OH (5)	Et_3N (5)	8:54:38:0	91: 5: 4	99: 1
9	4-MeO-C_6H_4OH (5)	Et_3N (200)	9: 5:81:5	66:24:10	87:13
10	4-MeO-C_6H_4OH (100)	Et_3N (200)	2:51:47:0	89: 5: 6	84:16

[a]Selectivity was determined based on the area% of LC/MS chart of the crude reaction mixture. [b]The selectivity refers to the ratio of single-aldol products/double-aldol products/triple-aldol products/quadruple-aldol products. [c]Diastereomeric ratio of double-aldol products. [d]Diastereomeric ratio of triple-aldol products.

entry 5). The same tendency was observed when using 4-methoxyphenol instead of 2-propanol (Table 1.12, entries 8-10).

To elucidate the effect of amine additive, NMR studies were conducted. ^{1}H NMR analysis of the reaction mixtures revealed that addition of triethylamine increased the concentration of aldehydes (Figure S2). ^{11}B NMR studies showed no amine−boron interaction. Based on these spectroscopic data as well as experimental results shown in Table 1.12, current hypothetical catalytic cycle is depicted in Figure 1.9. Lewis basic triethylamine coordinates to Cu(I), not boron atom. In this way, first, the nucleophilicity of copper(I) enolate would be increased due to the increased electron density of the metal center. Although the rate of aldol addition would become slow as the sequential aldol reaction proceeds, enhanced nucleophilicity would solve this hurdle. When there are proton sources, however, the reactive copper(I) enolate would easily be protonated and the corresponding aldehyde is generated (Table 1.12, entries 4 vs 5 and 9 vs 10). Second, the formation of hemiacetal **5** was prevented (Table 1.12, entries 1 vs 3 and 4, and 6 vs 8 and 9).[22] In the presence of triethylamine, the equilibrium would be located on the copper aldolate **7** and hemiacetal **5** is less likely to be produced. Third, after the double-aldol addition, copper aldolate **10'** would be generated. Without triethylamine, it seemed that boron/copper migration was the major reaction pathway generating unreactive hemiacetal **11'''**. In the presence of triethylamine, however, aldehyde moiety exists in a certain amount (Figure S2). One possibility is the existence of equilibrium between borate **10''** and hemiacetal **11**, where **10''** is trapped by borate **14** and go into the triple-aldol-catalytic cycle. Detailed studies to elucidate the origin of the amine's beneficial effects are a future task.[23]

[22] After reduction with $LiBH_4$, hemiacetal **5** generates diol **4** and alcohol derived from aldehyde **1**.
[23] Yamato is currently working on this mechanistic study as a part of his M.S. study.

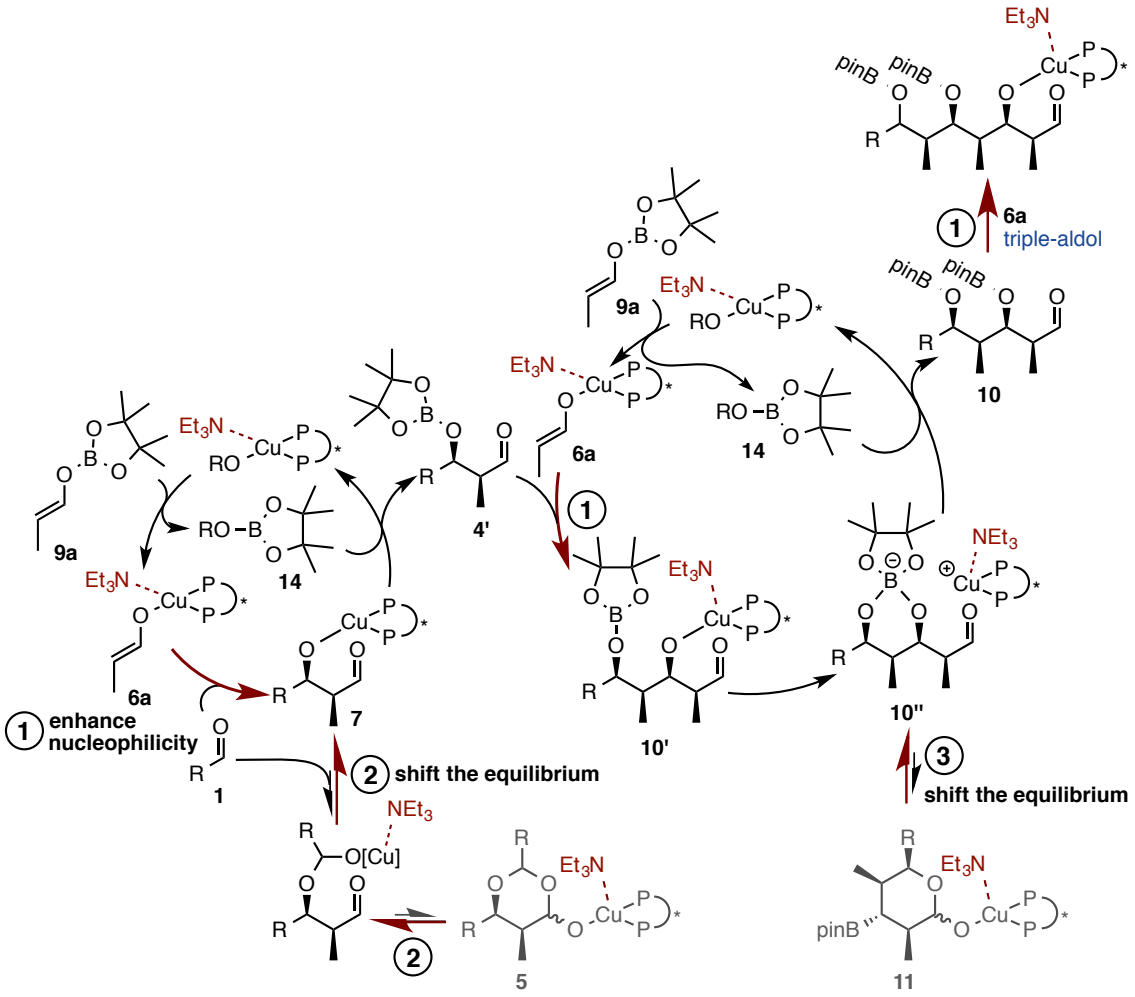
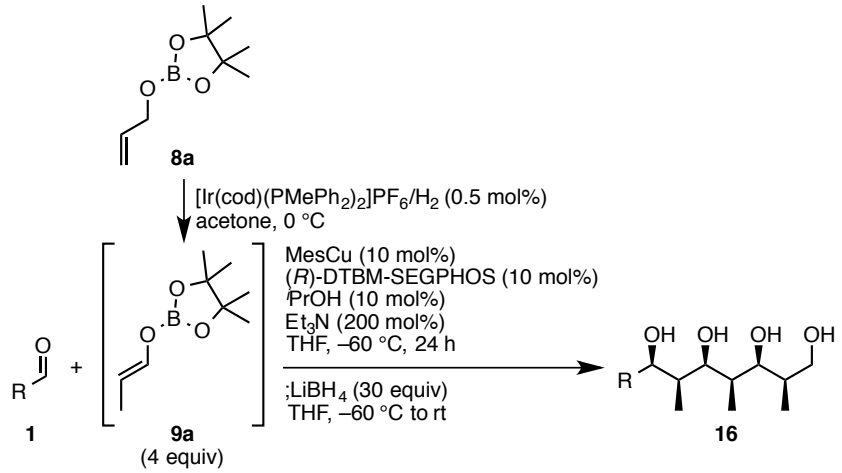
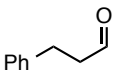
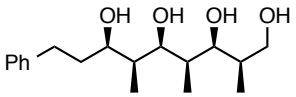
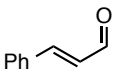
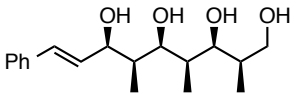
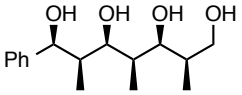


Figure 1.9 Hypothetical catalytic cycle for triple-aldol reaction.

Substrate generality was investigated for triple-aldol reaction (Table 1.13). As discussed above, tetraol **16a** derived from triple-aldol product was obtained after reduction in 71% yield, 90:10 dr (**16a**:other isomers), and >99% ee (Table 1.13, entry 1). The conditions were also applicable to α,β-unsaturated aldehyde **1l** and aromatic aldehyde **1m**, generating 1 of 64 possible isomers in high diastereo- and enantioselectivity (Table 1.13, entries 2 and 3). These results clearly demonstrate the robustness of the present method.

Table 1.13 Scope of Triple-Aldol Reaction



entry	acceptor	product	% yield[a]	dr (**16**:other isomers)[b]	% ee
1	 **1a**	 **16a**	71	90:10	>99
2	 **1l**	 **16l**	45	90:10	>99
3	 **1m**	 **16m**	77	98:2	95

[a]Yield refers to the combined yield of all diastereomers. [b]Diastereomeric ratio of triple-aldol products was determined based on the area% of LC/MS chart of the crude reaction mixture.

Chapter 2: xxx

CONCLUSION

While aldol reaction has long been recognized as one of the most useful and reliable reactions, the iterative *aldehyde* cross-aldol reactions demonstrate that there is untapped potential for the straightforward synthesis of enantiomerically and diastereomerically enriched 1,3-polyols. Realizing conceptually simple idea is often accompanied by “difficulties”, which has tended to be detoured. It is my hope that the work described in this thesis provides a breakthrough, and that my results may be useful for guiding future development.

The chiral copper(I) alkoxide catalyzed *syn*-selective cross-aldol reaction between acceptor aldehydes and boron enolates presented a broader substrate scope than the previously reported catalytic systems. This unit process was repeated using the aldol products in turn as an acceptor aldehyde for the second asymmetric aldol reaction. Flexible and stepwise switching of donors and stereoselectivity in the first and second steps of double-aldol reaction was achieved. Furthermore, the first catalytic asymmetric triple- and quadruple-aldol reactions were realized by 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 the rapid 1,3-polyol synthesis.

I believe that xxx.

EXPERIMENTAL

Materials and Methods

Reactions were carried out under argon atmosphere unless otherwise noted. Purified compounds were further dried under high vacuum. Diastereoselectivity of single-aldol products was determined by ^{1}H NMR analysis of the crude mixtures, comparing authentic samples. Diastereoselectivity of more than single-aldol products was determined by LC/MS analysis using 4.6 nm × 25 cm Daicel Chiralpak columns. Enantioselectivity was determined by high performance liquid chromatography (HPLC) using 4.6 nm × 25 cm Daicel Chiralpak columns. Yields refer to the diastereo mixture of compounds. Thin layer chromatography (TLC) was performed using EMD TLC plates pre-coated with 254 μm thickness silica gel 60 F_{254} plates and visualized by fluorescence quenching under UV light and $12MoO_3•H_3PO_4$ or *p*-anisaldehyde stains. Flash chromatography was performed using silica gel 60 (230-400 mesh ASTM) or silica gel 60N (40-100 μm) purchased from Merck or Kanto chemical, respectively. NMR spectra were recorded on either a JEOL ECX 500 spectrometer operating at 500 MHz and 125 MHz for ^{1}H and ^{13}C acquisitions, respectively, or a JEOL ECS 400 spectrometer operating at 400 MHz and 100 MHz for ^{1}H and ^{13}C acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (^{1}H: $CDCl_3$, δ 7.26; CD_3OD, δ 3.31; C_6D_6, δ 7.16), (^{13}C: $CDCl_3$, δ 77.16; CD_3OD, δ 49.00; C_6D_6, δ 128.06). Data is reported as follows: s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz; integration. All deuterated solvents were purchased form Kanto Chemical. IR spectra were measured on a JASCO FT/IR 410 spectrophotometer. High-resolution mass spectra were obtained using a JEOL JMS-T100LC AccuTOF spectrometer. LC/MS data

were obtained using an Agilent 6120 Series LC/MS-Agilent 1200 Series LC. Analytical HPLC was performed on either a Shimadzu SPD-20A/LC-20AT or a JASCO UV-2075/PU-2080. Preparative HPLC was performed on a Shimadzu SPD-20A/LC-20AT using 20 nm × 25 cm Daicel Chiralpak IC. Optical rotations were measured on a JASCO P-1010 polarimeter.

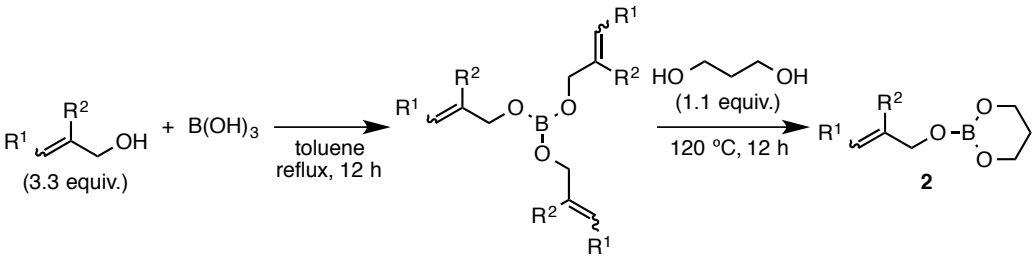
X-ray crystallographic analyses were performed on a Rigaku R-AXIS RAPID II imaging plate area detector with graphite-monochromated Cu-Kα radiation. Yadokari-XG 2009 program was used for crystal structure analysis. SHELX97 was used to refine structure.[1] MesCu was either purchased from Strem or synthesized according to the literature.[2] DTBM-segphos was donated by Takasago International Corporation. Liquid aldehydes and Et_3N were purified by distillation. All the other chemicals were used as received. THF was deoxidized and stabilizer free, organic synthesis grade; acetone was super dehydrated, organic synthesis grade; toluene was JIS special grade. These solvents were purchased from Wako Pure Chemical Industries and used as received without further purification.

[1] Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112.
[2] Tsuda, T.; Watanabe, K.; Miyata, K.; Yamamoto, H.; Saegusa, T. *Inorg. Chem.* **1981**, *20*, 2728.

Experimental Procedures and Compound Characterization for Chapter 1[3]

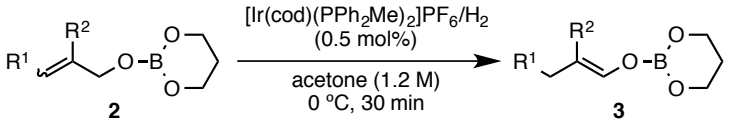
I. Preparation of Boron Enolates

Representative Procedure for the Preparation of Enolate Precursors



Allyl borate was prepared according to the literature.[4] Under air, allyl alcohol (3.3 equiv) and boronic acid were added to a round-bottom flask, followed by toluene at 23 °C. The reaction mixture was stirred for 12 hours at 120 °C using a Dean Stark trap to remove water. After distillation under reduced pressure, allyl borate was obtained as a colorless liquid. To this allyl borate, 1,3-propanediol (1.1 equiv) was added. After stirring for 12 hours at 120 °C, the enolate precursor **2** was obtained as a colorless liquid by distillation under reduced pressure. The product was stored under argon atmosphere to avoid hydrolysis.

Representative Procedure for the Preparation of Enolates

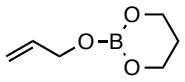


Boron enolate **3** was prepared by modifying the reported procedure[5] of isomerization of allyl silyl ethers. To the test tube, $[Ir(cod)(PPh_2Me)_2]PF_6$ (0.5 mol%) and acetone (1.2 M) were added under argon atmosphere. Dihydrogen was bubbled into

[3] I thank Luqing Lin, Harunobu Mitsunuma, Yamato Kanzaki for their contributions to the experiments described herein. Please see the footnotes throughout Chapter 1 for details of each of their individual contributions.
[4] Kuivila, H. G.; Slack, S. C.; Siiteri, P. K. *J. Am. Chem. Soc.* **1951**, *73*, 123.
[5] Ohmura, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413.

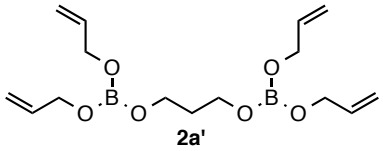
the solution at 23 °C for about 1 minute, at which point the color of the solution changed from red to colorless. The excess dihydrogen was replaced with argon and the reaction mixture was cooled to 0 °C. To this solution, enolate precursor **2** was added and stirred at 0 °C for 30 minutes. The solvent was evaporated at 0 °C and cooled to – 78 °C. To this colorless semi-solid, THF was added to give the enolate **3** solution, which immediately used for aldol reactions.

2-allyloxy-1,3,2-dioxaborinane (2a)



2a

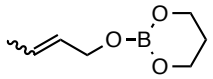
b.p.: 60 °C (0.3 kPa), NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.91 (m, 1H), 5.23 (m, 1H), 5.08 (m, 1H), 4.28 (m, 2H), 4.02 (m, 4H), 1.89 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.9, 114.6, 63.8, 62.7, 27.2. IR and HRMS were not measured due to lability of **2a** toward analytical conditions.



2a'

***2a** was obtained as a mixture of **2a** and **2a'** (**2a**:**2a'** = 6:1).

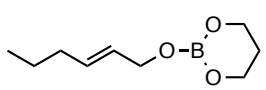
2-(but-2-en-1-yloxy)-1,3,2-dioxaborinane (2b)



2b

b.p.: 137 °C (0.5 kPa), NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.66 (m, 1H), 5.57 (m, 1H), 4.21 (d, *J* = 5.2 Hz, 2H), 4.03 (m, 4H), 1.90 (m, 2H), 1.68 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 128.9, 127.3, 63.6, 62.7, 27.3, 17.6. IR and HRMS were not measured due to lability of **2b** toward analytical conditions.

2-[(2*E*)-hex-2-en-1-yloxy]-1,3,2-dioxaborinane (2c)

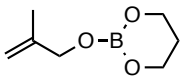


2c

b.p.: 162 °C (0.3 kPa), NMR spectroscopy: ^{1}H NMR (400 MHz,

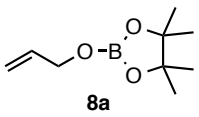
$CDCl_3$): δ = 5.64 (m, 1H), 5.55 (dt, *J* = 15.1, 5.5 Hz, 1H), 4.23 (d, *J* = 5.4 Hz, 2H), 4.03 (m, 4H), 2.00 (m, 2H), 1.90 (m, 2H), 1.39 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.4, 127.7, 63.7, 62.7, 34.3, 27.3, 22.3, 13.7. IR and HRMS were not measured due to lability of **2c** toward analytical conditions.

2-(2-methyl-2-propen-1-yloxy)-1,3,2-dioxaborinane (2d)


2d

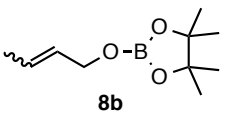
b.p.: 90 °C (0.5 kPa), NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.95 (s, 1H), 4.80 (s, 1H), 4.19 (s, 2H), 4.04 (m, 4H), 1.91 (m, 2H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.3, 109.7, 66.6, 62.7, 27.4, 19.0. IR and HRMS were not measured due to lability of **2d** toward analytical conditions.

2-allyloxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8a)


8a

b.p.: 88 °C (7.0 kPa), NMR spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (m, 1H), 5.28 (ddt, *J* = 17.4, 1.7, 1.7 Hz, 1H), 5.12 (ddt, *J* = 10.5, 1.7, 1.7 Hz, 1H), 4.36 (ddd, *J* = 4.8, 1.7, 1.7 Hz, 2H), 1.25 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.4, 115.0, 82.8, 65.5, 24.6. IR and HRMS were not measured due to lability toward analytical conditions.

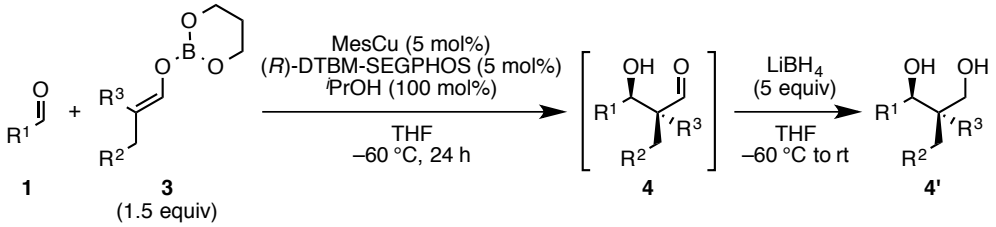
2-(but-2-en-1-yloxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8b)


8b

b.p.: 103 °C (4.9 kPa), NMR spectroscopy: ^{1}H NMR (400 MHz, C_6D_6): δ = 5.61-5.58 (m, 2H), 4.42 (m, 2H), 1.48 (m, 3H), 1.05 (s, 12H). ^{13}C NMR (100 MHz, C_6D_6): δ = 129.3, 127.3, 82.5, 65.6, 24.7, 17.6. IR and HRMS were not measured due to lability toward analytical conditions.

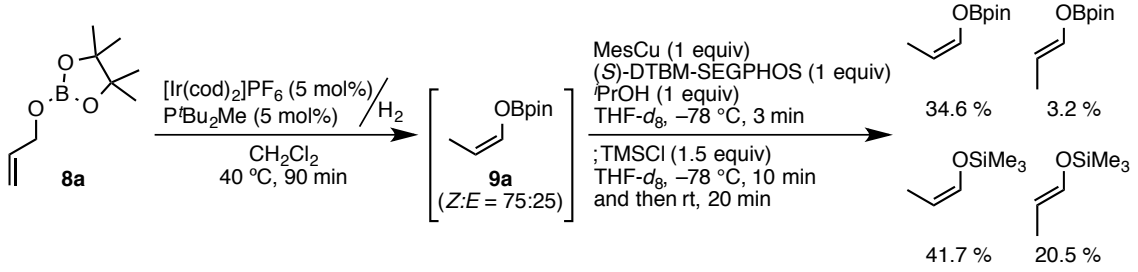
II. Single-Aldol Reaction

Representative Procedure



Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3** (0.3 mmol) in THF (0.4 mL) and a solution of aldehyde **1** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel. Enantioselectivity was determined by normal or reversed phase HPLC. Benzoylation of primary alcohol was conducted for HPLC analysis (if necessary).

Trapping Experiment of Copper Enolate with TMSCl



Procedure: To the test tube, $[Ir(cod)_2]PF_6$ (4.2 mg, 0.0075 mmol), P^{t}Bu$_2$Me (1.46

μL, 0.0075 mmol) and CH_2Cl_2 (2 mL) were added under argon atmosphere. Dihydrogen was bubbled into the solution at 23 °C for about 5 minutes and then the excess dihydrogen was replaced with argon. To this solution, enolate precursor **8a** (32.4 μL, 0.15 mmol) was added and stirred at 40 °C for 90 minutes. The solvent was evaporated at 23 °C and THF-d_8 (1.5 mL) was added to give the enolate **9a** (*Z*:*E* = 75:25) solution.

Under argon, mesityl copper (5.5 mg, 0.03 mmol) and (*S*)-DTBM-segphos (35.4 mg, 0.03 mmol) were added to a test tube, followed by THF-d_8 (0.4 mL) and 2-propanol (2.31 μL, 0.03 mmol) at 23 °C. After cooled to –78 °C, the solution of boron enolate **9a** (0.03 mmol) in THF-d_8 (0.3 mL) was added and stirred for 3 minutes at –78 °C. To this solution was added TMSCl (5.71 μL, 0.045 mmol) and stirred for 10 minutes at –78 °C. After stirred at 23 °C for 20 minutes, the reaction solution was moved to a NMR tube and ^{1}H NMR was taken at the same temperature. The ratio of (*Z*)-boron enolate/(*E*)-boron enolate/(*Z*)-silicon enolate/(*E*)-silicon enolate was 35:3:41:21, which indicated that the transmetalation of enolate proceeds with retention of the enolate geometry,[6] and that the transmetalation of (*E*)-enolate is faster than that of (*Z*)-enolate.[7]

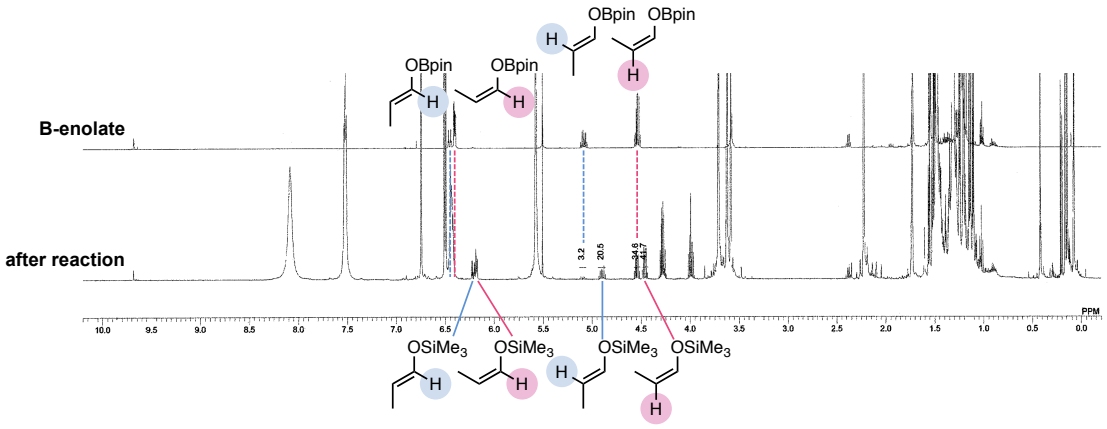
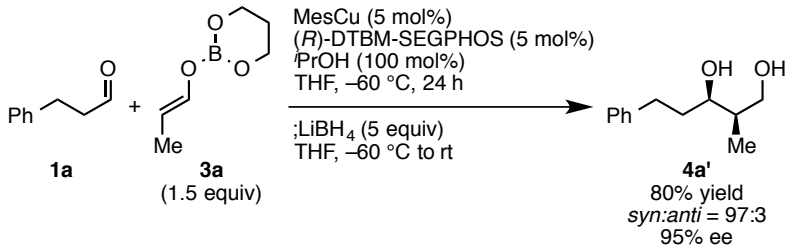


Figure S1 ^{1}H NMR of the reaction solutions, THF-d_8, 500 MHz.

[6] The ratio of (*Z*)-boron and silicon enolate/(*E*)-boron and silicon enolate was 76:24 after the reaction, which corresponds to the ratio of starting boron enolate (*Z*:*E* = 75:25).

[7] While 87% of (*E*)-boron enolate was converted to (*E*)-silicon enolate, 55% of (*Z*)-boron enolate was converted to (*Z*)-boron enolate.

(2*R*,3*R*)-2-methyl-5-phenylpentane-1,3-diol (4a')

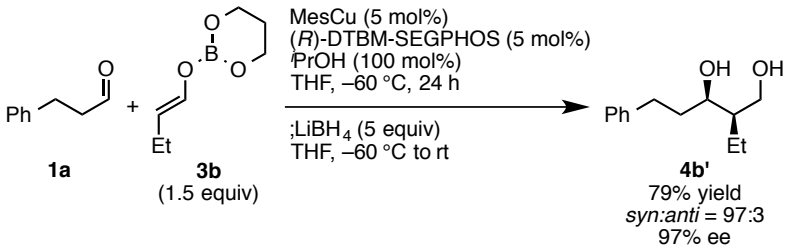


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3a** (0.3 mmol) in THF (0.4 mL) and a solution of hydrocinnamaldehyde **1a** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford the title compound (30.9 mg, 0.159 mmol, 80% yield) as a colorless liquid.

Known compound.[8] HPLC: Daicel Chiralpak IB-IF, H_2O (0.1% TFA)/MeCN = 5:1, flow rate = 1.0 mL/min, retention time; 68.9 min (minor) and 73.2 min (major). Optical rotation: $[\alpha]_D^{24.1}$ = +18.0 (*c* = 1.0, $CHCl_3$).

[8] Kano, T.; Sugimoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 18130.

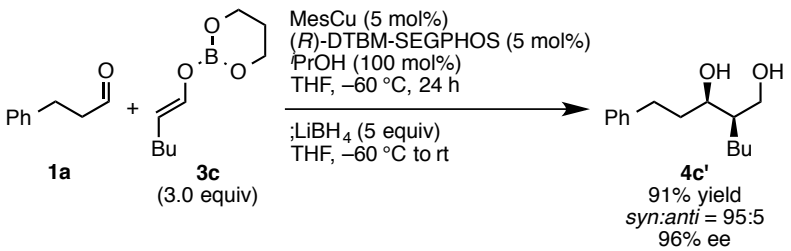
(2*R*,3*R*)-2-ethyl-5-phenylpentane-1,3-diol (4b')



Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3b** (0.3 mmol) in THF (0.4 mL) and a solution of hydrocinnamaldehyde **1a** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford the title compound (32.8 mg, 0.157 mmol, 79% yield) as a colorless liquid.

Known compound.[8] HPLC: Daicel Chiralpak IB, Hexane/EtOH = 20:1, flow rate = 0.5 mL/min, retention time; 22.8 min (minor) and 30.0 min (major). Optical rotation: $[\alpha]_D^{24.2}$ = +19.6 (*c* = 1.0, $CHCl_3$).

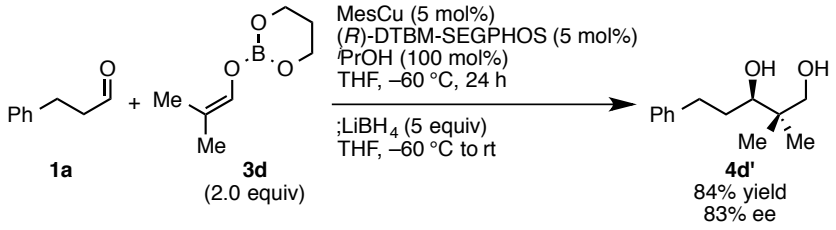
(2*R*,3*R*)-2-butyl-5-phenylpentane-1,3-diol (4c')



Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3c** (0.6 mmol) in THF (0.4 mL) and a solution of hydrocinnamaldehyde **1a** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 3:1 to afford the title compound (42.8 mg, 0.181 mmol, 91% yield) as a colorless liquid.

Known compound.[8] HPLC: Daicel Chiralpak OD-H-OD-H, Hexane/2-Propanol = 20:1, flow rate = 0.5 mL/min, retention time; 35.7 min (minor) and 53.5 min (major). Optical rotation: $[\alpha]_D^{24.1}$ = +17.4 (*c* = 1.0, $CHCl_3$).

(3*R*)-2,2-dimethyl-5-phenylpentane-1,3-diol (4d')

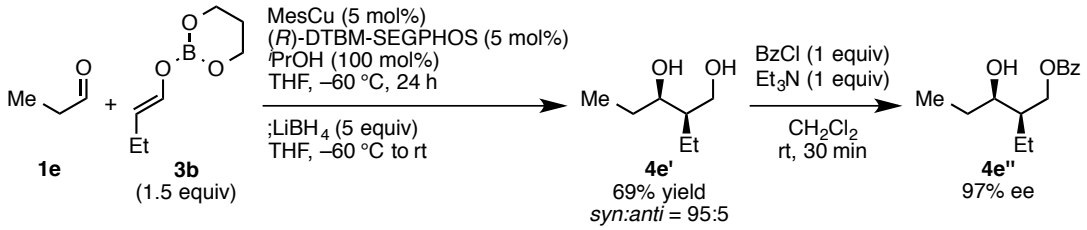


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3d** (0.4 mmol) in THF (0.4 mL) and a solution of hydrocinnamaldehyde **1a** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was

added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 2:1 to afford the title compound (34.9 mg, 0.168 mmol, 84% yield) as a white solid.

Known compound.[9] HPLC: Daicel Chiralpak AD-H, Hexane/EtOH = 20:1, flow rate = 0.5 mL/min, retention time; 31.6 min (minor) and 40.2 min (major). Optical rotation: $[\alpha]_D^{25.1}$ = +45.8 (*c* = 2.5, $CHCl_3$).

(2*R*,3*R*)-2-ethyl-3-hydroxypentyl benzoate (4e'')



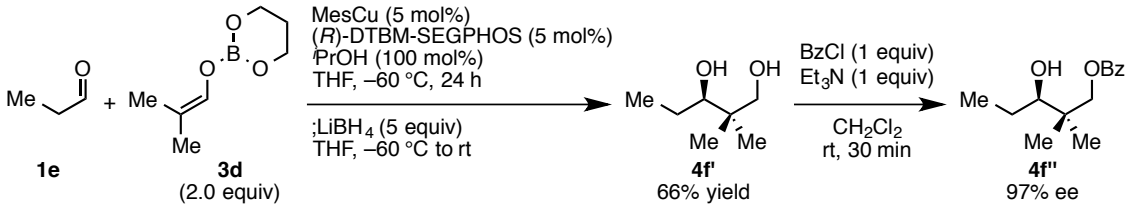
Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3b** (0.3 mmol) in THF (0.4 mL) and a solution of propanal **1e** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column

[9] Matsuda, F.; Kawatsura, M.; Hosaka, K.; Shirahama, H. *Chem. Eur. J.* 1999, *5*, 3252.

chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford **4e'** (18.3 mg, 0.138 mmol, 69% yield) as a colorless liquid. Enantioselectivity was determined by HPLC after the conversion into benzoate **4e''**.

4e'': R_f = 0.49 (Hexane/EtOAc = 3:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): 8.02 (d, *J* = 7.5 Hz, 2H), 7.56 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.43 (dd, *J* = 7.7, 7.7 Hz, 2H), 4.47 (dd, *J* = 11.5, 7.5 Hz, 1H), 4.33 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.67 (m, 1H), 1.82-1.76 (m, 2H), 1.65-1.50 (m, 3H), 1.41 (m, 1H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 166.8, 133.0, 130.2, 129.5, 128.4, 73.5, 65.1, 44.6, 26.9, 18.9, 12.2, 10.7. IR spectroscopy (neat, cm^{-1}): 2963, 1718, 1455, 1276. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{14}H_{20}O_3$ $[M+Na]^+$, 259.1305; found 259.1304. HPLC: Daicel Chiralpak IA-IA, Hexane/EtOH = 20:1, flow rate = 0.5 mL/min, retention time; 40.4 min (major) and 43.1 min (minor). Optical rotation: $[\alpha]_D^{25.0} = -20.4$ (*c* = 0.94, EtOH).

(*R*)-3-hydroxy-2,2-dimethylpentyl benzoate (4f'')

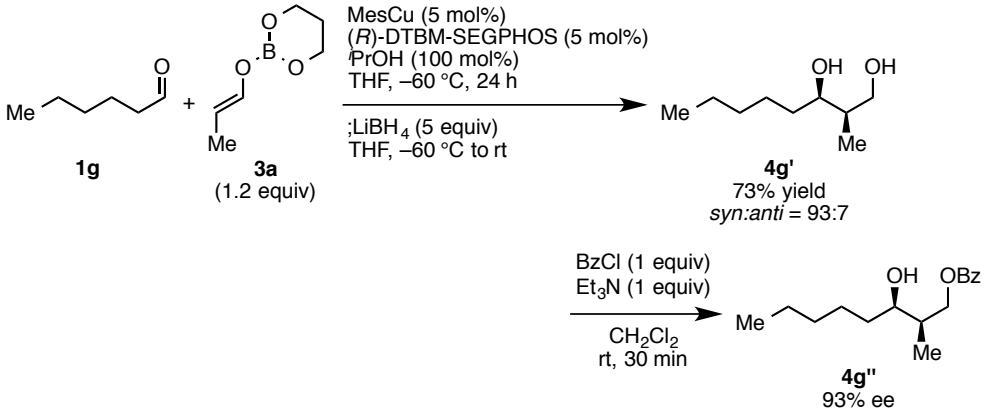


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3d** (0.4 mmol) in THF (0.4 mL) and a solution of propanal **1e** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for

overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 2:1 to afford **4f'** (17.4 mg, 0.132 mmol, 66% yield) as a white solid. Enantioselectivity was determined by HPLC after the conversion into benzoate **4f''**.

4f'': R_f = 0.54 (Hexane/EtOAc = 3:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): 8.04 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 4.45 (d, *J* = 10.9 Hz, 1H), 3.99 (d, *J* = 10.9 Hz, 1H), 3.34 (m, 1H), 2.13 (brs, 1H), 1.60 (m, 1H), 1.35 (m, 1H), 1.03 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 166.9, 133.0, 130.1, 129.6, 128.4, 71.3, 39.0, 23.9, 21.8, 19.2, 11.6. IR spectroscopy (neat, cm^{-1}): 3500, 2965, 1719, 1276, 1117. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{14}H_{20}O_3$ $[M+Na]^+$, 259.1305; found 259.1298. HPLC: Daicel Chiralpak IA, Hexane/EtOH = 20:1, flow rate = 1.0 mL/min, retention time; 8.2 min (major) and 8.6 min (minor). Optical rotation: $[\alpha]_D^{25.0} = -3.7$ (*c* = 0.75, EtOH).

(2*R*,3*R*)-3-hydroxy-2-methyloctyl benzoate (4g'')

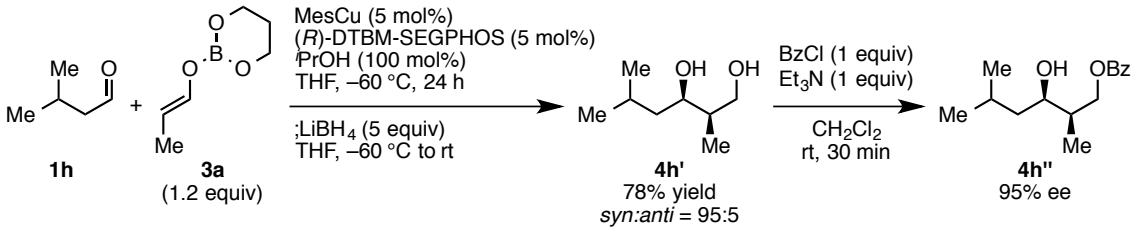


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8

mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3a** (0.24 mmol) in THF (0.4 mL) and a solution of hexanal **1g** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford **4g'** (23.3 mg, 0.145 mmol, 73% yield) as a colorless liquid. Enantioselectivity was determined by HPLC after the conversion into benzoate **4g''**.

4g'': R_f = 0.54 (Hexane/EtOAc = 3:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): 8.04 (d, *J* = 8.0 Hz, 2H), 7.57 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.45 (dd, *J* = 7.4, 7.4 Hz, 2H), 4.46 (dd, *J* = 11.2, 7.7 Hz, 1H), 4.19 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.72 (m, 1H), 2.02 (m, 1H), 1.80 (d, *J* = 5.2 Hz, 1H), 1.53-1.25 (m, 8H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 166.9, 133.0, 130.2, 129.6, 128.4, 71.4, 67.4, 37.8, 34.4, 31.8, 25.9, 22.6, 14.0, 10.1. IR spectroscopy (neat, cm^{-1}): 3481, 2930, 2858, 1720, 1277. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{16}H_{24}O_3$ $[M+Na]^+$, 287.1618; found 287.1608. HPLC: Daicel Chiralpak IA, Hexane/EtOH = 20:1, flow rate = 1.0 mL/min, retention time; 8.8 min (major) and 9.9 min (minor). Optical rotation: $[\alpha]_D^{24.3}$ = +2.7 (*c* = 0.30, $CHCl_3$).

(2*R*,3*R*)-3-hydroxy-2,5-dimethylhexyl benzoate (4h'')

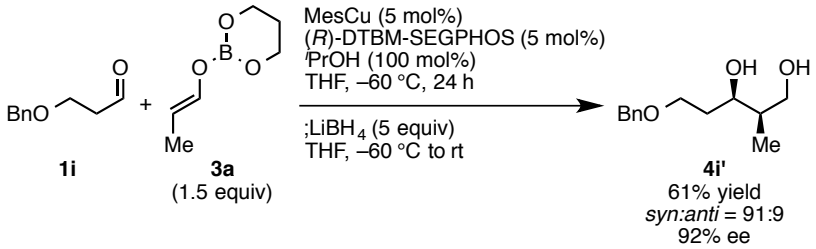


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3a** (0.24 mmol) in THF (0.4 mL) and a solution of isovaleraldehyde **1h** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford **4h'** (22.8 mg, 0.156 mmol, 78% yield) as a colorless liquid. Enantioselectivity was determined by HPLC after the conversion into benzoate **4h''**.

4h'': R_f = 0.51 (Hexane/EtOAc = 3:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): 8.04 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 4.46 (dd, *J* = 10.9, 7.5 Hz, 1H), 4.19 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.84 (m, 1H), 1.99 (m, 1H), 1.80-1.71 (m, 2H), 1.49 (m, 1H), 1.24 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 166.9, 133.0, 130.2, 129.6, 128.4, 69.3, 67.4, 43.5, 38.1, 24.8, 23.4, 22.0, 10.2. IR spectroscopy (neat, cm^{-1}): 3446, 2955, 1719, 1276. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{15}H_{22}O_3$ $[M+Na]^+$, 273.1461; found 273.1455. HPLC: Daicel Chiralpak IA, Hexane/EtOH = 20:1, flow rate = 1.0 mL/min,

retention time; 9.0 min (major) and 11.2 min (minor). Optical rotation: $[\alpha]_D^{24.3} = -3.6$ (c = 0.11, $CHCl_3$).

(2*R*,3*R*)-5-(benzyloxy)-2-methylpentane-1,3-diol (4i')

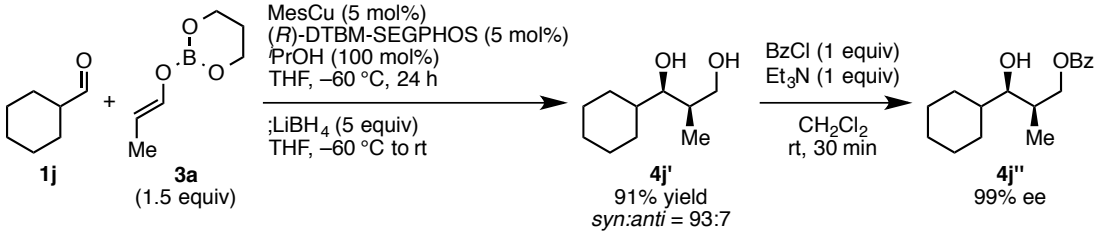


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.6 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –75 °C, a solution of boron enolate **3a** (0.3 mmol) in THF (0.25 mL) and a solution of 3-benzyloxypropionaldehyde **1i** (0.2 mmol) in THF (0.15 mL) were added, and stirred for 24 hours at –75 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 4:1 to 1:1. Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 5:1 afforded the title compound (27.5 mg, 0.123 mmol, 61% yield) as a colorless oil.

Known compound.[10] HPLC: Daicel Chiralpak IE-IF, H_2O (0.1% TFA)/MeCN = 5:1, flow rate = 1.0 mL/min, retention time; 44.5 min (minor) and 48.0 min (major). Optical rotation: $[\alpha]_D^{20.6} = -12.6$ (c = 1.0, $CHCl_3$).

[10] Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374.

(2*R*,3*R*)-3-cyclohexyl-3-hydroxy-2-methylpropyl benzoate (4j'')

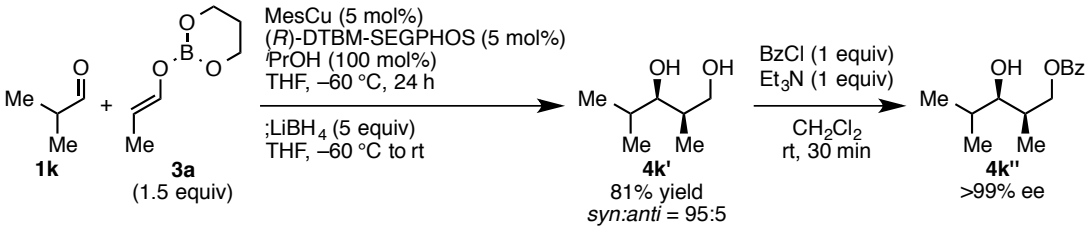


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3a** (0.3 mmol) in THF (0.4 mL) and a solution of cyclohexanecarboxaldehyde **1j** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford **4j'** (31.3 mg, 0.182 mmol, 91% yield) as a white solid. Enantioselectivity was determined by HPLC after the conversion into benzoate **4j''**.

4j'': R_f = 0.54 (Hexane/EtOAc = 3:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): 8.04 (d, *J* = 7.5 Hz, 2H), 7.57 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.45 (dd, *J* = 7.4, 7.4 Hz, 2H), 4.47 (d, *J* = 10.9, 8.0 Hz, 1H), 4.18 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.35 (m, 1H), 2.18 (m, 1H), 2.04 (m, 1H), 1.85 (d, *J* = 5.2 Hz, 1H), 1.78-1.73 (m, 2H), 1.67-1.62 (m, 2H), 1.44 (m, 1H), 1.29-1.20 (m, 2H), 1.14 (m, 1H), 1.00-0.89 (n, 2H), 0.99 (d, *J* = 9.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 166.9, 133.0, 130.2, 129.6, 128.4, 75.4, 67.7, 40.4, 34.4, 29.5, 29.1, 26.4, 26.1, 25.9, 9.6. IR spectroscopy (neat, cm^{-1}): 3502, 2924, 2851, 1719, 1450. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{17}H_{24}O_3$ $[M+Na]^+$,

299.1618; found 299.1607. HPLC: Daicel Chiralpak IA, Hexane/EtOH = 20:1, flow rate = 1.0 mL/min, retention time; 9.6 min (major) and 15.9 min (minor). Optical rotation: $[\alpha]_D^{26.8} = -2.0$ (c = 0.70, $CHCl_3$).

(2*R*,3*R*)-3-hydroxy-2,4-dimethylpentyl benzoate (4k'')

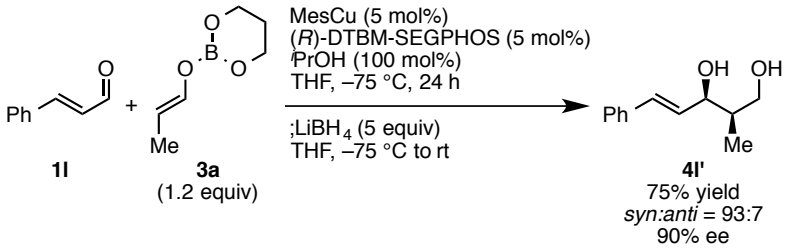


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3a** (0.3 mmol) in THF (0.4 mL) and a solution of isobutyraldehyde **1k** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford **4k'** (21.5 mg, 0.163 mmol, 81% yield) as a white solid. Enantioselectivity was determined by HPLC after the conversion into benzoate **4k''**.

4k'': R_f = 0.51 (Hexane/EtOAc = 3:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): 8.05 (d, J = 7.5 Hz, 2H), 7.57 (dd, J = 7.4, 7.4 Hz, 1H), 7.45 (dd, J = 7.7, 7.7 Hz, 2H), 4.46 (dd, J = 10.9, 8.0 Hz, 1H), 4.18 (dd, J = 10.9, 5.7 Hz, 1H), 3.29 (m, 1H), 2.18 (m, 1H), 1.85 (m, 1H), 1.76 (m, 1H), 1.02 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.9 Hz,

3H), 0.89 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$):166.9, 133.0, 130.2, 129.6, 128.4, 76.7, 67.7, 35.0, 30.9, 19.2, 19.1, 9.7. IR spectroscopy (neat, cm^{-1}): 3502, 2964, 1718, 1427, 1277. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{14}H_{20}O_3$ $[M+Na]^+$, 259.1305; found 259.1301. HPLC: Daicel Chiralpak IA, Hexane/2-Propanol = 20:1, flow rate = 1.0 mL/min, retention time; 9.3 min (major) and 11.4 min (minor). Optical rotation: $[\alpha]_D^{21.7} = -62.0$ (c = 0.1, $CHCl_3$).

(2*R*,3*R*)-2-methyl-5-phenyl-4-pentene-1,3-diol (4l')



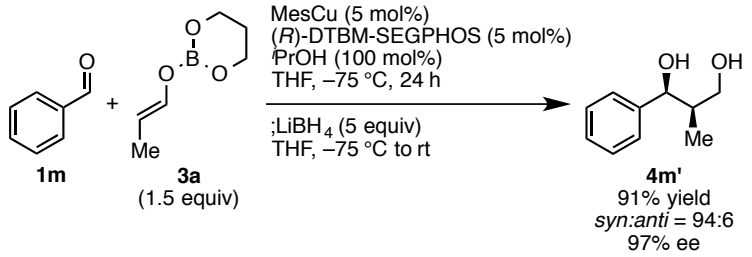
Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –75 °C, a solution of boron enolate **3a** (0.24 mmol) in THF (0.4 mL) and a solution of cinnamaldehyde **1l** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –75 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford the title compound (29.0 mg, 0.151 mmol, 75% yield) as a colorless liquid.

Known compound.[11] HPLC: Daicel Chiralpak AD-H, Hexane/EtOH = 20:1, flow

[11] Meyer, H. H. *Liebigs Ann. Chem*. **1984**, 791.

rate = 1.0 mL/min, retention time; 52.1 min (minor) and 62.1 min (major). Optical rotation: $[\alpha]_D^{23.8} = -12.4$ (c = 1.0, $CHCl_3$).

(1*R*,2*R*)-2-methyl-1-phenyl-propane-1,3-diol (4m')

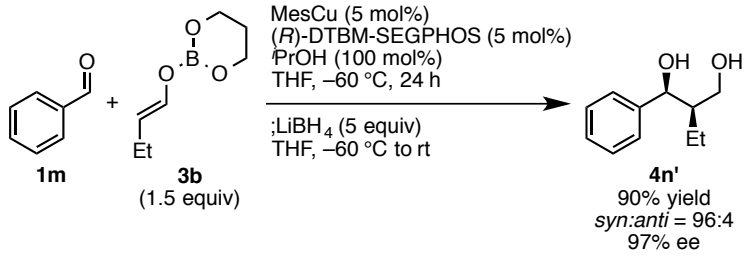


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –75 °C, a solution of boron enolate **3a** (0.3 mmol) in THF (0.4 mL) and a solution of benzaldehyde **1m** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –75 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford the title compound (30.2 mg, 0.182 mmol, 91% yield) as a colorless liquid.

Known compound.[12] HPLC: Daicel Chiralpak AD-H, Hexane/EtOH = 30:1, flow rate = 1.0 mL/min, retention time; 53.0 min (minor) and 59.9 min (major). Optical rotation: $[\alpha]_D^{24.1} = -58.9$ (c = 0.18, $CHCl_3$).

[12] Lin, L.; Yamamoto, K.; Matsunaga, S.; Kanai, M. *Chem. Asian J.* **2013**, *8*, 2974.

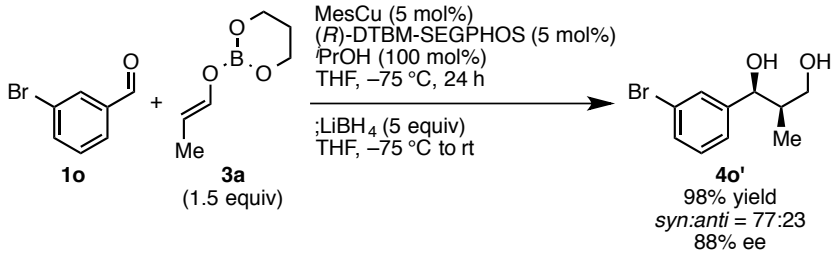
(1*R*,2*R*)-2-ethyl-1-phenyl-propane-1,3-diol (4n')



Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3b** (0.3 mmol) in THF (0.4 mL) and a solution of benzaldehyde **1m** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford the title compound (32.3 mg, 0.179 mmol, 90% yield) as a colorless liquid.

Known compound.[12] HPLC: Daicel Chiralpak IC, Hexane/EtOH = 20:1, flow rate = 1.0 mL/min, retention time; 16.4 min (major) and 18.1 min (minor). Optical rotation: $[\alpha]_D^{24.2} = -46.9$ (*c* = 0.26, $CHCl_3$).

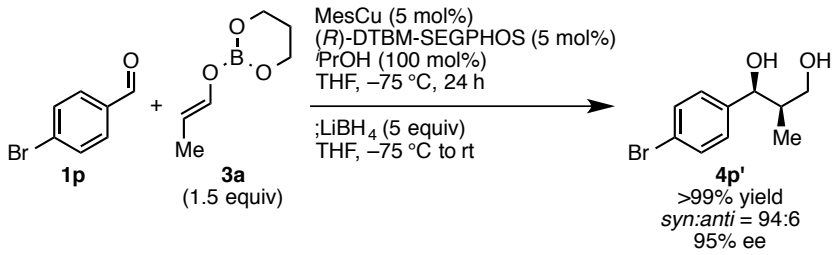
(1*R*,2*R*)-1-(3-bromophenyl)-2-methyl-propane-1,3-diol (4o')



Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –75 °C, a solution of boron enolate **3a** (0.3 mmol) in THF (0.4 mL) and a solution of 3-bromobenzaldehyde **1o** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –75 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford the title compound (48.0 mg, 0.196 mmol, 98% yield) as a colorless liquid.

Known compound.[12] HPLC: Daicel Chiralpak IC, Hexane/EtOH = 20:1, flow rate = 1.0 mL/min, retention time; 8.5 min (major) and 9.8 min (minor). Optical rotation: $[\alpha]_D^{24.2} = -14.0$ ($c = 0.50$, $CHCl_3$).

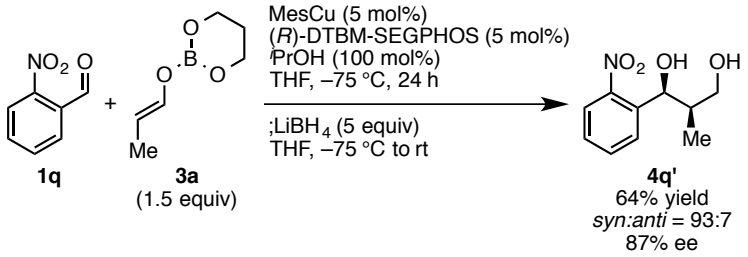
(1*R*,2*R*)-1-(4-bromophenyl)-2-methyl-propane-1,3-diol (4p')



Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –75 °C, a solution of boron enolate **3a** (0.3 mmol) in THF (0.4 mL) and a solution of 4-bromobenzaldehyde **1p** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –75 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford the title compound (48.8 mg, 0.199 mmol, >99% yield) as a white solid.

Known compound.[12] HPLC: Daicel Chiralpak IC, Hexane/EtOH = 30:1, flow rate = 1.0 mL/min, retention time; 14.4 min (major) and 15.5 min (minor). Optical rotation: $[\alpha]_D^{23.9} = -44.4$ (*c* = 0.50, $CHCl_3$).

(1*S*,2*R*)-2-methyl-1-(2-nitrophenyl)-propane-1,3-diol (4q')

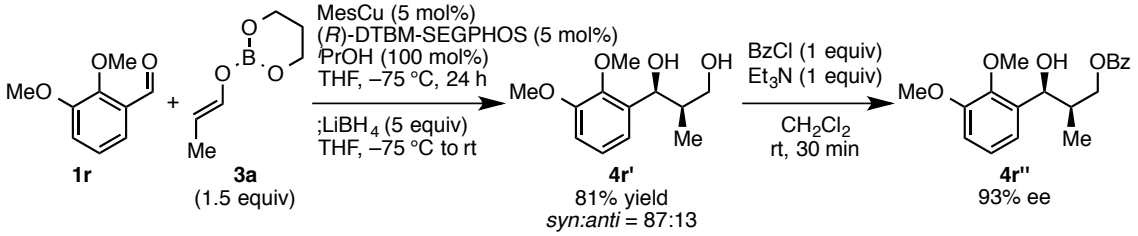


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –75 °C, a solution of boron enolate **3a** (0.3 mmol) in THF (0.4 mL) and a solution of 2-nitrobenzaldehyde **1q** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –75 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford the title compound (26.9 mg, 0.127 mmol, 64% yield) as yellow liquid.

Known compound.[13] HPLC: Daicel Chiralpak IC, Hexane/EtOH = 20:1, flow rate = 1.0 mL/min, retention time; 31.1 min (minor) and 48.4 min (major). Optical rotation: $[\alpha]_D^{24.1} = -26.0$ (*c* = 1.0, $CHCl_3$).

[13] Li, J.; Fu, N.; Li, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 4501.

(2*R*,3*S*)-3-(2,3-dimethoxyphenyl)-3-hydroxy-2-methylpropyl benzoate (4r'')

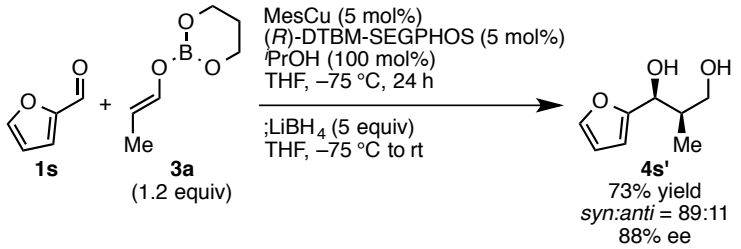


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –75 °C, a solution of boron enolate **3a** (0.3 mmol) in THF (0.4 mL) and a solution of 2,3-dimethoxybenzaldehyde **1r** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –75 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford **4r'** (36.7 mg, 0.162 mmol, 81% yield) as a colorless liquid. Enantioselectivity was determined by HPLC after the conversion into benzoate **4r''**.

4r'': R_f = 0.49 (Hexane/EtOAc = 3:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): 8.03 (m, 2H), 7.56 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.44 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.04 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.99 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.06 (dd, *J* = 4.9, 4.9 Hz, 1H), 4.39 (dd, *J* = 10.9, 7.5 Hz, 1H), 4.17 (dd, *J* = 10.9, 5.2, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.49 (d, *J* = 5.2, 1H), 2.37 (m, 1H), 1.05 (d, *J* = 6.9, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 166.7, 152.4, 146.0, 136.2, 132.9, 130.3, 129.6, 128.3, 123.8, 119.4, 111.5, 70.6, 67.3, 60.6, 55.7, 39.2, 11.3. IR spectroscopy (neat, cm^{-1}): 3502, 2936, 1717, 1478, 1274. Mass spectroscopy: HRMS-ESI (m/z): calcd for

$C_{19}H_{22}O_5$ $[M+Na]^+$, 353.1359; found 353.1368. HPLC: Daicel Chiralpak IA, Hexane/EtOH = 20:1, flow rate = 1.0 mL/min, retention time; 22.4 min (major) and 43.3 min (minor). Optical rotation: $[\alpha]_D^{27.4}$ = +36.0 (*c* = 0.70, $CHCl_3$).

(1*S*,2*R*)-1-(2-furyl)-2-methyl-propane-1,3-diol (4s')

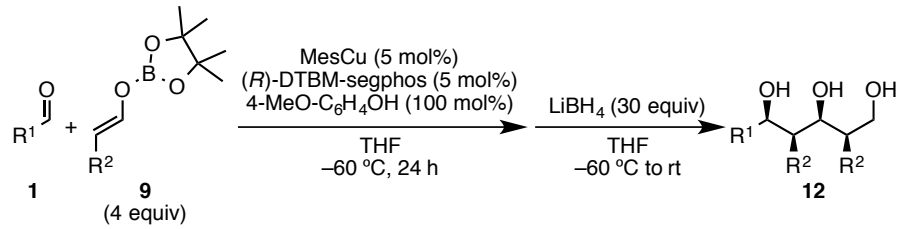


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and 2-propanol (15.4 μL, 0.2 mmol) at 23 °C. After cooled to –75 °C, a solution of boron enolate **3a** (0.24 mmol) in THF (0.4 mL) and a solution of furfural **1s** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –75 °C. To this solution was added a solution of $LiBH_4$ (1 mmol) in THF (0.5 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 to afford **4s'** (22.7 mg, 0.145 mmol, 73% yield) as a colorless liquid.

Known compound.[12] HPLC: Daicel Chiralpak IC, Hexane/EtOH = 20:1, flow rate = 1.0 mL/min, retention time; 37.1 min (major) and 42.0 min (minor). Optical rotation: $[\alpha]_D^{24.2}$ = −35.0 (*c* = 0.04, $CHCl_3$).

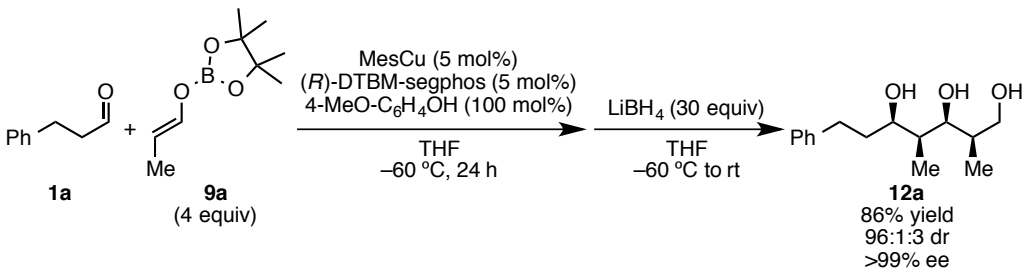
III. Double-Aldol Reaction

Representative Procedure



Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.8 mL) and a solution of 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) in THF (0.2 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9** (0.8 mmol) in THF (0.8 mL) and a solution of aldehyde **1** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity (if possible) by LC/MS analysis, the residue was purified by column chromatography on silica gel. After the determination of enantioselectivity (if necessary), further purification by reversed phase HPLC was conducted to give the pure product (if necessary).

(2*R*,3*S*,4*S*,5*R*)-2,4-dimethyl-7-phenylheptane-1,3,5-triol (12a)

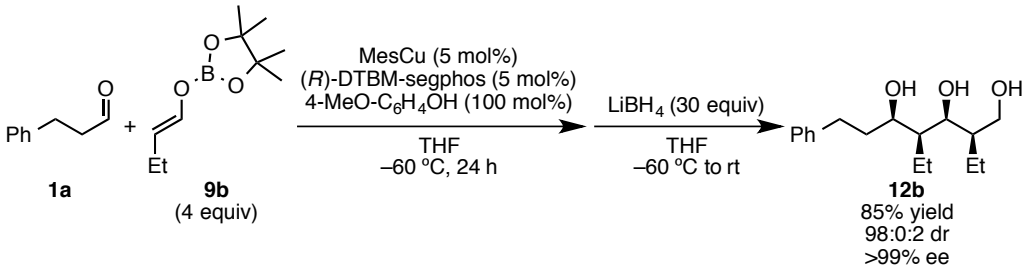


Under argon, mesityl copper (1.8 mg, 0.01 mmol), (*R*)-DTBM-segphos (11.8 mg,

0.01 mmol) and 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) were added to a test tube, followed by THF (0.5 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9a** (0.8 mmol) in THF (1.3 mL) and a solution of hydrocinnamaldehyde **1a** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity by LC/MS analysis using Daicel Chiralpak IA-ID, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 2:1 to EtOAc (10% MeOH). The enantiomeric purity was determined by HPLC analysis using Daicel Chiralpak IF (H_2O (0.1% TFA)/MeCN = 8:1, flow rate = 1.0 mL/min, retention time; 91.2 min (major) and 110.2 min (minor)). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 4:1 afforded the title compound (41.8 mg, 0.166 mmol, 83% yield) as a white solid. The relative configuration was determined by X-ray crystallographic analysis. The absolute configuration was elucidated from the single-aldol product.

R_f = 0.32 (EtOAc). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.22-7.18 (m, 3H), 3.84 (ddd, *J* = 8.7, 4.4, 2.1 Hz, 1H), 3.79 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.66-3.60 (m, 2H), 2.77 (m, 1H), 2.66 (m, 1H), 1.93-1.83 (m, 2H), 1.77-1.68 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8, 128.5, 128.4, 125.9, 78.5, 75.7, 66.4, 39.2, 38.3, 37.0, 32.5, 12.4, 6.0. IR spectroscopy (neat, cm^{-1}): 3365, 2923, 1654, 1456. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{15}H_{24}O_3$ $[M+Na]^+$, 275.1618; found 275.1620. Optical rotation: $[\alpha]_D^{29.7}$ = +10.9 (*c* = 0.77, $CHCl_3$).

(2*R*,3*S*,4*S*,5*R*)-2,4-diethyl-7-phenylheptane-1,3,5-triol (12b)

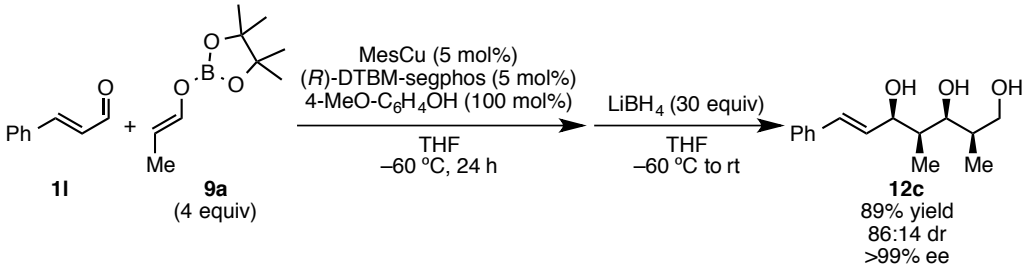


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.7 mL) and a solution of 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) in THF (0.1 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9b** (0.8 mmol) in THF (1.0 mL) and a solution of hydrocinnamaldehyde **1a** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity by LC/MS analysis using Daicel Chiralpak IC, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to EtOAc (10% MeOH). The enantiomeric purity was determined by HPLC analysis using Daicel Chiralpak IA (H_2O (0.1% TFA)/MeCN = 3:1, flow rate = 1.0 mL/min, retention time; 32.6 min (minor) and 36.4 min (major)). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 2:1 afforded the title compound (46.8 mg, 0.167 mmol, 83% yield) as a colorless oil.

R_f = 0.18 (hexane/EtOAc = 1:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.22-7.18 (m, 3H), 3.94 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.83 (m, 1H), 3.77 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.71 (dd, *J* = 10.9, 4.0 Hz, 1H), 2.81 (m, 1H), 2.66 (m, 1H),

2.29 (brs, 1H), 2.01 (brs, 1H), 1.93-1.78 (m, 2H), 1.66-1.39 (m, 6H), 1.02 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.8, 128.5, 128.4, 126.0, 77.6, 75.7, 63.2, 46.6, 44.9, 36.8, 32.8, 18.5, 16.0, 14.9, 11.7. IR spectroscopy (neat, cm^{-1}): 3389, 3027, 2960, 2876, 1636, 1604. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{17}H_{28}O_3$ $[M+Na]^+$, 303.1931; found 303.1916. Optical rotation: $[\alpha]_D^{20.4}$ = +11.2 (c = 1.0, $CHCl_3$).

(2*R*,3*S*,4*S*,5*R*,*E*)-2,4-dimethyl-7-phenylhept-6-ene-1,3,5-triol (12c)

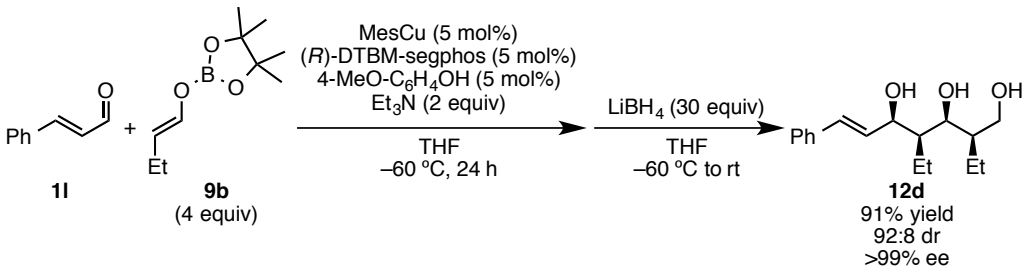


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.4 mL) and a solution of 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) in THF (0.4 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9a** (0.8 mmol) in THF (1.0 mL) and a solution of cinnamaldehyde **1l** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using Daicel Chiralpak IF, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 1:1 to 1:2 and then hexane/EtOAc (10% MeOH) = 1:4. Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with

H_2O/MeCN = 6:1 afforded the title compound (38.3 mg, 0.153 mmol, 76% yield) as a white solid.

R_f = 0.17 (hexane/EtOAc = 1:2). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7.5 Hz, 2H), 7.32 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 16.1 Hz, 1H), 6.27 (dd, *J* = 16.0, 5.2 Hz, 1H), 4.56 (m, 1H), 3.94 (m, 1H), 3.67 (m, 2H), 2.70 (brs, 1H), 2.49 (brs, 1H), 1.95-1.88 (m, 2H), 1.74 (brs, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ = 137.5, 131.9, 130.0, 128.8, 127.6, 126.8, 76.0, 75.6, 65.9, 41.0, 38.5, 12.2, 7.9. IR spectroscopy (neat, cm^{-1}): 3406, 3026, 2969, 2926, 2883, 1654, 1495, 1449. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{15}H_{22}O_3$ $[M+Na]^+$, 273.1461; found 273.1465. Optical rotation: $[\alpha]_D^{22.1}$ = +2.4 (*c* = 2.0, $CHCl_3$).

(2*R*,3*S*,4*S*,5*R*,*E*)-2,4-diethyl-7-phenylhept-6-ene-1,3,5-triol (12d)

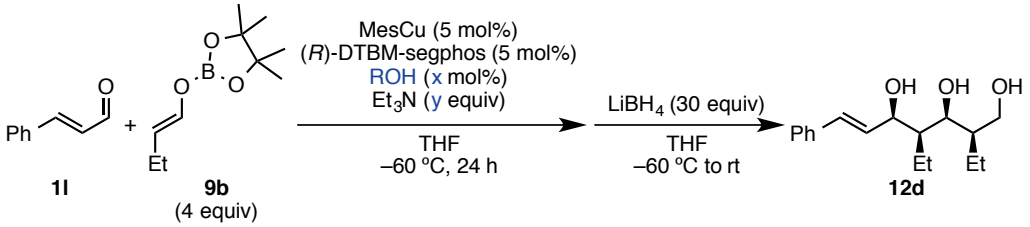


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.7 mL), a solution of 4-MeO-C_6H_4OH (1.2 mg, 0.01 mmol) in THF (0.1 mL) and triethylamine (55.8 μL, 0.4 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9b** (0.8 mmol) in THF (1.0 mL) and a solution of cinnamaldehyde **1l** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for

overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using Daicel Chiralpak IB, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:2 and then EtOAc (10% MeOH). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 7:3 afforded the title compound (46.7 mg, 0.168 mmol, 84% yield) as a colorless oil.

R_f = 0.42 (hexane/EtOAc = 1:2). NMR spectroscopy: ^{1}H NMR (500 MHz, CD_3OD): δ = 7.40 (d, *J* = 7.5 Hz, 2H), 7.29 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.19 (m, 1H), 6.59 (d, *J* = 15.5 Hz, 1H), 6.37 (dd, *J* = 15.8, 6.8 Hz, 1H), 4.45 (m, 1H), 3.90 (dd, *J* = 6.0, 4.0 Hz, 1H), 3.66 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.61 (dd, *J* = 11.0, 4.5 Hz, 1H), 1.73-1.48 (m, 5H), 1.39 (m, 1H), 1.04 (t, *J* = 7.8 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 138.6, 132.7, 131.1, 129.5, 128.3, 127.4, 75.8, 74.6, 62.5, 49.2, 46.5, 19.9, 18.8, 14.6, 12.1. IR spectroscopy (neat, cm^{-1}): 3362, 2961, 2932, 2876, 1495, 1448. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{17}H_{26}O_3$ $[M+Na]^+$, 301.1774; found 301.1789. Optical rotation: $[\alpha]_D^{21.9}$ = –6.0 (*c* = 2.0, $CHCl_3$).

Table S1 Optimization of the Reaction Conditions for 12d[a]

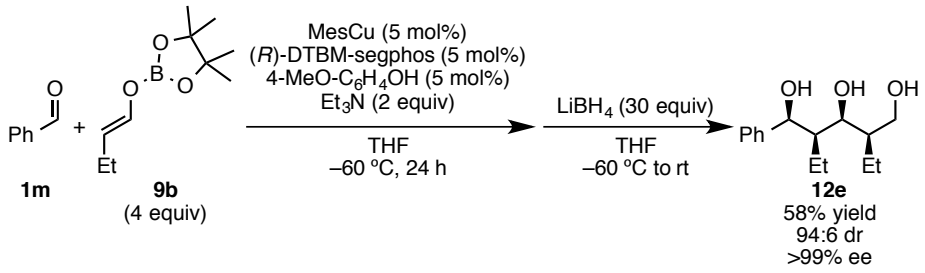


1l **9b** (4 equiv) **12d**

entry	ROH (x mol%)	Et_3N (y equiv)	single:double:triple[b]	dr (12d:other isomers)[c]	% ee	% yield[d]
1	4-MeO-C_6H_4OH (5)	0	59:41:0	66:34	97	ND
2	4-MeO-C_6H_4OH (5)	2	7:92:1	92: 8	>99	91
3	4-MeO-C_6H_4OH (100)	0	48:52:0	87:13	>99	ND
4	^{i}PrOH (5)	0	44:56:0	75:25	97	ND
5	^{i}PrOH (5)	2	5:95:0	90:10	>99	ND

[a]Selectivity was determined based on the area% of LC/MS chart of the crude reaction mixture. [b]The selectivity refers to the ratio of single-aldol products/double-aldol products/triple-aldol products. [c]Diastereomeric ratio of double-aldol products. [d]Yield refers to isolated yield after purification by column chromatography on silica gel.

(1*S*,2*R*,3*S*,4*R*)-2,4-diethyl-1-phenylpentane-1,3,5-triol (12e)

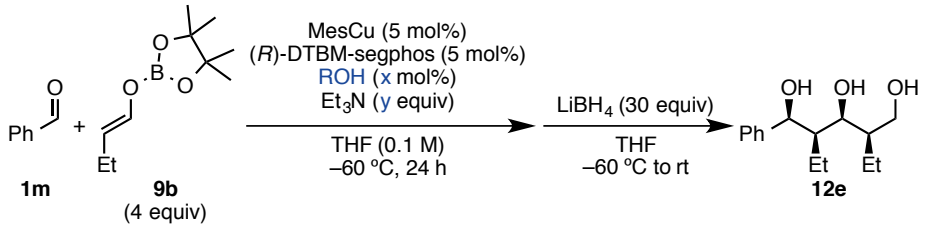


Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.7 mL), a solution of 4-MeO-C_6H_4OH (1.2 mg, 0.01 mmol) in THF (0.1 mL) and triethylamine (55.8 μL, 0.4 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9b** (0.8 mmol) in THF (1.0 mL) and a solution of benzaldehyde **1m** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using Daicel Chiralpak IC, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 2:1 and then hexane/EtOAc (10% MeOH) = 1:1. Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 5:1 afforded the title compound (27.3 mg, 0.108 mmol, 54% yield) as a colorless oil.

R_f = 0.45 (hexane/EtOAc = 1:2). NMR spectroscopy: ^{1}H NMR (500 MHz, CD_3OD): δ = 7.38 (d, *J* = 7.5 Hz, 2H), 7.32 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.22 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.91 (d, *J* = 4.6 Hz, 1H), 3.77 (dd, *J* = 6.3, 4.6 Hz, 1H), 3.65 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.57 (dd, *J* = 10.9, 4.6 Hz, 1H), 1.82 (m, 1H), 1.72-1.46 (m, 4H), 1.39 (m,

1H), 0.95 (t, J = 7.5 Hz, 3H), 0.68 (t, J = 7.7 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 145.7, 129.0, 127.8, 127.1, 77.3, 76.1, 62.4, 50.1, 46.1, 19.8, 17.9, 14.9, 12.0. IR spectroscopy (neat, cm^{-1}): 3375, 2961, 2931, 2876, 1650, 1604. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{15}H_{24}O_3$ $[M+Na]^+$, 275.1618; found 275.1621. Optical rotation: $[\alpha]_D^{22.6}$ = –35.3 (c = 2.0, $CHCl_3$).

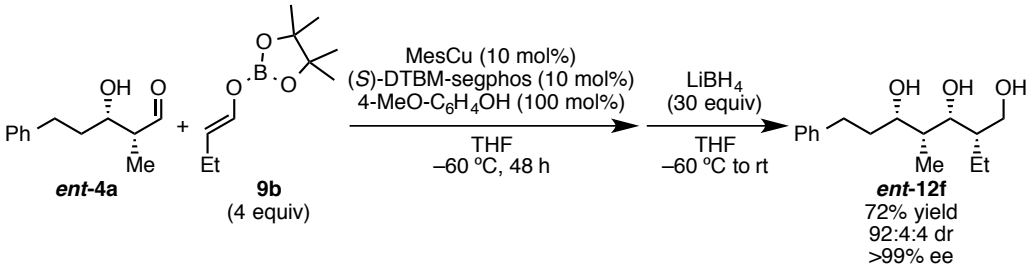
Table S2 Optimization of the Reaction Conditions for 12e[a]



entry	ROH (x mol%)	Et_3N (y equiv)	single:double:triple[b]	dr (**12e**:other isomers)[c]	% ee	% yield[d]
1	4-MeO-C_6H_4OH (5)	0	91: 9:0	76:24	>99	ND
2	4-MeO-C_6H_4OH (5)	2	22:77:0	94: 6	>99	58
3	4-MeO-C_6H_4OH (100)	0	31:69:0	98: 2	>99	ND
4	4-MeO-C_6H_4OH (100)	2	68:32:0	99: 1	>99	ND
5	^{i}PrOH (5)	0	73:27:0	66:34	>99	ND
6	^{i}PrOH (5)	2	34:66:0	98: 2	>99	ND
7	^{i}PrOH (100)	2	64:36:0	97: 3	>99	ND

[a]Selectivity was determined based on the area% of LC/MS chart of the crude reaction mixture. [b]The selectivity refers to the ratio of single-aldol products/double-aldol products/triple-aldol products. [c]Diastereomeric ratio of double-aldol products. [d]Yield refers to isolated yield after purification by column chromatography on silica gel.

(2*S*,3*R*,4*R*,5*S*)-2-ethyl-4-methyl-7-phenylheptane-1,3,5-triol (*ent*-12f)



Under argon, mesityl copper (18.3 mg, 0.1 mmol) and (*S*)-DTBM-segphos (119.1 mg, 0.101 mmol) were added to a round bottom flask, followed by THF (5.0 mL) and 2-propanol (153.9 μL, 2.0 mmol) at 23 °C. After cooled to –60 °C, a solution of boron

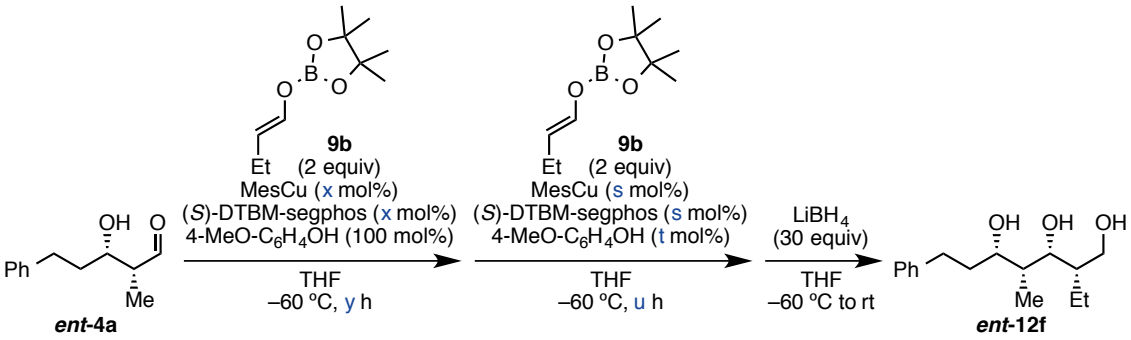
enolate **3a** (3.0 mmol) in THF (15 mL) and hydrocinnamaldehyde **1a** (263.4 μL, 2.0 mmol) were added, and stirred for 24 hours at –60 °C. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/Et_2O = 20:1 to 1.5:1 to afford ***ent*-4a** (145.5 mg, 38% yield) as a colorless oil.

Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*S*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.2 mL) and a solution of 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) in THF (0.1 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9b** (0.4 mmol) in THF (0.6 mL) and a solution of aldehyde ***ent*-4a** (0.2 mmol) in THF (0.6 mL) were added. After stirring for 24 hours at –60 °C, a solution of mesityl copper/(*S*)-DTBM-segphos (0.01 mmol) in THF (0.2 mL) and a solution of boron enolate **9b** (0.4 mmol) in THF (0.3 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity by LC/MS analysis using Daicel Chiralpak IC, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to 1:1 and then hexane/EtOAc (10% MeOH) = 1:1. The enantiomeric purity was determined by HPLC analysis using Daicel Chiralpak IB (H_2O (0.1% TFA)/MeCN = 5:1, flow rate = 1.0 mL/min, retention time; 49.3 min (major) and 61.9 min (minor)). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 4:1 afforded the title compound (35.2 mg, 0.132 mmol, 66% yield) as a colorless oil.

R_f = 0.14 (hexane/EtOAc = 1:1). NMR spectroscopy: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.22-7.18 (m, 3H), 3.88 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.84 (m, 1H), 3.76

(dd, J = 11.2, 4.9 Hz, 1H), 3.68 (dd, J = 10.9, 3.4 Hz, 1H), 2.77 (m, 1H), 2.66 (m, 1H), 1.89 (m, 1H), 1.77-1.71 (m, 2H), 1.63-1.52 (m, 2H), 1.43 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.8, 128.5, 128.4, 125.9, 78.1, 75.8, 62.9, 44.7, 38.8, 37.0, 32.5, 18.8, 11.7, 6.1. IR spectroscopy (neat, cm^{-1}): 3398, 3028, 2970, 1663, 1455. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{16}H_{26}O_3$ $[M+Na]^+$, 289.1774; found 289.1773. Optical rotation: $[\alpha]_D^{22.2}$ = –6.8 (c = 2.0, $CHCl_3$).

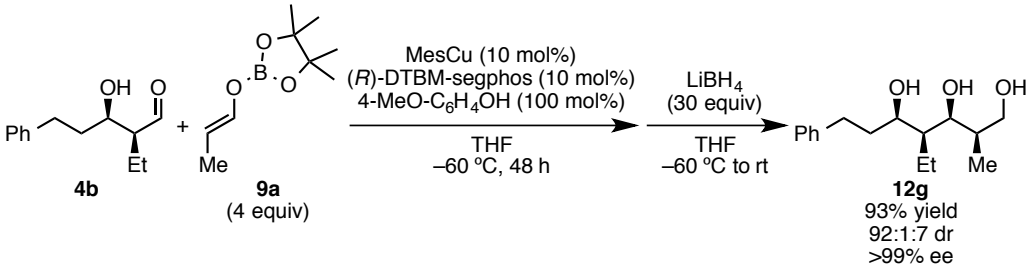
Table S3 Optimization of the Reaction Conditions for *ent*-12f[a]



entry	cat (x mol%)	y h	cat (s mol%)	ArOH (t mol%)	u h	single:double:triple[b]	dr (**12f**:**13f**:other isomers)[c]	% ee	% yield[d]
1	10	48	0	0	0	49:51:0	93:4:3	>99	ND
2	5	24	5	0	24	30:70:0	92:4:4	>99	72
3	5	24	5	100	24	54:46:0	94:0:6	ND	ND

[a]Selectivity was determined based on the area% of LC/MS chart of the crude reaction mixture. [b]The selectivity refers to the ratio of single-aldol products/double-aldol products/triple-aldol products. [c]Diastereomeric ratio of double-aldol products. [d]Yield refers to isolated yield after purification by column chromatography on silica gel.

(2*R*,3*S*,4*S*,5*R*)-4-ethyl-2-methyl-7-phenylheptane-1,3,5-triol (12g)



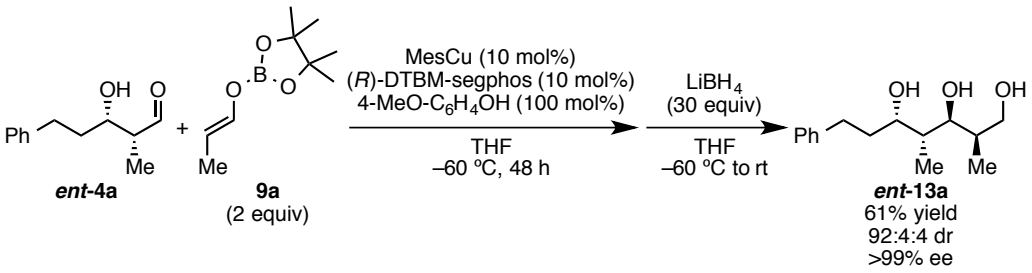
Under argon, mesityl copper (18.3 mg, 0.1 mmol) and (*R*)-DTBM-segphos (119.1

mg, 0.101 mmol) were added to a round bottom flask, followed by THF (5.0 mL) and 2-propanol (153.9 μL, 2.0 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3b** (3.0 mmol) in THF (15 mL) and hydrocinnamaldehyde **1a** (263.4 μL, 2.0 mmol) were added, and stirred for 24 hours at –60 °C. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/Et_2O = 5:1 to 2:1 to afford **4b** (331.5 mg, 80% yield) as a white solid.

Under argon, mesityl copper (1.8 mg, 0.01 mmol) and (*R*)-DTBM-segphos (11.8 mg, 0.01 mmol) were added to a test tube, followed by THF (0.5 mL) and a solution of 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) in THF (0.1 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9a** (0.4 mmol) in THF (0.4 mL) and a solution of aldehyde **4b** (0.2 mmol) in THF (0.5 mL) were added. After stirring for 24 hours at –60 °C, a solution of mesityl copper/(*R*)-DTBM-segphos (0.01 mmol) in THF (0.2 mL) and a solution of boron enolate **9a** (0.4 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity by LC/MS analysis using Daicel Chiralpak IE, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 2:1 to EtOAc (10% MeOH). The enantiomeric purity was determined by HPLC analysis using Daicel Chiralpak IA (H_2O (0.1% TFA)/MeCN = 5:1, flow rate = 1.0 mL/min, retention time; 37.0 min (minor) and 42.4 min (major)). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 4:1 afforded the title compound (45.8 mg, 0.172 mmol, 86% yield) as a white solid.

R_f = 0.11 (hexane/EtOAc = 1:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.22-7.18 (m, 3H), 3.88-3.83 (m, 2H), 3.67 (m, 2H), 2.81 (m, 1H), 2.66 (m, 1H), 1.93-1.78 (m, 4H), 1.57 (m, 2H), 1.02 (t, *J* = 7.7 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.9, 128.41, 128.37, 125.9, 76.1, 74.8, 66.2, 47.0, 38.2, 36.7, 32.8, 16.4, 14.9, 11.5. IR spectroscopy (neat, cm^{-1}): 3358, 2934, 2878, 1456. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{16}H_{26}O_3$ $[M+Na]^+$, 289.1774; found 289.1775. Optical rotation: $[\alpha]_D^{21.4}$ = +14.6 (*c* = 1.0, $CHCl_3$).

(2*R*,3*S*,4*R*,5*S*)-2,4-dimethyl-7-phenylheptane-1,3,5-triol (*ent*-13a)



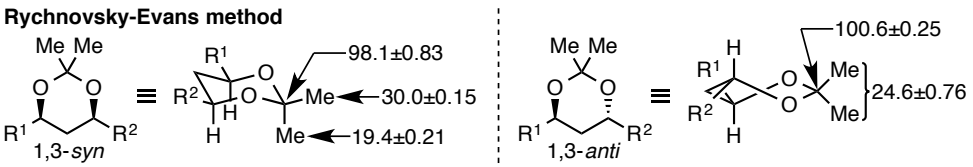
Under argon, mesityl copper (9.1 mg, 0.05 mmol) and (*S*)-DTBM-segphos (59.0 mg, 0.05 mmol) were added to a round bottom flask, followed by THF (3.0 mL) and 2-propanol (77.0 μL, 1.0 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3a** (1.5 mmol) in THF (7 mL) and hydrocinnamaldehyde **1a** (131.7 μL, 1.0 mmol) were added, and stirred for 24 hours at –60 °C. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/Et_2O = 10:1 to 2:1 to afford ***ent*-4a** (50.0 mg, 26% yield) as a colorless oil.

Under argon, mesityl copper (3.7 mg, 0.02 mmol) and (*R*)-DTBM-segphos (23.6 mg, 0.02 mmol) were added to a test tube, followed by THF (0.2 mL) and a solution of 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) in THF (0.2 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9a** (0.4 mmol) in THF (0.4 mL) and a solution of aldehyde

***ent*-4a** (0.2 mmol) in THF (1.2 mL) were added, and stirred for 48 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using Daicel Chiralpak IA-ID, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 2:1 to EtOAc (10% MeOH). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 4:1 afforded the title compound (28.3 mg, 0.112 mmol, 56% yield) as a colorless oil.

R_f = 0.42 (EtOAc). NMR spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.17 (m, 5H), 3.92 (dd, *J* = 9.4, 2.3 Hz, 1H), 3.85-3.79 (m, 2H), 3.73 (dd, *J* = 10.3, 4.9 Hz, 1H), 2.93 (m, 1H), 2.65 (m, 1H), 1.94-1.84 (m, 2H), 1.80-1.70 (m, 2H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.3, 128.40, 128.36, 125.8, 75.7, 73.9, 67.6, 39.9, 36.1, 34.6, 33.0, 11.8, 8.9. IR spectroscopy (neat, cm^{-1}): 3406, 2937, 1647, 1456, 1338. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{15}H_{24}O_3$ $[M+Na]^+$, 275.1618; found 275.1617. Optical rotation: $[\alpha]_D^{29.8}$ = –28.2 (*c* = 1.0, $CHCl_3$).

Stereochemical Determination of *ent*-13a

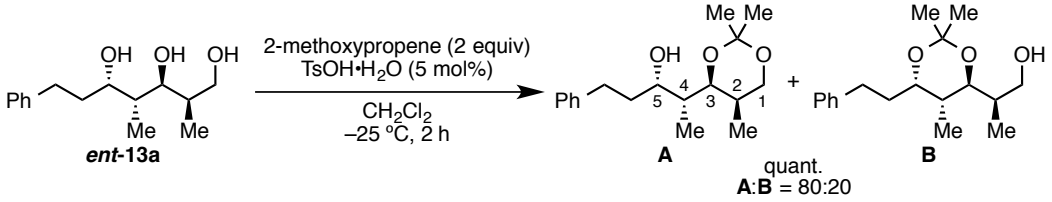


The relative configuration was determined according to the method of Rychnovsky[14] and Evans[15] after conversion to 1,3-diol acetonides. In this method,

[14] (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org.*

chemical shifts of ^{13}C NMR signals indicate a chair or a twist-boat configuration, which indicates the 1,3-*syn* or the 1,3-*anti* configuration, respectively. The 1,2-relative configuration was determined the coupling constants of ^{1}H NMR of 1,3-diol acetonides. The absolute configuration was elucidated from the single-aldol product.

(3*S*,4*R*)-1-phenyl-4-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl)pentan-3-ol (A)



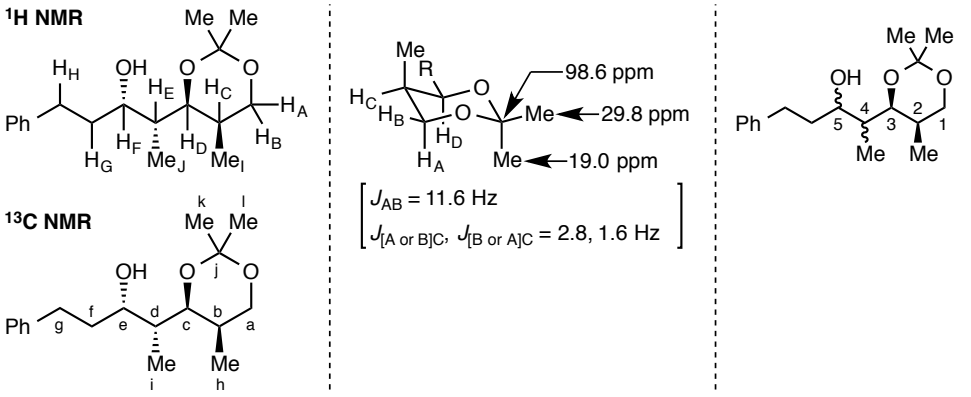
To a test tube, ***ent*-13a** (5.2 mg, 0.021 mmol) and CH_2Cl_2 (0.3 mL) were added, followed by 2-methoxypropene (3.8 μL, 0.041 mmol) and a solution of *p*-toluenesulfonic acid monohydrate (0.001 mmol) in THF (10.3 μL) at –25 °C. The reaction was stirred for 2 hours at –25 °C and quenched by the addition of sat. $NaHCO_3$ aq. EtOAc was added and the product was extracted from the aqueous mixture with EtOAc. The combined organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 6:1 to 5:1 to afford the mixture of **A** and **B** (A:B = 80:20) as a colorless oil.

R_f = 0.56 (hexane/EtOAc = 1:1). NMR spectroscopy of **A**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.23-7.16 (m, 3H), 4.10 (dd, *J* = 11.6, 2.8 Hz, 1H, $H_{A\text{ or }B}$), 3.97 (dd, *J* = 10.1, 2.4 Hz, 1H, H_D), 3.66 (m, 1H, H_F), 3.62 (dd, *J* = 11.6, 1.6 Hz, 1H, $H_{B\text{ or }A}$), 2.98 (m, 1H, H_H), 2.62 (m, 1H, H_H), 1.94 (m, 1H, H_E), 1.77-1.64 (m, 2H, H_G), 1.49 (m, 1H, H_C), 1.46 (s, 3H), 1.41 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H, Me_I), 0.74 (d, *J* =

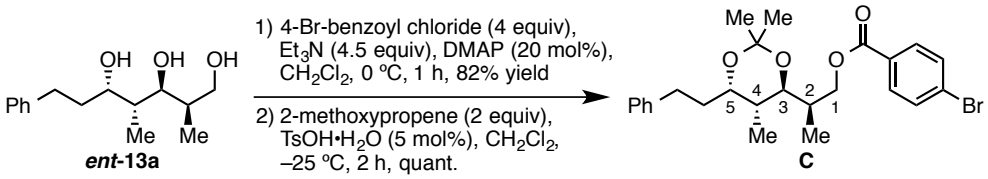
Chem. **1983**, *58*, 3511.
[15] Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

7.2 Hz, 3H, Me_J). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 128.4, 128.3, 125.7, 98.6 (C_j), 74.2 (C_e), 73.9 (C_c), 67.2 (C_a), 38.9 (C_d), 34.8 (C_f), 33.2 (C_g), 29.8 ($C_{b\ and\ k}$), 19.0 (C_l), 11.1 (C_i), 10.3 (C_h). IR spectroscopy (neat, cm^{-1}): 3479, 2936, 2876, 1456, 1380. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{18}H_{28}O_3$ $[M+Na]^+$, 315.1931; found 315.1938. Optical rotation: $[\alpha]_D^{19.5} = -12.5$ (c = 0.91, $CHCl_3$).

The 2,3-*syn* was identified by the $J_{[A\ or\ B]C}$ and $J_{[B\ or\ A]C}$ value of 2.8 and 1.6 Hz, respectively.



(*R*)-2-((4*S*,5*R*,6*S*)-2,2,5-trimethyl-6-phenethyl-1,3-dioxan-4-yl)propyl 4-bromobenzoate (C)



To a test tube, ***ent*-13a** (9.9 mg, 0.039 mmol) and CH_2Cl_2 (0.5 mL) were added, followed by 4-Br-benzoyl chloride (34.4 mg, 0.157 mmol), triethylamine (24.7 μL, 0.177 mmol) and *N,N*-dimethyl-4-aminopyridine (1.0 mg, 0.008 mmol) at 0 °C. The reaction was stirred for 1 hour at 0 °C and quenched by the addition of sat. NH_4Cl aq. CH_2Cl_2 was added and the product was extracted from the aqueous mixture with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated

under vacuum. The residue was purified by column chromatography on silica gel eluting with CH_2Cl_2/EtOAc = 20:1 to 5:1 to afford mono-benzoylated ***ent*-13a** (14.0 mg, 0.032 mmol, 82% yield) as a colorless oil.

To a test tube, this mono-benzoylated ***ent*-13a** (12.7 mg, 0.029 mmol) and CH_2Cl_2 (0.3 mL) were added, followed by 2-methoxypropene (5.5 μL, 0.058 mmol) and a solution of *p*-toluenesulfonic acid monohydrate (0.0015 mmol) in THF (14.6 μL) at –25 °C. The reaction was stirred for 2 hours at –25 °C and quenched by the addition of sat. $NaHCO_3$ aq. EtOAc was added and the product was extracted from the aqueous mixture with EtOAc. The combined organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the title compound **C** as a colorless oil.

R_f = 0.78 (hexane/EtOAc = 1:1). NMR spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (m, 2H), 7.58 (m, 2H), 7.29 (m, 2H), 7.22-7.17 (m, 3H), 4.28 (dd, *J* = 10.7, 7.6 Hz, 1H, $H_{A\text{ or }B}$), 4.23 (dd, *J* = 10.7, 6.5 Hz, 1H, $H_{B\text{ or }A}$), 3.79 (ddd, *J* = 10.0, 4.6, 4.6 Hz, 1H, H_F), 3.44 (dd, *J* = 8.5, 2.7 Hz, 1H, H_D), 2.81 (m, 1H, H_H), 2.55 (m, 1H, H_H), 2.06 (m, 1H, H_C), 1.90-1.74 (m, 2H, H_E and H_G), 1.63 (m, 1H, H_G), 1.32 (s, 3H), 1.31 (s, 3H), 1.01 (d, *J* = 7.2 Hz, 3H, Me_I), 0.84 (d, *J* = 6.7 Hz, 3H, Me_J). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 142.2, 131.7, 131.0, 129.2, 128.4, 128.3, 128.0, 125.8, 100.5 (C_j), 73.9 (C_c), 69.0 (C_e), 67.4 (C_a), 36.4 (C_d), 35.3 (C_b), 32.6 ($C_{f\text{ or }g}$), 32.4 ($C_{g\text{ or }f}$), 25.0 (C_k), 23.6 (C_l), 12.0 (C_i), 10.8 (C_h). IR spectroscopy (neat, cm^{-1}): 2934, 1723, 1591, 1455, 1381. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{25}H_{31}BrO_4$ $[M+Na]^+$, 497.1298; found 497.1316. Optical rotation: $[\alpha]_D^{20.0} = -5.8$ (*c* = 1.24, $CHCl_3$).

The 3,5-*anti* was identified by the acetal ^{13}C NMR chemical shifts of 100.5, 23.6 and 25.0 ppm. The 3,4-*anti* was identified by the J_{DE} value of 8.5 Hz.

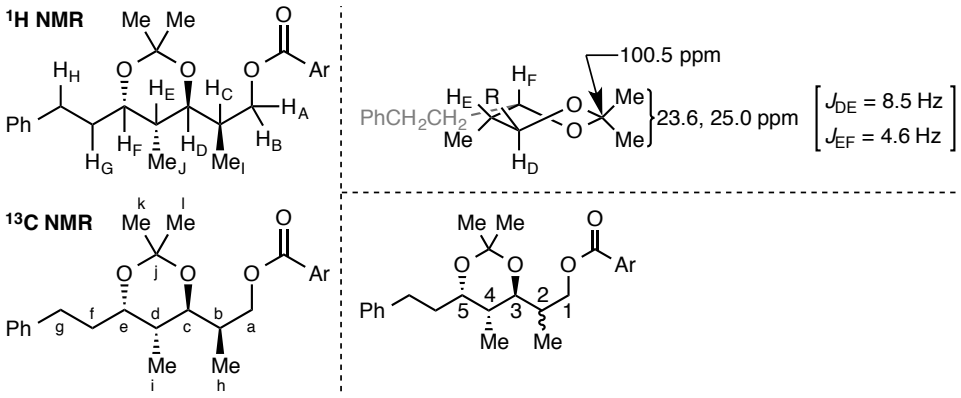
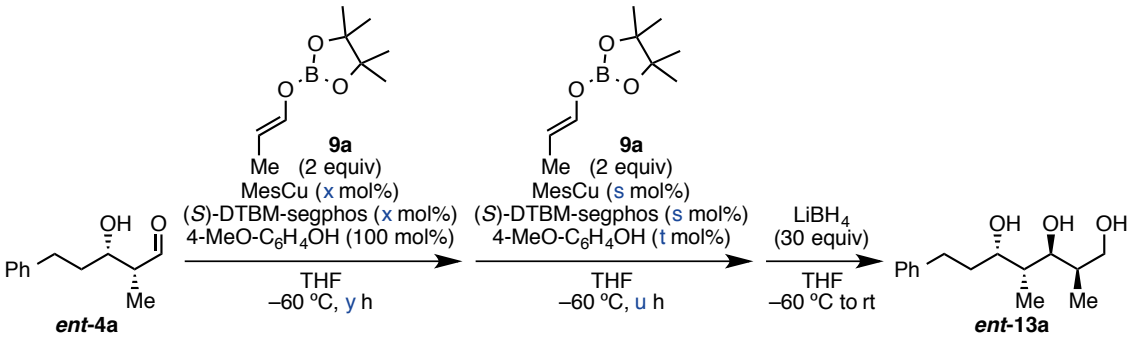


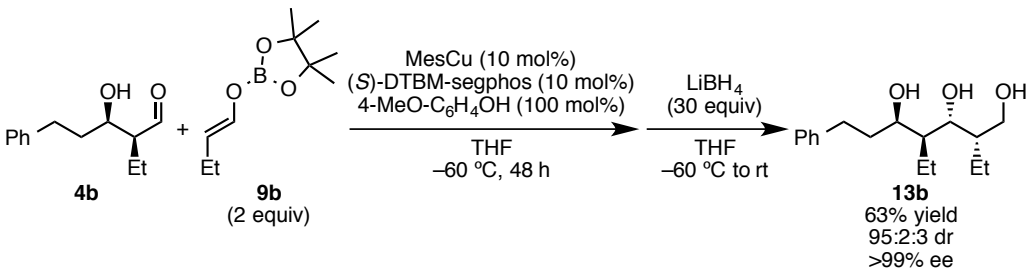
Table S4 Optimization of the Reaction Conditions for *ent*-13a[a]



entry	cat (x mol%)	y h	cat (s mol%)	ArOH (t mol%)	u h	single:double:triple[b]	dr (**12f**:**13f**:other isomers)[c]	% ee	% yield[d]
1	10	48	0	0	0	46:54:0	92:4: 4	>99	61
2	5	24	5	0	24	24:76:0	80:3:17	ND	ND
3	5	24	5	100	24	54:46:0	88:2:10	ND	ND

[a]Selectivity was determined based on the area% of LC/MS chart of the crude reaction mixture. [b]The selectivity refers to the ratio of single-aldol products/double-aldol products/triple-aldol products. [c]Diastereomeric ratio of double-aldol products. [d]Yield refers to isolated yield after purification by column chromatography on silica gel.

(2*S*,3*R*,4*S*,5*R*)-2,4-diethyl-7-phenylheptane-1,3,5-triol (13b)



Under argon, mesityl copper (18.3 mg, 0.1 mmol) and (*R*)-DTBM-segphos (119.1 mg, 0.101 mmol) were added to a round bottom flask, followed by THF (5.0 mL) and 2-propanol (153.9 μL, 2.0 mmol) at 23 °C. After cooled to –60 °C, a solution of boron

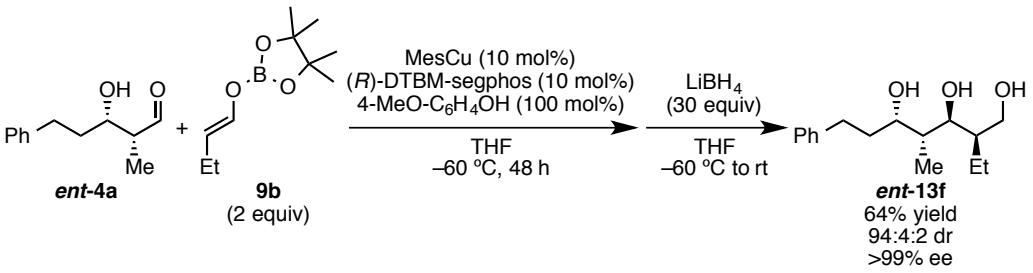
enolate **3b** (3.0 mmol) in THF (15 mL) and hydrocinnamaldehyde **1a** (263.4 μL, 2.0 mmol) were added, and stirred for 24 hours at –60 °C. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/Et_2O = 5:1 to 2:1 to afford **4b** (331.5 mg, 80% yield) as a white solid.

Under argon, mesityl copper (3.7 mg, 0.02 mmol) and (*S*)-DTBM-segphos (23.6 mg, 0.02 mmol) were added to a test tube, followed by THF (0.65 mL) and a solution of 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) in THF (0.1 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9b** (0.4 mmol) in THF (0.75 mL) and a solution of aldehyde **4b** (0.2 mmol) in THF (0.5 mL) were added, and stirred for 48 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using Daicel Chiralpak IC, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to EtOAc (10% MeOH). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 3:1 afforded the title compound (33.3 mg, 0.119 mmol, 59% yield) as a colorless oil.

R_f = 0.28 (hexane/EtOAc = 1:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.23 (d, *J* = 6.9 Hz, 2H), 7.19 (dd, *J* = 7.4, 7.4 Hz, 1H), 4.00 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.90-3.87 (m, 2H), 3.76 (dd, *J* = 10.9, 2.3 Hz, 1H), 2.96 (m, 1H), 2.66 (m, 1H), 1.94 (m, 1H), 1.79-1.72 (m, 2H), 1.63-1.49 (m, 2H), 1.45 (m, 1H), 1.30 (m, 1H), 1.12 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.4, 128.5, 128.4, 125.8, 77.4, 72.7, 64.6, 46.0, 43.0, 33.8, 33.0, 20.3, 16.1, 12.4, 12.0. IR spectroscopy (neat, cm^{-1}): 3419, 3027, 2961,

2876, 1647, 1636. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{17}H_{28}O_3$ $[M+Na]^+$, 303.1931; found 303.1917. Optical rotation: $[\alpha]_D^{20.9}$ = +38.8 (*c* = 0.50, $CHCl_3$).

(2*R*,3*S*,4*R*,5*S*)-2-ethyl-4-methyl-7-phenylheptane-1,3,5-triol (*ent*-13f)



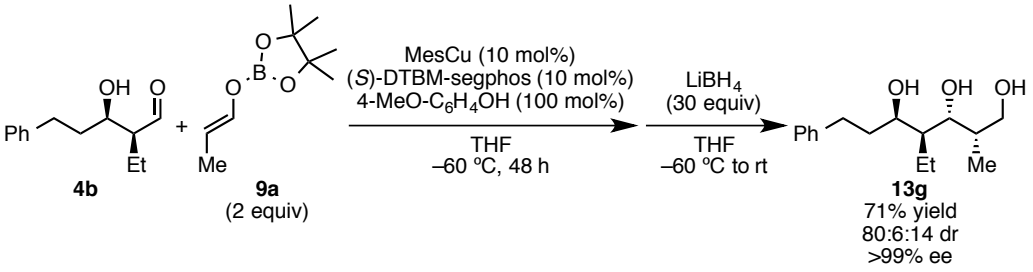
Under argon, mesityl copper (18.3 mg, 0.1 mmol) and (*S*)-DTBM-segphos (119.1 mg, 0.101 mmol) were added to a round bottom flask, followed by THF (5.0 mL) and 2-propanol (153.9 μL, 2.0 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3a** (3.0 mmol) in THF (15 mL) and hydrocinnamaldehyde **1a** (263.4 μL, 2.0 mmol) were added, and stirred for 24 hours at –60 °C. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/Et_2O = 20:1 to 1.5:1 to afford ***ent*-4a** (145.5 mg, 38% yield) as a colorless oil.

Under argon, mesityl copper (3.7 mg, 0.02 mmol) and (*R*)-DTBM-segphos (23.6 mg, 0.02 mmol) were added to a test tube, followed by THF (0.2 mL) and a solution of 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) in THF (0.2 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9b** (0.4 mmol) in THF (0.8 mL) and a solution of aldehyde ***ent*-4a** (0.2 mmol) in THF (0.8 mL) were added, and stirred for 48 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using

Daicel Chiralpak IC, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 1:1 to 1:2.5 to afford the title compound (31.9 mg, 0.120 mmol, 60% yield) as a colorless oil.

R_f = 0.20 (hexane/EtOAc = 1:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.23-7.18 (m, 3H), 3.95-3.90 (m, 2H), 3.85-3.78 (m, 2H), 3.58 (brs, 1H), 2.93 (m, 1H), 2.76 (brs, 1H), 2.65 (m, 1H), 2.16 (brs, 1H), 1.96 (m, 1H), 1.88 (m, 1H), 1.75 (m, 1H), 1.60-1.46 (m, 2H), 1.43 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.3, 128.42, 128.37, 125.8, 77.7, 74.2, 64.7, 42.8, 39.6, 34.5, 33.0, 15.6, 12.24, 12.16. IR spectroscopy (neat, cm^{-1}): 3407, 2962, 2934, 1653, 1456. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{16}H_{26}O_3$ $[M+Na]^+$, 289.1774; found 289.1762. Optical rotation: $[\alpha]_D^{23.0}$ = –31.5 (*c* = 2.0, $CHCl_3$).

(2*S*,3*R*,4*S*,5*R*)-4-ethyl-2-methyl-7-phenylheptane-1,3,5-triol (13g)



Under argon, mesityl copper (18.3 mg, 0.1 mmol) and (*R*)-DTBM-segphos (119.1 mg, 0.101 mmol) were added to a round bottom flask, followed by THF (5.0 mL) and 2-propanol (153.9 μL, 2.0 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **3b** (3.0 mmol) in THF (15 mL) and hydrocinnamaldehyde **1a** (263.4 μL, 2.0 mmol) were added, and stirred for 24 hours at –60 °C. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with

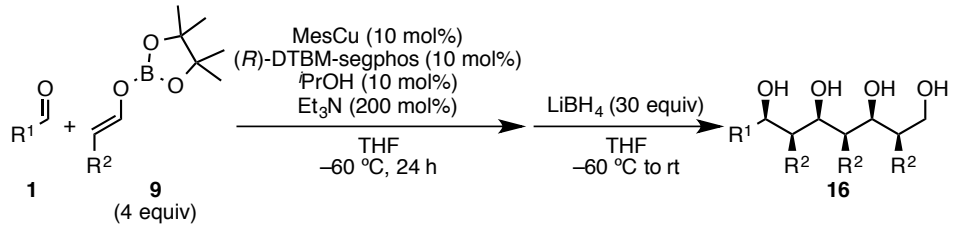
hexane/Et_2O = 5:1 to 2:1 to afford **4b** (331.5 mg, 80% yield) as a white solid.

Under argon, mesityl copper (3.7 mg, 0.02 mmol) and (*S*)-DTBM-segphos (23.6 mg, 0.02 mmol) were added to a test tube, followed by THF (1.0 mL) and a solution of 4-MeO-C_6H_4OH (24.8 mg, 0.2 mmol) in THF (0.1 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9a** (0.4 mmol) in THF (0.4 mL) and a solution of aldehyde **4b** (0.2 mmol) in THF (0.5 mL) were added, and stirred for 48 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using Daicel Chiralpak IE, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 2:1 to EtOAc (10% MeOH). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 2:1 afforded the title compound (30.3 mg, 0.114 mmol, 57% yield) as a colorless oil.

R_f = 0.18 (hexane/EtOAc = 1:1). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.23 (m, 2H), 7.19 (m, 1H), 3.97 (m, 1H), 3.91 (m, 1H), 3.77 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.72 (m, 1H), 2.96 (m, 1H), 2.66 (m, 1H), 1.94 (m, 1H), 1.80-1.74 (m, 2H), 1.68 (m, 1H), 1.30 (m, 1H), 1.11 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.3, 128.5, 128.4, 125.8, 76.0, 72.7, 67.8, 46.3, 36.2, 33.8, 33.0, 20.1, 12.4, 9.6. IR spectroscopy (neat, cm^{-1}): 3335, 2962, 2934, 2877, 1456. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{16}H_{26}O_3$ $[M+Na]^+$, 289.1774; found 289.1772. Optical rotation: $[\alpha]_D^{21.7}$ = +34.8 (*c* = 1.0, $CHCl_3$).

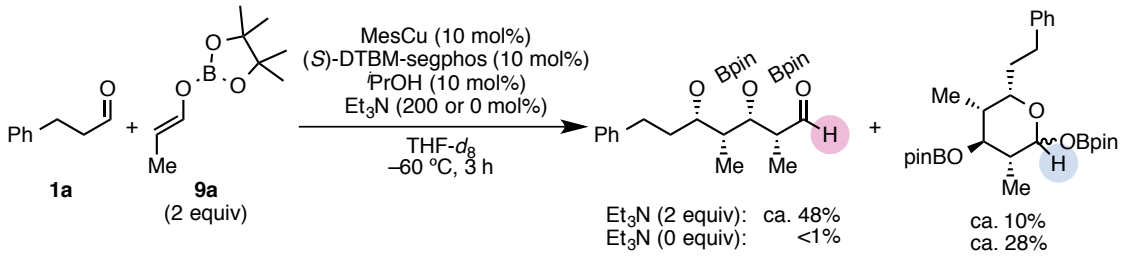
IV. Triple-Aldol Reaction

Representative Procedure



Under argon, mesityl copper (3.7 mg, 0.02 mmol) and (*R*)-DTBM-segphos (23.6 mg, 0.02 mmol) were added to a test tube, followed by THF (0.8 mL), a solution of 2-propanol (1.5 μL, 0.02 mmol) in THF (0.2 mL) and triethylamine (55.8 μL, 0.4 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9** (0.8 mmol) in THF (0.8 mL) and a solution of aldehyde **1** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity (if possible) by LC/MS analysis, the residue was purified by column chromatography on silica gel. After the determination of enantioselectivity (if necessary), further purification by reversed phase HPLC was conducted to give the pure product (if necessary).

^{1}H NMR Study of the Triple-Aldol Reaction



Procedure: Under argon, mesityl copper (1.8 mg, 0.01 mmol), (*S*)-DTBM-segphos (11.8 mg, 0.01 mmol) and triethylamine (27.9 μL, 0.2 mmol or none) were added to a NMR tube, followed by a solution of 2-propanol (0.01 mmol) in THF-d_8 (0.25 mL) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9a** (0.2 mmol) in THF-d_8 (0.25 mL) and hydrocinnamaldehyde **1a** (13.2 μL, 0.1 mmol) were added, and kept at –60 °C for 3 hours. To this solution was added 1,1,2,2-tetrachloroethane (5.29 μL, 0.05 mmol) as an internal standard. ^{1}H NMR of the reaction solution was taken at –60 °C. Peaks in the aldehyde region were observed only in the presence of triethylamine, indicating that the addition of triethylamine increased the concentration of reactive aldehyde form of the double-aldol intermediate.

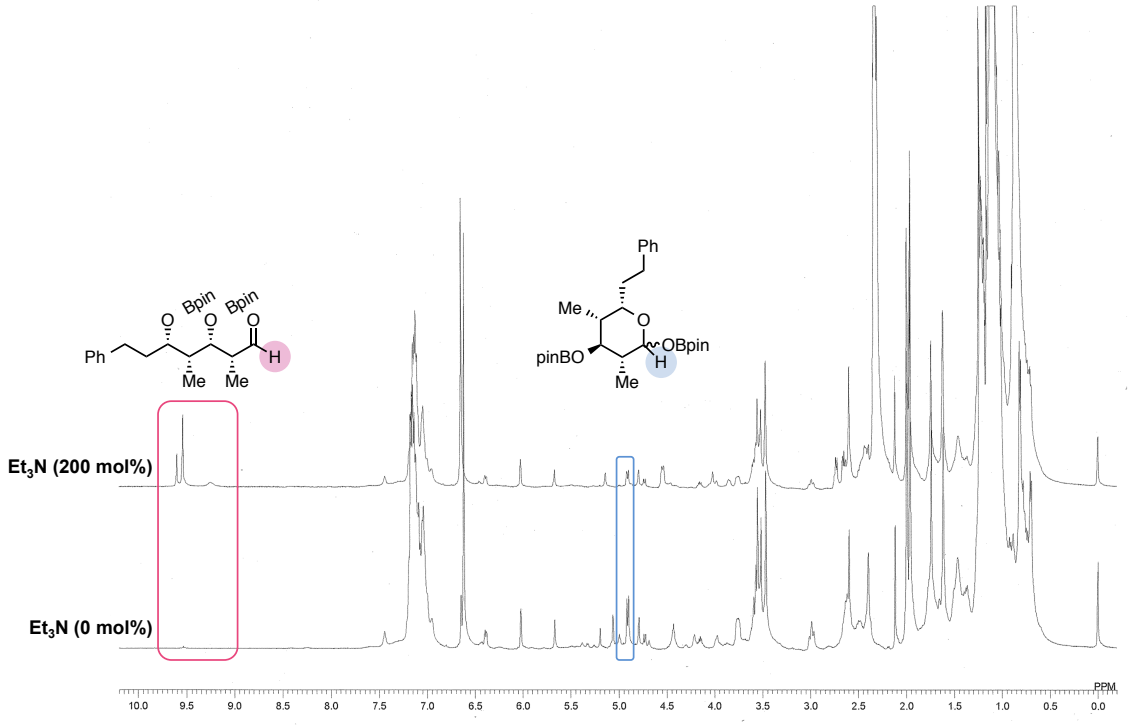
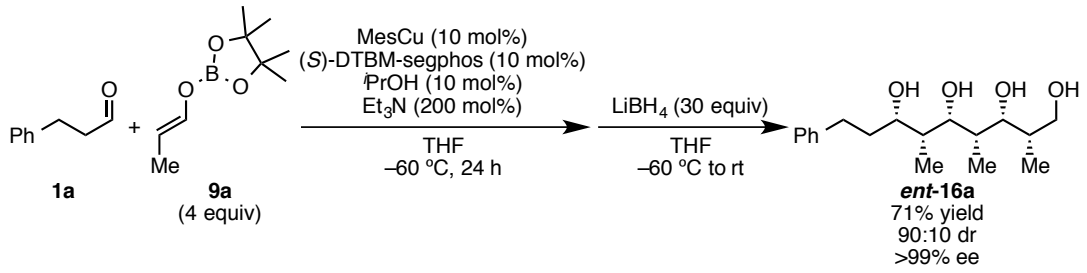


Figure S2 ^{1}H NMR of the reaction solutions, THF-d_8, 500 MHz, −60 °C.

(2*S*,3*R*,4*S*,5*S*,6*R*,7*S*)-2,4,6-trimethyl-9-phenylnonane-1,3,5,7-tetraol (*ent*-16a)

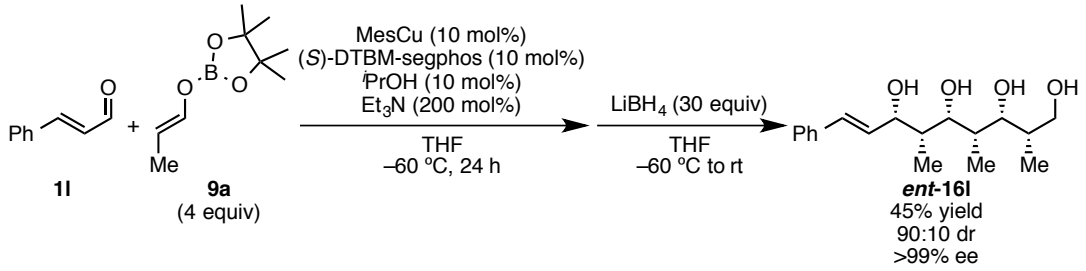


Under argon, mesityl copper (5.5 mg, 0.03 mmol) and (*S*)-DTBM-segphos (35.4 mg, 0.03 mmol) were added to a test tube, followed by a solution of 2-propanol (2.3 μL, 0.03 mmol) in THF (0.75 mL) and triethylamine (83.6 μL, 0.6 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9a** (1.2 mmol) in THF (1.0 mL) and hydrocinnamaldehyde **1a** (39.5 μL, 0.3 mmol) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (9 mmol) in THF (3 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of silica gel eluting with hexane/EtOAc = 2:1 to EtOAc/EtOH = 4:1 to remove less polar compounds. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using Daicel Chiralpak IB, the residue was purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH and then EtOAc/MeOH to afford the title compound (59.6 mg, 0.192 mmol, 64% yield) as a white solid. The relative configuration was determined by X-ray crystallographic analysis. The absolute configuration was elucidated from the single-aldol product.

R_f = 0.23 (CH_2Cl_2/MeOH = 10:1). NMR spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.21-7.17 (m, 3H), 3.84-3.79 (m, 2H), 3.71 (m, 1H), 3.62 (m, 2H), 2.80-2.61 (m, 2H), 2.37 (brs, 1H), 2.18 (brs, 1H), 1.92-1.65 (m, 5H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125 MHz,

$CDCl_3$): δ = 141.8, 128.5, 128.4, 126.0, 79.1, 77.0, 74.2, 66.0, 40.0, 38.4, 37.6, 37.1, 32.6, 12.9, 7.3, 7.0. IR spectroscopy (neat, cm^{-1}): 3358, 2970, 2939, 2878, 1455. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{18}H_{30}O_4$ $[M+Na]^+$, 333.2036; found 333.2044. Optical rotation: $[\alpha]_D^{29.0} = -13.0$ (*c* = 0.43, $CHCl_3$).

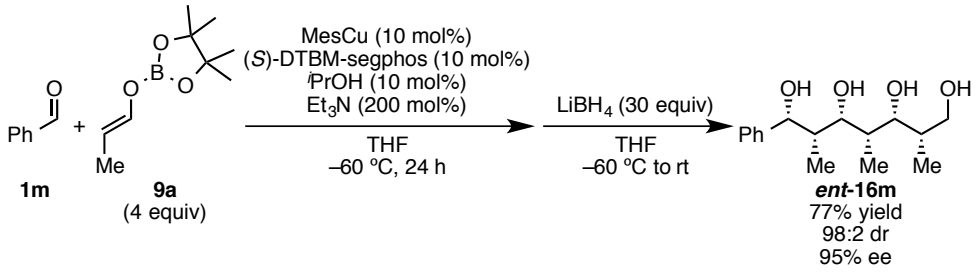
(2*S*,3*R*,4*S*,5*S*,6*R*,7*S*,*E*)-2,4,6-trimethyl-9-phenylnon-8-ene-1,3,5,7-tetraol (*ent*-16l)



Under argon, mesityl copper (3.7 mg, 0.02 mmol) and (*S*)-DTBM-segphos (23.6 mg, 0.02 mmol) were added to a test tube, followed by THF (0.7 mL), a solution of 2-propanol (0.02 mmol) in THF (0.1 mL) and triethylamine (55.8 μL, 0.4 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9a** (0.8 mmol) in THF (1.0 mL) and a solution of cinnamaldehyde **1l** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using Daicel Chiralpak IF, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc = 2:1 to EtOAc (10% MeOH). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 7:1 afforded the title compound (25.2 mg, 0.0817 mmol, 41% yield) as a white solid.

R_f = 0.25 (EtOAc). NMR spectroscopy: ^{1}H NMR (500 MHz, CD_3OD): δ = 7.40 (d, *J* = 7.5 Hz, 2H), 7.30 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.20 (m, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.30 (dd, *J* = 16.1, 6.3 Hz, 1H), 4.37 (m, 1H), 3.74 (m, 1H), 3.60-3.57 (m, 2H), 3.44 (d, *J* = 10.4, 6.3 Hz, 1H), 1.94 (m, 1H), 1.89-1.83 (m, 2H), 1.02-0.99 (m, 9H). ^{13}C NMR (125 MHz, CD_3OD): δ = 138.4, 132.8, 131.1, 129.6, 128.4, 127.4, 76.3, 75.4, 75.2, 65.9, 42.0, 39.2, 38.7, 12.8, 9.4, 9.1. IR spectroscopy (neat, cm^{-1}): 3389, 2970, 2931, 2883, 1638. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{18}H_{28}O_4$ $[M+Na]^+$, 331.1880; found 331.1864. Optical rotation: $[\alpha]_D^{20.7}$ = –15.4 (*c* = 1.0, MeOH).

(1*R*,2*S*,3*R*,4*S*,5*R*,6*S*)-2,4,6-trimethyl-1-phenylheptane-1,3,5,7-tetraol (*ent*-16m)



Under argon, mesityl copper (3.7 mg, 0.02 mmol) and (*S*)-DTBM-segphos (23.6 mg, 0.02 mmol) were added to a test tube, followed by THF (0.7 mL), a solution of 2-propanol (0.02 mmol) in THF (0.1 mL) and triethylamine (55.8 μL, 0.4 mmol) at 23 °C. After cooled to –60 °C, a solution of boron enolate **9a** (0.8 mmol) in THF (1.0 mL) and a solution of benzaldehyde **1m** (0.2 mmol) in THF (0.2 mL) were added, and stirred for 24 hours at –60 °C. To this solution was added a solution of $LiBH_4$ (6 mmol) in THF (2 mL) and allowed to warm up to room temperature for overnight. To this mixture was added HCl (1 M), and directly passed through a short pad of Na_2SO_4 eluting with Et_2O and EtOAc. After the determination of diastereoselectivity and enantioselectivity by LC/MS analysis using Daicel Chiralpak IB, the residue was

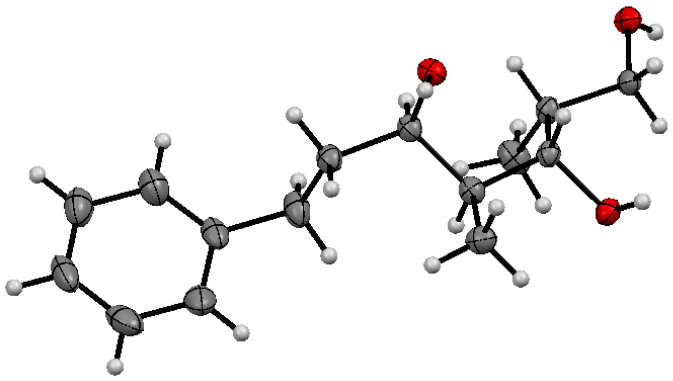
purified by column chromatography on silica gel eluting with hexane/EtOAc = 1:1 to EtOAc (10% MeOH). Further purification by reversed phase HPLC using Daicel Chiralpak IC eluting with H_2O/MeCN = 5:1 afforded the title compound (42.8 mg, 0.152 mmol, 76% yield) as a white solid.

R_f = 0.29 (EtOAc). NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37-7.32 (m, 4H), 7.26 (m, 1H), 5.02 (m, 1H), 4.01 (m, 1H), 3.75 (m, 1H), 3.64 (m, 2H), 2.66 (brs, 2H), 2.39 (brs, 1H), 1.99-1.95 (m, 2H), 1.86 (m, 1H), 1.69 (brs, 1H), 1.08-1.06 (m, 6H), 0.85 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ = 145.5, 129.0, 127.6, 127.0, 76.6, 76.0, 75.4, 65.9, 43.3, 39.1, 38.6, 12.5, 9.1, 8.6. IR spectroscopy (neat, cm^{-1}): 3390, 2970, 2936, 2883, 1724, 1642. Mass spectroscopy: HRMS-ESI (m/z): calcd for $C_{16}H_{26}O_4$ $[M+Na]^+$, 305.1723; found 305.1723. Optical rotation: $[\alpha]_D^{20.8}$ = +11.7 (c = 1.3, MeOH).

V. X-ray Crystallographic Analysis

(2*R*,3*S*,4*S*,5*R*)-2,4-dimethyl-7-phenylheptane-1,3,5-triol (12a)

12a was recrystallized from hexane/EtOH. The nonhydrogen atoms are depicted with 50% probability ellipsoids. The crystallographic data are summarized in the following table.

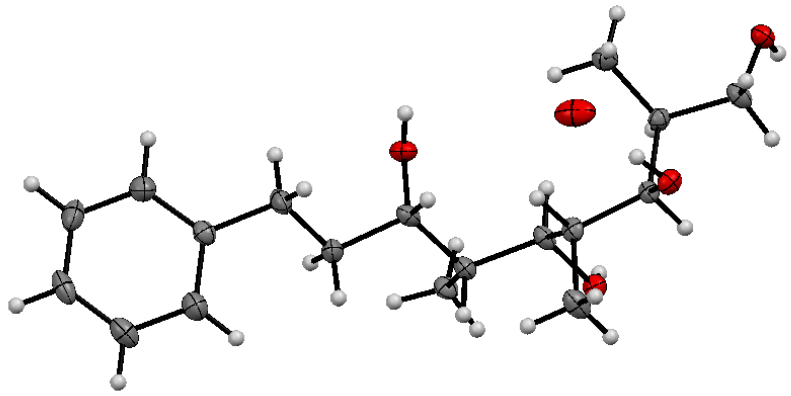


Empirical formula	$C_{15}H_{24}O_3$	
Formula weight	252.34	
Temperature	103(2) K	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.2912(2) Å	α = 90°.
	b = 6.8967(2) Å	β = 91.6756(17)°.
	c = 12.5196(3) Å	γ = 90°.
Volume	715.59(3) $Å^3$	
Z	2	
Density (calculated)	1.171 Mg/m^3	
Absorption coefficient	0.636 mm^{-1}	
F(000)	276	
Crystal size	0.22 × 0.16 × 0.06 mm^3	
Theta range for data collection	3.53 to 68.19°.	
Index ranges	-9<=h<=9, -7<=k<=8, -15<=l<=15	
Reflections collected	7499	

Independent reflections	2402 [R(int) = 0.0552]
Completeness to theta = 68.19°	99.6%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.7771
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2402 / 1 / 168
Goodness-of-fit on F^2	1.116
Final R indices [I>2sigma(I)]	R1 = 0.0356, wR2 = 0.0727
R indices (all data)	R1 = 0.0555, wR2 = 0.0903
Largest diff. peak and hole	0.261 and -0.217 e.Å^{-3}

(2*S*,3*R*,4*S*,5*S*,6*R*,7*S*)-2,4,6-trimethyl-9-phenylnonane-1,3,5,7-tetraol (*ent*-16a)

***ent*-16a•H_2O** was recrystallized from hexane/EtOH. The nonhydrogen atoms are depicted with 50% probability ellipsoids. The crystallographic data are summarized in the following table.



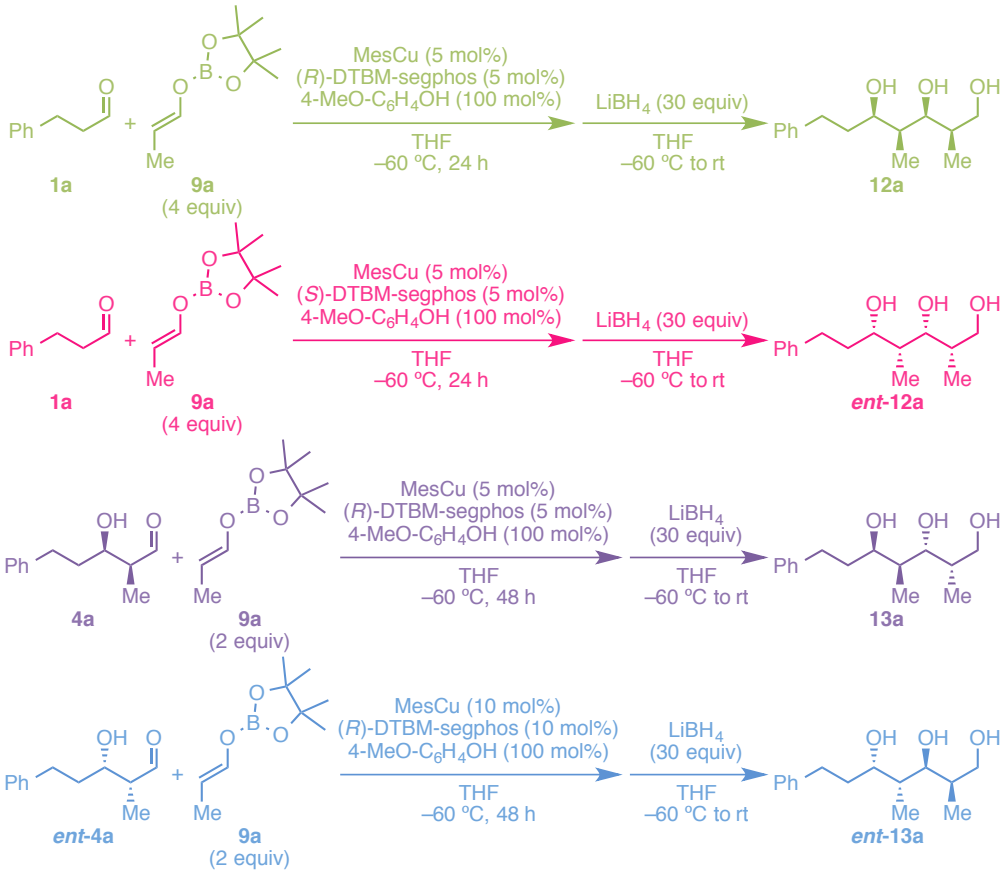
Empirical formula	$C_{18}H_{32}O_5$
Formula weight	328.44
Temperature	103(2) K
Wavelength	1.54187 Å
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 6.2435(2) Å α = 90°.

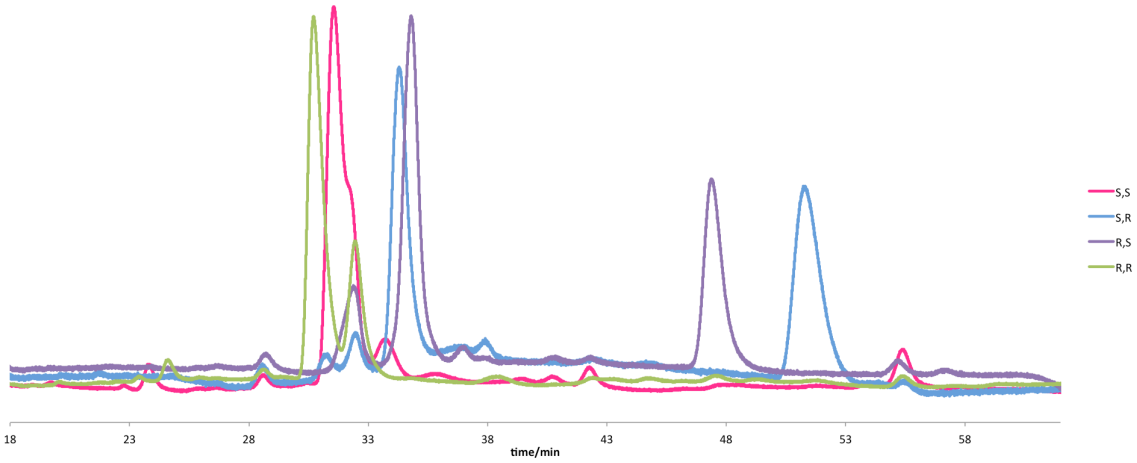
	b = 8.0069(2) Å β = 92.9155(19)°.
	c = 18.0851(4) Å γ = 90°.
Volume	902.92(4) $Å^3$
Z	2
Density (calculated)	1.208 Mg/m^3
Absorption coefficient	0.700 mm^{-1}
F(000)	360
Crystal size	0.20 × 0.18 × 0.14 mm^3
Theta range for data collection	4.90 to 68.22°.
Index ranges	-7<=h<=7, -9<=k<=9, -21<=l<=21
Reflections collected	9426
Independent reflections	3224 [R(int) = 0.0639]
Completeness to theta = 68.22°	99
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.7350
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3224 / 1 / 215
Goodness-of-fit on F^2	1.177
Final R indices [I>2sigma(I)]	R1 = 0.0430, wR2 = 0.1155
R indices (all data)	R1 = 0.0597, wR2 = 0.1536
Largest diff. peak and hole	0.395 and -0.308 $e.Å^{-3}$

VI. LC/MS Data

Authentic data for 2,4-dimethyl-7-phenylheptane-1,3,5-triol

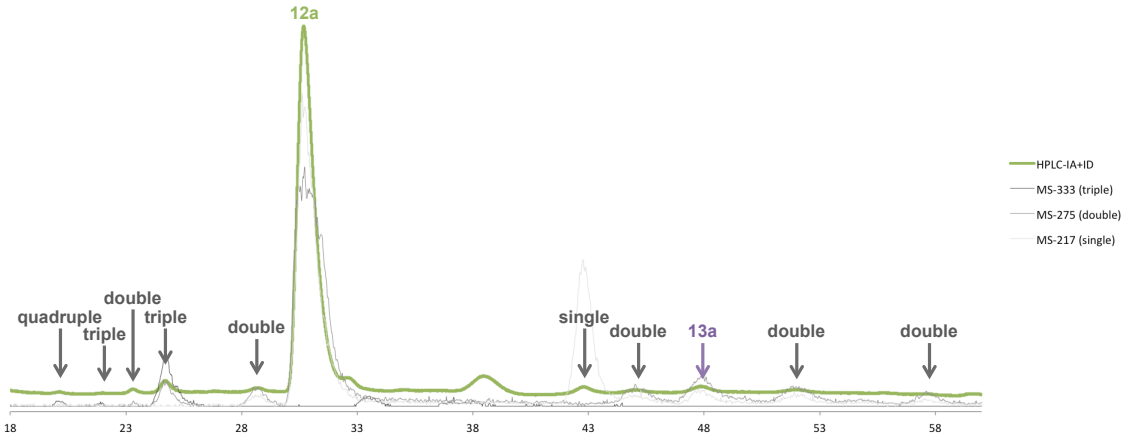
According to the above procedures, four reactions were conducted to dominantly generate **12a**, ***ent*-12a**, **13a** and ***ent*-13a**, respectively. Each crude residue was analyzed by LC/MS eluting with H_2O (0.1% TFA)/MeCN = 84:16 to 72:28 using Daicel Chiralpak IA-ID to give the following chart.





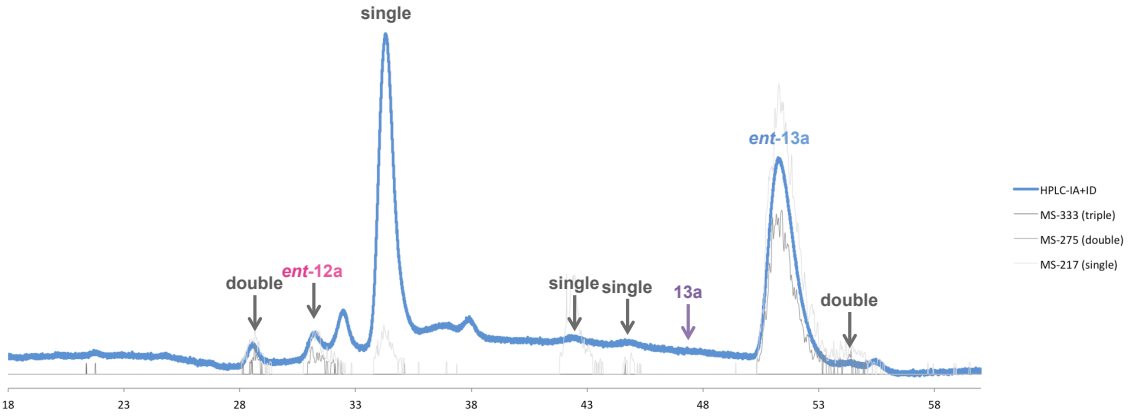
(2*R*,3*S*,4*S*,5*R*)-2,4-dimethyl-7-phenylheptane-1,3,5-triol (12a)

On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products : quadruple-aldol products = 1:97:2:0.1 and (**12a**+***ent*-12a**) : (**13a**+***ent*-13a**) : other isomers = 96:1:3.



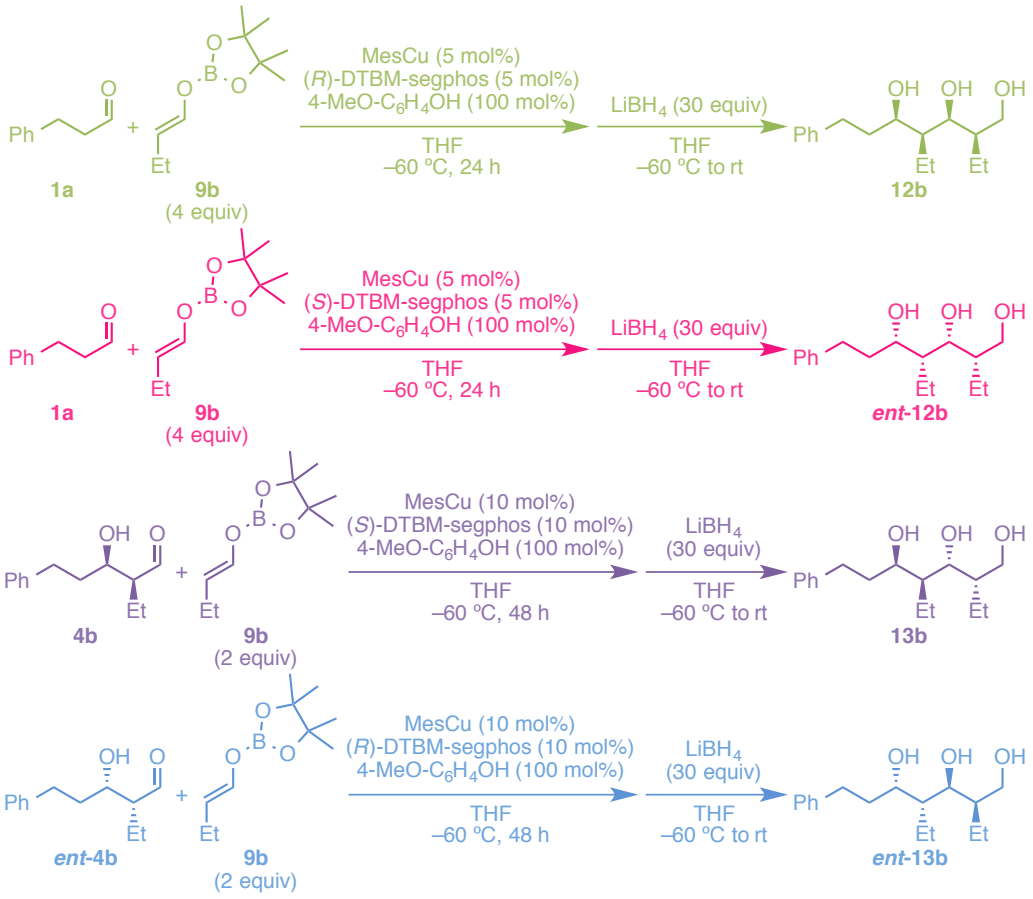
(2*R*,3*S*,4*R*,5*S*)-2,4-dimethyl-7-phenylheptane-1,3,5-triol (*ent*-13a)

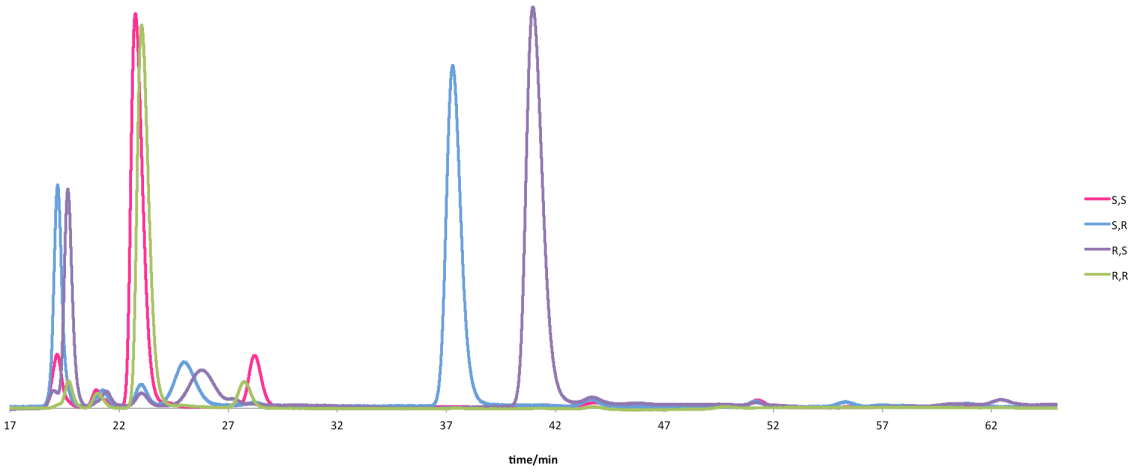
On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 47:53:0 and (**12a**+***ent*-12a**) : (**13a**+***ent*-13a**) : other isomers = 4:92:4, enantioselectivity; >99% ee [retention time; 47.3 min (minor) and 51.4 min (major)].



Authentic data for 2,4-diethyl-7-phenylheptane-1,3,5-triol

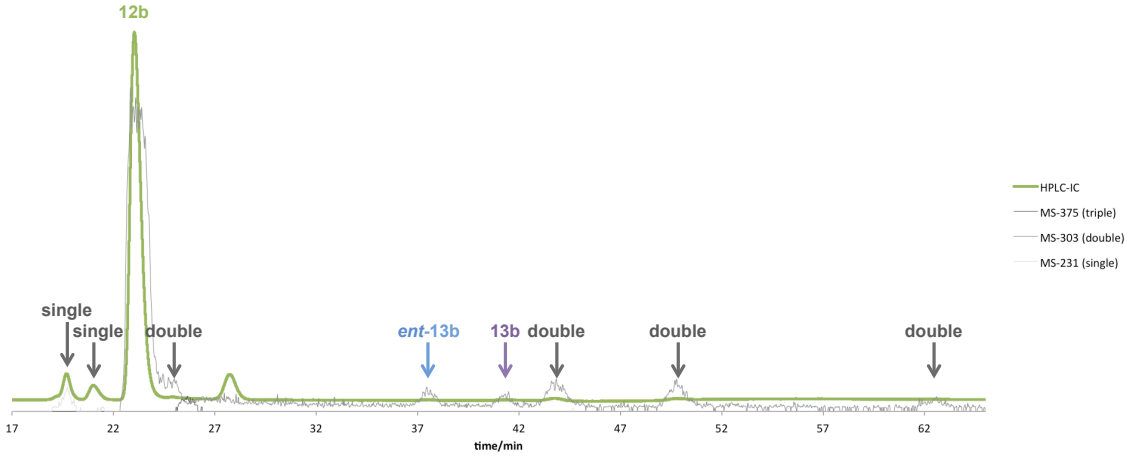
According to the above procedures, four reactions were conducted to dominantly generate **12b**, ***ent*-12b**, **13b** and ***ent*-13b**, respectively. Each crude residue was analyzed by LC/MS eluting with H_2O (0.1% TFA)/MeCN = 80:20 to 70:30 using Daicel Chiralpak IC to give the following chart.





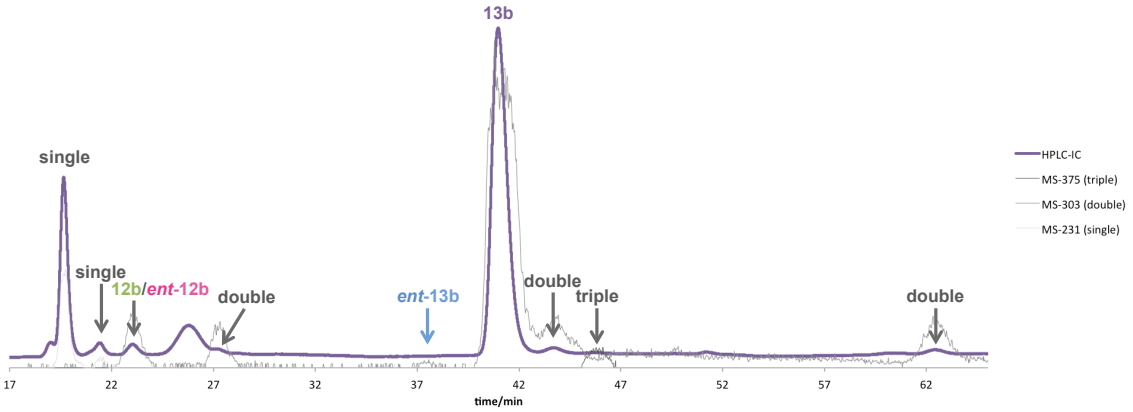
(2*R*,3*S*,4*S*,5*R*)-2,4-diethyl-7-phenylheptane-1,3,5-triol (12b)

On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 7:93:0 and (**12b**+***ent*-12b**) : (**13b**+***ent*-13b**) : other isomers = 98:0:2.



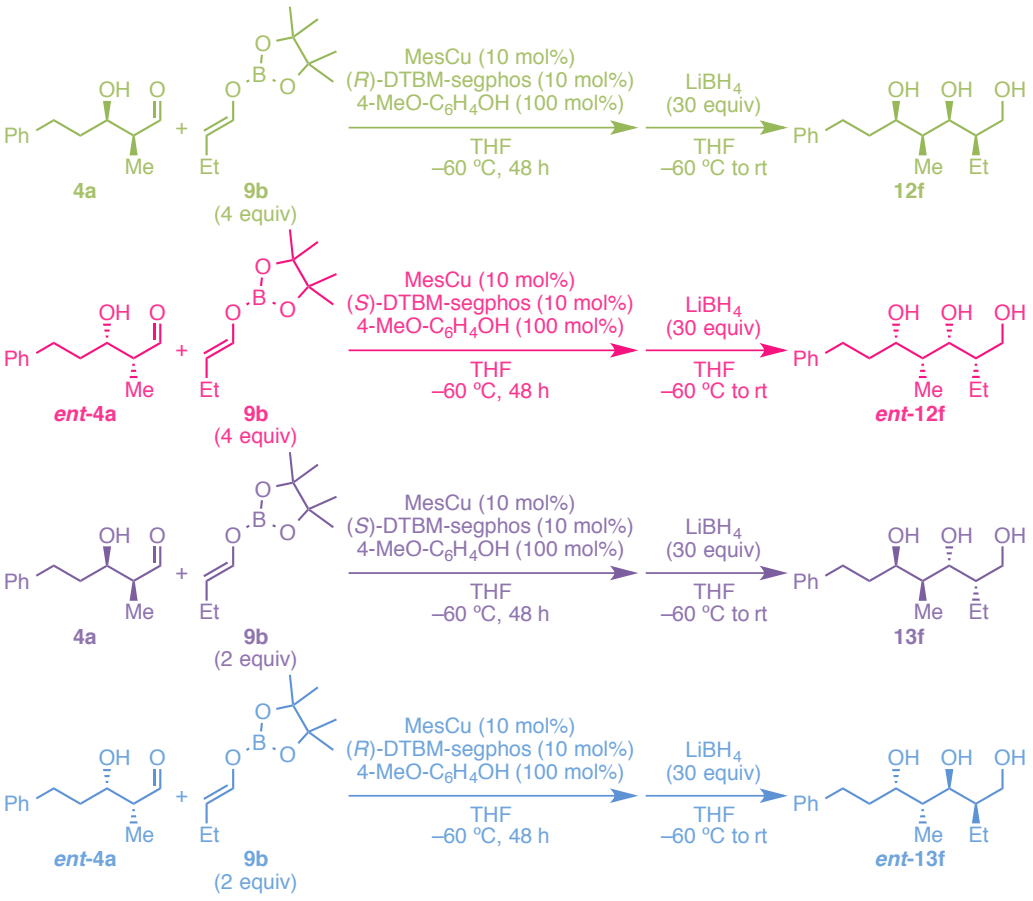
(2*S*,3*R*,4*S*,5*R*)-2,4-diethyl-7-phenylheptane-1,3,5-triol (13b)

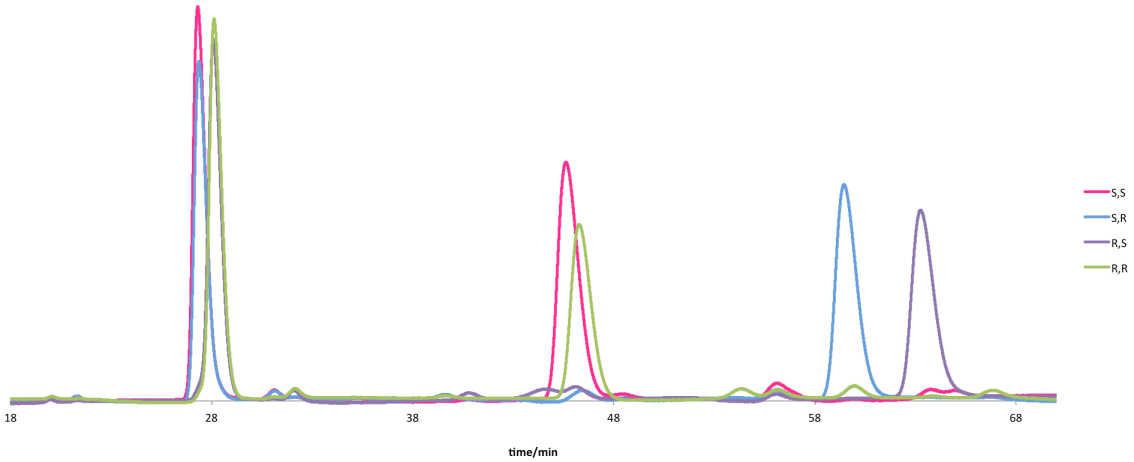
On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 22:78:0.2 and (**12b**+***ent*-12b**) : (**13b**+***ent*-13b**) : other isomers = 2:95:3, enantioselectivity; >99% ee [retention time; 37.3 min (minor) and 41.0 min (major)].



Authentic data for 2-ethyl-4-methyl-7-phenylheptane-1,3,5-triol

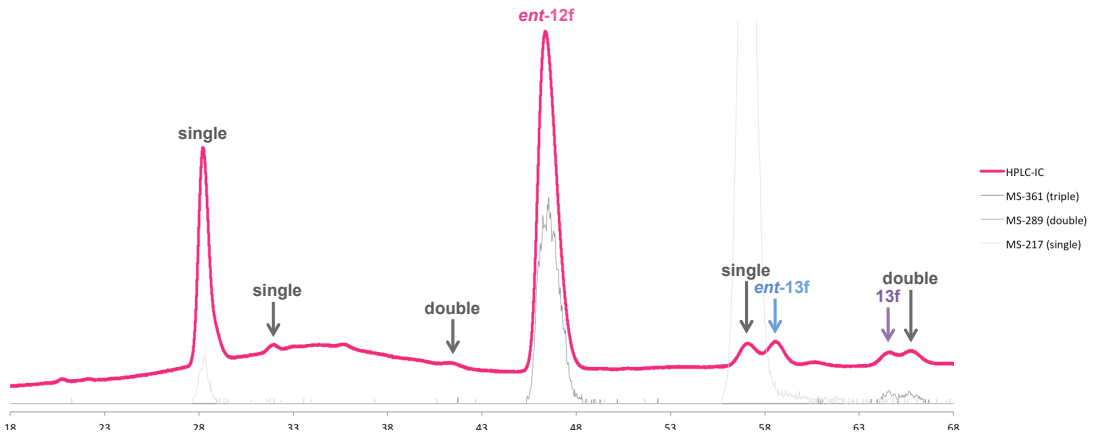
According to the above procedures, four reactions were conducted to dominantly generate **12f**, ***ent*-12f**, **13f** and ***ent*-13f**, respectively. Each crude residue was analyzed by LC/MS eluting with H_2O (0.1% TFA)/MeCN = 90:10 to 81:19 using Daicel Chiralpak IC to give the following chart.





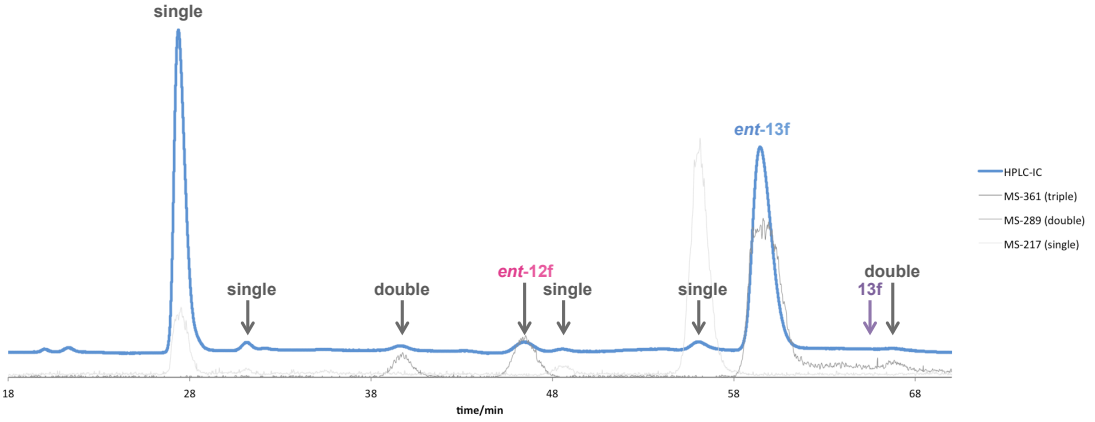
(2*S*,3*R*,4*R*,5*S*)-2-ethyl-4-methyl-7-phenylheptane-1,3,5-triol (*ent*-12f)

On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 30:70:0 and (**12f**+***ent*-12f**) : (**13f**+***ent*-13f**) : other isomers = 92:4:4.



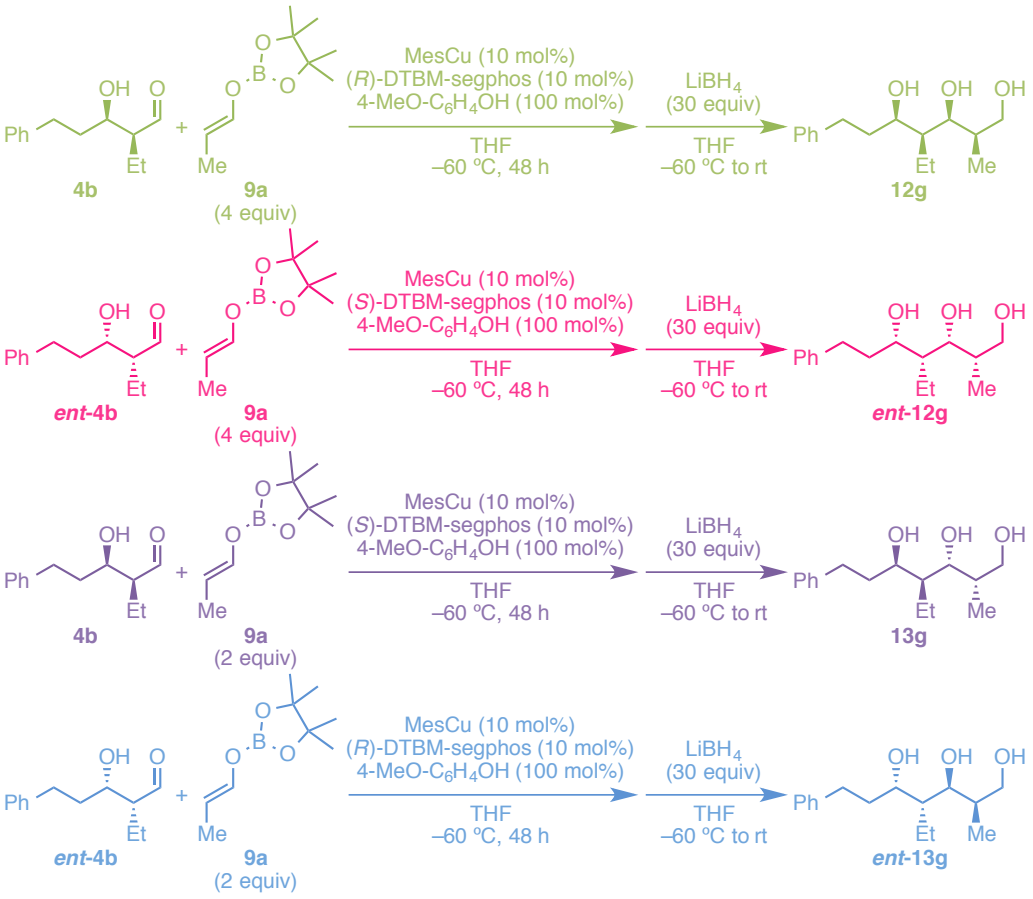
(2*R*,3*S*,4*R*,5*S*)-2-ethyl-4-methyl-7-phenylheptane-1,3,5-triol (*ent*-13f)

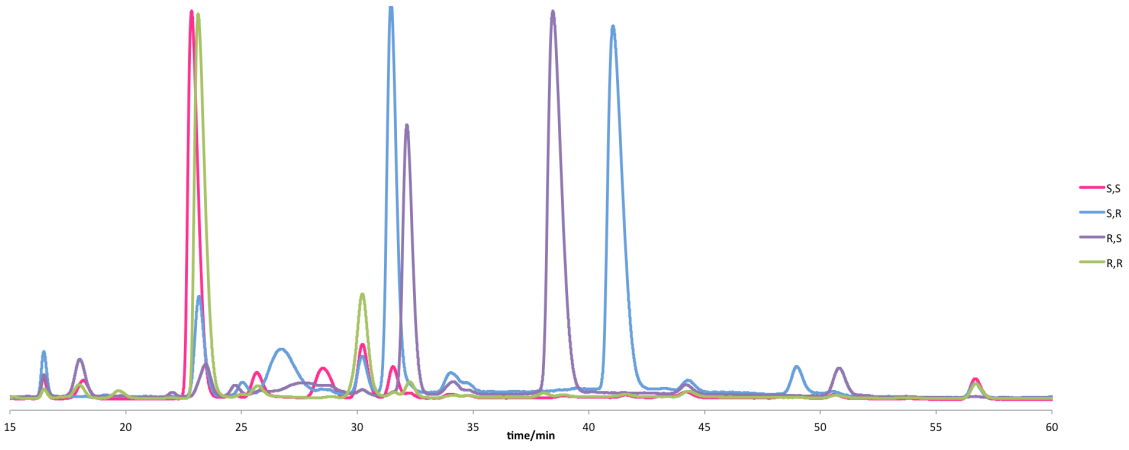
On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 49:51:0 and (**12f**+***ent*-12f**) : (**13f**+***ent*-13f**) : other isomers = 4:94:2, enantioselectivity; >99% ee [retention time; 59.5 min (major) and 63.3 min (minor)].



Authentic data for 4-ethyl-2-methyl-7-phenylheptane-1,3,5-triol

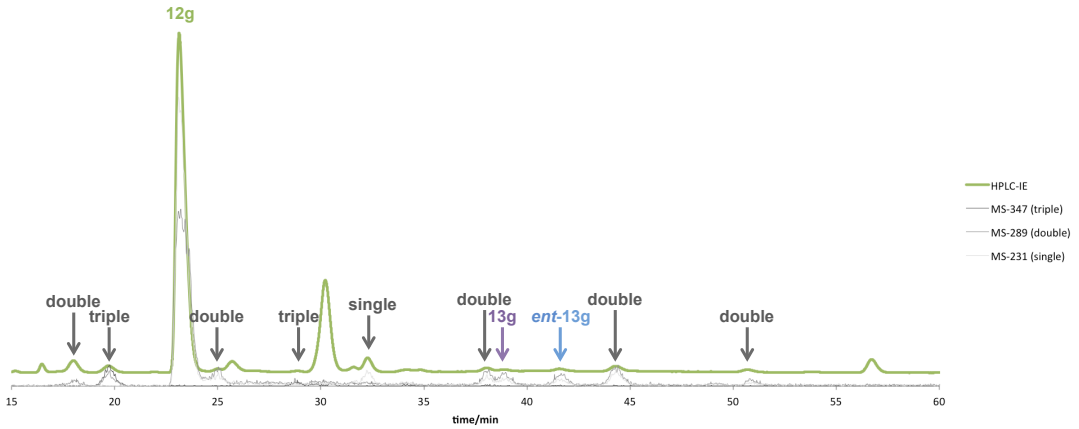
According to the above procedures, four reactions were conducted to dominantly generate **12g**, ***ent*-12g**, **13g** and ***ent*-13g**, respectively. Each crude residue was analyzed by LC/MS eluting with H_2O (0.1% TFA)/MeCN = 84:16 to 64:36 using Daicel Chiralpak IE to give the following chart.





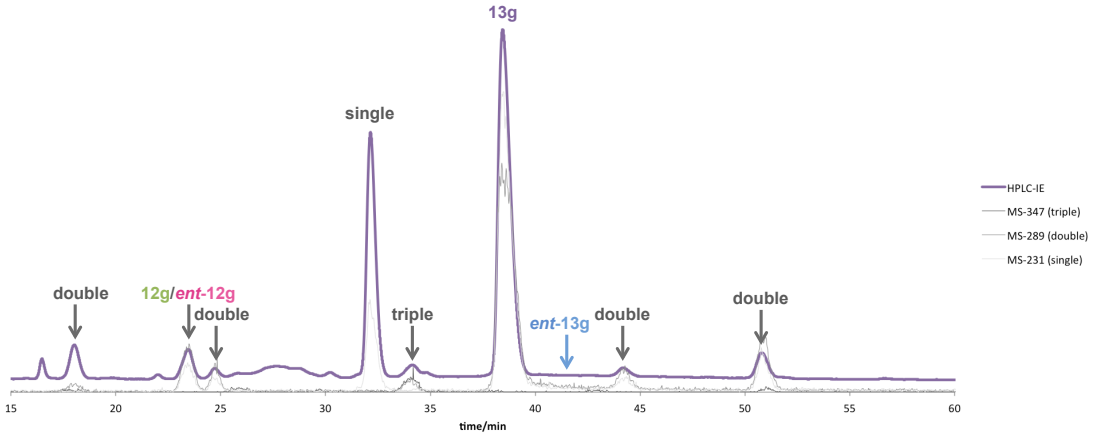
(2*R*,3*S*,4*S*,5*R*)-4-ethyl-2-methyl-7-phenylheptane-1,3,5-triol (12g)

On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 3:95:2 and (**12g**+***ent*-12g**) : (**13g**+***ent*-13g**) : other isomers = 92:1:7.



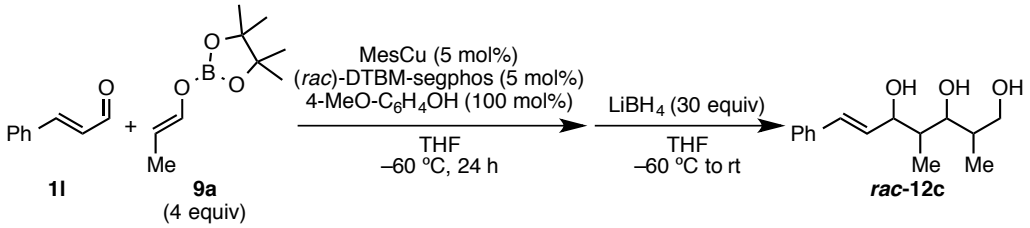
(2*S*,3*R*,4*S*,5*R*)-4-ethyl-2-methyl-7-phenylheptane-1,3,5-triol (13g)

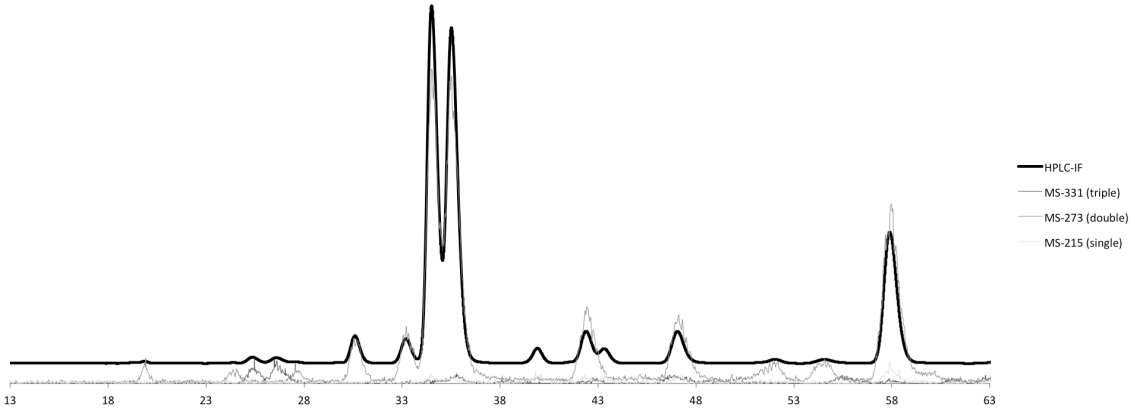
On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 29:69:2 and (**12g**+***ent*-12g**) : (**13g**+***ent*-13g**) : other isomers = 6:80:14, enantioselectivity; >99% ee [retention time; 38.4 min (major) and 41.0 min (minor)].



Authentic data for 2,4-dimethyl-7-phenylhept-6-ene-1,3,5-triol

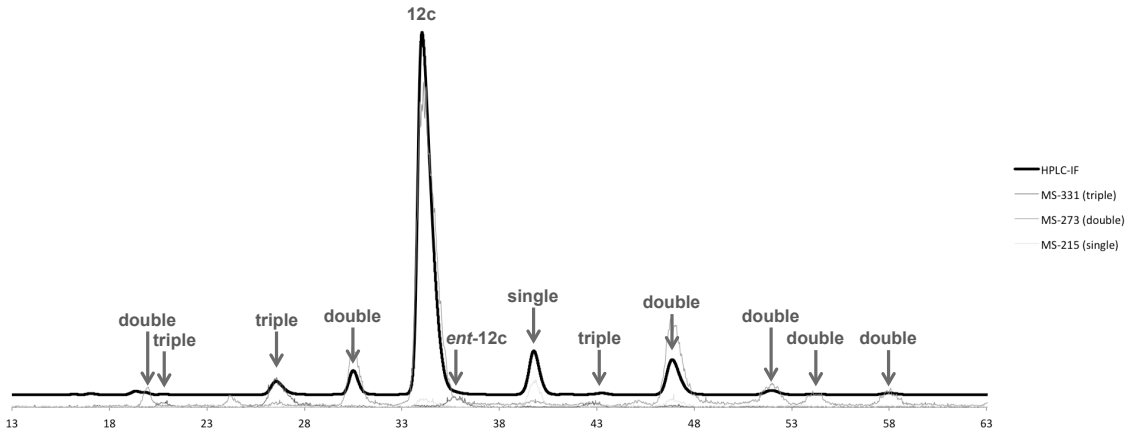
According to the above procedures, racemic reaction was conducted to dominantly generate **12c** and ***ent*-12c**. The crude residue was analyzed by LC/MS eluting with H_2O (0.1% TFA)/MeCN = 86:14 to 77:23 using Daicel Chiralpak IF to give the following chart.





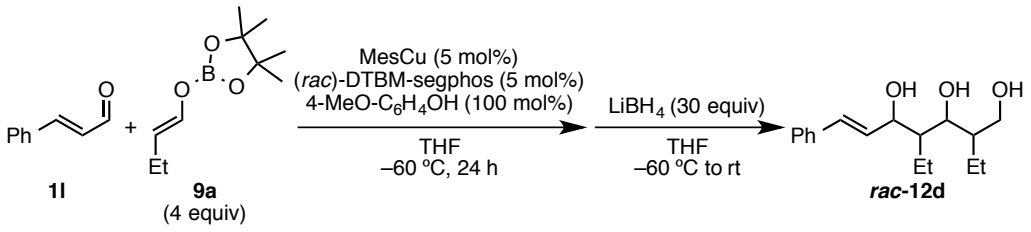
(2*S*,3*R*,4*S*,5*R*)-4-ethyl-2-methyl-7-phenylheptane-1,3,5-triol (12c)

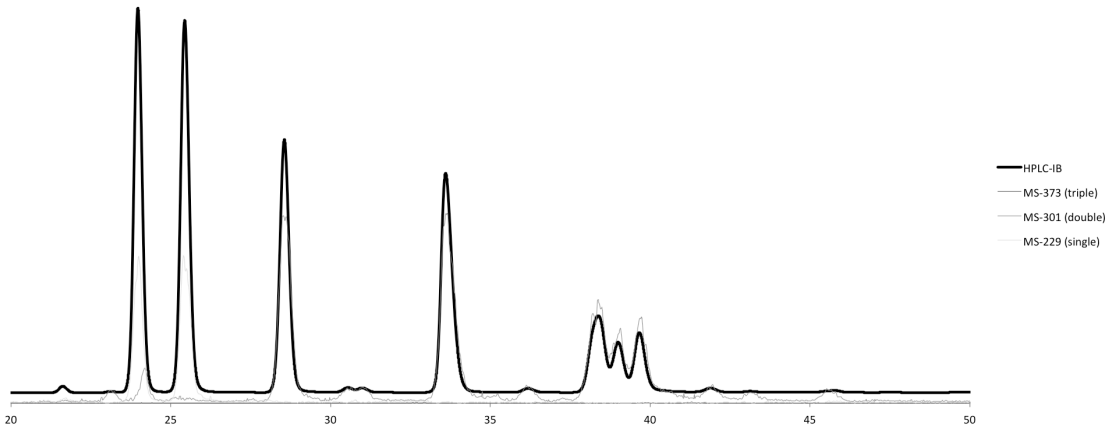
On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 7:90:3 and (**12c**+***ent*-12c**) : other isomers = 86:14, enantioselectivity; >99% ee [retention time; 34.0 min (major) and 35.5 min (minor)].



Authentic data for 2,4-dimethyl-7-phenylhept-6-ene-1,3,5-triol

According to the above procedures, racemic reaction was conducted to dominantly generate **12d** and ***ent*-12d**. The crude residue was analyzed by LC/MS eluting with H_2O (0.1% TFA)/MeCN = 80:20 to 50:50 using Daicel Chiralpak IB to give the following chart.

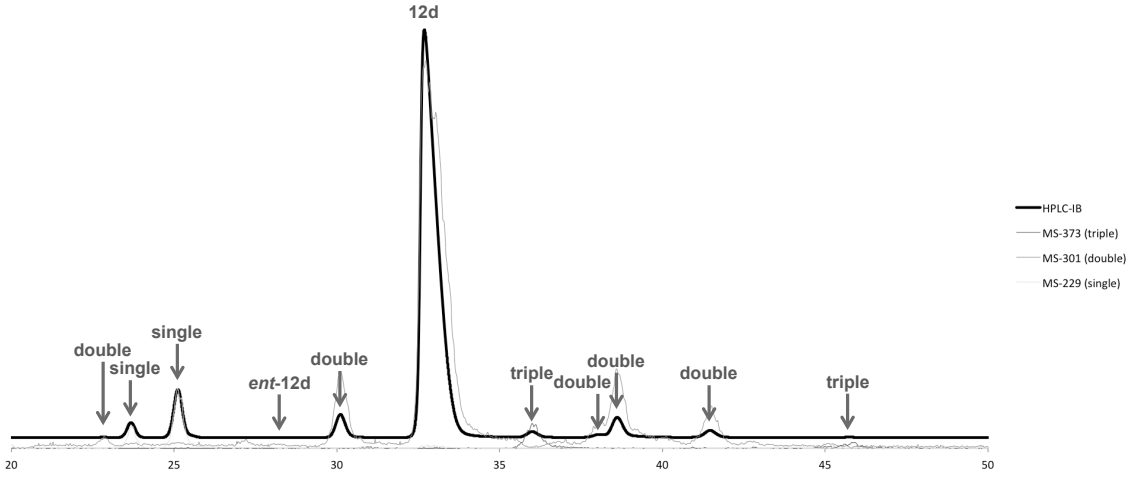




(2*R*,3*S*,4*S*,5*R*,*E*)-2,4-diethyl-7-phenylhept-6-ene-1,3,5-triol (12d)

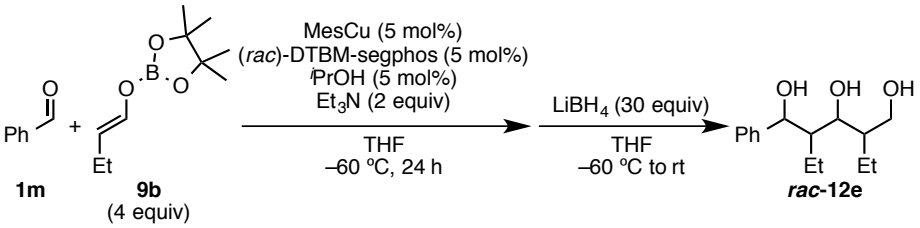
On the basis of both the authentic chart and MS data, each peak was characterized

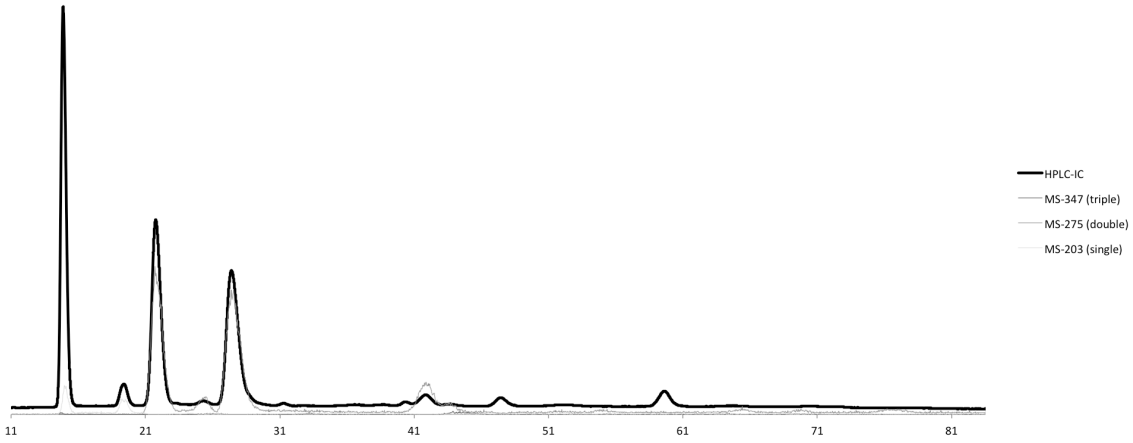
as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 7:92:1 and (**12d**+***ent*-12d**) : other isomers = 92:8, enantioselectivity; >99% ee [retention time; 28.2 min (minor) and 32.7 min (major)].



Authentic data for 2,4-diethyl-1-phenylpentane-1,3,5-triol

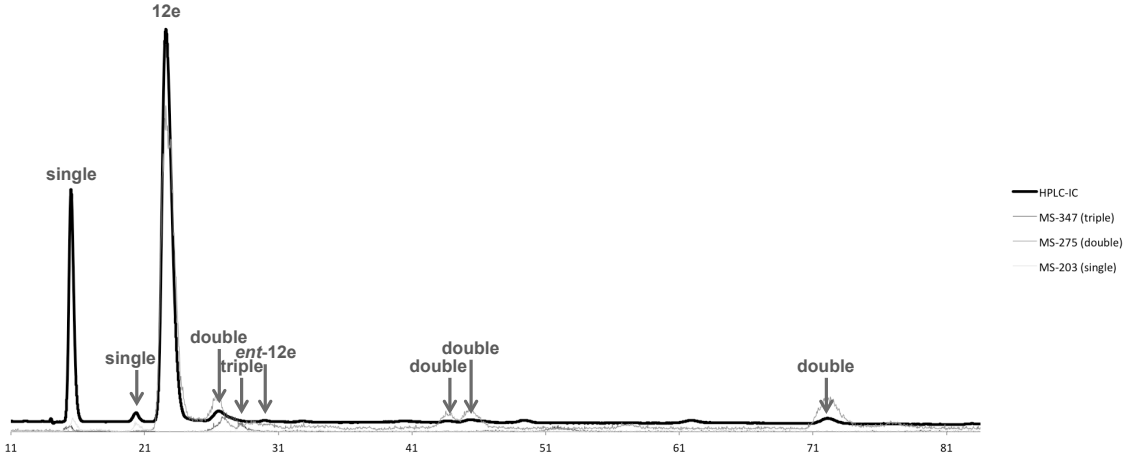
According to the above procedures, racemic reaction was conducted to dominantly generate **12e** and ***ent*-12e**. The crude residue was analyzed by LC/MS eluting with H_2O (0.1% TFA)/MeCN = 88:12 to 78:22 using Daicel Chiralpak IC to give the following chart.





(1*S*,2*R*,3*S*,4*R*)-2,4-diethyl-1-phenylpentane-1,3,5-triol (12e)

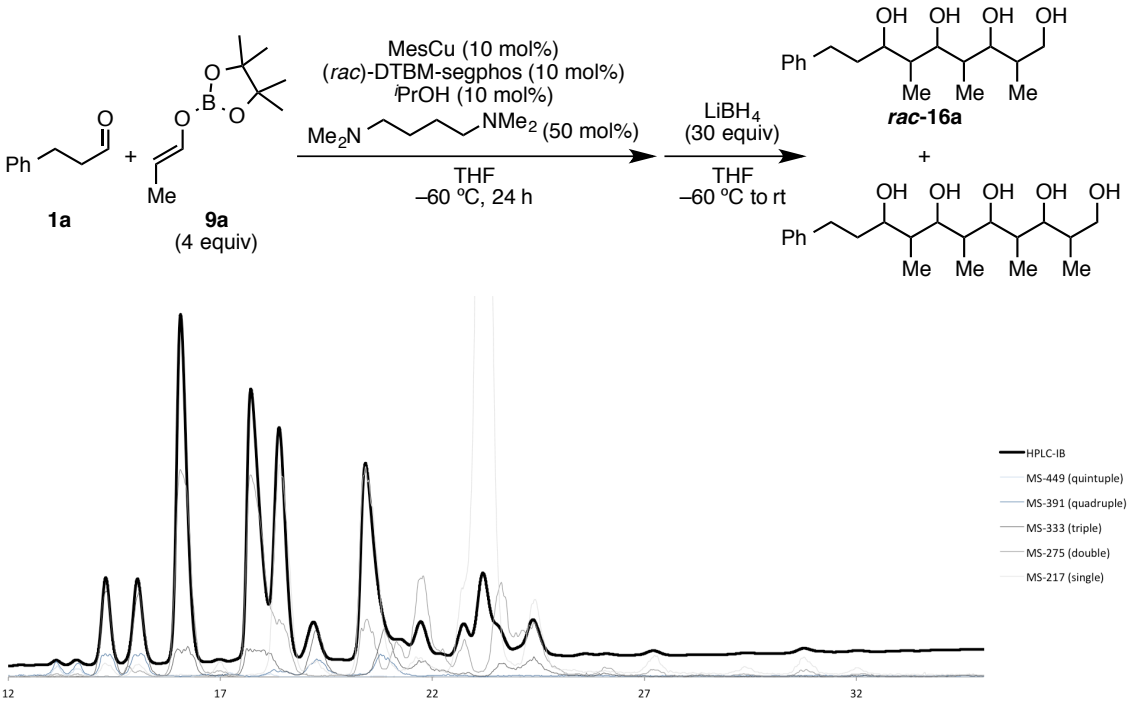
On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products = 22:78:0.4 and (**12e**+***ent*-12e**) : other isomers = 94:6, enantioselectivity; >99% ee [retention time; 22.6 min (major) and 29.9 min (minor)].



Authentic data for 2,4,6-trimethyl-9-phenylnonane-1,3,5,7-tetraol

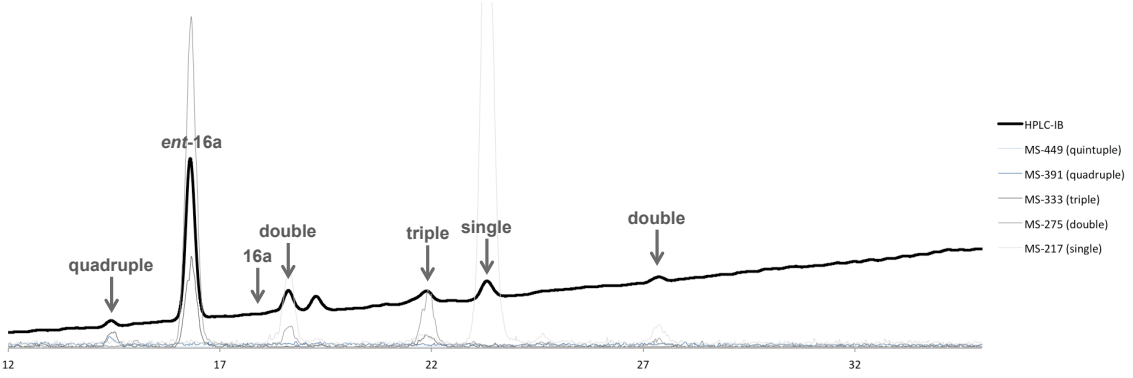
According to the above procedures, racemic reaction was conducted to dominantly generate **16a**, ***ent*-16a**, and pentaol derived from quadruple-aldol product. The crude

residue was analyzed by LC/MS eluting with H_2O (0.1% HCO_2H)/MeCN = 84:16 to 75:25 using Daicel Chiralpak IB to give the following chart.



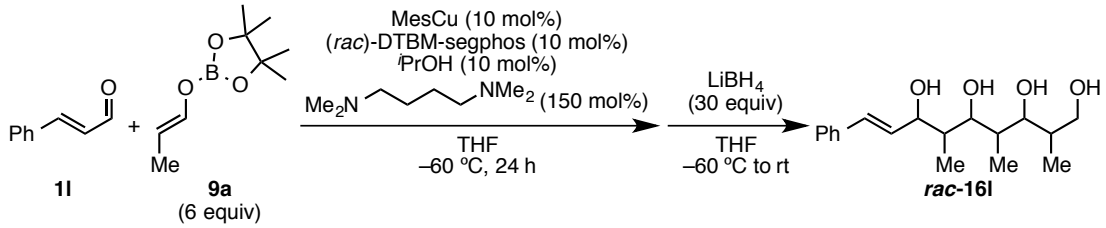
(2*S*,3*R*,4*S*,5*S*,6*R*,7*S*)-2,4,6-trimethyl-9-phenylnonane-1,3,5,7-tetraol (*ent*-16a)

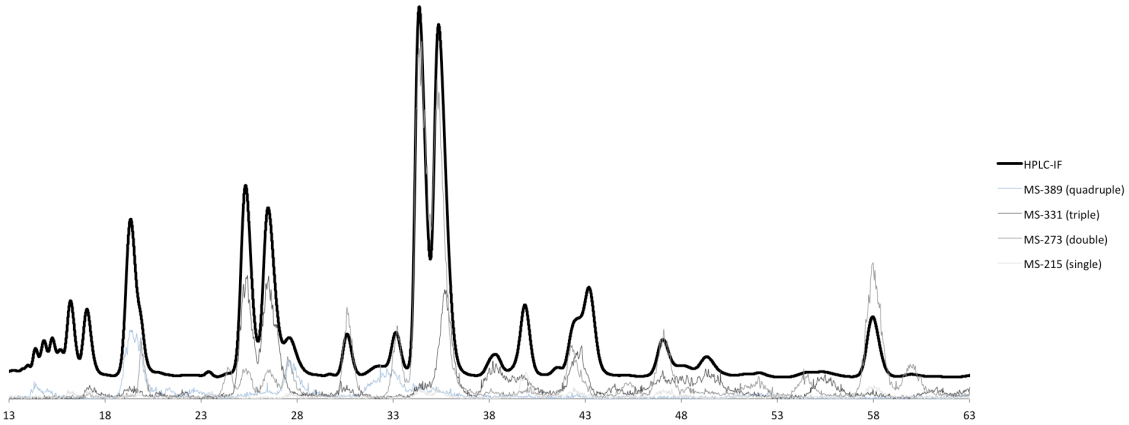
On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products : quadruple-aldol products = 10:12:76:2 and (**16a**+***ent*-16a**) : other isomers = 90:10, enantioselectivity; >99% ee [retention time; 16.3 min (major) and 18.0 min (minor)].



Authentic data for 2,4,6-trimethyl-9-phenylnon-8-ene-1,3,5,7-tetraol

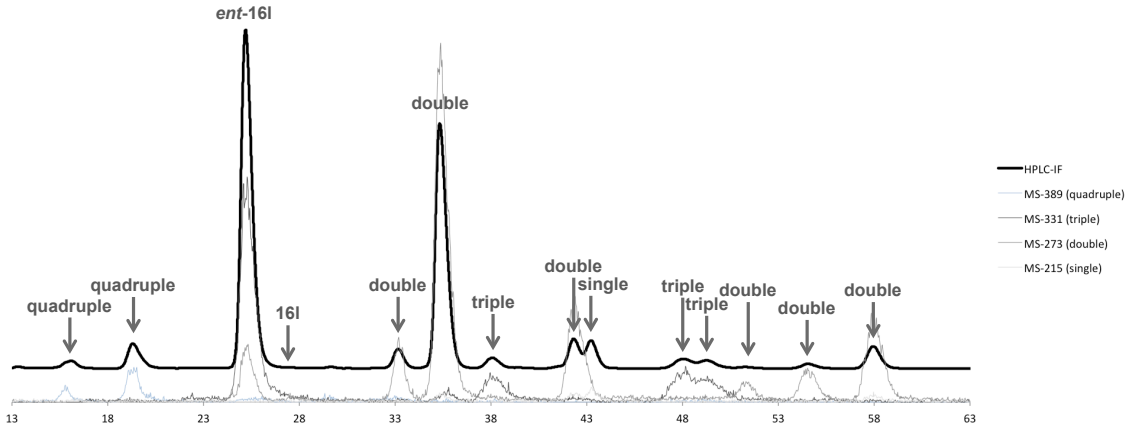
According to the above procedures, racemic reaction was conducted to dominantly generate **16l** and ***ent*-16l**. The crude residue was analyzed by LC/MS eluting with H_2O (0.1% TFA)/MeCN = 86:14 to 77:23 using Daicel Chiralpak IF to give the following chart.





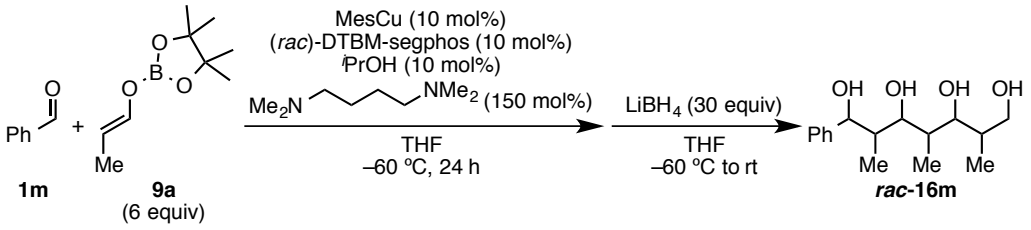
(2*S*,3*R*,4*S*,5*S*,6*R*,7*S*,*E*)-2,4,6-trimethyl-9-phenylnon-8-ene-1,3,5,7-tetraol (*ent*-16l)

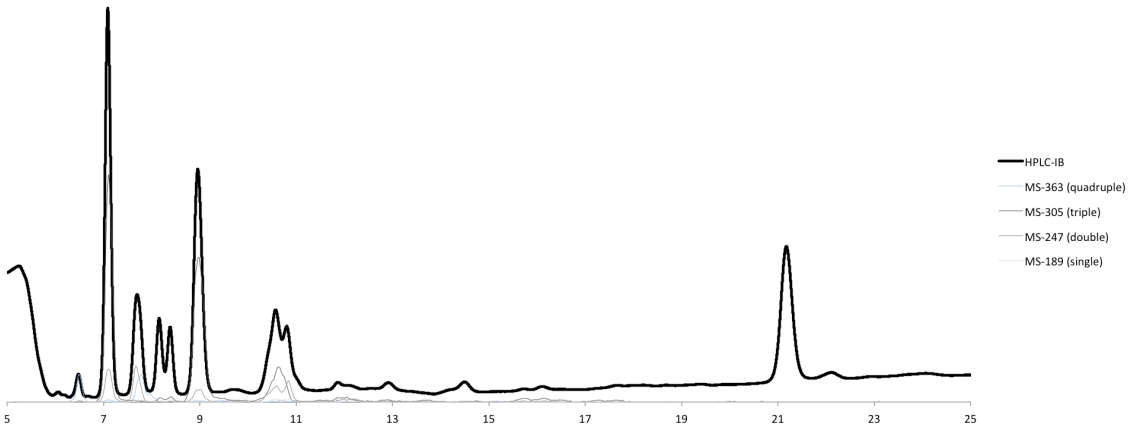
On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products : quadruple-aldol products = 3:42:50:5 and (**16l**+***ent*-16l**) : other isomers = 90:10, enantioselectivity; >99% ee [retention time; 25.2 min (major) and 27.2 min (minor)].



Authentic data for 2,4,6-trimethyl-1-phenylheptane-1,3,5,7-tetraol

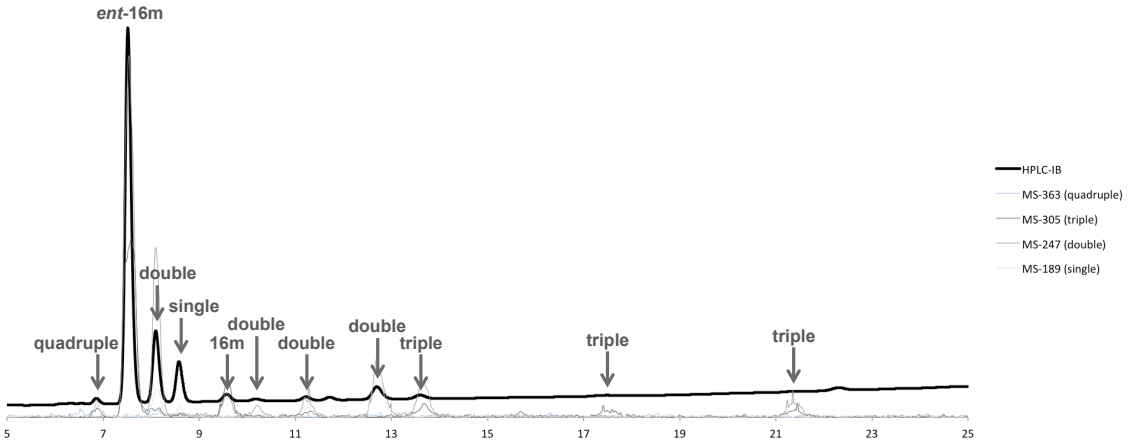
According to the above procedures, racemic reaction was conducted to dominantly generate **16m** and ***ent*-16m**. The crude residue was analyzed by LC/MS eluting with H_2O (0.1% HCO_2H)/MeCN = 84:16 to 72:28 using Daicel Chiralpak IB to give the following chart.





(1*R*,2*S*,3*R*,4*S*,5*R*,6*S*)-2,4,6-trimethyl-1-phenylheptane-1,3,5,7-tetraol (*ent*-16m)

On the basis of both the authentic chart and MS data, each peak was characterized as below. Based on the area %, the each selectivity was determined; single-aldol products : double-aldol products : triple-aldol products : quadruple-aldol products = 8:19:72:1 and (**16m**+***ent*-16m**) : other isomers = 98:2, enantioselectivity; 95% ee [retention time; 7.5 min (major) and 9.6 min (minor)].



Experimental Procedures and Compound Characterization for Chapter 2

I. xxx