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Reviews

Catalytic Asymmetric Carbon−Carbon Bond Formations: Their Evolution from Biocatalysis to Organocatalysis over the Millennium

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Abstract:

Illustrative discussion is made in chronological order on six select catalysts for asymmetric carbon−carbon bond formations that are scalable and are reported to be potentially scalable: (1) thiamine diphosphate (TPP)-bound pyruvate decarboxylase (PDC) used in the industrial production of (*R*)-L-phenyl acetyl carbinol (PAC; 5); (2) bimetallic Lewis acid−Brønsted base catalyst (9) for asymmetric Michael addition of dialkyl malonates; (3) Lewis acid−Lewis base catalyst (11) for asymmetric cyanosilylation of aryl alkyl ketones; (4) a chiral Schiff base chelated titanium(IV) alkoxide catalyst (32) for asymmetric addition of diketene to aldehydes; (5) 2-deoxyribose-5-phosphate aldolase (DERA) used in the preparation of (3*R*,5*S*)-6-chloro-2,4,6-trideoxy-*erythro*-hexose in its lactol form (50) from acetaldehyde (43)/chloroacetaldehyde (47) (2:1); and (6) chiral C_2-symmetric quaternary ammonium bromides, such as 63 of an *N*-spiro type, for asymmetric alkylation of Schiff bases of glycine and α-substituted glycine derivatives in the synthesis of nonproteogenic chiral α-amino acid derivatives.

Introduction

This minireview will deal with catalysts employed in scalable and potentially scalable asymmetric carbon−carbon bond formations in order of their evolution, which has taken the course involving the following four stages: (1) empirical application of fermentative power; (2) ligation of metallic ions with chiral organic ligands to mimic cooperative action of multiple functionalities in enzymatic catalysis; (3) creation of new and improved enzymes with the help of genetic engineering technologies; and (4) emergence of organic catalysts that can dispense with metallic species. Each stage is illustrated with epoch-making examples, where chemical transformations downstream of the asymmetric reactions are also discussed in the context of process research and development.

Diverting Fermentative Power to Unnatural Carboligation

The pharmaceutical industry has long been indebted to fermenting yeast (*Saccharomyces cerevisiae*) for asymmetric carbon−carbon bond formation.[1] At the penultimate stage of yeast's glycolytic pathway (anaerobic fermentation), pyruvate decarboxylase (PDC) helps thiamine diphosphate (TPP) in its ylide form (**2**) add to pyruvic acid (**1**) in a nucleophilic fashion to generate enamine (**3**) as an "active acetaldehyde" after decarboxylation (Scheme 1).[2] When benzaldehyde (**4**) is added to the briskly fermenting broth, the acetaldehyde synthon of inverted polarity (*Umpolung*) is transferred from **3** to **4** in a stereoselective manner to afford (*R*)-L-phenylacetylcarbinol (PAC; **5**).[1,2]

When **5** is treated with $MeNH_2$ in the presence of Pt under an atmosphere of hydrogen, L-ephedrine (**6**) is produced with an *erythro*-(1*R*,2*S*)-configuration (Scheme 1).[1,2] L-Norephedrine (**8**) can also be accessed from **5** via a two-step procedure: (1) reductive amination with $PhCH_2NH_2$ over 5% Pd/C to give *N*-benzyl norephedrine (**7**); and (2) selective removal of the *N*-benzyl group from **7** by hydrogenolysis over the same Pd catalyst, which leaves the hydroxy group at the benzylic position unaffected (Scheme 1).[3]

To mimic the unique mode of action associated with TPP-derived ylide (**2**) in the setting of asymmetric synthesis, chiral thiazolium and triazolium salts have been designed and tested for the ability to direct stereochemical courses in enantioselective benzoin[4] and intramolecular Stetter reactions,[5] which has now culminated in considerable success, as compiled in D. Enders' review on chiral nucleophilic carbenes.[6]

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(1) (a) Vasic-Racki, D. In *Industrial Biotransformations*, 2nd ed. completely revised and extended; Liese, A., Seelbach, K., Wandrey, C., Eds.; Wiley-VCH: Weinheim, 2006; pp 1−10. (b) Liese, A.; Seelbach, K.; Buchholz, A.; Haberland, J. In *Industrial Biotransformations*, 2nd ed. completely revised and extended; Liese, A., Seelbach, K., Wandrey, C., Eds.; Wiley-VCH: Weinheim, 2006; pp 447−448.

(2) (a) Pohl, A. *Adv. Biochem. Eng. Biotechnol.* **1997**, *58*, 15−43. (b) Sprenger, G. A.; Pohl, M. *J. Mol. Catal. B: Enzym.* **1999**, *6*, 145−159. (c) For benzoylformate decarboxylate (BFD) related to PDC, see: Iding, H.; Dünnwald, T.; Greiner, L.; Liese, A.; Müller, M.; Siegert, M.; Grötzinger, J.; Demir, A. S.; Pohl, M. *Chem.—Eur. J.* **2000**, *6*, 1483−1495.

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(5) (a) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195−197. (b) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654−1655. (c) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. (d) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934−1936. (e) de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284−6289.

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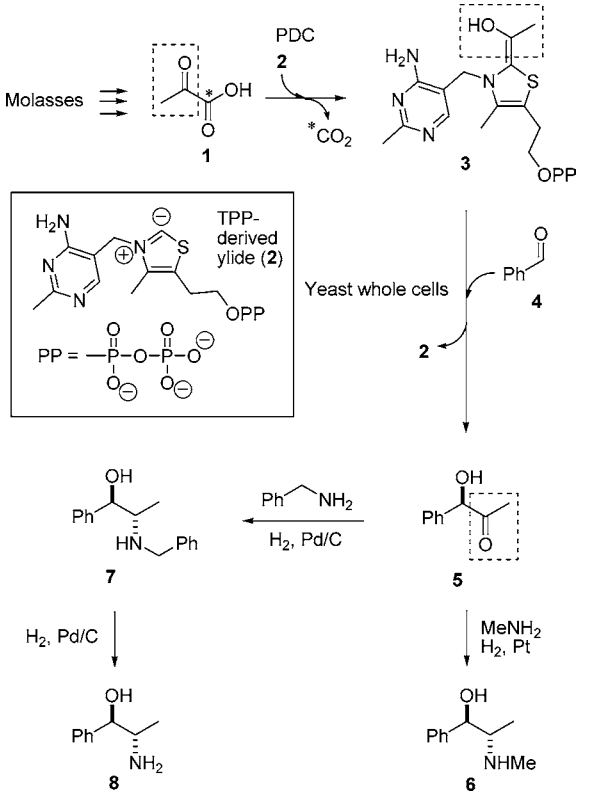
Scheme 1. **PDC/TPP-mediated production of (*R*)-L-PAC (5) and its conversion to L-ephedrine (6) and L-norephedrine (8)**



Beyond Mimicking Enzymes (Part 1): Enantioselective Addition of a C_2 Nucleophilic Synthon, Malonate, and a C_1 Nucleophilic Synthon, Cyanide Anion

Cooperative action of multiple, at least dual, functionalities is the key to the enzymatic catalysis as is the case with PDC effecting carboligation with the help of an ylide form of TPP (**2**).[2a] Exploiting this mechanistic concept, M. Shibasaki has devised two kinds of organometallic complex catalysts that can fulfill such enzyme-mimetic dual activity.[7] One is a heterobimetallic catalyst (**9**), such as (*R*)-ALB (**10**), in which a centrally chelated metallic cation (M^1) functions as a Lewis acid and a peripherally tethered one (M^2) as a Brønsted base. The other is a Lewis acid−Lewis base catalyst (**11**) in which a phosphine oxide oxygen atom functions as the Lewis base and a chelated metallic cation (M^3) functions as the Lewis acid (Figure 1).

1,1′-Bi-2-naphthol (BINOL)-based heterobimetallic complexes (**9**) varying in the species of metallic cations, M^1 and M^2, are prepared and assessed for the catalytic activity towards asymmetric Michael addition of dimethyl malonate (**12**) to 2-cyclohexenone (**13**) (Scheme 2).[8] For the given

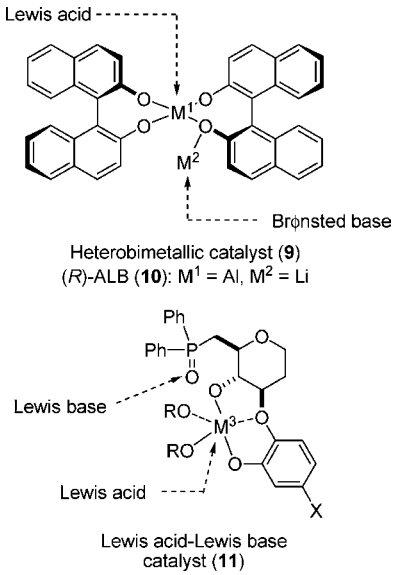
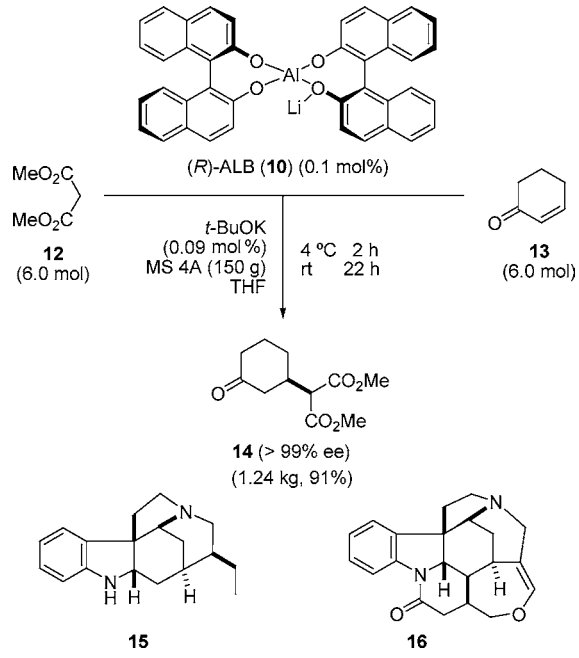


Figure 1. **General structures of heterobimetallic catalyst (9) and Lewis acid−Lewis base catalyst (11).**

Scheme 2. **(*R*)-ALB (10)-catalyzed asymmetric Michael addition and structures of (−)-tubifolidine (15) and (−)-strychnine (16)**



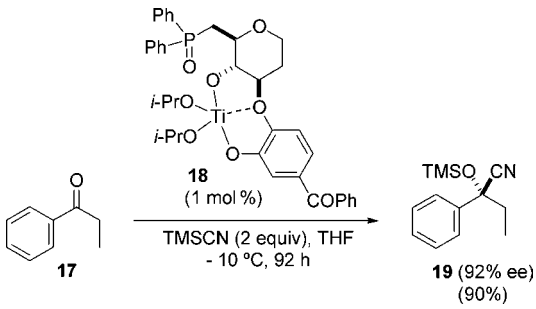
reaction, (*R*)-ALB [**10**; prepared from (*R*)-BINOL/$LiAlH_4$ (2:1) in THF at 0 °C] has turned out to be the catalyst of choice.[9] Under the optimized conditions using *t*-BuOK (0.09 mol %) and MS-4A (25 g/mol) as additives,[9d] the asymmetric Michael addition of **12** to **13** on a kilogram scale goes to completion under the catalysis of **10** (0.1 mol %) at room temperature in 22 h after setting up the reaction at 4 °C with ice-cooling over 2 h. Simple extractive workup followed by 3-fold crystallizations eventually provides (*R*)-3-[bis(methoxy-

(7) (a) Shibasaki, M.; Iida, T.; Yamada, Y. M. A. *J. Synth. Org. Chem. Jpn.* (*Yuki Gosei Kagaku Kyokaishi*) **1998**, *56*, 344−356. (b) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511−356. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187−2209. (d) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491−1508.

(8) (a) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571−1572. (b) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194−6198. (c) Arai, T.; Sasaki, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104−106. (d) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506−6507. (e) Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 466−14665.

(9) (a) Shimizu, S.; Ohri, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 7547−7551. (b) Xu, Y.; Ohri, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 2585−2588. (c) Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546−14547. (d) Ohshima, T.; Xu, Y.; Takita, R.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 9569−9588.

Scheme 3. **Lewis acid−Lewis base catalyst (18)-promoted enantioselective cyanosilylation of phenyl ethyl ketone (17)**



carbonyl)methyl]cyclohexanone (**14**) of >99% ee in 91% yield.

Being secured in quantity, the product (**14**) has served as the starting point in the two enantioselective total syntheses of *strychnos* alkaloids in natural forms, (−)-tubifolidine (**15**)[9a] and (−)-strychnine (**16**)[9c,d] (Scheme 2).

Because of its bifunctionality, chiral cyanohydrin TMS ethers are a versatile synthetic intermediate; in fact, they can be converted to chiral α-hydroxy acids, *β*-amino alcohols, and further elaborated derivatives thereof.

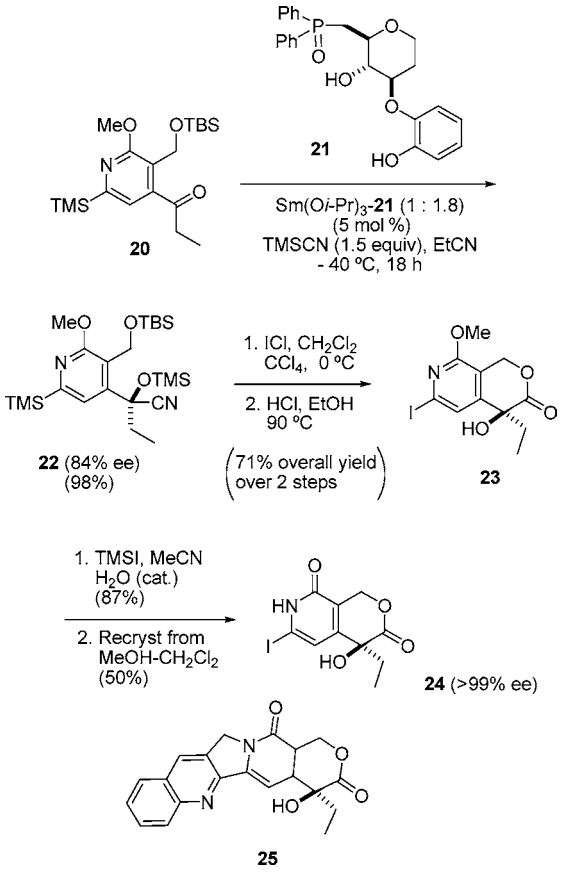
Indeed, the most expeditious method to access chiral cyanohydrin TMS ethers should be enantioselective cyanosilylation of carbonyl compounds; however, when compared with aldehydes, ketones had remained poor substrates until M. Shibasaki invented a Lewis acid−Lewis base catalyst (**11**) (Figure 1).[7b,10] When phenyl ethyl ketone (**17**) is treated with TMSCN (2 equiv) in the presence of a Ti(IV) complex (**18**; 1 mol %) in THF, enantioselective cyanosilylation proceeds at −10 °C to give (*R*)-cyanohydrin TMS ether (**19**) in 92% ee and 90% yield after 92 h (Scheme 3).[10b]

Another noteworthy feature of the catalyst (**11**) is that its enantioselectivity can be inverted only by switching the metallic species in it:[11] When a Sm(III) complex (5 mol %) [prepared from Sm(O*i*-Pr)$_3$/chiral ligand (**21**; possessing the same configuration as **18**) (1:1.8)] is employed in combination with TMSCN (1.5 equiv), 4-pyridyl ethyl ketone (**20**) undergoes cyanosilylation of an inverted stereochemical sense compared to that exerted by Ti(IV)-based **18** in EtCN at −40 °C to give (*S*)-cyanohydrin TMS ether (**22**) in 84% ee and 98% yield after 18 h (Scheme 4).

When **22** is treated with ICl in CH_2Cl_2−CCl_4 at 0 °C, its TMS group on the pyridine nucleus is exchanged for iodide. On acidic ethanolysis (HCl, EtOH, 90 °C), iodolactone (**23**) is isolated in a two-step overall yield of 71%. The methyl ether in **23** is then cleaved with TMSI in wet MeCN to give lactam (**24**) in 87% yield. Finally, recrystallization from MeOH−CH_2Cl_2 provides purified **24** of >99% ee in 50% yield, a key intermediate in the total synthesis of (*S*)-camptothecin (**25**).[11]

Exhibiting the same (*S*)-selectivity as the Sm(III) complex, a Gd(III) complex prepared from Gd(O*i*-Pr)$_3$/chiral ligand

Scheme 4. **Lewis acid−Lewis base catalyst-promoted enantioselective cyanosilylation and its application to the synthesis of 24, an eastern-hemisphere intermediate of (*S*)-camptothecin (25)**



(**21**) (1:2) proves effective in discerning a subtle stereoelectronic difference between the phenyl and cyclohexyl groups flanking the keto carbonyl group in ketone (**26**) (Scheme 5).[12a] Enantioselective cyanosilylation proceeds with **26** (100 g) uneventfully when it is treated with TMSCN (1.2 equiv) in the presence of Gd(O*i*-Pr)$_3$ (1 mol %) and **21** (2 mol %) at −40 °C for 40 h. Short pad silica gel chromatography permits simple isolation of (*S*)-cyanohydrin TMS ether (**27**; 152 g, quantitative) as well as efficient recovery of the chiral ligand (**21**; 98% yield) in a pure state.

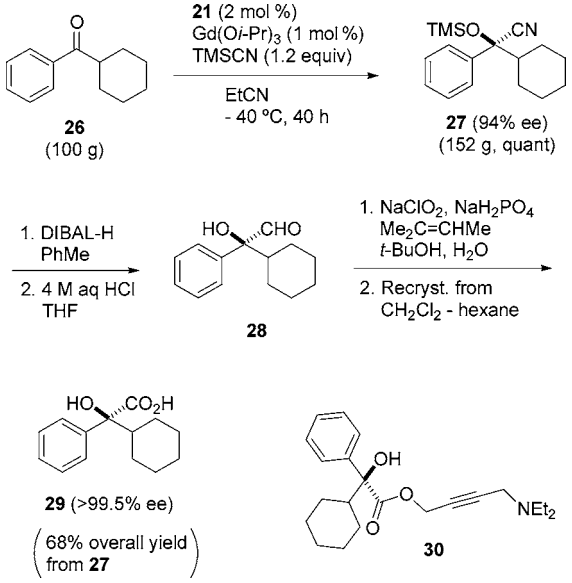
To convert **27** to α-hydroxy carboxylic acid (**29**), a key intermediate for (*S*)-oxybutynin (**30**), not only acidic hydrolysis of **27** but also basic hydrolysis of its derived THP ether has been attempted, but to no avail. However, this unforeseen obstacle has been overcome successfully by making a detour in which **27** is first reduced with DIBAL-H in PhMe and the resulting aldehyde (**28**) is next oxidized to the desired carboxylic acid (**29**) with sodium chlorite ($NaClO_2$).[12] Finally, recrystallization from hexane−CH_2Cl_2 affords purified **29** in >99.5% ee and a three-step overall yield of 68% from **27** (Scheme 5).[12a]

(10) (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413. (b) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691−694.

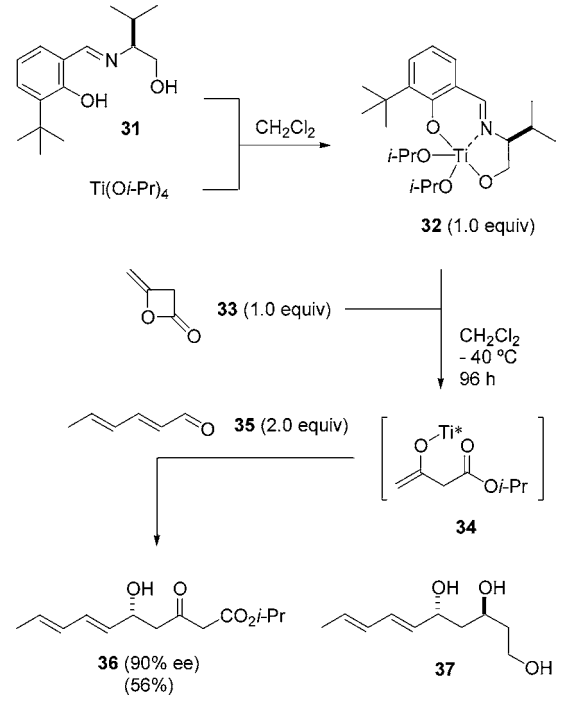
(11) Yabu, K.; Matsumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908−9909.

(12) (a) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 8647−8651. (b) Suzuki, M.; Kato, N.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 2527−2530.

Scheme 5. **Lewis acid−Lewis base catalyst-promoted enantioselective cyanosilylation and its application to the synthesis of (*S*)-α-hydroxy carboxylic acid (29) and structure of (*S*)-oxybutynin (30)**



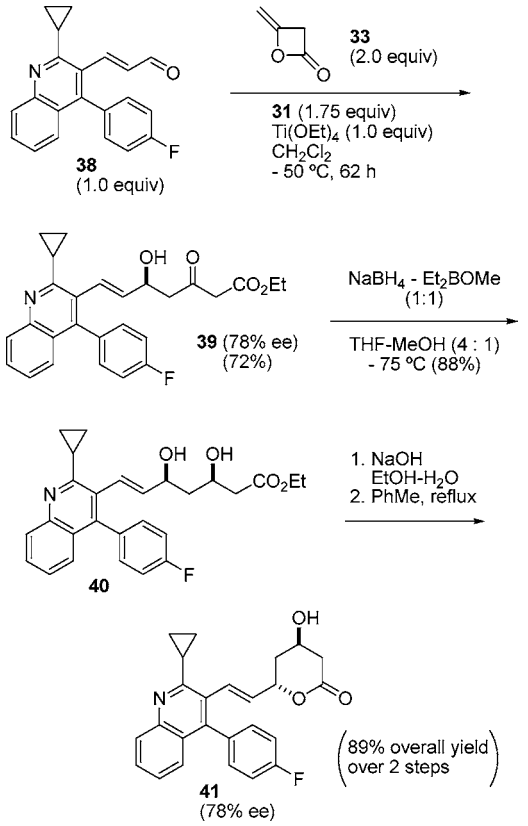
Scheme 6. **Chiral Schiff base chelated Ti(IV) alkoxide-promoted asymmetric addition of diketene (33) to unsaturated aldehyde (35) and structure of a *Streptomyces fimbriatus* metabolite (37)**



Beyond Mimicking Enzymes (Part 2): Enantioselective Addition of a C_4 Nucleophilic Synthon, γ-Enolate of Acetoacetate

Aldol reactions should gain wider applicability when methyl ketone enolates with extra functionalities for further manipulation [$CH_2{=}C(O^-)CHR^1R^2$], such as **34** depicted in Scheme 6, can be added enantioselectively to aldehydes of elaborate structures. M. Hayashi has succeeded in addressing

Scheme 7. **Enantioselective synthesis of pitavastatin lactone (41)**



such synthetic issues[13] by reacting diketene (**33**;1.0 equiv) with 2,4-hexadienal (**35**; 2.0 equiv) in CH_2Cl_2 at −40 °C in the presence of a Ti(IV) complex [**32**; 1.0 equiv; prepared from Ti(O*i*-Pr)$_4$/chiral β-aminoalcohol Schiff base (**31**) (1:1)] to obtain (*R*)-δ-hydroxy-β-ketoester (**36**) in 90% ee and 56% yield (Scheme 6).[14] It is assumed that the chiral Schiff base chelated Ti(IV) complex (**32**) reacts with **33** stoichiometrically to generate titanium enolate (**34**), which then adds to the unsaturated aldehyde (**35**; 2.0 equiv) enantioselectively.[13b] As regards the product (**36**), $Me_4NB(OAc)_4H$-mediated *anti*-selective reduction of its β-hydroxy keto moiety and further functional group manipulations give a concise access to (3*S*,5*R*,6*E*,8*E*)-deca-6,9-diene-1,3,5-triol (**37**), a metabolite of *Streptomyces fimbriatus*.[14]

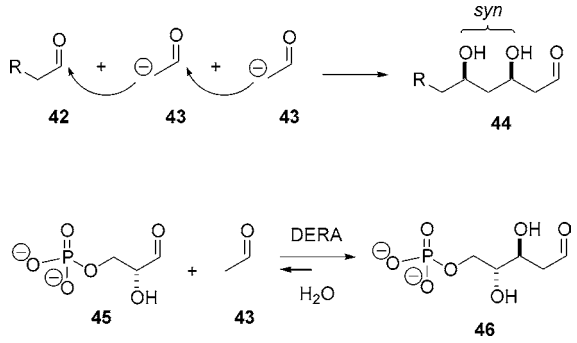
A Ti(IV) complex prepared from $Ti(OEt)_4$ (1.0 equiv) and a chiral β-aminoalcohol Schiff base (**31**; 1.75 equiv) in CH_2Cl_2 has also proven to be effective in adding **33** (2.0 equiv) to 3-(3-quinolyl)-2-propenal (**38**; 1.0 equiv) enantioselectively (Scheme 7).[15] When the reaction is conducted in CH_2Cl_2 at −50 °C for 62 h, (*S*)-δ-hydroxy-β-ketoester (**39**) is produced in 78% ee and 72% yield. Reduction of **39** with $NaBH_4$/Et_2BOMe (1:1) in THF/MeOH (4:1) at −75 °C gives a 1,3-*syn* diol (**40**) in 88% yield, which, on heat-promoted lactonization, is converted into (4*R*,6*S*)-4-hydroxy-6-[3-(3-

(13) Hayashi, M.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1994**, 341−342. (b) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385−4398.

(14) Hayashi, M.; Kaneda, H.; Oguni, N. *Tetrahedron: Asymmetry* **1995**, *6*, 2511−2516.

(15) Hayashi, M.; Yoshimoto, K.; Hirata, N.; Tanaka, K.; Oguni, N.; Harada, K.; Matsushita, A.; Kawachi, Y.; Sasaki, H. *Isr. J. Chem.* **2001**, *41*, 241−246.

Scheme 8. **Double aldol reactions leading to (3*R*)-3,5-*syn*-dihydroxy-6-substituted-hexanal (44) and 2-deoxyribose-5-phosphate aldolase (DERA)-catalyzed aldol reaction between D-glyceraldehyde 3-phosphate (45) and acetaldehyde (43)**



quinolyl)-2-propenyl]-3,4,5,6-tetrahydro-*2H*-pyran-2-one (**41**), a δ-lactone of pitavastatin, in 78% ee and 89% yield without erosion of the stereochemical integrity over the three-step transformations.[15]

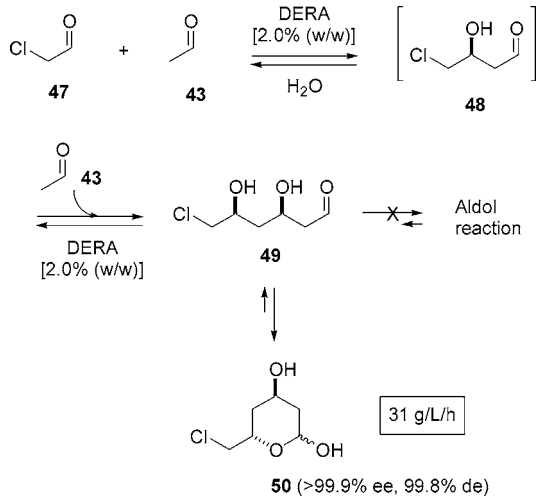
Enzyme Development in the Genomic Era: Stereocontrolled Aldol Reactions by Enzymatic Catalysis

Even if participating carbonyl substrates are of simple structure, aldol reactions should make a difference provided that they proceed successively under strict control of the reaction order, recurring times, and enantioselectivity. In fact, the most logical and expeditious approach to a (3*R*)-3,5-*syn*-3,5-dihydroxycarboxylic acid derivative, such as **40** (Scheme 7), is to assemble (3*R*)-6-substituted-2,4,6-trideoxy-3,5-*erythro*-hexose (**44**) as its penultimate precursor via the enantioselective *syn*-aldol reaction in which α-substituted acetaldehyde (**42**; a starting acceptor substrate) undergoes 2-fold addition of acetaldehyde (**43**; a donor substrate) (Scheme 8). To achieve this synthetic goal, C.-H. Wong has turned to Nature and demonstrated that 2-deoxyribose-5-phosphate aldolase (DERA) is able to catalyze the successive enantioselective aldol reaction in question.[16]

Being a type I aldolase that converts donor substrates, such as **43**, to enamine via Schiff base formation in enhancing their nucleophilicity, DERA catalyzes in Nature a reversible aldol reaction in which D-glyceraldehyde 3-phosphate (G3P; **45**) participates as an acceptor (electrophile) and acetaldehyde (**43**) participates as a donor (nucleophile) thereby to form D-2-deoxyribose-5-phosphate (DRP; **46**) (Scheme 8).[17] Nonetheless, accommodating the α-substituted acetaldehyde (**42**) rather than G3P (**45**), DERA shows some intrinsic tolerance to acceptor substrates, which should add to its potential applicability.[17,18] Hence, C.-H. Wong has cloned the *Escherichia coli* DERA gene and overexpressed it in engineered *E. coli* cells such that DERA can be applied advantageously to his chemoenzymatic endeavor to build

(16) Chen, L.; Dumas, D. P.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 241−246.
(17) DeSantis, G.; Liu, J.; Clark, D. P.; Heine, A.; Wilson, I. A.; Wong, C.-H. *Bioorg. Med. Chem.* **2003**, *11*, 43−52.
(18) (a) Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 8422−8423. (b) Liu, J.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1404−1407.

Scheme 9. **Conversion of chloroacetaldehyde (47)/acetaldehyde (43) (1:2) into (3*R*,5*S*)-6-chloro-2,4,6-trideoxy-*erythro*-hexose lactol (50) by the catalysis of 2-deoxyribose-5-phosphate aldolase (DERA)**



carbohydrate-related derivatives.[19] In parallel, the wild-type *E. coli* DERA has been subjected to site-directed mutagenesis to further expand its substrate specificity, which leads to identification of the S238D mutant that can accommodate 2-azidopropionaldehyde preferably as an acceptor substrate.[17]

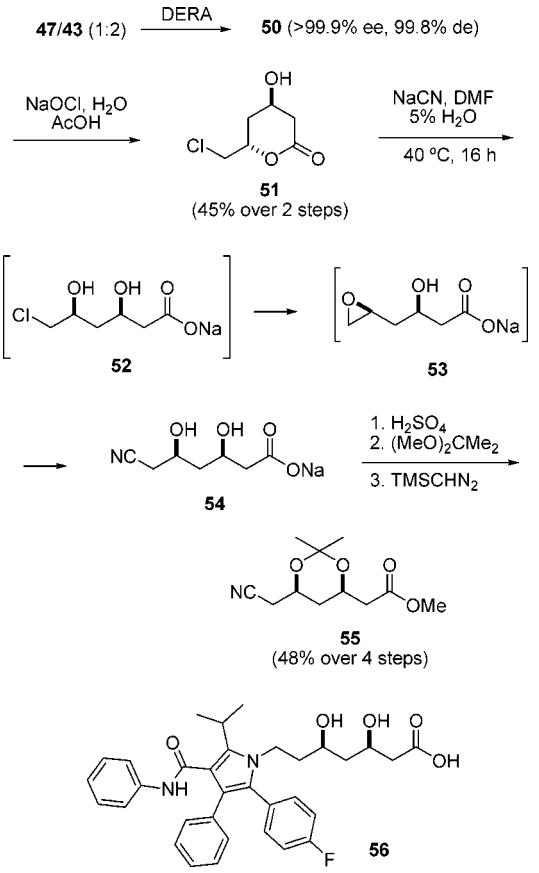
In the meantime, M. J. Burk has explored huge environmental DNA libraries for DERAs with both improved activity (reduced catalyst load) and increased tolerance to high substrate concentrations.[20] High throughput screening has identified a new and improved DERA of which the organism source is still unknown, its protein sequence homology to that of *E. coli* being <30%. In the synthesis of lactol (**50**) by sequential aldol reactions starting with chloroacetaldehyde (**47**; an acceptor substrate)/acetaldehyde (**43**; a donor substrate) (1:2) (Scheme 9), the newly identified DERA shows 400-fold and 10-fold improvement over the *E. coli* DERA in terms of volumetric productivity and catalyst load, respectively, once a fed-batch process is used to overcome the substrate inhibition caused by **47**.[20]

As regards the DERA-catalyzed aldol reaction that yields (3*R*,5*S*)-6-chloro-3,5-dihydroxyhexanal (**49**) from **47**/**43** (1:2) via (*S*)-4-chloro-3-hydroxy-butanal (**48**), the steps involved are all reversible; hence, the whole reaction sequence reaches equilibrium irrespective of the type of DERA employed (Scheme 9). Actually, the equilibrium is driven far in the forward direction as the double-aldol product (**49**) cyclizes spontaneously to lactol (**50**); what is better, such cyclization protects the aldehyde (**49**) from being attacked further by the acetaldehyde (**43**) in the presence of DERA.[18] When the improved DERA discovered by M. J. Burk is used at a catalyst load of 2.0% (w/w), lactol (**50**) can be produced in >99.9% ee and 99.8% de with an industrially viable productivity of 31 g/L/h.[20]

Once the DERA-catalyzed double aldol reaction between **47**/**43** (1:2) goes to completion, crude lactol (**50**) is extracted

(19) Wong, C.-H.; Garcia-Junceda, E.; Chen, L.; Blanco, O.; Gijsen, H. J. M.; Steensma, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 8422−8423.
(20) Greenberg, W. A.; Varvak, A.; Hanson, S. R.; Wong, K.; Huang, H.; Chen, P.; Burk, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5788−5793.

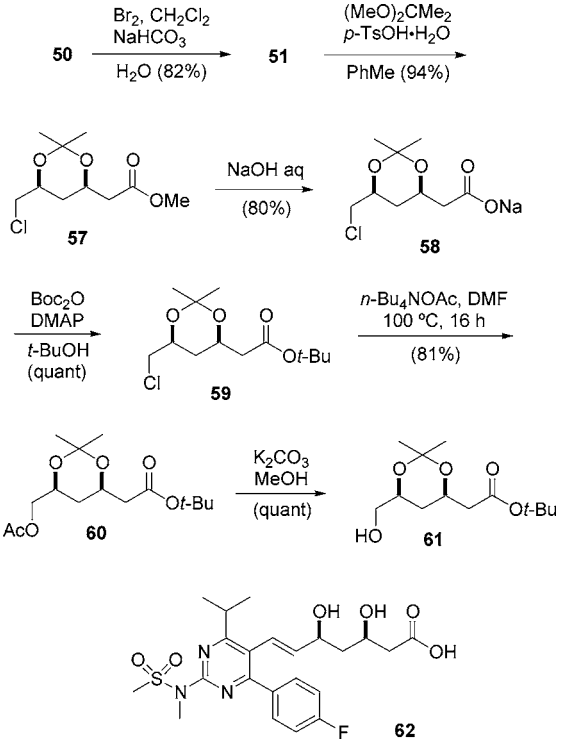
Scheme 10. **Synthesis of methyl (3*R*,5*R*)-6-cyano-3,5-dihydroxyhexanoate 3,5-acetonide (55) and structure of atorvastatin (56)**



into AcOEt and is carried on to the next step without further purification (Scheme 10).[20] When crude **51** is treated with aqueous sodium hypochlorite (NaOCl) in AcOH, crystalline lactone (**51**) is obtained in a two-step overall yield of 45% from **47**. On treatment with NaCN in wet DMF at 40 °C for 16 h, chloride (**51**) is converted to sodium (3*R*,5*R*)-6-cyano-3,5-dihydroxyhexanote (**54**) with concomitant lactone-ring opening. ^{1}H and ^{13}C NMR analysis indicates that this displacement en route to **54** has proceeded via saponification (**51** → **52**) followed by epoxide formation (**52** → 5**3**) under basic conditions caused by NaCN. Treatment of **54** with H_2SO_4 liberates the free acid, which then undergoes acetal formation with 2,2-dimethoxypropane. Finally, methyl ester formation with $TMSCHN_2$ furnishes acetonide ester (**55**), akey chiral intermediate that permits convergent access to atorvastatin (**56**), in a three-step overall yield of 48% from **51**.[21]

Lactol (**50**) is also converted to *tert*-butyl (3*R*,5*R*)-3,5,6-trihydroxyhexanoate 3,5-acetonide (**61**), a key intermediate in the production of rosuvastatin (**62**), at DSM as outlined in Scheme 11.[22] When **50** is subjected to bromine-mediated oxidation, lactone (**51**) is obtained in 82% yield from **50** which, in turn, has been secured in quantity by the *E. coli*

Scheme 11. **Synthesis of *tert*-butyl (3*R*,5*R*)-3,5,6-trihydroxyhexanoate 3,5-acetonide (61) and structure of rosuvastatin (62)**



DERA-catalyzed aldol reaction.[22a] On treatment with 2,2-dimethoxypropane in the presence of catalytic *p*-TsOH·H_2O, **51** undergoes acetal formation concomitant with methyl ester formation to give methyl (3*R*,5*R*)-6-chloro-3,5-dihydroxyhexanoate 3,5-acetonide (**57**) in 94% yield.[22b] Saponification of **57** with aqueous NaOH solution affords sodium carboxylate (**58**) in 80% yield, which is converted to *tert*-butyl ester (**59**) quantitatively through the agency of $(Boc)_2O$ and catalytic DMAP in *t*-BuOH. When **59** is treated with $(n\text{-}Bu)_4NOAc$ in DMF at 100 °C for 16 h, the chloride in **59** is displaced with acetate to give acetoxy ester (**60**) in 81% yield. Finally, K_2CO_3-mediated methanolysis affords **61** quantitatively.[22b]

Metal-Free Designer Catalysts for Enantioselective Alkylation of the Enolates Arising from Glycine and α-Substituted Glycine Derivatives

Molecular catalysts in the paradigm of the 20th century, such as **9**, **11**, and **32**, fail to outdo enzymes, such as TPP-dependent PDC and DERA, in that such biocatalysts can do without metallic cations in promoting carbon−carbon bond formations. However, the situation changed at the dawn of the 21st century when K. Maruoka introduced his designer organocatalysts. In fact, his C_2-symmetric chiral quaternary ammonium bromides, such as **63**,[23] **64**,[24] and **65**,[25] have opened new avenues to enantioselective assemblage of

(21) For a compilation of chemoenzymatic approaches to statin side chains of the (3*R*)-*syn*-3,5-dihydroxy-6-substituted-hexanoate motif, see: Müller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 362−365.

(22) (a) Kierkels, J. G. T.; Mink, D.; Panke, S.; Lommen, F. A. M.; Heemskerk, D. (DSM). WO 03/006656. (b) Kooistra, J. M. H. H.; Zeegers, H. J. M.; Mink, D.; Mulders, J. M. C. A. (DSM). WO 02/06266.

(23) (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228−5229. (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139−5151.

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(25) Han, Z.; Yamaguchi, Y.; Kitamura, M.; Maruoka, K. *Tetrahedron Lett.* **2005**, *46*, 8555−8558.

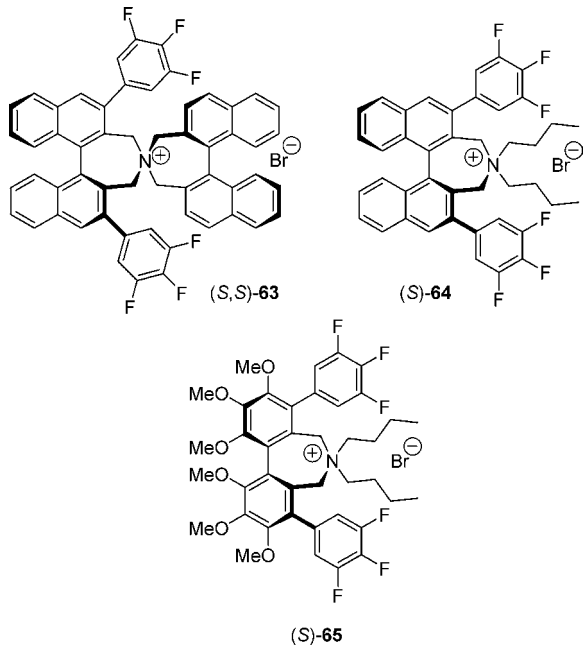


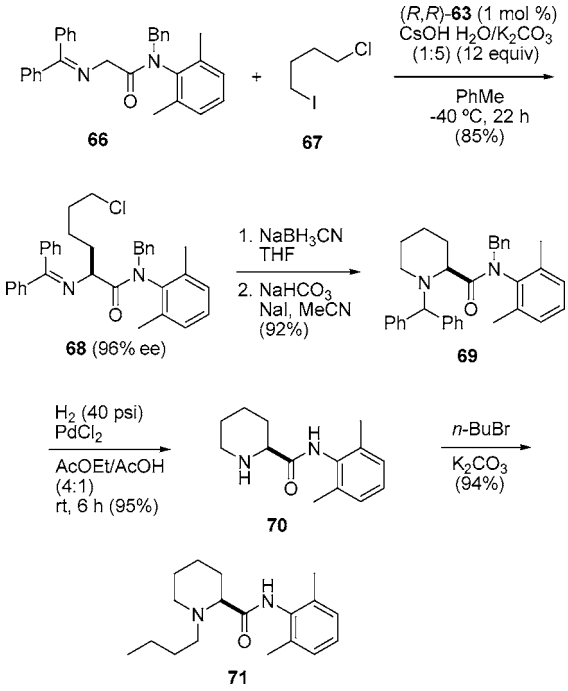
Figure 2. **Structures of C_2-symmetric chiral quaternary ammonium bromides, 63, 64, and 65.**

nonproteogenic α-amino acids[26] and derivatives thereof (Figure 2).[27,28] In fact, such chiral quaternary ammonium organocatalysts have found their increasing synthetic applications even outside the inventor's laboratory because oftheir intrinsic power of superb enantioselection ever since the first advent of their prototype in 1999.[29]

Asymmetric alkylation catalyzed by (*R*,*R*)-*N*-spiro-quaternary ammonium bromide (**63**) is used to advantage in an enantioselective access to levobupivacaine (**71**), a local anaesthetic with less CNS side effects compared to its racemic progenitor, bupivacaine, as outlined in Scheme 12.[30] When *N*-diphenylmethylideneamino-[*N*-benzyl-*N*-(2,6-dimethylphenyl)]acetamide (**66**) is treated with 1-chloro-4-iodobutane (**67**) in the presence of (*R*,*R*)-**63** (1 mol %) and $CsOH{\cdot}H_2O/K_2CO_3$ (1:5; 12 equiv in total) at −40 °C for 22 h, the (*S*)-configured alkylated product (**68**) is isolated in 96% ee and 85% yield.

The imine function in **68** is reduced with $NaBH_3CN$ in THF, and the resulting secondary amine is subjected to NaI-assisted intramolecular *N*-alkylation using $NaHCO_3$ as an acid scavenger in MeCN to give *N*-diphenylmethylpiperidine (**69**) in 92% yield. The benzyl and diphenylmethyl groups are removed from the amine and amide functionalities, respectively, in one pot by catalytic hydrogenolysis [H_2, 40 psi; $PdCl_2$, AcOEt/AcOH (4:1); rt, 6 h] to give protection-

Scheme 12. **Synthesis of levobupivacaine (71)**



free **70** in 95% yield. Finally, *N*-alkylation with *n*-BuBr in the presence of K_2CO_3 affords **71** in 94% yield without incident.

More elaborate quaternary stereogenic centers can be built enantioselectively when (*R*,*R*)-(**63**) is applied to the catalytic asymmetric alkylation of α-substituted α-amino acids. In fact, (*S*)-α-allyl phenylglycine methyl ester (**74**), prepared according to such asymmetric alkylation tactics, can be converted to a (2*S*,4*R*)-4-hydroxy-2-phenylproline framework (**79**), a core structure in a drug candidate being developed jointly at Banyu and Merck (Scheme 13).[31] When a 4-chlorobenzaldehyde Schiff base of (±)-phenylglycine *tert*-butyl ester (**72**) is treated with allyl bromide in the presence of (*S*,*S*)-**63** (1 mol %) and $CsOH{\cdot}H_2O$ (5 equiv) in PhMe at −40 °C for 25 h under an Ar atmosphere,[32] the aldimine of (*S*)-α-allyl phenylglycine *tert*-butyl ester (**73**) is generated in 91% ee.

On subjection to H_2SO_4-mediated methanolysis (50 °C), **73** undergoes both imine hydrolysis and transesterification in one pot to afford methyl ester (**74**) in a two-step overall yield of 72%. *N*-Tosylation of **74** [TsCl, $Me_2N(CH_2)_6NMe_2$, MeCN, room temperature] provides (*S*)-tosylamide (**75**)

(26) Ooi, T.; Arimura, Y.; Hiraiwa, Y.; Yuan, L. M.; Kano, T.; Inoue, T.; Matsumoto, J.; Maruoka, K. *Tetrahedron: Asymmetry* **2006**, *17*, 603−606.
(27) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013−3028.
(28) For the streamlined synthesis of **63** and **64**, see: (a) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576−4578. (b) Ikunaka, M.; Maruoka, K.; Okuda, Y.; Ooi, T. *Org. Process Res. Dev.* **2003**, *7*, 644−648. (c) Yamamoto, K.; Inoue, T.; Ikunaka, M. *Abstract Papers of the 2005 Summer Symposium*; the Japanese Society for Process Chemistry, Tokyo, July 28−29, 2005; the Japanese Society for Process Chemistry: Nagoya, 2005; pp 94−95.
(29) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519−6520.
(30) Kumar, S.; Ramachandran, U. *Tetrahedron Lett.* **2005**, *46*, 19−21.
(31) Maeda, K.; Miller, R. A.; Szumigala, R. H., Jr.; Shafiee, A.; Karady, S.; Armstrong, J. D., III. *Tetrahedron Lett.* **2005**, *46*, 1545−1549.
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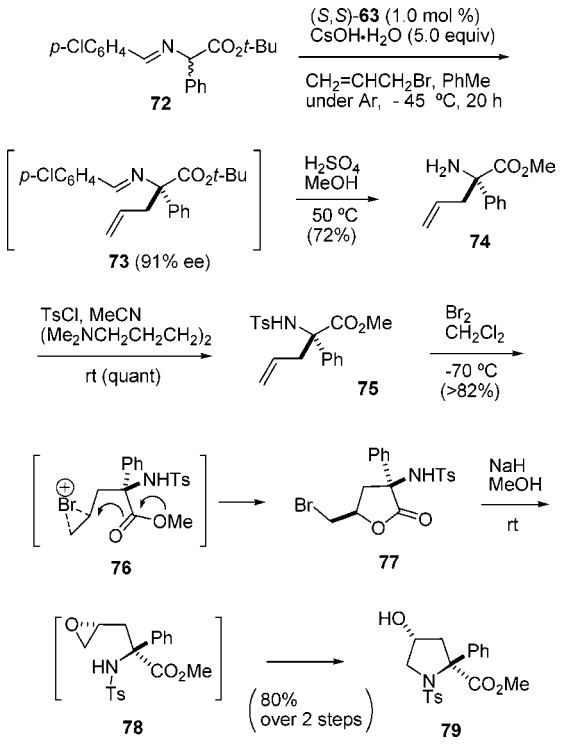
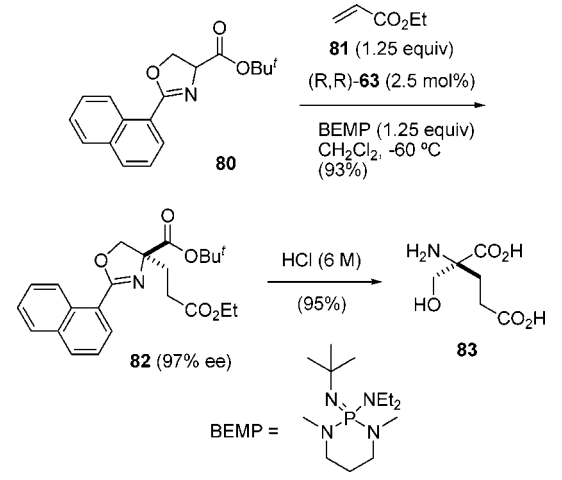
(33) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Jew, S.; Park, H. *Org. Lett.* **2005**, *7*, 3207−3209.
(34) For recent progress in the chemoenzymatic approaches to the chiral intermediates to build the side chains of synthetic statins, see: Thayer, A. N. *Chem. Eng. News* **2006**, *84* (Aug 14), 26−27.
(35) For Shibasaki's successful application of his concept of catalyst design to the synthesis of tamiflu, see: Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312−6313.
(36) For the mechanistic discussion on the catalytic cycle involving C_2-symmetric chiral quaternary ammonium bromide **64** of a truncated structure, see ref 24.
(37) For further application of the C_2-symmetric chiral quaternary ammonium bromides explored at Maruoka's laboratory, see: Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073−5083.

Scheme 13. **Synthesis of (2*S*,4*R*)-*N*-tosyl-4-hydroxy-2-phenylproline methyl ester (79)**



Scheme 14. **Synthesis of (*S*)-α-(hydroxymethyl)glutamic acid (83)**



quantitatively, which, on bromolactonizaion (Br_2, CH_2Cl_2, −70 °C), is converted to γ-lactone (**77**) in high diastereoselectivity (>20:1) and >82% yield by way of **76**. Finally, **77** is treated with NaH in MeOH to effect NaOMe-mediated opening of the γ-lactone ring, which is immediately followed by intramolecular nucleophilic attack of the tosylamide nitrogen on the epoxide terminus in the incipiently formed **78** to furnish **79** in a two-step overall yield of 80% yield.

The (*S*,*S*)-quaternary ammonium bromide (**63**) of the *N*-spiro type is also effective in an asymmetric Michael reaction as depicted in Scheme 14, which has culminated in an expeditious enantioselective access to (*S*)-α-(hydroxymethyl)glutaric acid (HMG; **83**), a strong antagonist for the matabotropic glutamate receptor 2 (mGluR2) and a weak agonist for mGluR3.[33] When 2-(1-naphthyl)-1,3-oxazoline-4-carboxylic acid *tert*-butyl ester (**80**) is treated with ethyl acrylate (**81**; 1.25 equiv) in the presence of (*R*,*R*)-**63** (2.5 mol %) and BEMP (1.25 equiv), a nonionic phosphazene base, in CH_2Cl_2 at −60 °C for 20 h, an (*S*)-configured Michael adduct (**82**) of 97% ee is obtained in 93% yield. Hydrolysis with 6 M aqueous HCl then provides (*S*)-HMG (**83**) in 95% yield.

Conclusions

As far as asymmetric carbon−carbon bond formation is concerned, the pharmaceutical industry benefits from chemoenzymatic processes, such as the DERA-promoted aldol reactions in assembling the lactol of (3*R*,5*S*)-6-chloro-2,4,6-trideoxy-*erythro*-hexose (**50**), a key intermediate for statin drugs,[34] not to mention carboligation between active acetaldehyde [Me(O)C$^-$] and PhCHO by the catalysis of TPP-dependent PDC in the classical production of (*R*)-L-PAC (**5**), a penultimate intermediate for L-ephedrine (**6**). In addition, recent advances in molecular catalysis and organocatalysis have opened up new horizons where the catalyst performance can be tailored to specific synthetic campaigns at will, as illustrated by Shibasaki's multifunctional catalysts for asymmetric Michael addition of malonate esters and asymmetric cyanosilylation of ketones,[35] Hayashi's chiral Schiff base chelated Ti(IV) alkoxide catalysts for asymmetric addition of diketene to aldehydes, and Maruoka's chiral quaternary ammonium catalysts[36] for the production of nonproteogenic chiral α-amino acids, in particular, those of an α,α-dialkyl type.[37]

Acknowledgment

Dedicated to Prof. Emeritus Yasuhiro Yamada, Osaka University, on the occasion of his 70th birthday.

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