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SYNTHETIC STRATEGIES OF FOSTRIECIN

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Abstract – Fostriecin is a naturally occurring triene-containing phosphate ester, which exhibits a potent and selective PP2A inhibitory activity. Due to its interesting chemical structure and biological activity, strategically unique total syntheses of fostriecin were reported from several groups. An overview of the synthesis and chemistry-based structure-activity relationships of fostriecin is described in this review.

INTRODUCTION

Fostriecin (**1**, CI-920) is a structurally unique antibiotic isolated from *Streptomyces pulveraceus* by a research group at Warner Lambert-Parke Davis in 1983.¹ It displays cytotoxic activity against a broad range of cancerous cell lines such as leukemia, lung cancer, breast cancer, and ovarian cancer *in vitro*, and also antitumor activity against leukemia *in vivo*.² It is proposed that the anticancer activity is derived from perturbation of the mitotic entry checkpoint through potent inhibition of protein phosphatases (PP). Specifically, fostriecin produces the most selective serine/threonine phosphatase 2A (PP2A) inhibition known to date: its IC₅₀ values against PP1 and PP2A are 45 mM and 1.5 nM, respectively (10⁴ times greater selectivity for PP2A versus PP1).³ Due to this unique property, fostriecin is expected to be a novel and potent lead compound for antitumor drugs.⁴ Unfortunately, the clinical trial of fostriecin at the National Institute of Cancer was halted in phase I due to its instability and unpredictable purity.⁴ Therefore, more stable analogues of fostriecin that retain high PP subtype selectivity are in high demand. Considering the importance of protein phosphorylation and dephosphorylation reactions in living organisms, however, fostriecin itself is still a valuable biological tool.

The structural characteristics of fostriecin are as follows: (1) four stereogenic centers including the allylic tertiary hydroxy group at C-8, (2) an α,β -unsaturated lactone at one end, (3) a phosphate ester at C-9, and

(4) (*Z,Z,E*)-triene at the other end. The three-dimensional structure of fostriecin was first determined in 1997 through synthetic and degradation studies by Boger *et al.*⁵ Since then, eight groups including ours have succeeded in total synthesis or formal total synthesis of fostriecin in a short period (from 2001 to 2005). In this review, we survey the synthetic strategies and methodologies utilized in the total synthesis of fostriecin,⁶ and recent chemistry-based structure-activity relationships.

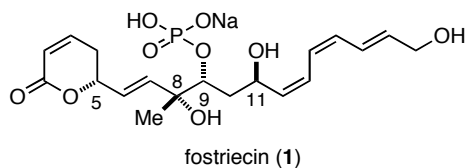


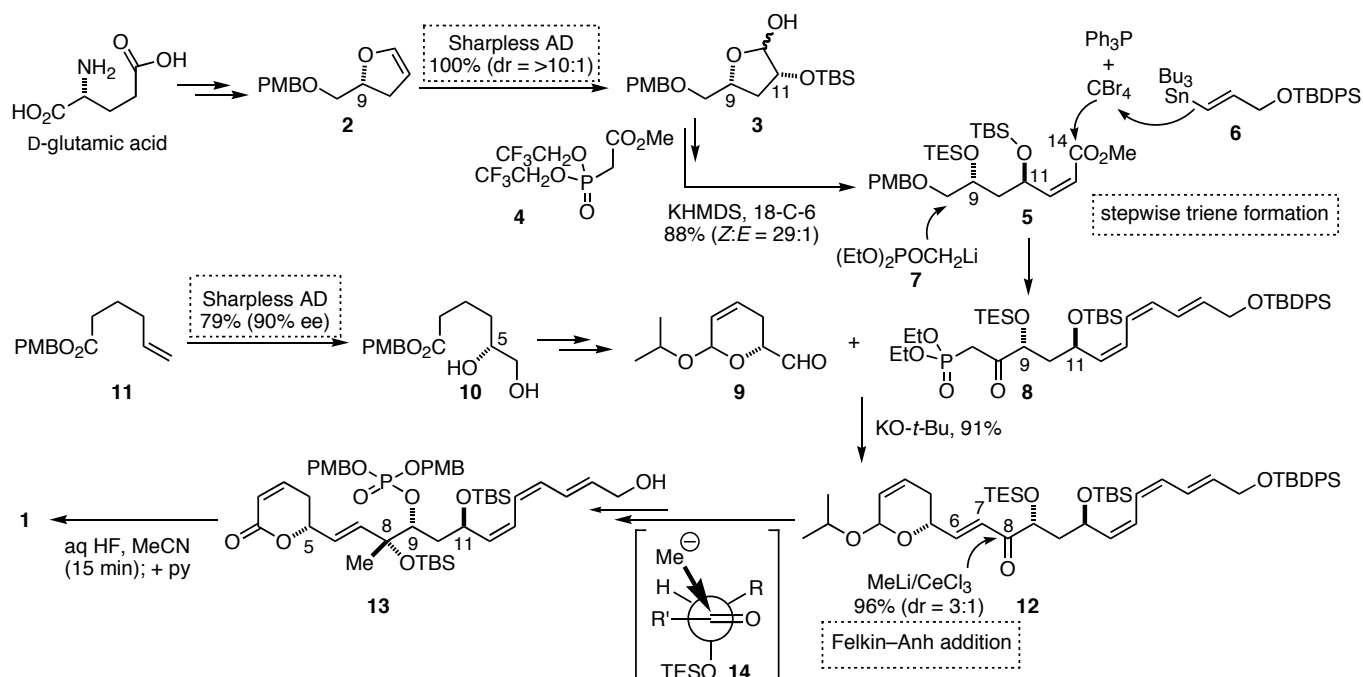
Figure 1

BOGER'S TOTAL SYNTHESIS

The first total synthesis of fostriecin was accomplished by the Boger's group (Scheme 1).⁷ Their synthesis utilized a Wadsworth–Hornor–Emmons reaction to couple two building blocks (**8**) and (**9**), constructing the *E*-olefin between C-6 and C-7. Synthesis of **8** began from D-glutamic acid, which was converted to **2** in several steps. The chirality of D-glutamic acid was eventually transformed to the chirality at C-9 of fostriecin. Sharpless catalytic asymmetric dihydroxylation of **2** using (DHQD)₂AQN⁸ constructed the chiral secondary hydroxy group at C-11 in quantitative yield with >10:1 selectivity. After protection, the resulting lactol was condensed with Still-Gennari phosphonate (**4**)⁹ to afford *Z*-enone (**5**) with excellent selectivity (*Z:E* = 29:1). The *Z,Z,E*-triene was constructed in a stepwise fashion. Thus, after converting the methyl ester to the corresponding aldehyde, Corey-Fuchs homologation (CBr₄, PPh₃),¹⁰ *E*-selective debromination with Bu₃SnH–Pd(PPh₃)₄,¹¹ and Stille coupling with *E*-alkenyl tin **6** in Hünig base as solvent afforded the desired *Z,Z,E*-triene with nearly perfect stereoselectivity. Addition of lithiated phosphonate (**7**) to the corresponding aldehyde at C-8, followed by oxidation with Dess–Martin periodinane produced the key phosphonate (**8**). On the other hand, the coupling partner aldehyde (**9**) was synthesized from (**11**) using Sharpless AD as a key step, providing the chiral center at C-5 with 90% ee.

The key Wadsworth–Hornor–Emmons reaction between **8** and **9** was carried out using KO-*t*-Bu as a base to give the desired enone (**12**) in 91% yield. Next, the chiral tertiary hydroxy group at C-8 was constructed through a Felkin–Anh controlled methylation of **12** through proposed transition state (**14**). Unexpectedly, MeLi proved unsatisfactory for this purpose, giving the undesired 1,4-adduct predominantly. This problem was solved by addition of ketone (**12**) in toluene solution to a MeLi/CeCl₃ slurry in THF. This procedure produced the desired 1,2-adduct (>20:1) in 96% yield with a 3:1 diastereoselectivity. After proper protection of the hydroxyl groups and introduction of the phosphate

under Evans conditions (1. PCl_3 ; 2. PMBOH ; 3. H_2O_2),¹² global deprotection was necessary. The proper choice of the protective groups was essential, especially for such a labile natural product as fostriecin (fostriecin is only stable within the pH range of 5.5–7.5 according to the isolation paper¹). In the last step, the PMB group was removed by treatment of **13** with aqueous HF (5%) in MeCN for 15 min followed by addition of pyridine to remove silyl groups (rt, 4 days).



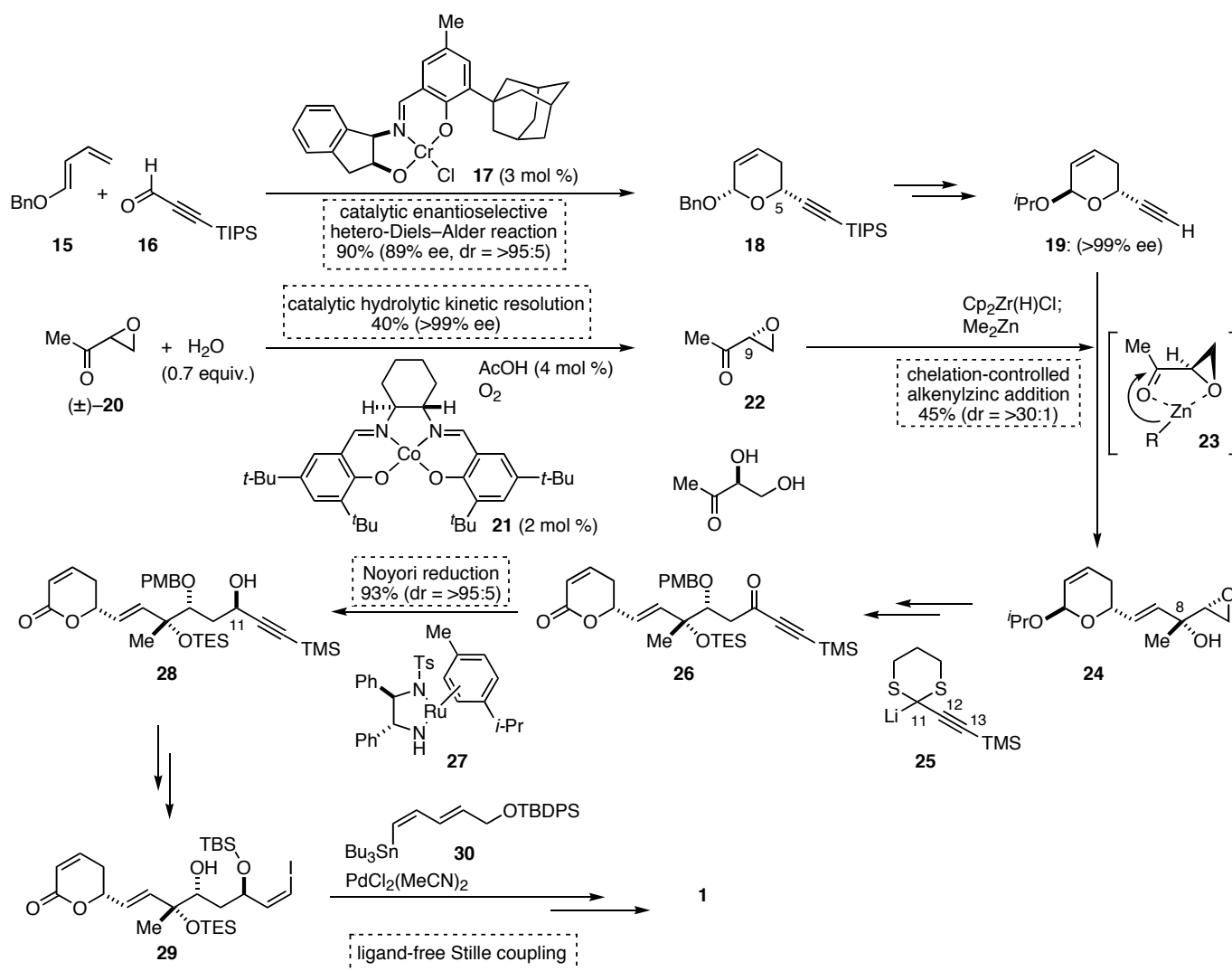
Scheme 1 Boger's Synthesis

JACOBSEN'S TOTAL SYNTHESIS

In the same year as Boger's first total synthesis, Jacobsen's group also succeeded in a total synthesis of fostriecin (Scheme 2).¹³ Their approach integrates three catalytic enantioselective reactions to generate key chiral building blocks containing the trisubstituted stereogenic centers at C-5, 9, and 11. These building blocks were assembled using efficient coupling reactions. For example, the tertiary hydroxy group at C-8 was formed through chelation-controlled vinylzinc addition to ketone (**22**). The unstable triene moiety was constructed at a late stage of the synthesis through Stille coupling of *Z*-alkenyl iodide (**29**) and *E,Z*-dienyl tin compound (**30**).

Jacobsen's group has developed a catalytic enantioselective hetero-Diels–Alder reaction using tridentate Schiff base–Cr complex (**17**).¹⁴ Applying this reaction to diene (**15**) and ynal (**16**) using 3 mol % catalyst, product (**18**) containing the C-5 chiral center was obtained in 90% yield with 89% ee and >95:5 dr. After conversion to a crystalline compound, the enantiomeric purity was enriched to >99% ee by recrystallization. Meanwhile, another enantiomerically pure coupling partner, the epoxy ketone (**22**), was

synthesized through the [(salen)Co] (**21**)-catalyzed hydrolytic kinetic resolution¹⁵ of a racemic **20**. Initially, the yield of this reaction was low due to undesired reductive deactivation of the catalyst, forming inactive [(salen)CO^{II}] precipitate under the normal reaction conditions. This catalyst deactivation appeared to be related to the presence of the ketone functionality in the substrate (**20**). This problem was overcome by conducting the reaction under O₂, giving product (**22**), containing the C-9 chiral center, in 40% yield (max = 50% yield) with >99% ee.



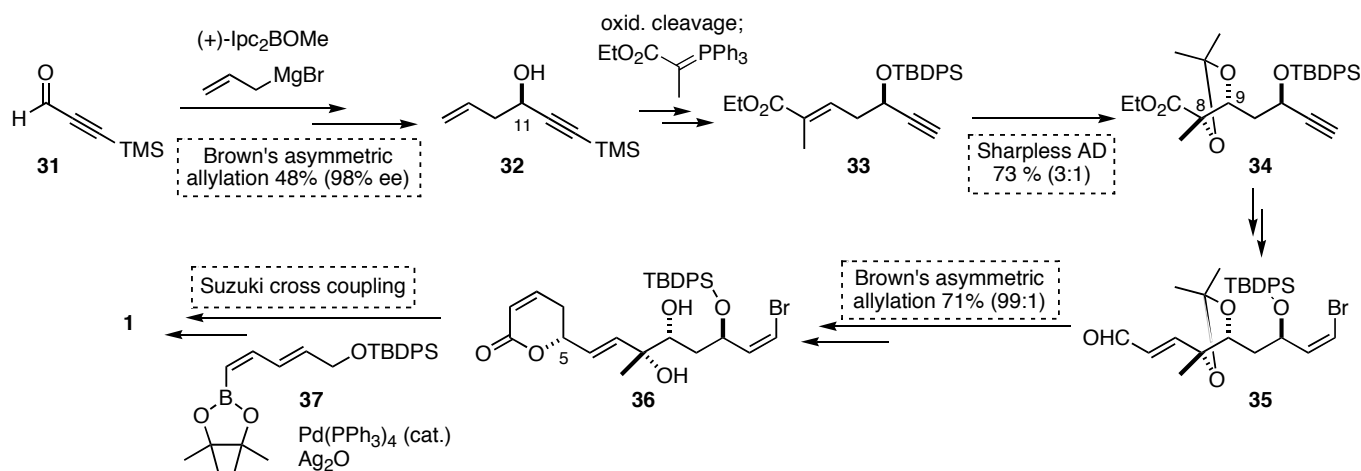
Scheme 2 Jacobsen's Synthesis

To effect the coupling between the two components, **18** was first converted to **19**. Then, terminal vinyl-zinc reagent was produced under Wipf conditions through hydrozirconation and transmetalation.¹⁶ This vinyl zinc was coupled with ketone (**22**) through a possible chelation transition state (**23**), producing the tertiary hydroxy group at C-8 with >30:1 selectivity. The C-11–C-13 unit was introduced to **24** through an epoxide-opening by dithiane-derived anion (**25**). After the ketone at C-11 was deprotected,

Noyori transfer hydrogenation using catalyst (**27**)¹⁷ produced the secondary propargyl alcohol at C-11 with >25:1 selectivity. Protection of the propargyl alcohol, iododesilylation, PMB removal, and *cis*-reduction of the acetylene using diimide provided vinyl iodide (**29**). The “ligand-free” Stille coupling¹⁸ between **29** and *Z,E*-stannane (**30**), followed by introduction of the phosphate at C-9, and global deprotection gave **1**.

REDDY AND FALCK'S TOTAL SYNTHESIS

Reddy and Falck's total synthesis¹⁹ utilized Brown's asymmetric allylation²⁰ of aldehydes (**31**) and (**35**) with allyldiisopinocampheylborane to construct the chiral secondary hydroxy function at C-11 and C-5, respectively, in excellent stereoselectivity (Scheme 3). The contiguous stereogenic centers at C-8 and C-9 were constructed in one step *via* Sharpless catalytic asymmetric dihydroxylation of *E*- α,β -unsaturated ester (**33**) using AD-mix β (from **33** to **34**). After construction of the α,β -unsaturated lactone in **36** using Grubbs ring-closing metathesis,²¹ the triene moiety was built up using Suzuki cross coupling between vinyl bromide (**36**) and vinyl boronate (**37**) in the presence of Ag₂O.²² Trimethylsilylethyl phosphate formation (1. PCl₃, py; 2. TMSCH₂CH₂OH; 3. H₂O₂) and global desilylation using HF•py produced **1**.

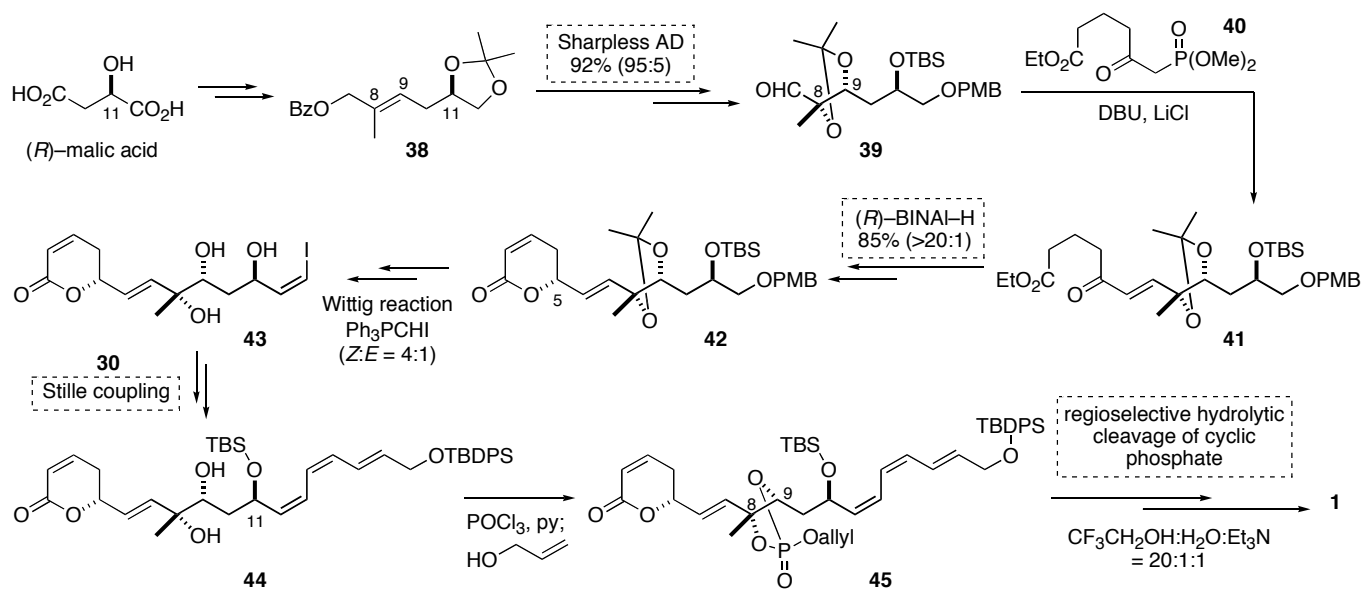


Scheme 3 Reddy and Falck's Synthesis

IMANISHI'S TOTAL SYNTHESIS

Imanishi's total synthesis²³ began with (*R*)-malic acid as a chiral source for the C-11 secondary hydroxy group (Scheme 4). After *E*-selective Wittig olefination, Sharpless asymmetric dihydroxylation of **38** using (DHQD)₂PHAL as a ligand afforded the desired diol with a 95:5 ratio. The stereoselectivity of this reaction using substrate (**38**) was much higher than that of the related reaction in Reddy and Falck's synthesis (Scheme 3, from **33** to **34**). The lactone moiety was constructed using a Hornor–Emmons reaction between **39** and **40** to give **41** under Masamune–Roush conditions and a stereoselective (>20:1)

ketone reduction by (*R*)-BINAL-H²⁴ to form the chiral secondary alcohol at C-5, as key steps. (*S*)-CBS-catalyzed reduction of **41** also gave the desired C-5 epimer, however with lower selectivity (3:1). Wittig homologation of the aldehyde derived from **41** with Ph₃PCHI produced the *Z*-vinyl iodide (**43**) in a 4:1 ratio. Stille coupling of **43** with vinyltin (**30**) under the same conditions used by Jacobsen, followed by protection of the least sterically hindered hydroxy group at C-11 with a TBS group gave diol **44**. A synthetically useful regioselective phosphate formation was developed starting from **44**. Thus, treatment of **44** with POCl₃ and allyl alcohol produced the cyclic phosphate triester (**45**) as a diastereomeric mixture derived from the chirality at the phosphorous atom. Without purification, **45** was then hydrolyzed with CF₃CH₂OH:H₂O:Et₃N = 20:1:1, giving the desired C-9 phosphate as the major isomer [C-9 phosphate:C-8 phosphate:cyclic phosphate diester (allyl ester hydrolysis) = 80 (65% yield):12:8]. It was proposed that this selectivity is derived from a combination of stereoelectronic effects (explaining the selectivity for *endo*-cyclic vs. *exo*-cyclic P–O bond cleavage) and steric effects (explaining the preferential generation of the C-9 phosphate over the C-8 phosphate), as well as hydrogen bonding effects. Finally, reductive allyl phosphate cleavage using a Pd catalyst (originally used in Hatakeyama's synthesis as described below) and desilylation with HF•pyridine gave **1**.



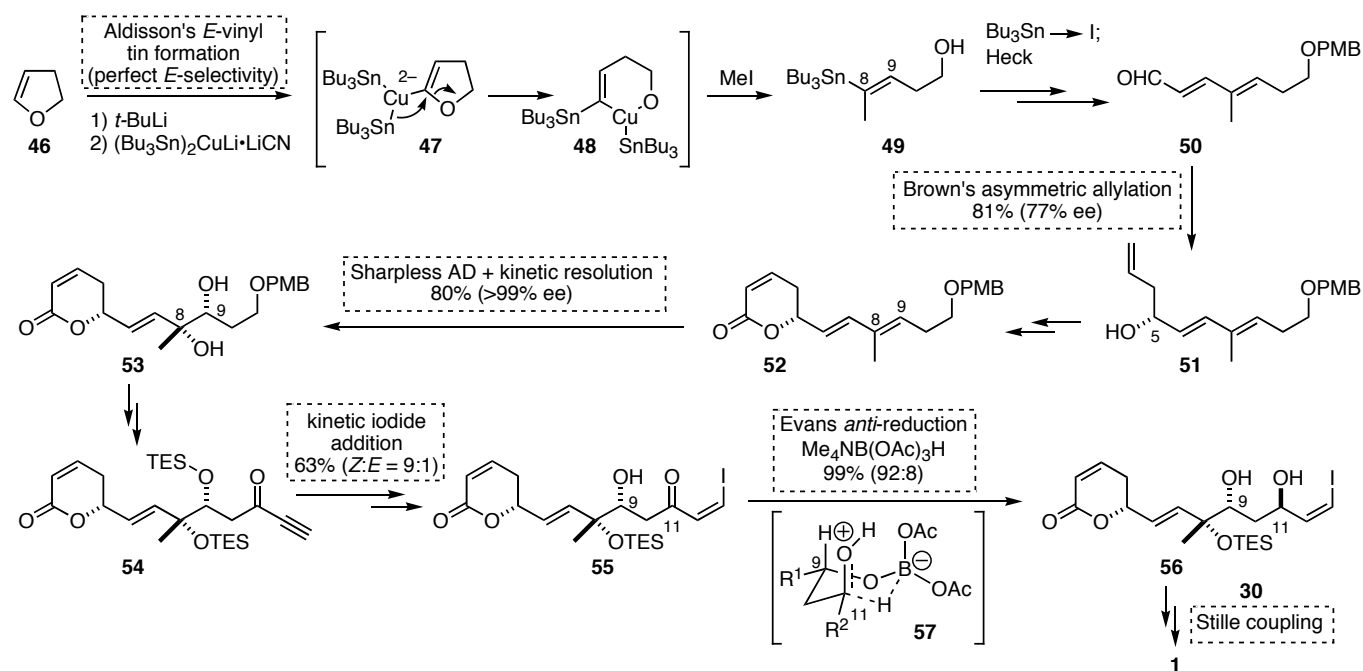
Scheme 4 Imanishi's Synthesis

HATAKEYAMA'S TOTAL SYNTHESIS

Hatakeyama's total synthesis²⁵ started by forming the *E*-alkene between C-8 and C-9 according to Aldisson's procedure (Scheme 5).²⁶ Intramolecular migration of the tributyltin cuprate (**47**) generated from dihydrofuran (**46**), followed by trapping the resulting vinyl cuprate (**48**) with MeI produced vinyltin

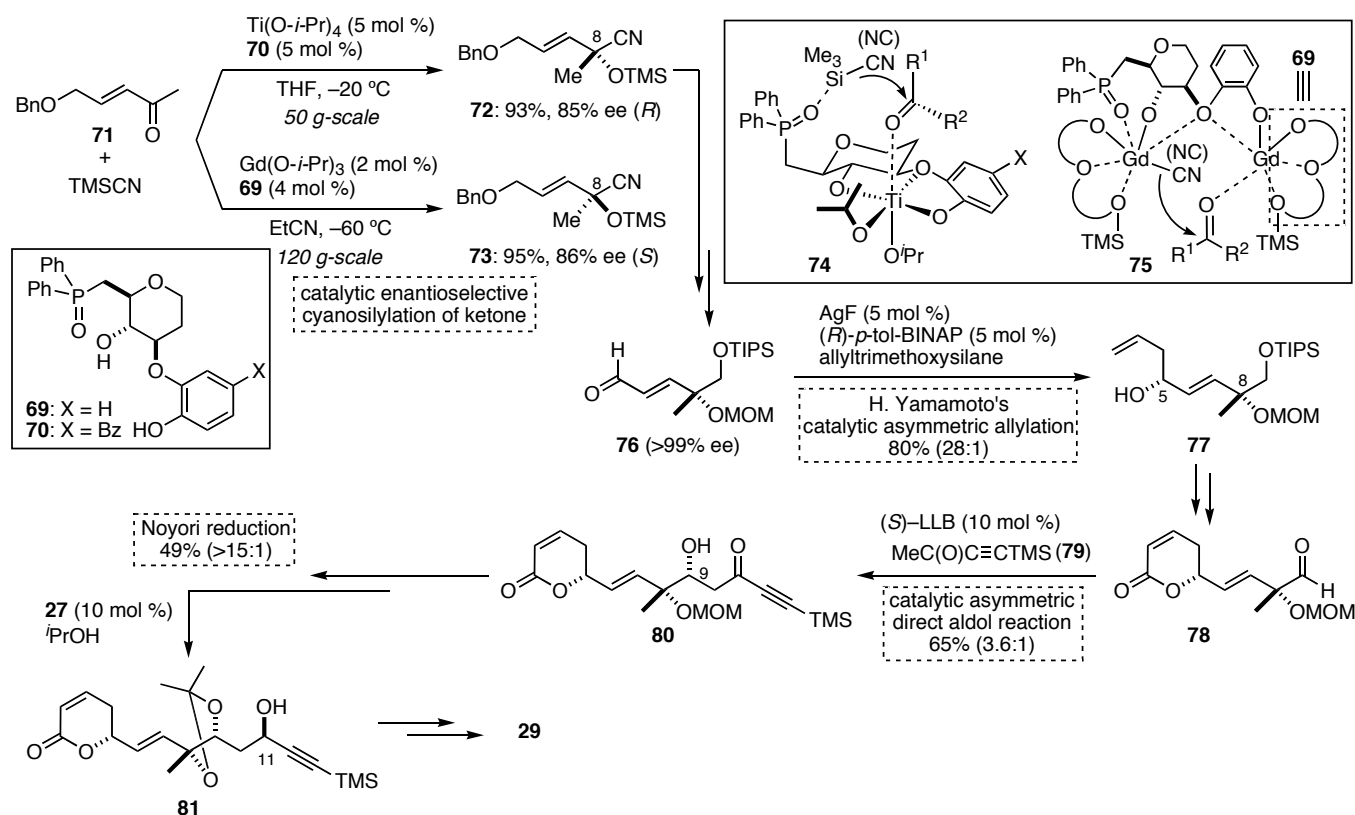
(**49**) with perfect *E*-selectivity. After elongation of the carbon chain via Heck reaction to give aldehyde (**50**), Brown's asymmetric allylation²⁰ was used to produce **51**, containing the C-5 chiral center, in 81% yield with 77% ee. Subsequent acryloylation and ring-closing metathesis using Grubbs catalyst gave lactone (**52**), which was subjected to Sharpless asymmetric dihydroxylation using AD-mix- β .⁸ This reaction produced enantiomerically pure product (**53**) (from starting material with 77% ee). Thus, this Sharpless AD functioned as a kinetic resolution with perfect regio- and diastereoselectivity, constructing the two chiral centers at C-8 and C-9.

After converting **53** to acetylenic ketone (**54**) via Grignard addition, a conjugate addition of NaI in the presence of 1 equiv. AcOH in acetone gave the *Z*-vinyl iodide (**55**). 1,3-Chirality transfer under Evans conditions²⁷ produced the chiral secondary hydroxy function at C-11 through a possible 6-membered transition state (**57**) relying on the minimization of 1,3-diaxial repulsion. Stille coupling between **56** and **30** gave the phosphorylation precursor containing a free hydroxyl group at C-9. The final global deprotection had been problematic in the previous four syntheses, proceeding only with long reaction times, in moderate yield. An allyl group was used for protection of the phosphate moiety in Hatakeyama's synthesis. This protecting group was removed in a clean and high-yielding deallylation under Pd catalysis (10 mol % Pd(PPh₃)₄, HCONH₂). In conjunction with the final global desilylation with HF•py, the deprotection yield was significantly improved to 79%.



Scheme 5 Hatakeyama's Synthesis

Our synthesis began with the catalytic enantioselective cyanosilylation of ketone (**71**) using the Ti-complex (**5 mol %**). The desired (*R*)-product (**72**) was obtained in 94% yield with 71% ee using ligand (**69**), and 93% yield with 85% ee using ligand (**70**). A bifunctional transition state model (**74**) is proposed for this (*R*)-selective reaction: the Ti works as a Lewis acid to activate the ketone while the phosphine oxide functions as a Lewis base to activate TMSCN. The improved enantioselectivity observed using ligand (**70**) is attributed to higher Lewis acidity and more effective shielding of the undesired reaction site (α -side) by the benzoyl group on the catechol. This reaction was performed in a 50 g-scale.



Scheme 7 Shibasaki-Kanai's Synthesis

Enantiomerically pure aldehyde (**76**) was obtained from **72** through 10-step conversion including recrystallization. Lactone (**78**) was synthesized from aldehyde (**76**) using catalytic asymmetric allylation under Yamamoto's conditions³⁵ followed by acryloylation and ring-closing metathesis. Lactone (**78**) was next subjected to a direct catalytic asymmetric aldol reaction with alkynyl ketone (**79**) using LLB³⁶ as a catalyst. Although chemical yield and diastereoselectivity were moderate (65% yield with 3.6:1 selectivity), this is the first example of direct catalytic asymmetric aldol reaction using an alkynyl ketone as a donor. Due to the high acidity of alkynyl ketone α -protons, the retro-aldol reaction is facile and effective promotion of this aldol reaction was difficult. The aldol product was not obtained in synthetically useful yield if a lithium- or zinc enolate of **79** was used as a donor. The use of LLB, having

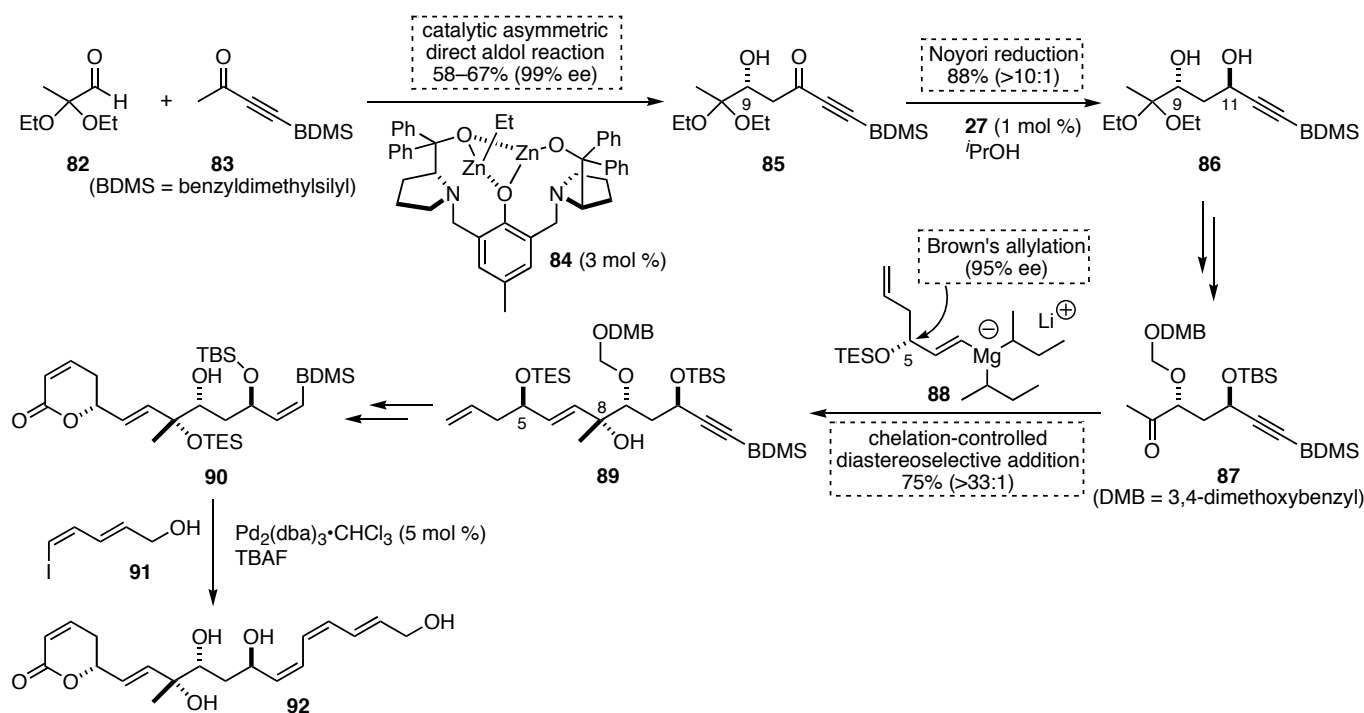
both Lewis acidic and Brønsted basic functionality, is essential for the production of **80** in reasonable yield. From the alkynyl ketone (**80**), Noyori reduction proceeded with excellent selectivity (>15:1). After vinyl iodide formation and protecting group conversion, Jacobsen's intermediate **29** was synthesized. Our synthesis is unique in so far as all the chiral carbons are constructed using catalytic asymmetric reactions. This strategy is especially advantageous for the synthesis of stereoisomeric analogues of fostriecin. If the reactions that set the carbon stereocenters proceed under catalyst-control, any stereoisomer can be synthesized by simply switching the stereoselectivity of the appropriate catalytic asymmetric reactions. Based on this idea, we synthesized 8-*epi*-fostriecin using the (*S*)-selective catalytic enantioselective cyanosilylation of ketone (**71**). Thus, using 5 mol % Gd-complex prepared from Gd(*O-i*-Pr)₃ and **69** in a 1:2 ratio, (*S*)-ketone cyanohydrin (**73**) was produced in 95% yield with 86% ee. The reaction was conducted on a 120 g-scale without difficulty. The proposed transition state model for this (*S*)-selective reaction is depicted as **75**. The active catalyst structure was proposed as a 2:3 complex of Gd and ligand (**69**) based on ESI-MS studies. One of the Gd atoms works as a Lewis acid to activate a substrate ketone, and the other Gd cyanide (or isonitrile) that is generated through transmetalation from TMSCN works as a nucleophile. Intramolecular cyanide transfer should determine the enantioselectivity. From the (*S*)-cyanohydrin (**73**), we have succeeded in synthesizing 8-*epi*-fostriecin following almost the same synthetic route as that used for natural fostriecin. The other three catalytic asymmetric reactions indeed proceeded under catalyst-control. Our synthesis demonstrates the power of asymmetric catalysis, especially in the synthesis of linear molecules such as fostriecin.

TROST'S FORMAL TOTAL SYNTHESIS

After our use of alkynyl ketone (**79**) as a donor in a catalytic asymmetric direct aldol reaction toward the synthesis of fostriecin, the Trost group reported a highly enantioselective direct aldol reaction of alkynyl ketones to α -ketal aldehydes using their dinuclear Zn catalyst (**84**).³⁷ In this reaction, enantioselectivity depended on reaction time: at early conversion the major product exhibited the opposite absolute configuration to that obtained at the end of the reaction. They proposed that a new catalyst containing the aldol product is generated during the reaction, and that this is the highly enantioselective catalyst in this reaction.

Trost's synthesis³⁸ began with the catalytic enantioselective direct aldol reaction between **82** and **83** using 3 mol % of catalyst (**84**) (Scheme 8). The advantage of using a benzyldimethylsilyl (BDMS) alkyne is its applicability toward Pd-catalyzed cross coupling at a late stage of the synthesis, after conversion to an alkenylsilane.³⁹ The aldol product (**85**) containing the C-9 chiral secondary hydroxy group was obtained in reasonable yield with 99% ee. Noyori transfer hydrogenation of **85** produced diol (**86**) with >10:1 selectivity. Selective protection of the diol and deprotection of the ketone produced **87**, a precursor for the

tetrasubstituted carbon construction. The coupling partner (**88**), containing the C-5 stereogenic center, was synthesized using Brown's asymmetric allylation as a key step. Addition of vinyl magnesiate (**88**) to ketone (**87**) produced compound (**89**), containing all the chiral centers of fostriecin, with perfect stereoselectivity at C-8 via chelation control. After diimide reduction of the alkyne, Pd-catalyzed cross coupling between vinyl silane (**90**) and vinyl iodide (**91**) in the presence of TBAF gave the triene **92**, an intermediate in Boger's total synthesis.



Scheme 8 Trost's Synthesis

CHEMISTRY-BASED BIOLOGICAL STUDIES

The structure-activity relationships of fostriecin have not been intensively studied yet. Recently, Boger's group reported a synthesis-based structure-activity relationship of fostriecin for the first time (Figure 2).⁴⁰ The relevance of the α,β -unsaturated lactone and the phosphate to the PP2A inhibitory activity was the focus of their interest. If the α,β -unsaturated lactone was reduced (**93**) or hydrolyzed (**94**), the PP2A inhibitory activity was found to be 200-fold less than that of natural fostriecin (**1**). In control experiments, it was demonstrated that the α,β -unsaturated lactone acts as a good Michael acceptor for conjugate addition of a thiol. Based on these results as well as molecular modeling studies, they proposed that fostriecin might inhibit PP2A through covalent bonding of its α,β -unsaturated lactone to the C269 residue of PP2A. This proposal is supported by the observation by another group that PP2A C269S and C269F mutants are much less sensitive to fostriecin (>10 fold).⁴¹ Surprisingly, compound (**95**), lacking the entire

lactone subunit, still displayed a comparable PP2A inhibitory activity to **93** and **94**. On the other hand, the phosphate proved to be critical to PP inhibition. Thus, compound (**96**), lacking the phosphate moiety, exhibited a 10^5 -fold loss of PP2A inhibitory activity. Although the PP2A inhibitory activity of **96** is very weak, its cytotoxic activity against L1210 cells is relatively high (20 μ M vs. 0.3 μ M for fostriecin). Analogue (**96**) might inhibit cancer cell growth via a mechanism other than PP2A inhibition.

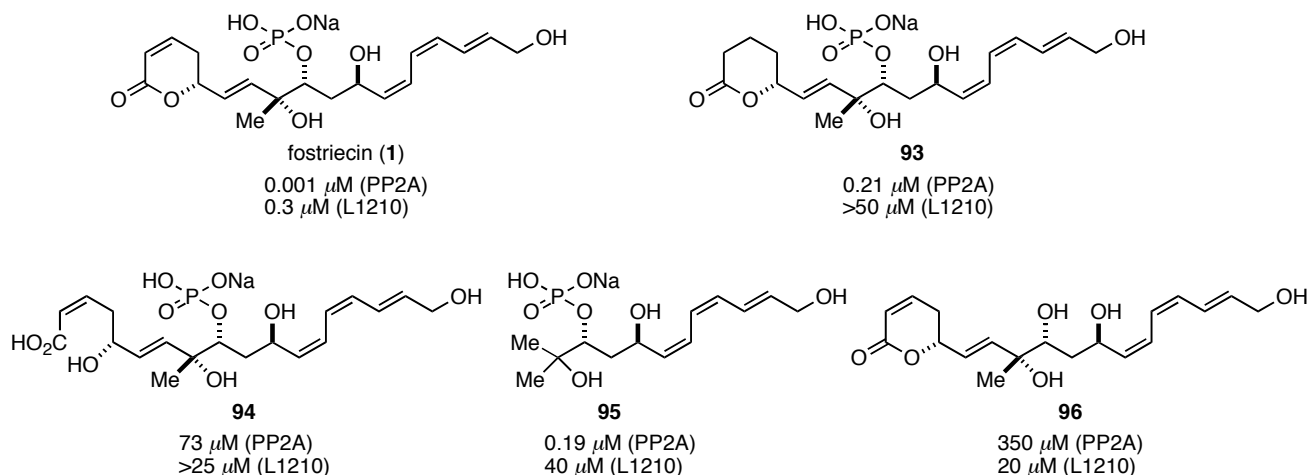


Figure 2 IC_{50} Values for PP2A Inhibition and Cytotoxic Activity against L1210 Cell Lines

There have been no reports concerning the effect of the chirality of fostriecin's four stereogenic centers upon the biologic activity. As described above, our group synthesized 8-*epi*-fostriecin. Our preliminary evaluation of PP2A and PP1 inhibitory activity suggested that 8-*epi*-fostriecin is a slightly weaker, but more selective PP2A inhibitor compared to natural fostriecin. Detailed evaluation of the biological activity of 8-*epi*-fostriecin is ongoing, and will be reported in due course.⁴²

CONCLUSION

Strategies used in the total synthesis of fostriecin are reviewed. Catalytic asymmetric reactions play key roles in the construction of its stereogenic centers. Specifically, Sharpless dihydroxylation and Noyori reduction are quite often utilized due to the broad substrate generality and the high enantioselectivity of these reactions. At the same time, it is clear that catalytic asymmetric carbon-carbon bond-forming reactions are extremely powerful when synthetically useful stereoselectivity is obtained (e.g. the catalytic enantioselective hetero-Diels-Alder reaction of Jacobsen's synthesis and the catalytic enantioselective aldol reaction of Trost's synthesis). Allylation of carbonyl compounds is a useful reaction in the total synthesis of complex molecules. Brown's asymmetric allylation reaction, which uses a stoichiometric amount of chiral reagent, however, is still the most often utilized asymmetric allylation. Our synthesis demonstrated that Yamamoto's Ag-catalyzed asymmetric allylation can produce excellent selectivity

when applied to an α,β -unsaturated aldehyde. Construction of chiral tertiary hydroxy groups depends heavily on intramolecular stereocontrol at present. Our catalytic enantioselective cyanosilylation is advantageous for flexible construction of chiral tertiary alcohols. Intensive research is focused today on the development of asymmetric catalysts that can produce chiral tetrasubstituted carbons.⁴³ Continuing efforts toward new synthetic methodology development should make synthesis of pharmaceutical leads simpler and more flexible.

REFERENCES

1. (a) J. B. Tunac, B. D. Graham, and W. E. Dobson, *J. Antibiot.*, 1983, **36**, 1595. (b) S. S. Stampwala, R. H. Bunge, T. R. Hurley, N. E. Wilmer, A. J. Brankiewicz, C. E. Steinman, T. A. Smitka, and J. C. French, *J. Antibiot.*, 1983, **36**, 1601. (c) G. C. Honkanson and J. C. French, *J. Org. Chem.*, 1985, **50**, 462.
2. Reviews: (a) D. S. Lewy, C. -M. Gauss, D. R. Soenen, and D. L. Boger, *Curr. Med. Chem.*, 2002, **9**, 2005. (b) R. C. Jackson, D. W. Fry, T. J. Boritzki, B. J. Roberts, K. E. Hook, and W. R. Leopold, *Adv. Enzyme Regul.*, 1985, **23**, 193. (c) R. S. De Jong, E. G. E. De Vries, and N. H. Mulder, *Anti-Cancer Drugs.*, 1997, **8**, 413. (d) W. Scheithauer, D. D. V. Hoff, G. M. Clark. J. L. Shillis, and E. F. Elslager, *Eur. J. Clin. Oncol.*, 1986, **22**, 921.
3. T. J. Boritzki, T. S. Wolfard, J. A. Besserer, R. C. Jackson, and D. W. Fry, *Biochem. Pharmacol.*, 1998, **37**, 4063.
4. R. S. De Jong, N. H. Mulder, D. R. A. Uges, D. Th. Sleijfer, F. J. P. Hoppener, H. J. M. Groen, P. H. B. Willemse, W. T. A. Van der Graaf, and E. G. E. De Vries, *Br. J. Cancer*, 1999, **79**, 882.
5. D. L. Boger, M. Hikota, and B. M. Lewis, *J. Org. Chem.*, 1997, **62**, 1748.
6. Synthetic studies of fostiecin are not described in this review. See: (a) G. Just and B. O'Connor, *Tetrahedron Lett.*, 1988, **29**, 753. (b) S. U. Liu, D. F. Huang, H. H. Huang, and L. Huang., *Chin. Chem. Lett.*, 2000, **11**, 957. (c) J. Cossy, F. Pradaux, and S. BouzBouz, *Org. Lett.*, 2001, **3**, 2233. (d) Y. Kiyotsuka, J. Igarashi, and Y. Kobayashi, *Tetrahedron Lett.*, 2002, **43**, 2725. (e) J. A., Marshall and M. P. Bourbeau, *Org. Lett.*, 2003, **5**, 3197. (f) P. V., Ramachandran, H. P. Liu, M. V. R. Reddy, and H. C. Brown, *Org. Lett.*, 2003, **5**, 3755.
7. D. L. Boger, S. Ichikawa, and W. Zhong, *J. Am. Chem. Soc.*, **2001**, *123*, 4161.
8. (a) H. Becker and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 448. (b) H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
9. W. C. Still and C. Gennari *Tetrahedron Lett.*, **1983**, *24*, 4405.
10. E. J. Corey and P. L. Fuchs *Tetrahedron Lett.*, 1972, 3769.
11. J. Uenishi, R. Kawahama, O. Yonemitsu, and J. Tsuji, *J. Org. Chem.*, 1998, **63**, 8965.

12. D. A. Evans, J. R. Gage, and J. L. Leighton, *J. Am. Chem. Soc.*, 1992, **114**, 9434.
13. D. E. Chavez and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2001, **40**, 3667.
14. A. G. Dossetter, T. F. Jamison, E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 1999, **38**, 2398.
15. M. Tokunaga, J. F. Larrow, F. Kakiuchi, and E. N. Jacobsen, *Science*, 1997, **277**, 936.
16. P. Wipf and W. Xu, *Tetrahedron Lett.*, 1994, **35**, 5197.
17. K. Matsumura, S. Hashiguchi, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738.
18. J. K. Stille and B. L. Groh, *J. Am. Chem. Soc.*, 1987, **109**, 813.
19. Y. K. Reddy and J. R. Falck, *Org. Lett.*, **2002**, **4**, 969.
20. H. C. Brown and P. K. Jadhav, *J. Am. Chem. Soc.*, 1983, **105**, 2092.
21. R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413.
22. N. Miyaoura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
23. (a) K. Miyashita, M. Ikejiri, H. Kawasaki, S. Maemura, and T. Imanishi, *Chem. Commun.*, 2002, 742.
(b) K. Miyashita, M. Ikejiri, H. Kawasaki, S. Maemura, and T. Imanishi, *J. Am. Chem. Soc.*, 2003, **125**, 8238.
24. R. Noyori, I. Tamino, Y. Tanimoto, M. Yamada, and M. Nishizawa, *J. Am. Chem. Soc.*, 1984, **106**, 6709.
25. T. Esumi, N. Okamoto, and S. Hatakeyama, *Chem. Commun.*, 2002, 3042.
26. V. Fargeas, P. L. Ménez, I. Berque, J. Aldisson, and A. Panctazi, *Tetrahedron*, 1996, **52**, 6613.
27. D. A. Evans, T. Chapman, and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.
28. Y. -G. Wang and Y. Kobayashi, *Org. Lett.*, 2002, **4**, 4615.
29. (a) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974. (b) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237. (c) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
30. S. Okamoto, T. Shimazaki, Y. Kobayashi, and F. Sato, *Tetrahedron Lett.*, 1987, **28**, 2033.
31. For a recent review, see: M. Kanai, N. Kato, E. Ichikawa, and M. Shibasaki, *Synlett*, 2005, 1491.
32. For (*R*)-selective cyanosilylation of ketones using Ti complex, see: (a) Y. Hamashima, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.*, 2000, **122**, 7412. (b) Y. Hamashima, M. Kanai, and M. Shibasaki, *Tetrahedron Lett.*, 2001, **42**, 691.
33. For (*S*)-selective cyanosilylation of ketones using Gd complex, see: K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 9908.
34. K. Fujii, K. Maki, M. Kanai, and M. Shibasaki, *Org. Lett.*, 2003, **5**, 733.
35. A. Yanagisawa, H. Kageyama, Y. Nakatsuka, K. Asakawa, Y. Matsumoto, and H. Yamamoto,

- Angew. Chem., Int. Ed.*, 1999, **38**, 3701.
36. (a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, and M. Shibasaki, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1871. (b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, and M. Shibasaki, *J. Am. Chem. Soc.*, 1999, **121**, 4168.
37. B. M. Trost, A. Fettes, and B. T. Shireman, *J. Am. Chem. Soc.*, 2004, **126**, 2660.
38. B. M. Trost, M. U. Frederiksen, J. P. N. Papillon, P. E. Harrington, S. Shin, and B. T. Shireman, *J. Am. Chem. Soc.*, 2005, **127**, 3666.
39. B. M. Trost, M. R. Machacek, Z. and T. Ball, *Org. Lett.* 2003, **5**, 1895.
40. S. B. Buck, C. Hardouin, S. Ichikawa, D. R. Soenen, G. -M. Gauss, I. Hwang, M. R. Swingle, K. M. Bonness, R. E. Honkanen, and D. L. Boger, *J. Am. Chem. Soc.*, 2003, **125**, 15694.
41. D. R. H. Evans and J. A. Simon, *FEBS Lett.*, 2001, **498**, 110.
42. K. Maki, R. Motoki, K. Fujii, M. Kanai, T. Kobayashi, S. Tamura, and M. Shibasaki, *J. Am. Chem. Soc.*, in press.
43. For recent examples of advances in this field, see: (a) P. I. Dosa and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 445. (b) S. E. Denmark and Y. Fan, *J. Am. Chem. Soc.*, 2002, **124**, 4233. (c) S.-J. Jeon and P. J. Walsh, *J. Am. Chem. Soc.*, 2003, **125**, 9544. (d) D. J. Ramon and M. Yus, *Tetrahedron*, 1998, **54**, 5651. (e) N. Kato, M. Suzuki, M. Kanai, and M. Shibasaki, *Tetrahedron Lett.*, 2004, **45**, 3153. (f) R. Wada, K. Oisaki, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 8910. (g) K. Oisaki, D. Zhao, Y. Suto, M. Kanai, and M. Shibasaki, *Tetrahedron Lett.*, 2005, **46**, 4325.