

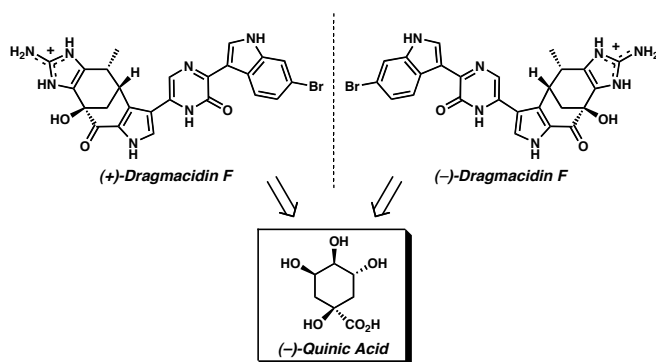
Recent Advances in Enantiodivergent Strategies

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ABSTRACT



Many chiral building blocks, ligands, and catalysts are only readily available in a single absolute configuration. This limitation often prevents expedient access to both enantiomers of a target molecule. A powerful solution to this problem is enantiodivergence, where the stereogenicity from a single enantiomer intermediate is used to produce both antipodes of a desired product.

The demand for single enantiomer compounds has been progressively increasing during the past decade, particularly within the pharmaceutical industry.¹ However, despite the current vogue of asymmetric methodology development, expedient access to both enantiomers of a target compound is not always viable. Many chiral building blocks, ligands, and catalysts (e.g. amino acids, sugars, amines, enzymes) are derived from natural sources, and are often only readily available in one absolute configuration. The other antipode may have a cost premium associated with it, may require an expensive and lengthy synthesis, or, in some cases, may not be available at all. For an asymmetric process, these limitations can occasionally be overcome by employing a more accessible pseudo enantiomer or enantiomer surrogate^{2,3} of the chiral ligand or reagent, such as the

cinchona alkaloid derivatives (DHQD)₂PHAL (**3**) and (DHQ)₂PHAL (**4**) popularized by Sharpless (Figure 1).⁴ However, locating enantiocomplementary relationships between molecules can be extremely challenging, and it is not always feasible.

A considerably more powerful approach in asymmetric synthesis is to exploit the chirality of a single enantiomer intermediate to produce both absolute configurations of a desired product, i.e. an *enantiodivergent* approach. By using a carefully planned route that makes efficient and creative use of symmetry properties and functional groups, an enantiodivergent synthesis can often be achieved.⁵ In this brief review, highlights of some recent examples from the literature will be discussed.

¹ Agranat, I.; Caner, H.; Caldwell, J. *Nat. Rev. Drug Discov.* **2002**, *1*, 753-768.

² For a recent example of a (+)-sparteine mimic, see: Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870-11871.

³ For an example using peptide-based catalysts, see: Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653-11656.

⁴ Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968-1970.

⁵ Ho, T.-I. In *Symmetry: A Basis for Synthesis Design*; Wiley-Interscience: New York, 1995. pp 24-34.

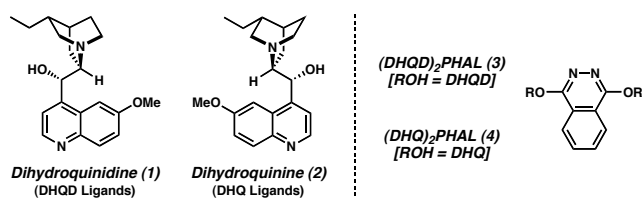
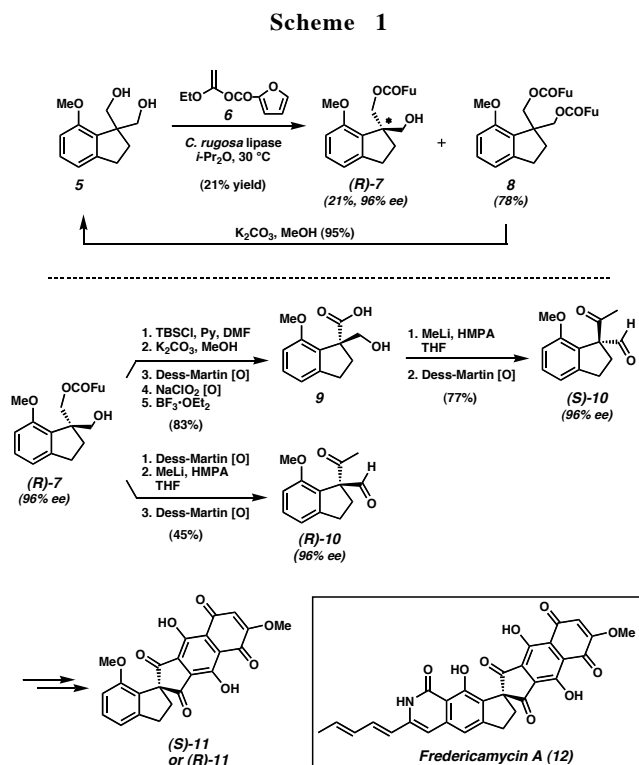


Figure 1. Dihydroquinidine and dihydroquinine ligands.

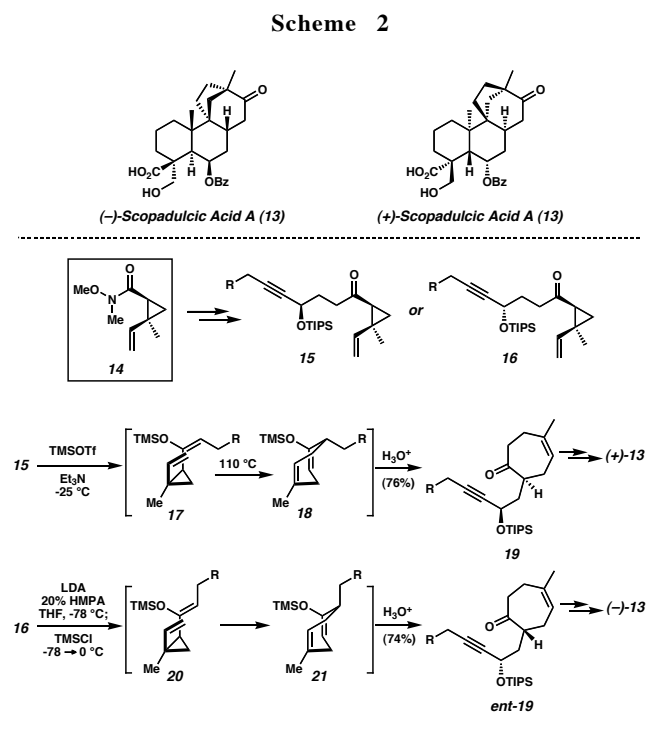
A straightforward demonstration of enantiodivergent synthesis was described by Kita for a model system of the antibiotic fredericamycin A (**12**).⁶ Using lipase catalysis, the authors were able to desymmetrize prochiral diol **5** to set the key benzylic quaternary stereocenter in 96% ee (Scheme 1). Although this transformation furnished a low yield of **7**, the overall mass recovery was excellent and the byproduct diester (**8**) could be recycled. By differentiating the primary alcohol from the furoate of **7** using oxidation and protection sequences, the authors were able to generate both enantiomers of keto-aldehyde **10** with perfect retention of chiral integrity. In turn, **10** was carried on to pentacyclic **11**, which served as a model system for fredericamycin A (**12**).

In a less intuitive approach, the Overman group executed an enantiodivergent synthesis of pharmacologically active scopadulcic acid (**13**) by distinguishing between



⁶ Akai, S.; Tsujino, T.; Fukuda, N.; Iio, K.; Takeda, Y.; Kawaguchi, K.-i.; Naka, T.; Higuchi, K.; Kita, Y. *Org. Lett.* **2001**, *3*, 4015-4018.

diastereomeric transition states for a divinylcyclopropane rearrangement.⁷ Beginning from a single enantiomer of cyclopropane **14**, diastereomeric alkynes **15** and **16** could be assembled in short order (Scheme 2). By optimizing protocols for the highly selective formation of the *E*- (**17**) or *Z*-isomer (**20**) of the TMS enol ethers, excellent yields of corresponding cycloheptenones **19** and *ent*-**19** could be obtained through well-organized boat transition states. Both enantiomers of **19** could then be carried on through Heck cyclizations to ultimately complete the synthesis of the natural product (**13**).



Along similar lines of substrate manipulations, an enantiodivergent route to both antipodes of drarmacidin F was recently reported by Stoltz.⁸ The starting material employed in the synthesis, (–)-quinic acid (**22**), was rapidly converted to bicyclic lactone **23**. Using straightforward functional group manipulations, lactone **23** could be converted into carbonate **25** in a facile manner. Taking advantage of a reductive isomerization reaction,⁹ Stoltz and co-workers were able to selectively generate cyclohexenes **24** and **26** by using the lactone or carbonate functionality present in the starting materials as a leaving group. These cyclohexene products could, in turn, be advanced to diastereomeric pyrrole-appended bicycles (**27** and **28**) and carried on to both enantiomers of drarmacidin F (**29**). Even though the pyrrole-appended bicycles **27** and **28** are not

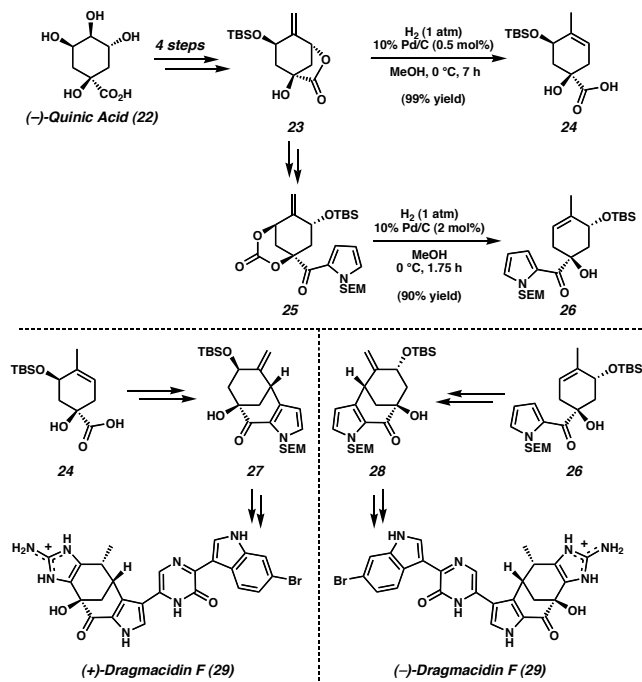
⁷ Fox, M. E.; Li, C.; Marino, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467-5480.

⁸ (a) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552-9553. (b) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5970-5978.

⁹ Caspi, D. D.; Garg, N. K.; Stoltz, B. M. *Org. Lett.* **2005**, *7*, 2513-2516.

enantiomeric, the stereochemistry of the silyl-protected secondary alcohol is not present in the final target (**29**) and was converted into the aminoimidazole functionality later in the synthesis.

Scheme 3



Mascareñas demonstrated an elegant example of enantiodivergence using a specialized chiral auxiliary for a [5 + 2] pyrone-alkene cycloaddition.¹⁰ Heating pyrone **31**, containing a sulfinyl chiral auxiliary, at reflux followed by desulfinylation using Raney Ni¹¹ led to an excellent yield of oxabicyclo[3.2.1]octane (*S*)-**30** (Scheme 4). The stereochemical outcome of this reaction is believed to arise from **32**, where the S-O bond is situated in an *S-trans* conformation with respect to the alkene in order to avoid dipole-dipole interactions with the oxidopyrylium ylide, and the approach on the less hindered face avoids a steric interaction with the bulky *p*-tolyl group.¹² A switch in enantioselectivity was observed, however, when the lone pair on sulfur in **31** was converted into a sulfoximide (NTf) using a two-step procedure employing MSH (*o*-mesitylsulfonylhydroxylamine) and triflic anhydride. Refluxing this sulfoximide in toluene, followed by desulfurization using Raney Ni,¹¹ furnished (*R*)-**30**. The incorporation of the NTf group at sulfur reversed the diastereofacial selectivity of the cycloaddition by altering the conformational preference of the sulfinyl moiety; using

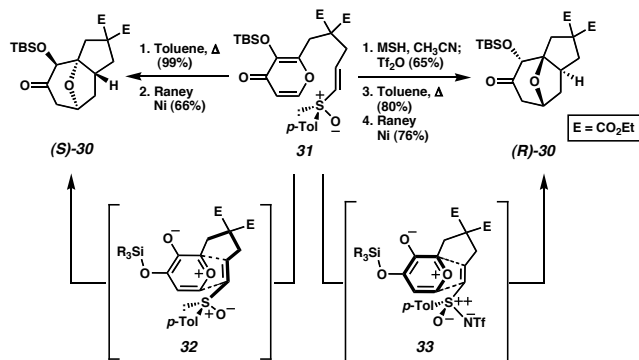
¹⁰ López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2001**, *3*, 623-625.

¹¹ The need to use an excess of Raney Ni caused concomitant reduction of the enone system. See ref 10.

¹² For a theoretical rationalization, see: López, F.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **2003**, *68*, 9780-9786.

this auxiliary, the reaction is believed to occur via intermediate **33**.¹² The S-N bond is positioned in an *S-trans* arrangement with respect to the alkene in order to avoid dipole-dipole interactions with the oxidopyrylium ylide. As in the case of **32**, the facial preference of the cycloaddition avoids steric interactions with the bulky *p*-tolyl group.

Scheme 4



Not only is enantiodivergence an effective synthetic strategy, but its broad definition also encompasses the fascinating area of enantiodivergent catalysis. In this scenario, the asymmetry from a single absolute configuration of a *ligand or reagent* can be used to generate either enantiomer of a desired product. This concept, commonly referred to as dual or reversible enantioselective control, can be implemented in a number of ways. While reports of this effect have been largely empirical, altering the metal, employing additives, or modifying reaction parameters such as solvent or temperature are techniques that have been used successfully.^{13,14} Although the mechanistic rationale for the observed switch in selectivity is often not well understood, this general phenomenon has certainly captured the attention of organic chemists.

Sibi has reported a highly selective transformation using enantioselective tandem radical addition/trapping chemistry.¹⁵ Reaction of oxazolidinone **34** with *t*-BuI and bisoxazoline **35** using MgI₂ as a Lewis acid provided 97% ee of the desired product (**36**, Scheme 5) in excellent yield. However, by simply switching the Lewis acid from MgI₂ to Cu(OTf)₂, a 96% ee of the desired product was produced in the opposite absolute configuration (*ent*-**36**).¹⁶ Sibi's work has shown that the initial addition of the nucleophilic

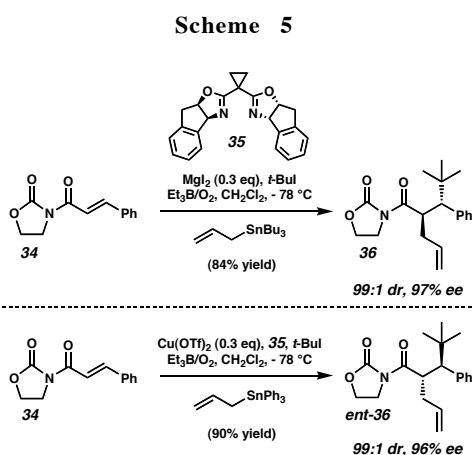
¹³ Changes in reaction conditions can also lead to switches in diastereoselectivity. For recent examples, see: (a) Huang, Z.-Z.; Kang, Y.-B.; Zhou, J.; Ye, M.-C.; Tang, Y. *Org. Lett.* **2004**, *6*, 1677-1679. (b) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752-1755.

¹⁴ For reviews, see: (a) Zanoni, G.; Castronovo, F.; Franzini, M.; Vidari, G.; Giannini, E. *Chem. Soc. Rev.* **2003**, *32*, 115-129. (b) Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719-755. (c) Kim, Y. H. *Acc. Chem. Res.* **2001**, *34*, 955-962.

¹⁵ Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472-9473.

¹⁶ A completely temperature-dependent reversal of stereochemistry has also been reported, see: Sibi, M. P.; Gorikunti, U.; Liu, M. *Tetrahedron* **2002**, *58*, 8357-8363.

t-Bu radical is the origin of enantiodiscrimination, and that subsequent trapping with the allyltin reagent occurs in an anti manner regardless of the Lewis acid employed (Mg or Cu). A working model for Mg-catalyzed additions has been proposed,¹⁷ but the formation of the enantiomeric product with the Cu Lewis acids suggests an alternate binding arrangement.



Wagner and Mioskowski have recently reported an impressive chiral switch that was observed during studies of a kinetic resolution of amines.¹⁸ Using **38** as an *N*-acylating agent, reaction of acetamide **37** in THF or toluene led to modest enantiomeric excesses of acetamide **39** (entries 1-2, Table 1). However, the use of a more polar solvent such as DMPU (entry 3), or the addition of *n*-Oct₃NMeCl salt (entries 4-6), led to not only a significant increase in selectivity factors, but also a complete switch from *R* to *S*-enantiomers of **39**. There is some evidence that supports a change in mechanism; namely, strong

Table 1. Influence of salt and solvent on enantioselectivity.

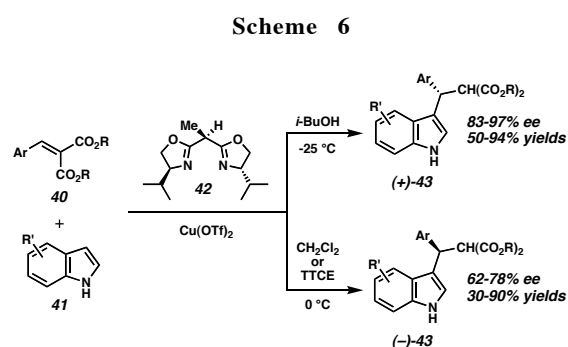
entry	solvent	salt	temperature (°C)	<i>s</i>	ee% 39
1	toluene	-	23	6.6	58 (<i>R</i>)
2	THF	-	23	3.6	42 (<i>R</i>)
3	DMPU	-	23	30.3	84 (<i>S</i>)
4	THF	<i>n</i> -Oct ₃ NMeCl (0.01 M)	23		30 (<i>S</i>)
5	THF	<i>n</i> -Oct ₃ NMeCl (1 M)	23		90 (<i>S</i>)
6	THF	<i>n</i> -Oct ₃ NMeCl (1 M)	-20	115	94 (<i>S</i>)

¹⁷ Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163-171.

¹⁸ (a) Arseniyadis, S.; Subhash, P. V.; Valleix, A.; Mathew, S. P.; Blackmond, D. G.; Wagner, A.; Mioskowski, C. *J. Am. Chem. Soc.* **2005**, *127*, 6138-6139. (b) Arseniyadis, S.; Valleix, A.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3314-3317.

hydrogen bonding with the acidic sulfonamide of **38** guides the attack of amine **37** in polar solvents (e.g., DMPU), whereas only steric interactions dictate selectivity in nonpolar solvents (e.g., THF or toluene). Kinetic profiles obtained by reaction calorimetry reveal that the addition of the *n*-Oct₃NMeCl salt significantly increases the reactivity of acylating reagent **38** toward the *S*-enantiomer of **37**, whereas only a moderate change in reactivity is observed toward the *R*-enantiomer.

Yang has described a Friedel-Crafts reaction of arylidene malonates (**40**) with indoles (**41**) using a bisoxazoline (**42**)-Cu catalyst framework.¹⁹ By switching from *i*-BuOH to halogenated solvents (dichloromethane or 1,1,2,2-tetrachloroethane), a complete shift in enantioselectivity was observed (Scheme 6). Mechanistic details are uncertain; however, it is postulated that the enantioselectivity in different solvents originates from the coordination geometry of the copper center.



Enantiodivergent synthesis and catalysis are methods that are well suited to circumvent the problems associated with access to both enantiomers of a desired molecule if only one antipode of a necessary reagent is available. Enantiodivergence is not generally considered to be an intuitive concept, but it can produce excellent results when it is used successfully. Presently, enantiodivergent synthesis has a distinct advantage over enantiodivergent catalysis since it far more conducive to rational design elements such as retrosynthesis. On the other hand, the field of enantiodivergent catalysis is still largely in its infancy, and many of the reports in this area have been the product of empirical observations. There is still enormous potential for enantiodivergent catalysis as an enhanced understanding of how to effect an enantioselective switch is acquired.

¹⁹ Zhou, J.; Tang, Y. *Chem. Commun.* **2004**, *4*, 432-433.