Design of Novel Titanium(IV) Schiff Base Complexes for Catalytic, Enantioselective Aldol Additions to Aldehydes

Thesis by

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The person to whom I am most grateful is my wife Lori. Without her support and companionship this project would never have been completed.

I would also like to express my appreciation to the Carriera group and my father for the insightful discussions that we have had.

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Abstract

A novel chiral Schiff base ligand derived from 2-amino-2'-hydroxy-1,1'-binaphthyl and 3-bromo-5-*t*butylsalicylaldehyde has been prepared. When binding the chiral ligand to titanium(IV) with 3,5-di-*t*butylsalicylic acid, the complex formed functions as an efficient catalyst for the Mukaiyama aldol addition reaction. Using only 1-2 mol% of the catalyst, silyl ketene acetal additions to aldehydes were carried out in good chemical yield and in excellent levels of enantioselectivity. Unsaturated aldehydes tended to produce adducts in 95-99% ee, while aliphatic aldehyde products were typically obtained in 94-95% ee.

The methodology was extended to include dienolate additions to aldehydes by utilizing silyl enol ethers of dioxinones. Optimal selectivities in the dienolate additions were obtained with unsaturated, unbranched aldehydes (90-94% ee). Aromatic and aliphatic aldehydes were usually isolated in 80-84% ee. Since many of the adducts were crystalline solids, the optical purity was enhanced by recrystallization. By heating the dioxinone adduct in the presence of an alcohol or amine, the products were transformed to more useful β-ketoesters or β-ketoamides.

To demonstrate the utility of the methodology developed, the asymmetric addition reactions have been applied to the total synthesis of (*R*)-epinephrine and macrolactin A. After carrying out an enantioselective acetate addition to 3,4-dimethoxybenzaldehyde in 95% ee, the β-hydroxyester was converted to the amino-alcohol by a Hoffman rearrangement and a reduction. After deprotecting the catechol, (*R*)-epinephrine was obtained in 5 steps overall. Dienolate additions to β-stannylpropenal were employed to prepare two key fragments of macrolactin A. The convergent route involved stitching together three fragments with a Stille coupling and a Horner-Emmons olefination. Macrocyclization was accomplished by an intramolecular Stille coupling.

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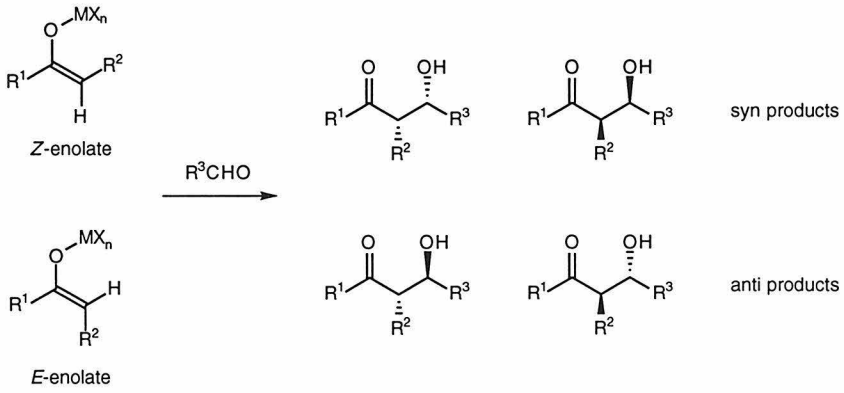
Chapter 1

Introduction

One of the most powerful reactions available to the organic chemist is the aldol addition reaction.[1] In a single transformation a carbon-carbon bond is formed between an enolized carbonyl compound and an aldehyde or ketone with concomitant introduction of a stereocenter in the form of an alcohol. Reactions involving substituted enolates (substituent R^2 at the α-carbon) incorporate a second stereocenter as well (Scheme 1).

Scheme 1



Nature carries out the equivalent of an aldol reaction in a two step sequence involving a Claisen addition and a reduction. After adding an enolized acetate to a thioester (Scheme 2), the resulting ketone is stereoselectively reduced. Iteration of this process results in the biosynthesis of skipped 1,3–polyol natural products such as the amphotericins.[2]

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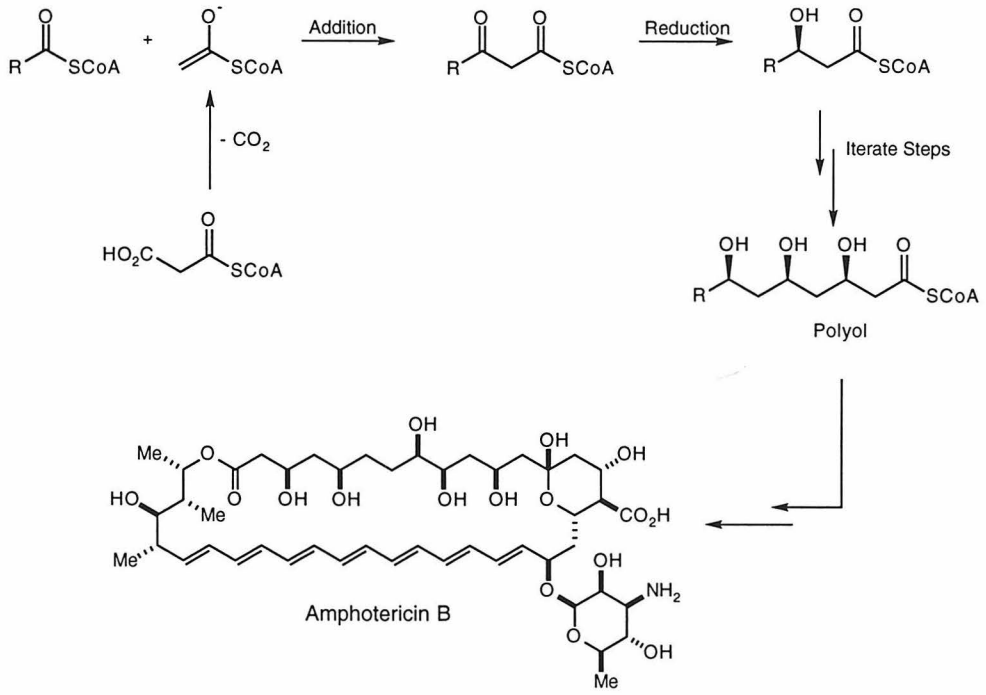
1. (a) Heathcock, C. H. In *Asymmetric Synthesis, Vol 3*; Morrison, J. D., Ed.; Academic Press: New York, **1984**; Chapter 2. (b) Heathcock, C. H. In *Comprehensive Organic Synthesis, Vol II*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, **1991**; Chapter 1.6.

2. (a) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, **1984**; 351-404. (b) Norcross, R. D.;

Scheme 2



The strategies that have been developed for the asymmetric synthesis of aldol fragments may be classified in two general categories. The first involves the use of stoichiometric auxiliaries or promoters, while the second employs substoichiometric quantities of chiral catalysts. The early efforts to carry out asymmetric aldols utilized chiral auxiliaries (moieties present in both the substrates and products) appended to enolates.[3] For the propionate aldol addition, which simultaneously sets two stereocenters, the alcohol and the adjacent methyl group, Evans and co-workers[4] exploited chiral acyloxazolidinones

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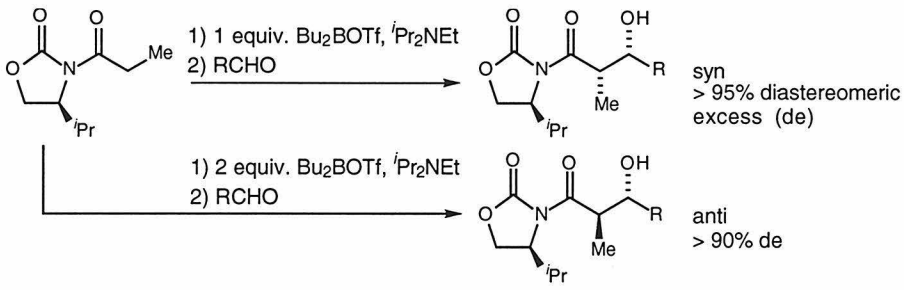
Patterson, I. *Chem. Rev.* **1995**, *95*, 2041. (c) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.

3. For review see: Braun, M.; Sacha, H. *J. Prakt. Chem.* **1993**, *335*, 653.

4. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Sjogren, E. B.; Weber, E. A.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39.

as chiral enolate precursors. Subjecting the α-substituted chiral acyloxazolidinone to base (diisopropylethylamine) and a Lewis acid (dibutylboron triflate) results in exclusive formation of the *Z*-borylenolate. This enolate was found to undergo highly diastereoselective additions to aldehydes as shown in Scheme 3. The preparation of members in complementary stereochemical families can be accomplished in two ways. The choice of one of the two possible antipodes of the acyloxazolidinone determines the absolute stereochemistry of the aldol products. In addition, Heathcock and co–workers have demonstrated that changing the nature and stoichiometry of the Lewis acid can deliver either the diastereomeric syn or anti aldol adducts.[5]

Scheme 3



In contrast to the additions involving propionates, those employing the unsubstituted acetylated oxazolidinones give a stereorandom mixture of products (eq 1). Other chiral auxiliaries have been developed to carry out acetate aldol additions to aldehydes with a greater degree of stereocontrol. However, it is important to note that in all cases the levels of induction of the acetate aldol additions are poorer than the corresponding propionate additions. Some of the best systems have been reported by Braun and Oppolzer which utilize chiral enolates derived from mandelic acid and camphor, respectively

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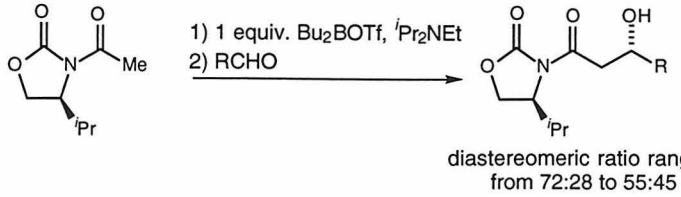
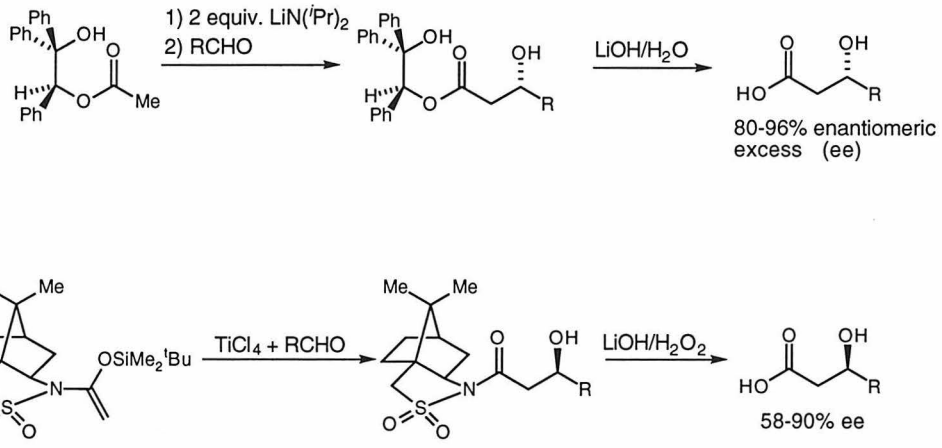
5. Danda, H.; Hansen, M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173.



(1)

(Scheme 4).[6,7] While these auxiliary based systems can afford adducts with useful diastereoselectivity, the methodology tends to be limited in substrate scope. Moreover, inherent in these chiral auxiliary based methods is the fact that a subsequent step must be used to remove the controlling group.

Scheme 4



An alternative approach which does not necessitate derivatization of the products employs chiral Lewis acids in stoichiometric amounts to promote additions to aldehydes . Corey and co-workers[8] have shown that chiral Lewis acid **1** (eq 2) and

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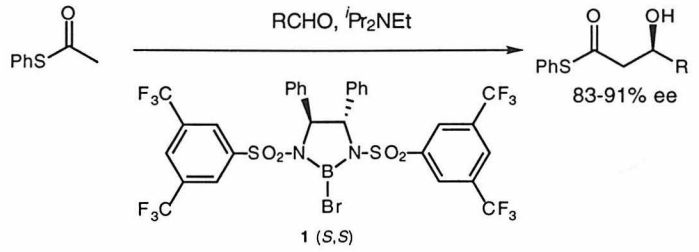
6. (a) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031. (b) Braun, M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 24. (c) Devant, R.; Mahler, U.; Braun, M. *Chem. Ber.* **1988**, *121*, 397. (d) Mahler, U.; Devant, R. M.; Braun, M. *Chem. Ber.* **1988**, *121*, 2035.

7. Oppolozer, W.; Starkemann, C. *Tetrahedron Lett.* **1992**, *33*, 2439.

8. (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (b) Corey, E. J.; Lee, D-H. *Tetrahedron Lett.* **1993**, *34*, 1737.

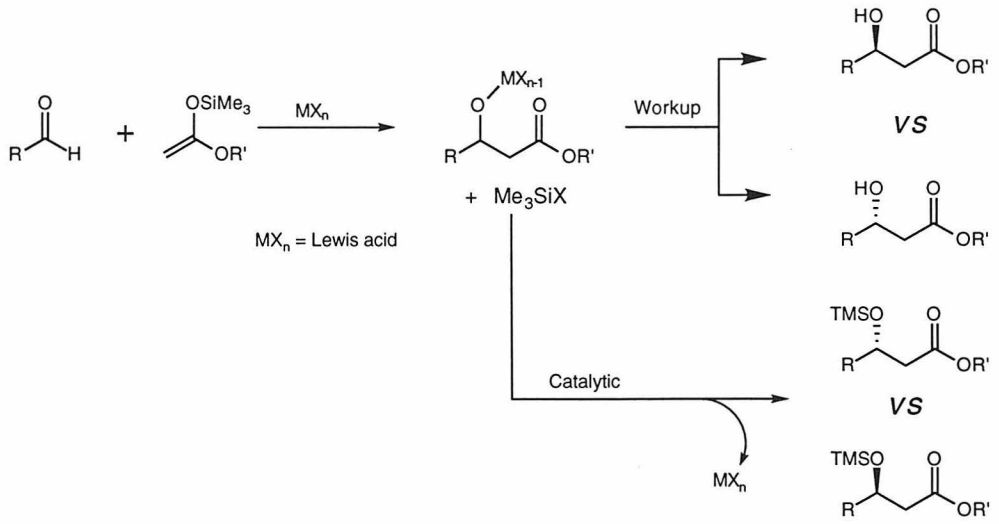
diisopropylethylamine generate a chiral enolate which undergoes enantioselective additions to aldehydes. This system and the auxiliary methods still have the disadvantage of requiring stoichiometric quantities of the chiral promoter which may be expensive and experimentally difficult to handle.[9]



(2)

The second general approach to control the asymmetric aldol addition reaction entails the use of chiral Lewis acids as catalysts (Scheme 5). This stems from the discovery by Mukaiyama and co-workers[10] that silyl enol ethers attack aldehydes in the

Scheme 5



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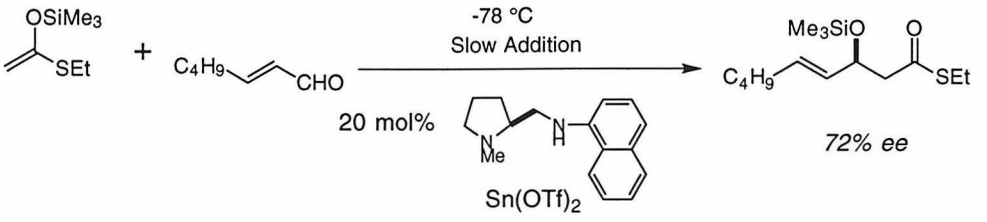
9. Other Lewis acid promoters: (c) Masamune, S.; Sato, T.; Kim, B. M.; Wollman, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (d) Duthaler, R. O.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Angew. Chem.* **1989**, *101*, 490.

10. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

presence of a Lewis acid. The initial reports employed achiral Lewis acids (BF_3•OEt_2, $TiCl_4$, $MgBr_2$ and $SnCl_4$) to activate the aldehyde towards addition. Subsequently, the incorporation of chiral ligands led to promoters which gave aldol adducts in high levels of induction (eq 3).[11] Further modification of the promoter procedure allowed the system to be catalytic. For example, slow addition of the substrates to the reaction mixture and the use of polar donor solvent propionitrile at low temperature –78 °C allowed the promoter to be used in catalytic quantities (10–20 mol%).[12]



(3)

This pioneering work by Mukaiyama and co–workers encouraged others to design novel chiral Lewis acids (Figure 1) to mediate the aldol addition reaction of silyl ketene acetals.[13] In addition to the Sn(II) Lewis acids, complexes derived from boron and Ti(IV)

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11. Kobayshi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247.

12. Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *Tetrahedron: Asymm.* **1991**, *2*, 635.

13. (a) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. (b) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077. (c) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761. (d) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (e) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729. (f) Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927. (g) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (h) Furuta, K.; Maruyama, T.; Yamamoto, H. *Synlett* **1991**, 439. (i) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (j) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276.

have given promising leads. While these catalysts may operate more efficiently than auxiliary or promoter based systems by using substoichiometric levels of chiral

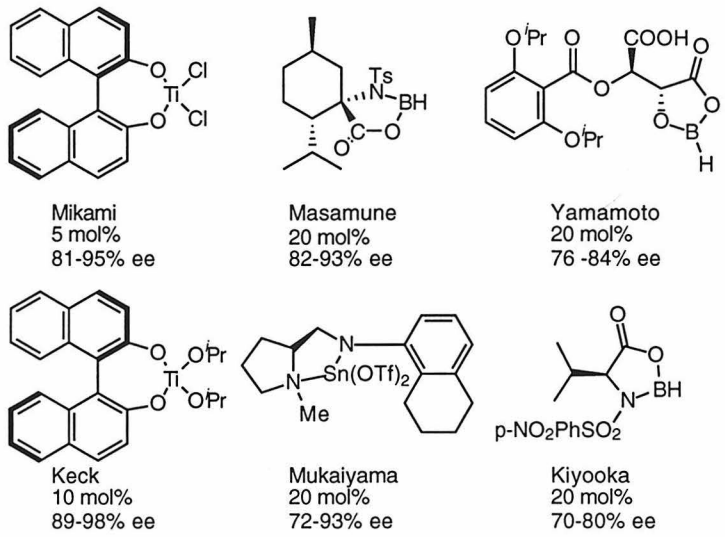


Figure 1. Enantioselective aldol catalysts.

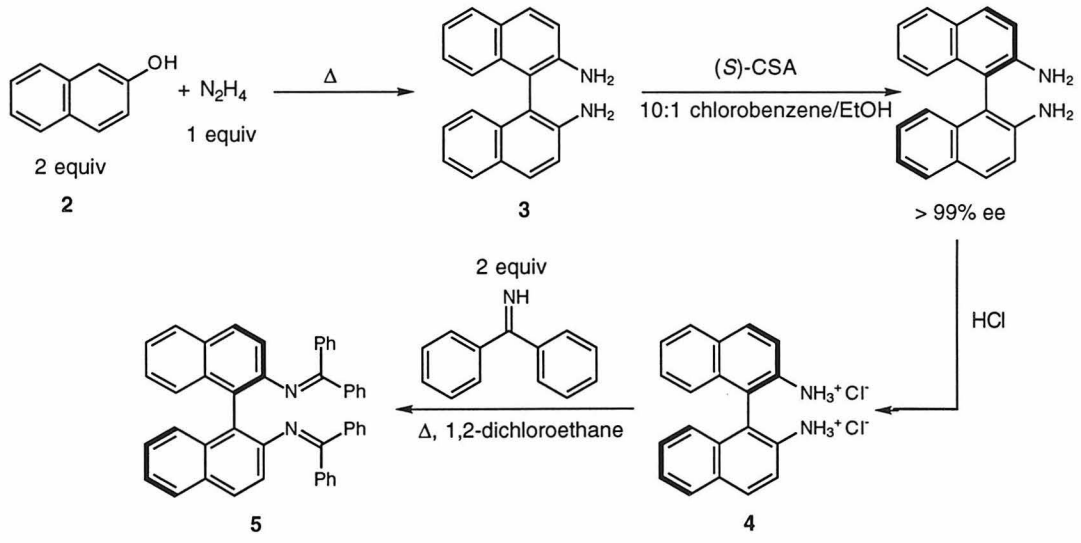
material, generally the selectivities were not significantly better than the comparable chiral auxiliary approaches. In addition, they require high catalyst loadings (10 to 20 mol%), reactions at low temperature and cumbersome experimental protocols (slow addition of substrates). For a catalytic method to be competitive in performance with the auxiliary methods, it would be desirable to employ minimal catalyst loadings (< 5 mol%), to obtain products in synthetically useful levels of enantioselectivity (> 90% ee) and chemical yield, for it to be compatible with a broad range of substrates, and to be able to execute the procedure easily.

Chapter 2

Preliminary Investigations in Chiral Ligand Design

The initial design of ligands was based on a family of C_2-symmetric ligands derived from a 2,2'-diamino-1,1'-binaphthyl (**3**) core.[14] We envisioned forming complexes with Sn(II), Mg(II), Zn(II), or Yb(III) in order to obtain weak chiral Lewis acids with which to catalyze the Mukaiyama aldol addition. It was hypothesized that the metathesis process necessary for turnover might be easier to execute with these metals as opposed to metals at higher oxidation states. Bidentate bis-imine ligands (**5** in Scheme 6) were easily prepared from (+) or (–)–2,2'-diamino-1,1'-binaphthyl.[15] It was expected that using ligands possessing weakly basic imine nitrogens would generate complxes with sufficient Lewis

Scheme 6

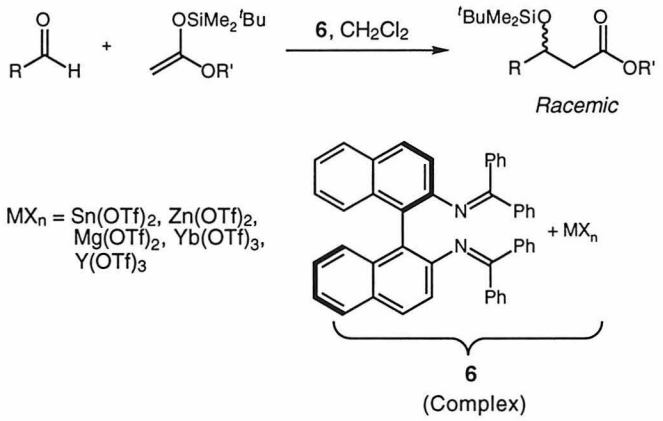


14. For a review on binaphthyl ligands and their application in organic synthesis see: Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503.

15. Yamamoto, Y.; Sakamoto, A.; Nishioka, T.; Oda, J. *J. Org. Chem.* **1991**, *56*, 1112.

acidity to mediate aldol additions. The binaphthyl diamine (**3**) was prepared by heating 2 equiv of β-naphthol (**2**) with 1 equiv of hydrazine hydrate at 180 °C for 48 h (Scheme 6).[15] The racemic binaphthyl was isolated in 36% yield and subsequently resolved with (*R*)– or (*S*)–camphorsulfonic acid in 10:1 chlorobenzene/ethanol.[16] The camphorsulfonate salt was treated with pyridine to give the optically pure diamine following recrystallization. Treatment of the diamine with gaseous HCl in CH_2Cl_2 provided the bis-hydrochloride salt, **4**, which upon heating with diphenyl ketimine[17] produced the desired bis-imine ligand **5**.[18]

The complexes (**6**) derived from ligand **5** were formed from treatment of a suspension of $Sn(OTf)_2$, $Zn(OTf)_2$, $Mg(OTf)_2$, $Yb(OTf)_3$, or $Y(OTf)_3$ with solutions of the ligand **5** (eq 4). We speculated that ligand **5** was binding with the metals on the basis of the dissolution of the metal salts in the presence of ligands. The aldol addition reactions were carried out by adding aldehyde to a solution of the metal complexes (20 mol%) at -78



(4)

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16. Miyano, S.; Nawa, M.; Mori, A.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2171.

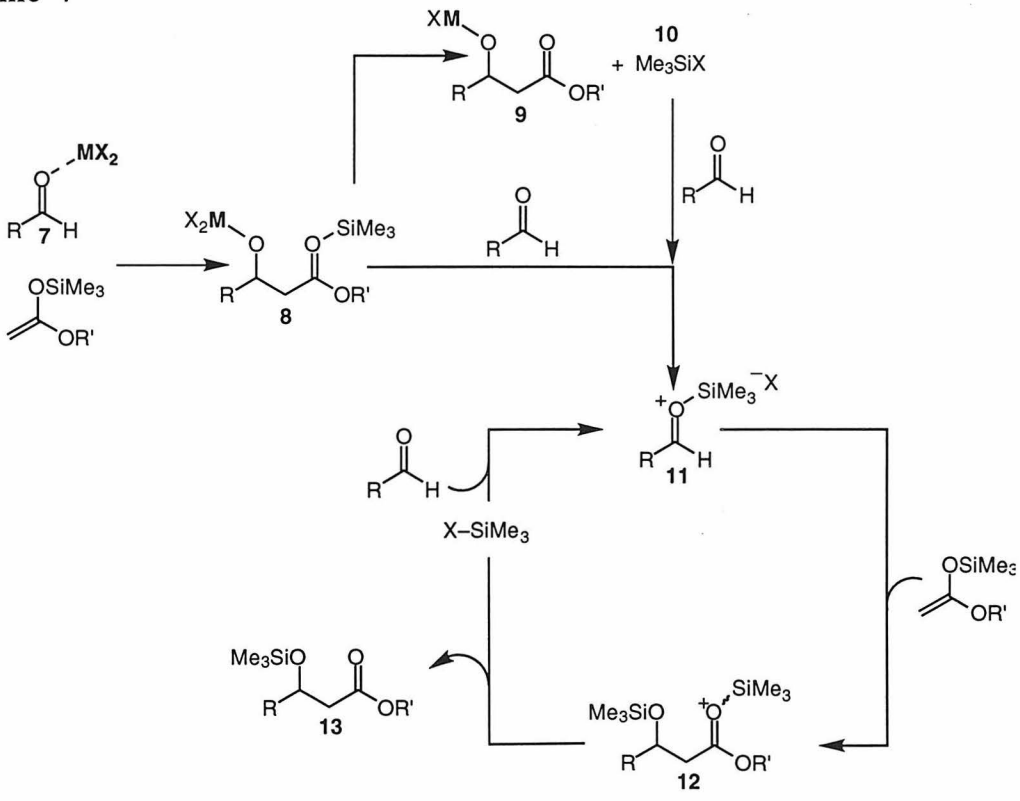
17. Pickard, P.; Tolbert, T. In *Organic Syntheses*, *Coll. Vol. 5*, Wiley: New York, **1973**, 520.

18. O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

°C followed by the silyl ketene acetal. The reactions were allowed to gradually warm to 0 °C over several hours. The isolated adducts were desilylated (Bu_4NF) and converted to the corresponding alcohol in order to facilitate determination of the enantioselectity. Conversion to the corresponding (*S*)–MTPA esters ((*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate)[19] gave diastereomeric mixtures of products which could be analyzed by ^1H NMR spectroscopy. In all cases examined, the products were isolated as racemic mixtures. We speculated that the lack of enantioselectivity in the products arose from a competing achiral reaction involving a silicon catalyzed pathway.

Since all of the metals employed included weakly coordinating anions (such as triflate (OTf), iodine, or perchlorate), we suspected that the corersponding trimethylsilyl species might be generated *in situ* and function as an aldol catalyst (Scheme 7). A possible

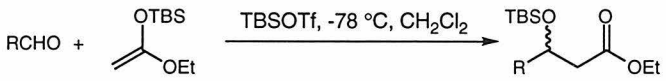
Scheme 7



19. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

mechanism to account for these results. The dissolved metal complex coordinates and activates an aldehyde (**7**) to attack by a silyl ketene acetal (Scheme 7). If silylation of the metal bound aldolate (**8**) is slow then the trimethyl silyl group could either be trapped by the weakly coordinating anion to form **10**, or by a free aldehyde to form **11** in solution. If the trimethylsilyl species is trapped by an anion of the metal, it may then silylate an aldehyde in solution to form **11**. In both of these scenarios, the trimethylsilyl–activated aldehyde (**11**) may then be attacked by a silyl ketene acetal. Following the addition, the same trimethylsilyl species (Me_3SiX) could be reformed to propagate the silyl catalyzed process. It should be noted that such a process involving achiral silyl catalysis provides racemic products (**13**).

The viability of these mechanistic pathways rest on the ability of a silyl species to catalyze aldol addition reactions. To explore this, *tert*–butyldimethylsilyl triflate (TBSOTf) was first investigated as an aldol catalyst. As expected TBSOTf was found to be capable of catalyzing the Mukaiyama aldol reaction in dichloromethane with benzaldehyde (-78 °C, 30 min) and hydrocinnamaldehyde (23 °C, 2 hours) (eq 5).[20] This result demonstrates the ability of a trialkylsilyl triflate to function as a powerful Lewis acid catalyst of the Mukaiyama aldol.



(5)

We then were interested in determining whether the trialkylsilyl group is transferred intramolecularly or intermolecularly in the catalytic Mukaiyama aldol addition reaction. In a metal mediated process there are at least two modes for turnover and silylation of the metal aldolate as shown in Scheme 8. The Lewis acid may be regenerated by either direct

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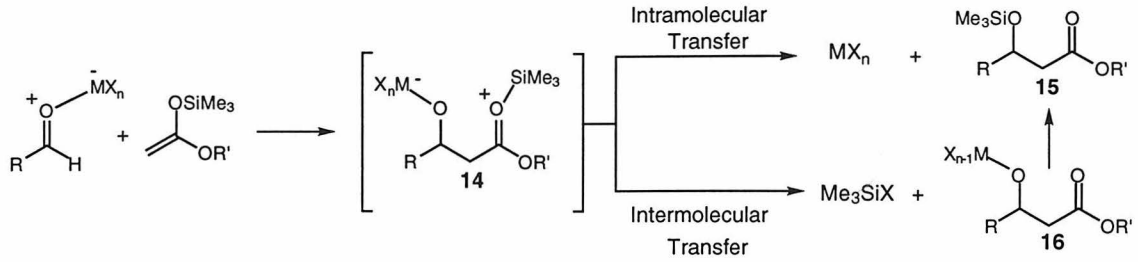
20. Precedence for $Me_3Si(OTf)$ catalysis in silyl enol ether addition to acetals: Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.

transfer of the trialkylsilyl group (**14** → **15**) in an intramolecualr fashion or through a stepwise intermolecular silylation of the aldolate (**14** → **16** → **15**).

Scheme 8



To elucidate the nature of the silyl–transfer mechanism, crossover experiments were carried out using labeled silyl ketene acetals. Two silyl ketene acetals of similar steric and electronic demands **17** and **18** were prepared (Scheme 9).[21] Two experimental results may be anticipated. Intramolecular silyl transfer in **14** should afford aldol adducts **22** and **23** (Scheme 9); in contrast, intermolecular silyl transfer should give a mixture of **21**, **22**, **23**, and **24**. A 1:1 mixture of **17** and **18** (0.50 equiv of each) and benzaldehyde were allowed to react in dichloromethane at -78 °C in the presence of 20 mol% Lewis acid ($Yb(OTf)_3$, $Sn(OTf)_2$, $Zn(OTf)_2$, $LiClO_4$, or $BF_3{\bullet}OEt_2$). In all cases examined, the reaction mixtures were maintained at -78 °C and were complete in less than 30 min. Upon work-up, the product composition was subsequently determined by GC chromatography. As shown in Scheme 9 (R = Ph), the aldol addition reactions employing $Yb(OTf)_3$, $Sn(OTf)_2$, $Zn(OTf)_2$, and $LiClO_4$ reproducibly gave 1–3 % alcohol product along with a mixture of silyl ethers **21**, **22**, **23**, and **24**. The $BF_3{\bullet}OEt_2$ aldol addition reaction gave 20% alcohol product (equivalent to the amount of Lewis acid employed) along with a mixture of the four silyl-scrambled products.

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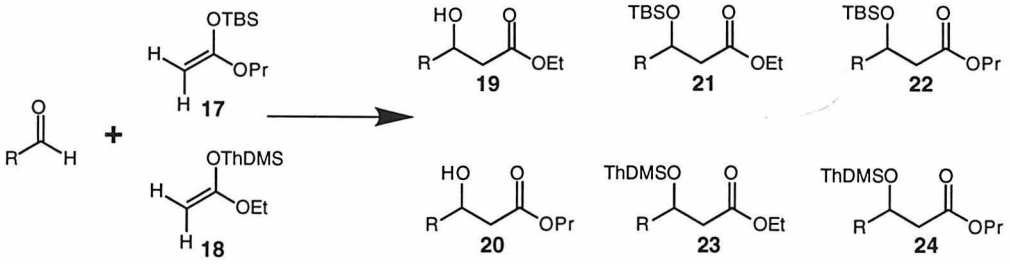
21. (a) Colvin, E. W., *Silicon in Organic Synthesis*, Butterworths: London, **1981**. (b) Weber, W. P., *Silicon Reagents for Organic Synthesis*, Springer-Verlag: Berlin, **1983**.

The analogous reactions were conducted with hydrocinnamaldehyde, (R = CH_2CH_2Ph, Scheme 9). With the exception of BF_3•OEt_2, the aldol addition reactions

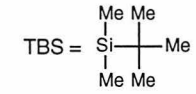
Scheme 9

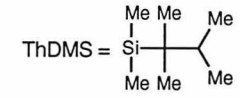


R = Ph	%(19+20)	21 : 22 : 23 : 24
$Yb(OTf)_3$	3	1 : 1.0 : 1.0 : 0.98
$Sn(OTf)_2$	2	1 : 1.1 : 0.88 : 0.93
$Zn(OTf)_2$	1	1 : 1.0 : 1.2 : 1.2
$LiClO_4$	1	1 : 1.1 : 1.1 : 1.1
BF_3•OEt_2	20	1 : 1.0 : 1.9 : 2.0

R = $(CH_2)_2Ph$	%(19+20)	21 : 22 : 23 : 24
$Yb(OTf)_3$	6	1 : 0.82 : 0.98 : 0.98
$Sn(OTf)_2$	0	1 : 0.81 : 0.94 : 0.86
$Zn(OTf)_2$	4	1 : 0.93 : 0.95 : 0.93
$LiClO_4$	1	1 : 1.1 : 0.97 : 0.87
BF_3•OEt_2	20	–

Yields based on GC analysis





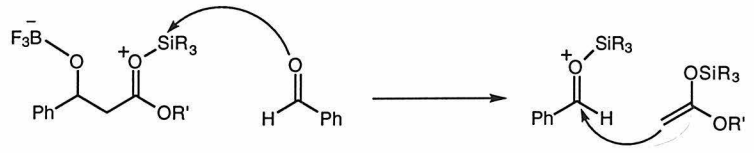
were markedly slower, proceeding in 6-8 hours at 23 °C. In the $Sn(OTf)_2$–mediated reaction, alcohol product was observed initially and was consumed during the course of the reaction giving only a mixture of **21**, **22**, **23**, and **24**. In the $Yb(OTf)_3$, $Zn(OTf)_2$, and $LiClO_4$ mediated reactions, all four products resulting from trialkylsilyl group scrambling are observed along with 1-6% alcohol product. With BF_3•OEt_2, the aldol addition reaction of hydrocinnamaldehyde exclusively afforded alcohol product in proportion to the amount

of Lewis acid present in the reaction mixture; no silylated aldolates **21**, **22**, **23**, or **24** were observed. In order to rule out catalysis by adventitious Bronsted acid, the aldol addition reactions with both aldehydes were repeated in the presence of 20 mol% 2,6-di-*tert*-butyl-4-methylpyridine; in all cases, identical results were obtained. Additional control experiments indicated that the silylated aldol adducts (**21**, **22**, **23**, **24**) were stable at 23 °C in the presence of 20 mol% Lewis acid, showing no evidence of scrambling over 8 hours. Moreover, 1:1 mixtures of the silyl ketene acetals in CH_2Cl_2 did not show evidence of silyl scrambling at 23 °C in the presence of any of the Lewis acids investigated. These results along with the observation of silyl–scrambled products for both aldehydes tested exclude a reaction mechanism in which the metal catalyst is regenerated via intramolecular silylation (**14** $\rightarrow$ **15**, Scheme 8).

The presence of alcohol product after the reaction has reached completion indicates that the metal aldolates were not silylated at a rate comparable to that observed for silyl product formation. In such a case, the Lewis acidic silicon species generated (**14** or R_3SiX) may subsequently catalyze the Mukaiyama aldol. In this regard, it was mentioned earlier that TBSOTf catalyzed the aldol addition reactions of benzaldehyde and hydrocinnamaldehyde. We have conducted experiments to determine the relative rate of silylation of the metal aldolate for Lewis acids which yielded >1% alcohol product.

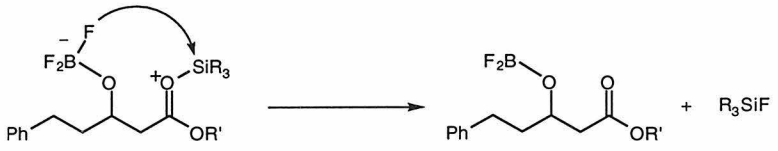
The aldolate formed in the $Sn(OTf)_2$ mediated aldol addition to benzaldehyde was consumed in 1.5 hours upon warming the reaction mixture to 23 °C. In contrast, the alcohol formed in the $Yb(OTf)_3$ and $BF_3{\bullet}OEt_2$ mediated reactions persisted after 16 hours at 23 °C. These carbinols (derived from $Yb(OTf)_3$, $BF_3{\bullet}OEt_2$) were not observed to silylate at 23 °C with added TBSOTf (20 mol%) and 2,6-di-*tert*-butyl-4-methylpyridine (20 mol%). Thus, the metal aldolates derived from $Yb(OTf)_3$, $Sn(OTf)_2$ and $BF_3{\bullet}OEt_2$ silylate at slower rates than that observed for silyl product formation at -78 °C. This suggests that these metal mediated reactions with benzaldehyde are metal initiated and subsequently silicon catalyzed. For the reaction involving $BF_3{\bullet}OEt_2$, transfer of the trialkylsilyl group to

one of the fluoride anions would not generate a silylating agent. Consequently, the metal initiated silyl catalyzed pathway must result from the trialkylsilyl group transferring directly to a free aldehyde (eq 6).



(6)

Analogous experiments were conducted with hydrocinnamaldehyde. The alcohol products produced in the $Yb(OTf)_3$ and $Zn(OTf)_2$ mediated reactions were observed throughout the course of the reaction and were not consumed upon prolonged stirring at 23 °C. Moreover, the addition of TBSOTf (20 mol %) and 2,6-di-*tert*-butyl-4-methylpyridine (20 mol%) did not lead to alcohol silylation. Thus, silicon catalysis is implicated in the aldol additions mediated by $Yb(OTf)_3$ and $Zn(OTf)_2$. For the $Sn(OTf)_2$ mediated reaction, the fact that alcohol formation is observed initially and is subsequently consumed during the course of the reaction (as mentioned earlier) does not permit the silicon and metal catalyzed processes to be differentiated. Since the benzaldehyde-derived Sn(II)–aldolate silylates at 23 °C in 1.5 hours, the $Sn(OTf)_2$ mediated addition to hydrocinnamaldehyde may proceed through either metal or silicon catalysis, or both. The exclusive formation of alcohol products in the $BF_3{\bullet}OEt_2$ mediated reaction at 0 °C may be rationalized by assuming that the silylating species (eq 7) is quenched at a faster rate by fluoride than it can silylate hydrocinnamaldehyde.



(7)

The observations from the crossover experiments and related control experiments exclude a metal catalyzed aldol addition from operating as the sole reaction pathway. For

metals that have weakly coordinating anions, a trialkylsilyl species is generated (Scheme 7, **8** → **10**) which can compete with the metal as a catalyst. For metals lacking weakly coordinating anions (BF_3•OEt_2) a direct transfer of the trialkylsilyl group to an aldehyde may be invoked as a competing pathway (eq 6), especially for the more nucleophilic aromatic aldehydes. Overall, for any system designed to catalyze the Mukaiyama aldol two issues must be dealt with. First, steps must be taken to prevent silicon catalysis from competing with the metal mediated process, and second, the system must account for a mechanism which allows for the silylation of the metal bound aldolate.

Experimental Section

General Procedures

All non–aqueous reactions were performed using oven dried glassware under an atmosphere of dry nitrogen. All chemicals were purchased from Aldrich and used without further purification unless otherwise noted. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Acetonitrile, butyl alcohol, chloroform, diisopropylamine, diisopropylethylamine, dichloromethane, 1,2-dichloroethane, 2,6-lutidine, pyridine, and triethylamine were distilled from calcium hydride prior to use. Methanol was distilled from magnesium turnings prior to use. Toluene, mesitylene, and benzene were distilled from sodium prior to use. *N*,*N*-Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were dried over 4 Å sieves prior to usage. Spectroscopy grade chloroform (with 1.0% ethanol) was used for all optical rotation data. Chromatographic purification of products was accomplished using forced flow chromatography on Baker 7024-R silica gel according to the method of Still.[22] Analytical gas-liquid chromatography was carried out on a Hewlett Packard 5890 chromatograph, equipped with a split mode capillary injection system and a flame ionization detector, using a 25 m x 0.2 mm HP-5 fused silica capillary column wall coated with phenyl methyl silicone. Helium was used as the carrier gas. Analytical high performance liquid chromatography was performed on a Hewlett Packard 1050 quaternary pumping system, equipped with a variable UV-visible wavelength detector using a 250 x 4.6 mm Chiralcel OD column. NMR spectra were recorded on a General Electric QE Plus operating at 300 and 75 MHz for ^1H and ^{13}C, respectively, and are referenced to internal solvent signals. Data for ^1H are reported as follows: chemical shift (δ in ppm), integration, multiplicity (s singlet, bs broad singlet, d doublet, t triplet, q quartet, dd doublet of

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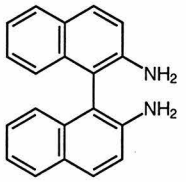
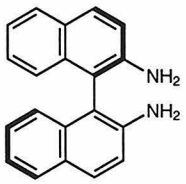
22. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

doublets, ddd doublet of doublet of doublets, m multiplet) and coupling constant (*J* in Hz). IR spectra were recorded on a Perkin-Elmer 1600 Series spectrometer. Optical rotations were determined on a JASCO DIP-181 polarimeter operating at the sodium D line or the mercury 365 nm line and are reported as follows: $[\alpha]_D^{23}$, or $[\alpha]_{365}^{23}$, concentration (g/100 mL), and solvent. High-resolution mass spectrometry was performed by the Midwest Center for Mass Spectrometry at the University of Nebraska and at the University of Washington at St. Louis, with partial support by the National Science Foundation, Biology Division (Grant No. DIR9017262).

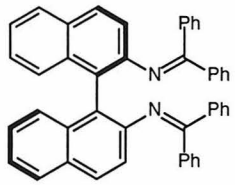


Preparation of (±)-3.[15] A glass sleeve with 10 g of β-naphthol (69 mmol) and 2.3 mL of hydrazine hydrate (46 mmol) was placed in a stainless steel bomb. The sealed system was heated to 180 °C for 48 hours after which time the reaction vessel was cooled to 23 °C and the contents were removed. The yellow viscous material was triturated with 1:1 hexane/EtOAc to crystallize the product. The product was isolated from the hexane/EtOAc solution by filtration and was washed three times with 15 mL of 1:1 hexane/EtOAc. The powder was recrystallized from ethanol and dried under vacuum to give a total of 3.5 g (36%) of needle shaped crystals.



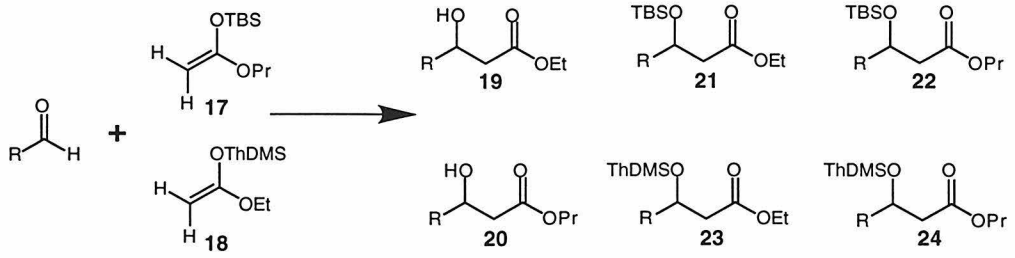
Resolution of (±)-3 to afford (+)-(*R*)-3.[16] A suspension of 6.1 g of (±)-**3** (2.1 mmol) in 175 mL of chlorobenzene was heated to 70 °C with stirring to dissolve diamine **3**. The brown solution was allowed to slowly cool with continued stirring. When the

temperature of the solution reached 50 °C 5.2 g of (S)-camphorsulfonic acid (2.2 mmol) was slowly added in 35 mL of absolute ethanol. As the last of the camphorsulfonic acid was being added a white precipitate began forming in the dark stirred solution. The solution was allowed to continue cooling with stirring until reaching 23 °C, at which point the suspension was allowed to stand for 12 hours. The precipitate was isolated by filtration through filter paper (crystals were too fine to be collected with a frit) and was washed three times with 15 mL of chlorobenzene. The solid was dissolved in 35 mL of pyridine and was poured onto 290 mL of warm water. A precipitate formed which was collected by filtration. The solid was dissolved in 120 mL of 2.0 M HCl and was treated with charcoal. After filtering to remove the charcoal, the acidic solution was made alkaline with a solution of aqueous ammonium hydroxide causing a white precipitate to form. The white solid was collected by filtration and was recrystallized from ethanol. After drying the needle shaped crystals under vacuum, 1.2 g of (*R*)-**3** were isolated in 39% yield.



Preparation of (*R*)-bis-imine 5.[18] HCl gas was bubbled through a solution of 0.21 g of (*R*)-**3** (0.75 mmol) in 25 mL of CH_2Cl_2 for 1 minute. A white precipitate formed and after stirring the solution for 5 minutes, it was concentrated *in vacuo*. The solid was taken up in 5 mL of benzene and concentrated *in vacuo* (carried out twice) to remove water. After drying the solid under vacuum, it was treated with 0.81 g of diphenyl ketimine[17] (4.5 mmol) and dissolved in 25 mL of toluene. The resulting solution was heated to reflux for 12 hours. The yellow solution was then cooled to 23 °C and was filtered to remove the ammonium chloride salt side product. The solution was concentrated in vacuo and the

product was isolated by flash chromatography on silica gel using 6:1 hexane/EtOAc as eluent. A yellow powder was isolated in 74% yield (0.34 g).



General Procedure for Crossover Experiments

The metal salts were dried for 6 hours under vacuum (2mm Hg) at 150 °C. A 1.0 M solution of BF_3•OEt_2 in dichloromethane was purchased from Aldrich. To the Lewis acid (8.0 μmol, 0.20 equiv) in 2 mL of CH_2Cl_2 was added a solution of the aldehyde (40 μmol, 1.0 equiv) in 1 mL of CH_2Cl_2 via cannula. The reaction mixture was cooled to -78 °C and a solution containing 4.3 mg of **18** (20 μmol, 0.50 equiv) and 4.6 mg of **17** (20 μmol, 0.50 equiv) in 1 mL of CH_2Cl_2 was added dropwise. The reactions were stirred at -78 °C for 2 hours and allowed to gradually warm toward 23 °C over 1 hour. They were maintained at 23 °C until complete (as monitored by thin layer chromatography, products at R_f = 0.68 in 4:1 hexane/ethyl acetate) before being treated with water. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 ml); the combined organic layers were washed with brine (15 ml) and dried over anhydrous Na_2SO_4. The solution was then passed through a small plug of silica and concentrated *in vacuo*. Each sample was subjected to analysis by gas chromatography. Two slightly different conditions were employed for each of the aldehydes investigated. Column condition 1: initial time: 3 min, intial temp.: 225 °C, rate: 10 °C/min, final temp.: 275 °C; column condition 2: initial time: 3 min, intial temp.: 250 °C, rate: 10 °C/min, final temp.: 275 °C. Retention times for benzaldehyde derived products under column condition 1: **19** (R = Ph, t_R = 4.14), **20** (R = Ph, t_R = 4.82), **21** (R = Ph, t_R = 5.88 min), **22** (R = Ph, t_R = 6.72 min), **23** (R = Ph, t_R = 8.13 min), **24** (t_R = 9.11 min). Retention times for hydrocinnamaldehyde derived products under column condition

2: **19** (R = CH_2CH_2Ph, t_R = 4.31), **20** (R = CH_2CH_2Ph, t_R = 4.92), **21** (R = CH_2CH_2Ph, t_R = 6.35 min), **22** (R = CH_2CH_2Ph, t_R = 7.20 min), **23** (R = CH_2CH_2Ph, t_R = 8.98 min), **24** (R = CH_2CH_2Ph, t_R = 10.30 min).

Reactions with $Yb(OTf)_3$: For R = Ph isolated 3% of **19** and **20**; isolated silylated products in ratio of 1.0: 1.0:1.0:0.98 (**21**:**22**:**23**:**24**). For R = $(CH_2)_2Ph$ isolated 6% of **19** and **20**; isolated silylated products in ratio of 1.0: 0.82:0.98:0.98 (**21**:**22**:**23**:**24**).

Reactions with $Sn(OTf)_2$: For R = Ph isolated 2% of **19** and **20**; isolated silylated products in ratio of 1.0: 1.1:0.88:0.93 (**21**:**22**:**23**:**24**). For R = $(CH_2)_2Ph$ isolated none of **19** and **20**; isolated silylated products in ratio of 1.0: 0.81:0.94:0.86 (**21**:**22**:**23**:**24**).

Reactions with $Zn(OTf)_2$: For R = Ph isolated 1% of **19** and **20**; isolated silylated products in ratio of 1.0: 1.0:1.2:1.2 (**21**:**22**:**23**:**24**). For R = $(CH_2)_2Ph$ isolated 4% of **19** and **20**; isolated silylated products in ratio of 1.0: 0.93:0.95:0.93 (**21**:**22**:**23**:**24**).

Reactions with $LiClO_4$: For R = Ph isolated 1% of **19** and **20**; isolated silylated products in ratio of 1.0: 1.1:1.1:1.1 (**21**:**22**:**23**:**24**). For R = $(CH_2)_2Ph$ isolated 1% of **19** and **20**; isolated silylated products in ratio of 1.0: 1.1:0.97:0.87 (**21**:**22**:**23**:**24**).

Reactions with $BF_3 \bullet OEt_2$: For R = Ph isolated 20% of **19** and **20**; isolated silylated products in ratio of 1.0: 1.0:1.9:2.0 (**21**:**22**:**23**:**24**). For R = $(CH_2)_2Ph$ isolated 20% of **19** and **20**; isolated no silylated products.

General Procedure for Aldol Reactions Mediated by TBSOTf

To a of the aldehyde (0.10 mmol) in 1.0 mL of CH_2Cl_2 were added 2,6-di-tert-butyl-4-methylpyridine (0.020 mmol) and *O*-ethyl-*O*-trimethylsilyl ketene acetal (0.12

mmol) in 1.0 mL of CH_2Cl_2. The resulting solution was cooled to -78 °C. To the solution was added TBSOTf (0.0050 mmol). The reaction was kept at -78 °C for 1 hour and then allowed to warm to 23 °C to reach completion if necessary. When complete, the reaction was poured onto water and extracted twice with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. The organic solution was passed through a small plug of silica gel and was concentrated *in vacuo*. The sample was subjected to analysis by gas chromatography.

Reaction with benzaldehyde (R = Ph): Isolated 99% of compound **19** by GC.

Reaction with hydrocinnamaldehyde (R = $(CH_2)_2Ph$): Isolated 99% of compound **19** by GC.

Chapter 3

Development of an Enantioselective Ti(IV) Aldol Catalyst

In light of the mechanistic studies described in chapter 2, we decided to design a chiral Lewis acid with a covalently bound multidentate ligand lacking weakly coordinating anions. Titanium(IV) was employed to prepare new complexes because it would be able to retain Lewis acidity in spite of having multiple relatively strong donors bound.[23] It was hoped that by employing a multidentate ligand, only a single coordination geometry would be accessible to the complex and thus minimize the possible binding modes of substrates. In addition, by encapsulating the titanium complex within a relatively bulky ligand, it might be less prone to aggregation in solution, resulting in a well-defined, monomeric complex.[24] Furthermore, exchange of ligands on titanium is well precedented and facile.[25]

We were concerned that the functionalized amines of the binaphthyl-2,2'-diamine derived ligands may operate as neutral donors on Ti(IV). In such a scenario, the ligand would saturate the coordination sphere of Ti(IV), because Ti can only accomodate 2 neutral donors beyond its four ionic donors. To avoid this, a new family of ligands was prepared derived from the 2-amino-2'-hydroxy-1,1'-binaphthyl scaffold (**25**).[26]

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23. Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807.

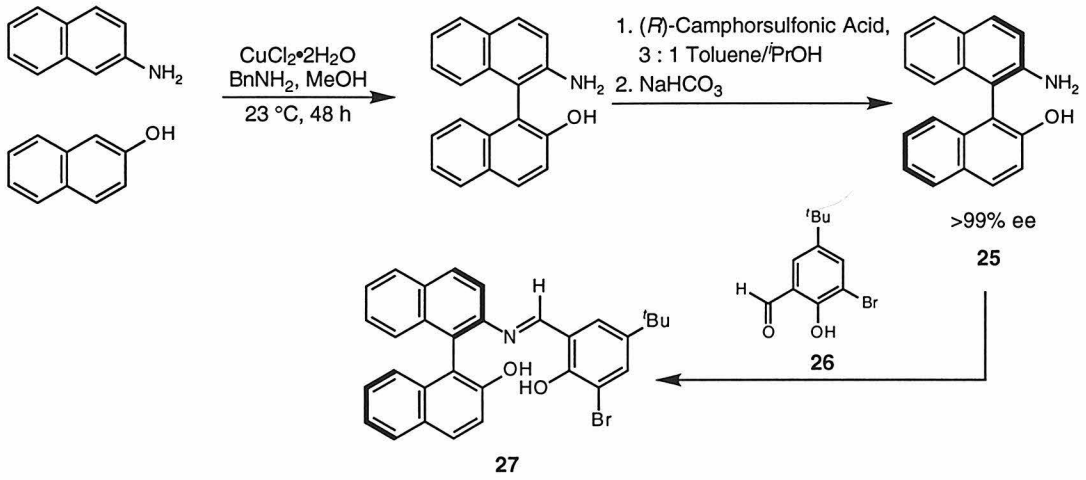
24. Aggregation of Ti complexes is well precedented: (a) Finn, M. G.; Sharpless K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113. (b) Corey, E. J.; Letavic, M. A.; Noe, M. C.; Sarsher, S. *Tetrahedron Lett.* **1994**, *35*, 7553.

25. (a) Seebach, D.; Plattner, D. P.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171. (b) Narasaka, K.; Inoue, M., Yamada, T., *Chem. Lett.*, **1986**, 1967.

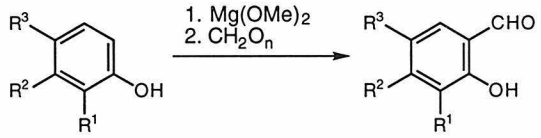
26. Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem.* **1993**, *58*, 4534.

With 2-amino-2'-hydroxy-1,1'-binaphthyl (**25**), Schiff base ligands could be readily prepared by the condensation with the appropriate salicylaldehyde (Scheme 10).

Scheme 10



The sterics and electronics of the complex could be tuned systematically[27] by varying the structure of the salicylaldehyde (eq 8).[28] Consequently, rapid screening of complexes with varied salicylimine functionality (Figure 2) was possible due to the convergent ligand synthesis.



(8)

When attempting to prepare the 1:1 complex by combining Schiff base ligand **27** and $Ti(O^iPr)_4$ in toluene and concentrating *in vacuo* (eq 9), 2:1 complex **39** was isolated

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27. For a discussion of electronic tuning in asymmetric catalysis, see: Jacobsen, E. N.; Zhang, W.; Guler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.

28. Jacobsen has described the preparation of a large range of substituted salicylaldehydes, see: Larrow, J. F.; Jacobsen, E. N. Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939.

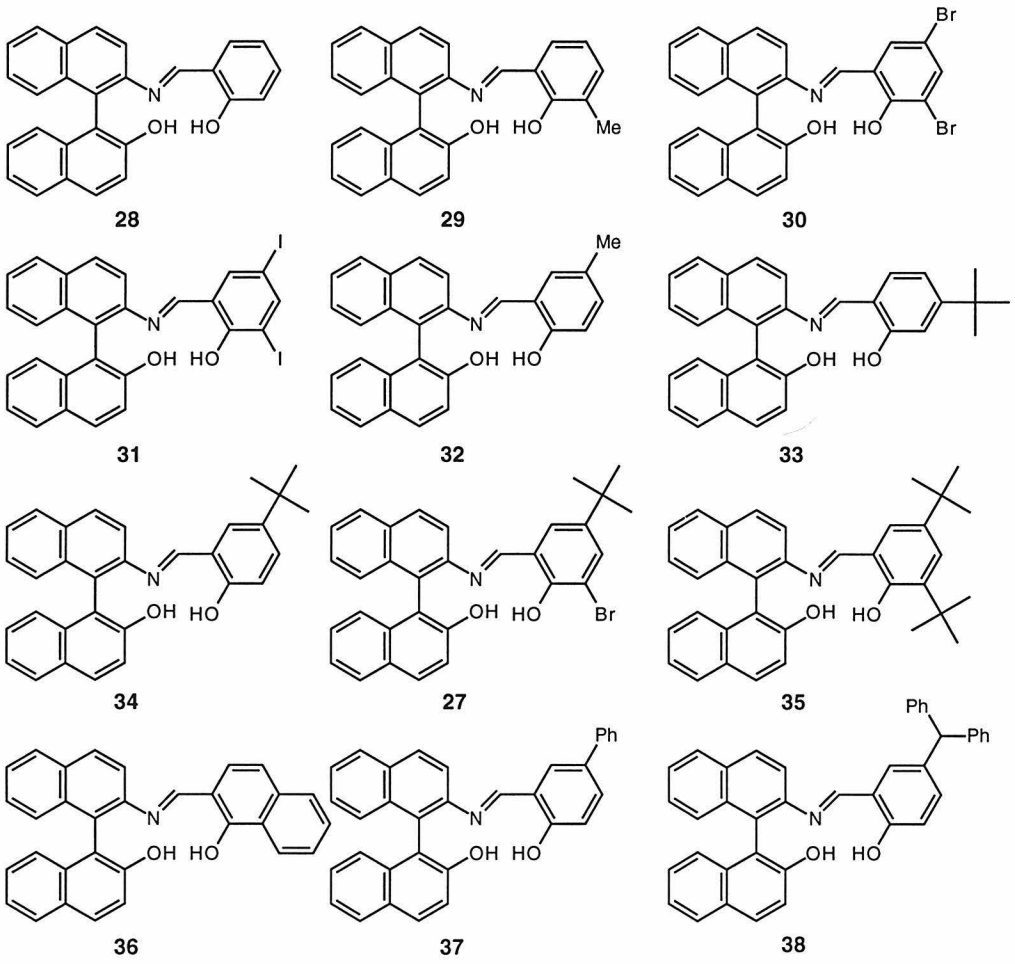
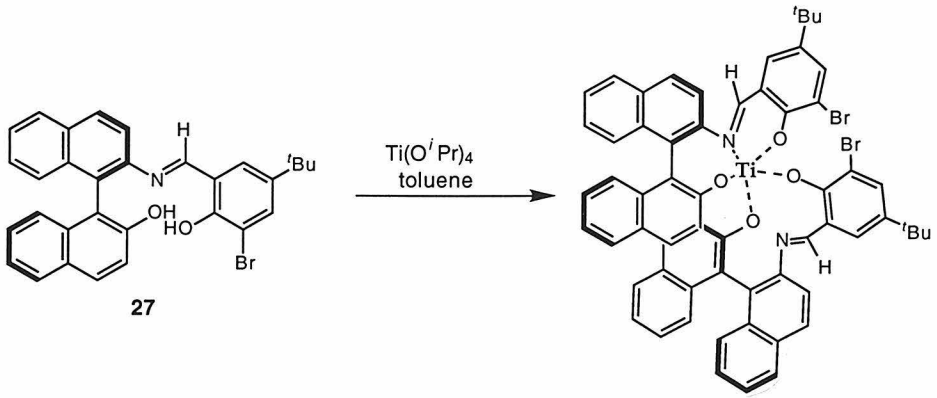


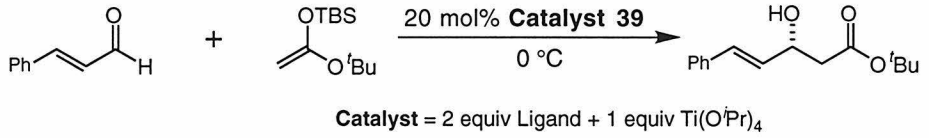
Figure 2. Various Schiff base ligands prepared.

instead. Apparently, concentrating the solution of ligand and Ti(IV) *in vacuo* drives the formation of **39** to completion. As a result, it was not possible to isolate a complex with only a single Schiff base ligand (**27**) bound to Ti. The two ligands could not both be bound statically in a tridentate fashion, since the complex operated as a competent aldol catalyst, implying that the coordination sphere was not constantly saturated with six donors. Molecular weight determination experiments described in chapter 7 were found to be consistent with a 2:1 monomer (**39**).



(9)

Initial experiments employing this 2:1 complex (**39**) involved reactions with benzaldehyde and a *tert*-butyl acetate derived silyl ketene acetal possesing a *tert*-butyldimethylsilyl (TBS) group (Table 1). The 2:1 complex was prepared by combining



(10)

Table 1. Enantioselective Aldol Reactions with 2:1 Complex

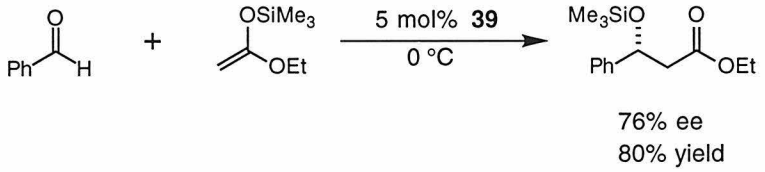
Entry	**Ligand**	ee[a]	Yield
1	**28**	40%	22%
2	**30**	50%	23%
3	**31**	43%	28%
4	**27**	60%	21%
5	**29**	10%	18%

[a] Enantiomeric excesses were determined by preparation of the (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) esters[29] and analysis by ^{1}H NMR spectroscopy.

29. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

two equivalents of the Schiff base ligand in toluene with 1 equivalent of $Ti(O^iPr)_4$, and removing the volatiles *in vacuo* after stirring the solution for 30 minutes at 23 °C. The 2:1 complex was redissolved in the reaction solvent and cooled to 0 °C. To the solution was added aldehyde followed by silyl ketene acetal. The salicylimine portion of the ligand was varied to optimize enantioselectivity. It was found that including a 5-*tert*-butyl group on the salicylimine improved selectivity, while incorporating a bromine ortho to the phenol led to faster rates of addition and enhanced enantioselectivity.

Further optimization of the system involved the preparation of additional silyl ketene acetals. Decreasing the sterics of both the silicon group and the ester of the acetate precursor improved the enantioselectivity. In addition we observed that **39** could be employed catalytically. Using *O*-ethyl-*O*-trimethylsilyl ketene acetal, the catalyst load could be lowered to 5 mol% (eq 11). Still, the catalyst loads necessary to carry out the reactions were not substantially improved over existing systems and the enantioselectivities of products were competitive at best.



(11)

To optimize the system further, a carboxylate chelate was incorporated as a ligand on the Ti(IV) complex to enhance the reactivity. We speculated that the carboxylate chelate may function as a silicon transfer agent to accelerate the turnover process.[30] After the silyl ketene acetal attacks the aldehyde, the ester product (**B**, Scheme 11) silylates the carboxylate ligand. The original catalyst is regenerated by transferring the trimethylsilyl group from the carboxylate chelate (**C**) to the metal bound aldolate. This process might not

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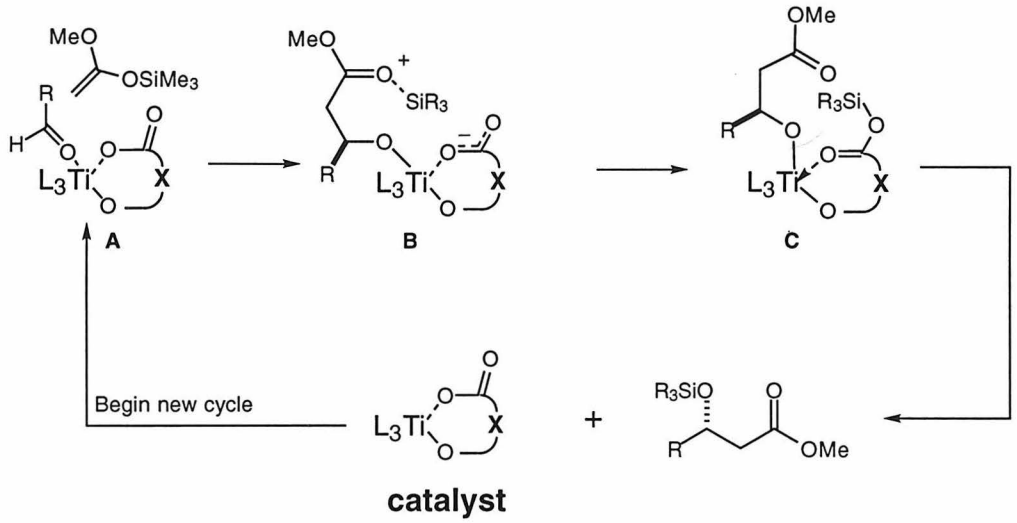
30. (a) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (b) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365.

only improve the reactivity but also might enhance the enantioselectivity through a directing effect of the nucleophile's silyl group aligning with the carboxylate ligand early in the transition state.

Scheme 11



A carboxylate donor was introduced into the Ti(IV) complex by exchanging one of the bound ligands (**27**) for a salicylic acid to obtain **41** (Scheme 12). The complex was prepared by initially combining two equivalents of Schiff base ligand **27** and Ti(O^{i}Pr)$_4$ in toluene. After stirring the solution for 1 hour at 23 °C, salicylic acid **40** was added and allowed to stir for an additional hour. The volatiles were then removed *in vacuo* and the residue was dissolved in ether. After cooling the solution, the reactants were added. With incorporation of the carboxylate ligand on the Ti(IV) complex, the reaction proceeded much more rapidly and in excellent enantioselectivity. Using only 2 mol% of catalyst **41**, the adduct derived from benzaldehyde and *O*-methyl-*O*-trimethylsilyl ketene acetal (**42**) was isolated after desilylation (with 10% trifluoroacetic acid (TFA) in tetrahydrofuran (THF)) in 92% yield and 96% ee.[31]

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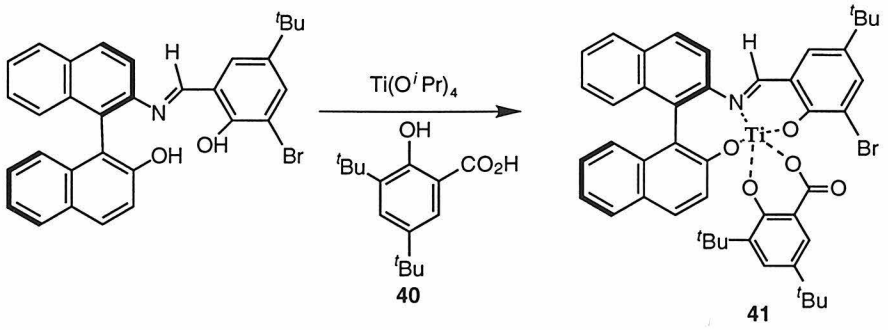
31. Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837.

Scheme 12

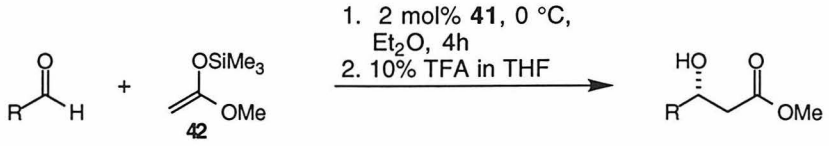


Scope and Characteristics of Catalyst 41

While 3,5-di-*tert*-butylsalicylic acid was initially used in complex **41** due to its superior solubility in organic media, it was later found that any salicylic acid with ortho substituents to the phenol, such as a bromine, or a methyl group, allowed the catalyst to perform optimally. In the absence of an ortho substituent, the catalyst reacted slightly slower. With the unsubstituted salicylic acid, the reaction proceeded at about half the rate, affording adduct in comparable enantioselectivity but in only 50% yield. This may be due to inadvertent silylation of the phenol or a slight change in conformation of the complex that leads to slower turnover.

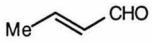
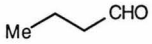
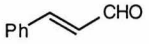
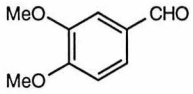
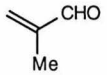
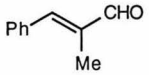
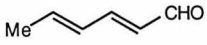
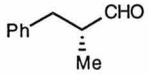
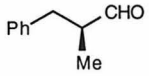
In general, it was found that less bulky substrates function the best with catalyst **41** (Table 2). The best substrates included unsaturated aldehydes, aromatic aldehydes and propargaldehydes (96-99% ee). Aliphatic aldehydes usually gave slightly lower levels of enantioselectivity (93-95% ee) and the poorest substrates were those with α-heteroatoms (80% ee). The trend was also seen with the silyl ketene acetals, the smaller alkoxy groups giving the best selectivities (Table 3). In the extreme case with the *tert*-butyl acetate derived silyl ketene acetal, the selectivity was substantially poorer and turnover was inhibited. Swapping the trimethylsilyl group for a triethylsilyl group led to slower turnover (41% yield in 4 hours at 0 °C) and diminished optical purity (86% ee for cinnamaldehyde). These findings were consistent with the steric constraints of the hypothetical model of the catalyst

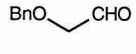
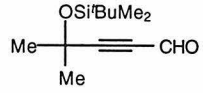
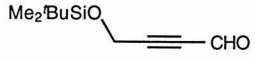
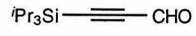
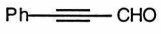
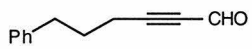
shown in Figure 3. The salicylimine and one of the binaphthyl rings serve as the borders of a chiral pocket surrounding the aldehyde.



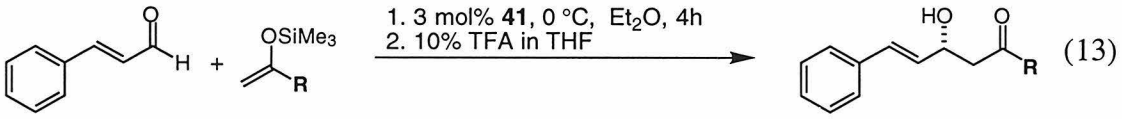
(12)

Table 2. Enantioselectivities for Various Aldehydes in Acetate Aldol

Entry	Aldehyde	ee[a]	Yield
1		98%	82%
2		95%	76%
3		98%	99%
4		94%	98%
5	$C_6H_{11}CHO$	95%	81%
6	PhCHO	96%	84%
7		95%	93%
8		95%	74%
9		95%	92%
10		99%	83%
11		95%	91%
12		88%	88%

13		80%	86%
14		96%	88%
15		96%	91%
16		97%	88%
17		94%	96%
18		96%	84%

[a] Enantiomeric excesses were determined by preparation of the (*S*)-MTPA esters and analysis by ^{1}H NMR spectroscopy.



(13)

Table 3. Trend in Enantioselectivity for Silyl Ketene Acetals

Entry	**R**	Adduct ee[b]
1	O^{t}Bu	64%
2	OBn	91%
3	O^{i}Pr	92%
4	OEt	92%
5	OMe	98%
6	SEt	NR[a]
7	SPh	NR[a]

[a] No reaction (NR) occurred. [b] Optical purity determined by conversion to the corresponding (*S*)-MTPA ester for analysis by ^{1}H NMR spectroscopy.

The working model of the catalyst proposed in Figure 3 is based on the coordination constraints of the ligands and the absolute sense of induction observed in the products, as well as the relationship between the structure of the salicylimine and its effect on the enantioselectivity observed in the adducts. Since the three donors of Schiff base ligand **27** must coordinate cis to each other on Ti,[32] the aldehyde is believed to bind in an axial position, resting against the salicylimine aromatic ring and leaving the Re face of the aldehyde open to attack as shown in Figure 3. With the aldehyde situated in the axial position, the carboxylate could occupy a position cis to the aldehyde, prepared to accept the trimethylsilyl group from the incoming silyl ketene acetal (**42**).

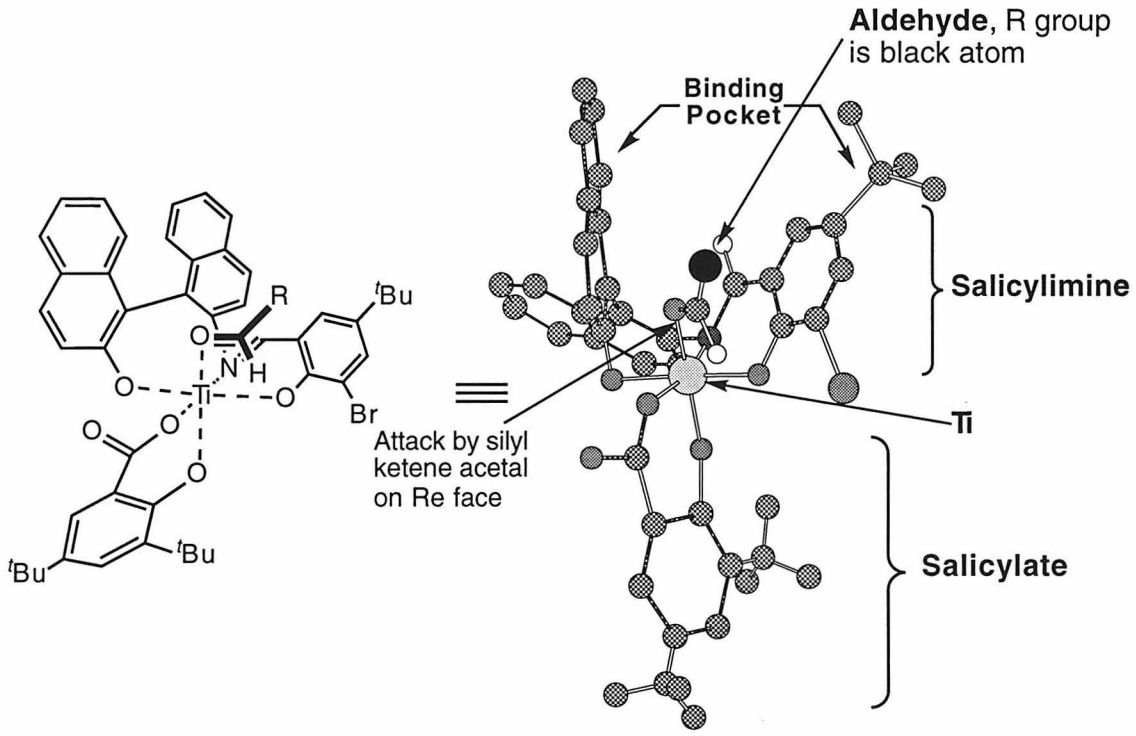


Figure 3. Working model of titanium catalyst with bound aldehyde.

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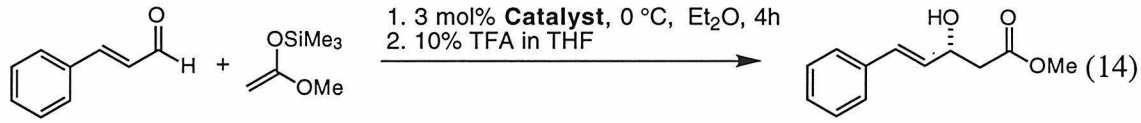
32. Crystal structure of Ti(IV) Schiff base complex: Aoyama, T.; Ohba, S.; Saito, Y.; Sasaki, C.; Kojima, M.; Fujita, J.; Nakajima, K. *Acta Cryst.* **1988**, *C44*, 1309.

Noting how changes in the salicylimine sterics of complex **41** influenced the selectivity and reactivity in the reaction between cinnamaldehyde and **42** (Table 4) provided the most convincing evidence for the model in Figure 3. Placing a *tert*-butyl group ortho to the phenol shuts down the reactivity, while a *tert*-butyl group para to the salicylimine hinders reactivity (4% yield) and diminishes enantioselectivity significantly (33% ee). Removing the bromine ortho to the phenol reduces reactivity (64% yield) and lowers selectivity slightly (95% ee). Replacing the *tert*-butyl group para to the phenol with a smaller substituent such as a methyl group or a proton lowered the selectivity (86% ee), and increasing the sterics to a benzhydryl group eroded the selectivity as well (81% ee). These structure and function relationships of the Ti(IV) complex with aldol adduct stereoselectivities are consistent with the proposed model in Figure 3.



(14)

Table 4. Enantioselective Aldol Additions Showing Dependence on Schiff Base Ligand

Entry	Schiff base Ligand	ee[a]	Yield
1	**35**	NA	NR
2	**33**	33%	4%
3	**34**	95%	64%
4	**28**	86%	40%
5	**32**	86%	85%
6	**38**	81%	85%

[a] Enantiomeric excesses were determined by preparation of the (*S*)-MTPA esters and analysis by ^{1}H NMR spectroscopy.

The efficiency of the catalyst was evaluated in various solvents (Table 5). Reaction solvents with moderate and high polarity such as dichloromethane and acetonitrile, which tend to support charge separation and silicon catalysis better, produced adducts with substantially poorer selectivity, while nonpolar solvents such as toluene, ether and chloroform resulted in optimal performance. In solvents with higher dielectric constants, direct transfer of a trimethylsilyl group to an unactivated aldehyde should become more favorable, and may result in initiating achiral silicon catalysis.

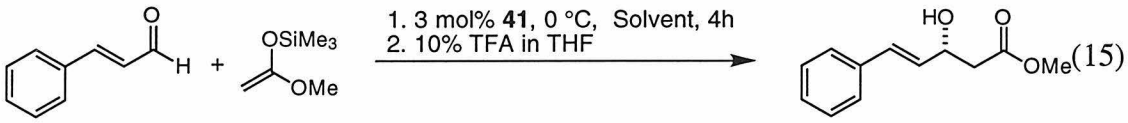


Table 5. Effect of Solvent on Catalytic, Enantioselective Aldol

Entry	Solvent	Dielectric Constant	ee[c]
1	mesitylene	2.27	95%
2	benzene	2.28	94%[a]
3	toluene	2.44	98%
4	ether	4.34	98%
5	chloroform	4.81	97%
6	tetrahydrofuran	7.58	NR[b]
7	dichloromethane	9.08	50%
8	dichloroethane	10.36	53%
9	acetonitrile	37.5	17%

[a] Reaction run at 23 °C. [b] No reaction (NR) occurred.
[c] Enantiomeric excess determined by ^{1}H NMR spectroscopic analysis of the derived (*S*)-MTPA ester.

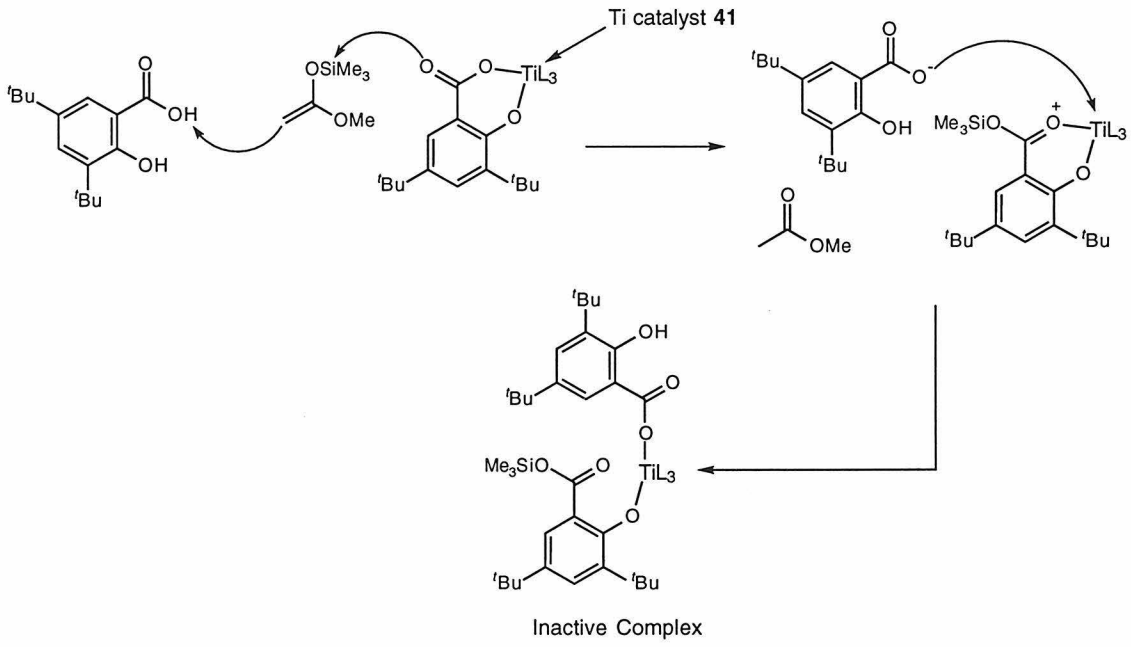
Further Optimization of the System

Additional optimization of the reactions involved including an amine base to prevent the silyl ketene acetal from attacking excess salicylic acid in solution. Generally, the

catalyst was the most compatible with hindered bases (Table 6). With stronger bases such as triethylamine and diisopropylethylamine, the rate of the reaction slowed down slightly.

Although the base was incorporated into the protocol to stabilize the silyl ketene acetal, it is likely that it plays a larger role in extending the life of the catalyst as well. Given that a silyl ketene acetal becomes an effective silylating agent when protonated, adding triethylamine should prevent the silyl ketene acetal from attacking any excess salicylic acid or extraneous proton source in solution. Should the silyl ketene acetal abstract a proton from free salicylic acid in solution, it may silylate the carboxylate chelate of complex **41** (Scheme 13). The newly formed salicylate may bind to the Ti(IV) complex leading to an inactive or less active catalyst. Consistent with this theory is the observation that excess salicylic acid used to prepare the catalyst can lead to slower reaction rates and partial conversions of substrates. When preparing the catalyst with 1 fold excess salicylic acid (relative to Ti) and operating with 1 mol% catalyst in the absence of base, the catalyst became inactive after 30-40 turnovers. Consequently, adding base to the reactions gave reliable performance from the catalyst.

Scheme 13



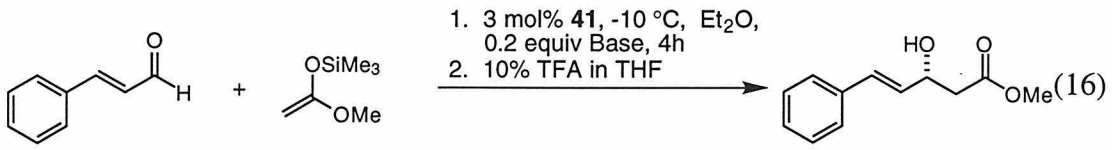


Table 6. Effect of Base on Asymmetric Acetate Aldol

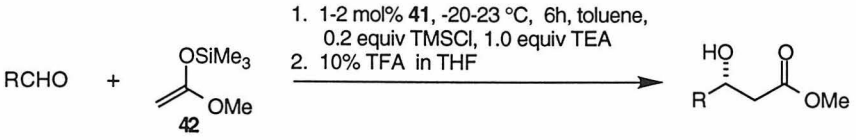
Entry	Base	Yield	ee[a]
1	2,6-di-*t*butyl-4-methylpyridine	90%	97%
2	2,6-lutidine	93%	98%
3	pyridine	17%	87%
4	triethylamine	45%	98%
5	diisopropylethylamine	67%	98%

[a] Enantiomeric excess determined by ^{1}H NMR spectroscopic assay of (*S*)-MTPA derived ester.

Improvement of the Catalyst Preparation

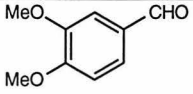
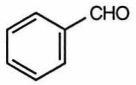
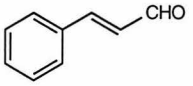
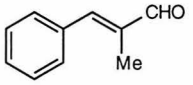
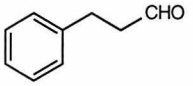
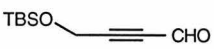
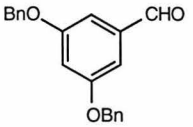
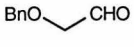
One final adaptation of the catalyst preparation avoids removal of the volatiles *in vacuo* by adding 0.2 equivalents of trimethylsilyl chloride (TMSCl) and 1.0 equivalent of triethylamine (TEA) to silylate the isopropanol liberated from the ligand exchange process (eq 17). Such a protocol is more amenable for large scale preparation of the catalyst since this circumvents the need for the removal of toluene. The catalyst is equally efficient using this preparation and is possibly even improved (Table 7). With the original protocol, preparing catalyst from 1.0 g of Schiff base ligand **27** required the eventual removal of 500 mL of toluene under vacuum. The new procedure allows facile preparation of the catalyst and has been successfully carried out on 4.0 g scale (relative to aldehyde). The reaction protocol was made more facile by demonstrating that other less volatile silyl ketene acetals could be used in place of **42**. The benzyl acetate derived silyl ketene acetal (**43**) was

$$^{i}PrOH + Me_3SiCl + Et_3N \longrightarrow {}^{i}PrOSiMe_3 + Et_3NH^{+}\ Cl^{-} \qquad (17)$$



(18)

Table 7. Enantioselective Mukaiyama Aldol Additions and Preparing the Catalyst Without Solvent Removal

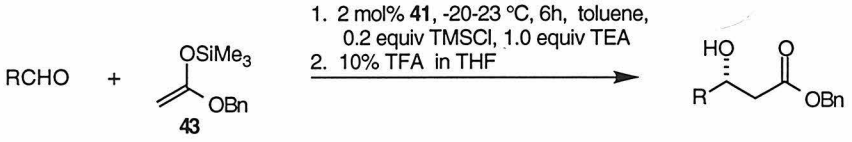
Entry	Aldehyde	Catalyst Load	ee	Yield
1		2 mol%	97%[a]	89%
2		1 mol%	96%[a]	93%
3		2 mol%	96%[a]	94%
4		1 mol%	94%[a]	87%
5		2 mol%	98%[a]	95%
6		1 mol%	97%[a]	92%
7		2 mol%	97%[b]	89%
8		1 mol%	97%[a]	92%
9		2 mol%	93%[a]	98%
10		2 mol%	99%[b]	91%
11		2 mol%	92%[b]	85%
12		2 mol%	81%[a]	86%

[a] Optical purity assayed by HPLC using a Chiralcel OD column.

[b] Optical purity of (*S*)-MTPA ester derivative assayed by ^{1}H NMR spectroscopy.

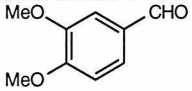
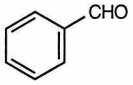
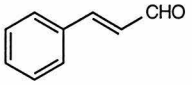
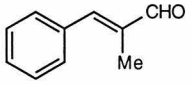
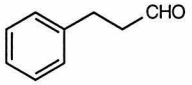
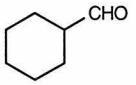
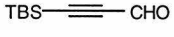
shown to be a suitable substitute for the methyl acetate derived silyl ketene acetal (**42**), (Table 8) and is far easier to prepare.[33]

With the new protocol, the reactions were started at low temperature (-20 °C) to avoid proton abstraction by silyl ketene acetal upon addition of reactants. The reactions were allowed to gradually warm to 23 °C to compensate for the slightly poorer reactivity of the catalyst in the presence of triethylamine.



(19)

Table 8. Enantioselective Aldol Additions with Benzyl Acetate Derived Nucleophile and Catalyst Prepared Without Solvent Removal

Entry	Aldehyde	ee	Yield
1		96%[a]	92%
2		96%[a]	94%
3		96%[a]	98%
4		97%[a]	91%
5		91%[a]	95%
6		90%[a]	95%
7		99%[b]	99%

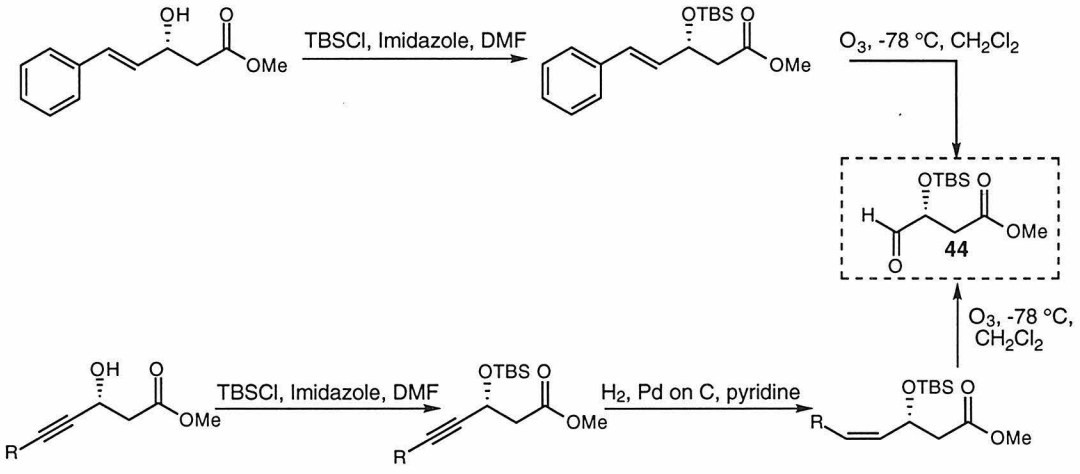
[a] Optical purity assayed by HPLC using a Chiralcel OD column.
[b] Optical purity of (*S*)-MTPA ester derivative assayed by ^{1}H NMR spectroscopy.

33. Weber, W. P., *Silicon Reagents for Organic Synthesis*, Springer-Verlag, Berlin, **1983**, 100.

The performance of the catalyst was evaluated in the presence of powdered 4 Å molecular sieves to find out whether sieves would be a suitable substitute for the trimethylsilyl chloride. Using 2 mol% of **41** to carry out an addition between cinnamaldehyde and **43** in toluene, alcohol product was isolated exclusively in 5% yield and in 80% ee. This observation demonstrates that molecular sieves are incompatible with catalyst **41**.

Structural Analysis of Aldol Products

Scheme 14



The absolute configuration of many of the products was determined by correlation to the known diols.[30] The propargaldehyde derived adducts were correlated to the cinnamaldehyde derived product by degradation to a common fragment (**44**, Scheme 14). The propargyl alcohol was protected as the *t*butyldimethylsilyl ether and partially reduced by hydrogenolysis in pyridine to the cis-olefin. Oxidative cleavage of the olefin with a dilute stream of ozone at -78 °C produced a fragment (**44**) that was also derived from the cinnamaldehyde adduct using a similar degradation sequence.

Appendix (Crystal Structure Data)

Crystals of Schiff base ligand **28** were grown from a solution of 6:1 hexane/ethyl acetate. The yellow crystals were needle shaped, and a crystal of suitable dimensions for x-ray diffraction was obtained. The solution structure confirms the connectivity and geometry that was proposed for this class of ligands. For the free ligand, the x-ray structure (Figure 5) depicts the salicylimine in plane with the adjacent naphthalene. In addition hydrogen bonding appears to be occurring between the phenol and imine nitrogen of the salicylimine.

Table 9. Crystal Data and Structure Refinement for Schiff Base Ligand **28**

Empirical formula	$C_{27}H_{19}NO_2$
Formula weight	389.43
Crystal color	yellow
Solvent of crystallization	6:1 hexane/ethyl acetate
Type of diffractometer	*Enraf-Nonius CAD-4*
Data collection method	Omega
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	P2(1)2(1)2(1) (#19)
Unit cell dimensions	a = 9.232(2) Å $\alpha = 90°$ b = 11.454(2) Å $\beta = 90°$ c = 19.123(4) Å $\gamma = 90°$
Volume	2022.1(7) $Å^3$
Z	4
Density (calculated)	1.279 mg/m^3
Absorption coefficient	0.081 mm^{-1}

F(000)	816
Crystal size	0.48 x 0.10 x0.08 mm
Theta range for data collection	2.07 to 24.94°
Index ranges	$0 \leq h \leq 10$, $0 \leq k \leq 13$, $0 \leq l \leq 22$
Reflection collected	6657
Independent reflections	2035 [R(merge) = 0.0942]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2032/0/347
Goodness-of-fit on F^2	1.351
Final R indices [$I>2\sigma(I)$]	$R_1 = 0.0521$, $wR_2 = 0.0656$
R indices (all data)	$R_1 = 0.1024$, $wR_2 = 0.0798$
Absolute structure parameter	4(3)
Largest diff. peak and hole	0.132 and -0.139 $e \cdot A^{-3}$
Lattice parameter determination	# of reflections = 25; range = $7° \leq \theta \leq 8°$
Number of standard relfections	3
Interval (minutes)	150
Coefficients in weighting scheme	a = 0, b = 0, c = 0, d = 0, e = 0
$(\Delta/\sigma)_{max}$ in final least squares cycle	-0.028

Table 10. Atomic Coordinates ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **28**. U(eq) is Defined as One Third of the Trace of the Orthogonalized U_{ij} Tensor

Atom	x	y	z	U(eq)
N(1)	4179(4)	5976(3)	8405(2)	50(1)
O(1)	2063(3)	8367(3)	9436(2)	62(1)
O(2)	5975(3)	5636(3)	9371(2)	72(1)
C(1)	3449(4)	7950(4)	8178(2)	44(1)
C(2)	3442(4)	6796(4)	7967(2)	47(1)
C(3)	2743(6)	6446(5)	7341(2)	62(1)
C(4)	2002(5)	7242(5)	6961(3)	65(1)
C(5)	1895(4)	8411(5)	7173(2)	54(1)
C(6)	1057(5)	9251(5)	6795(3)	68(1)
C(7)	941(6)	10364(6)	7026(3)	78(2)
C(8)	1654(6)	10724(5)	7636(3)	79(2)
C(9)	2499(6)	9959(4)	7995(3)	60(1)
C(10)	2630(4)	8777(4)	7783(2)	49(1)
C(11)	4252(4)	8319(3)	8824(2)	41(1)
C(12)	3517(4)	8526(4)	9431(2)	46(1)
C(13)	4255(6)	8889(4)	10047(2)	55(1)
C(14)	5705(6)	9076(4)	10031(3)	59(1)
C(15)	6498(4)	8893(4)	9418(2)	52(1)
C(16)	8027(5)	9075(5)	9393(3)	70(2)
C(17)	8777(5)	8884(5)	8802(3)	73(2)
C(18)	8104(5)	8461(4)	8206(3)	65(1)
C(19)	6618(5)	8268(4)	8202(3)	53(1)
C(20)	5787(4)	8488(4)	8807(2)	44(1)
C(21)	3867(5)	4888(4)	8414(2)	59(1)
C(22)	4602(4)	4090(4)	8872(2)	54(1)
C(23)	5646(5)	4494(4)	9343(2)	58(1)
C(24)	6313(7)	3705(6)	9791(3)	82(2)
C(25)	5980(7)	2548(6)	9757(3)	86(2)
C(26)	4973(7)	2122(6)	9294(3)	84(2)
C(27)	4287(6)	2889(5)	8860(3)	72(2)

Table 11. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2x10^3$) for **28**.

Atom	x	y	z	U(eq)
H(1)	1566(59)	8666(47)	9769(25)	105(23)
H(2)	5370(57)	6099(50)	8958(29)	145(23)
H(3)	2846(41)	5604(34)	7178(18)	59(12)
H(4)	1594(43)	6923(37)	6549(20)	69(15)
H(6)	587(38)	8927(35)	6351(20)	63(13)
H(7)	333(45)	10915(40)	6804(24)	84(17)
H(8)	1566(54)	11614(50)	7769(26)	124(22)
H(9)	2999(42)	10212(33)	8440(19)	60(14)
H(13)	3704(36)	9040(34)	10476(19)	54(12)
H(14)	6183(40)	9376(34)	10459(20)	58(12)
H(16)	8445(53)	9401(45)	9895(27)	121(20)
H(17)	9905(42)	8959(34)	8742(19)	65(12)
H(18)	8603(47)	8284(41)	7753(23)	84(16)
H(19)	6165(38)	8027(32)	7772(19)	47(12)
H(21)	3114(40)	4544(34)	8134(21)	59(13)
H(24)	7053(52)	4041(43)	10097(24)	106(19)
H(25)	6509(56)	1974(44)	10034(27)	113(21)
H(26)	4762(55)	1280(52)	9248(27)	119(22)
H(27)	3524(43)	2639(38)	8521(23)	85(18)

The structure was solved using SHELXS-86. Twenty seven non-hydrogen atoms were located and most hydrogen atoms were visible in the solution results as well. All hydrogen atoms, except those on O_1 and O_2, were placed in calculated positions. H_1 and H_2 were attached to O_1 and O_2 respectively, located in ΔF map. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically.

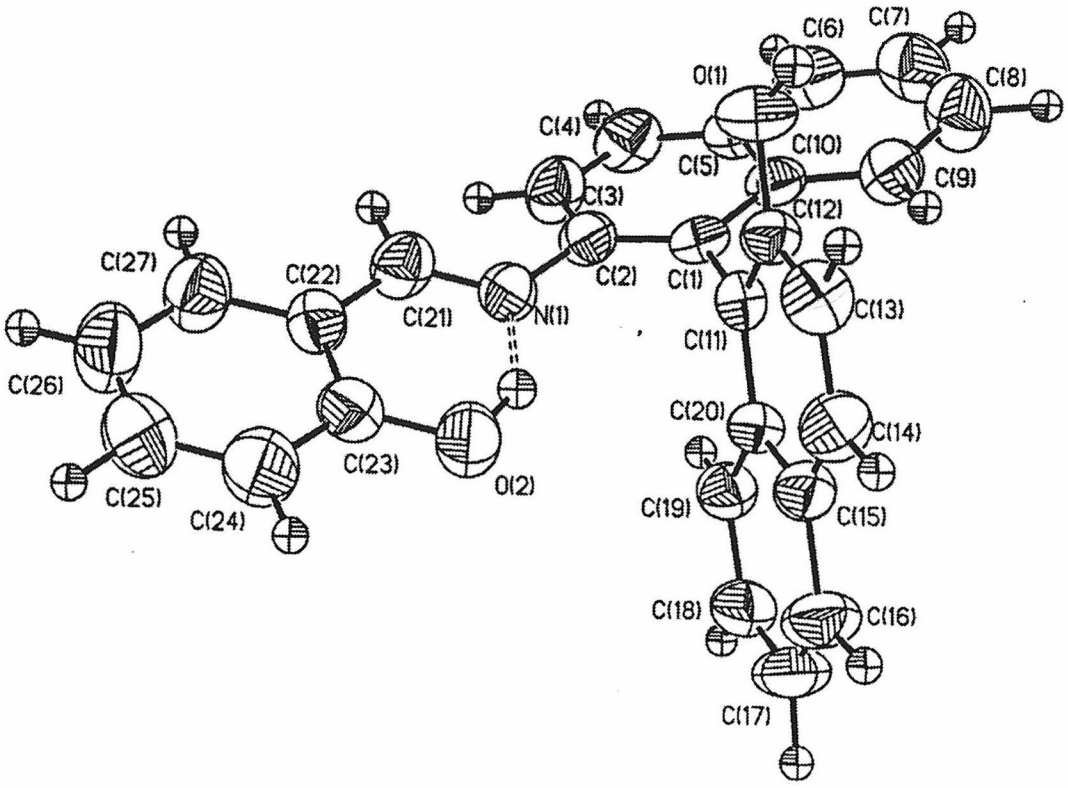


Figure 4. Schiff base **28** crystal structure.

Bond lengths [A] and angles [deg]

N(1)-C(21)	1.279(5)
N(1)-C(2)	1.430(5)
N(1)-H(2)	1.53(6)
O(1)-C(12)	1.355(4)
O(1)-H(1)	0.85(5)
O(2)-C(23)	1.344(5)
O(2)-H(2)	1.10(6)
C(1)-C(2)	1.381(6)
C(1)-C(10)	1.428(5)
C(1)-C(11)	1.503(5)
C(2)-C(3)	1.418(6)
C(3)-C(4)	1.352(6)
C(3)-H(3)	1.02(4)
C(4)-C(5)	1.402(6)
C(4)-H(4)	0.95(4)
C(5)-C(10)	1.413(5)
C(5)-C(6)	1.430(6)
C(6)-C(7)	1.353(7)
C(6)-H(6)	1.02(4)
C(7)-C(8)	1.402(8)
C(7)-H(7)	0.94(4)
C(8)-C(9)	1.359(7)
C(8)-H(8)	1.05(5)
C(9)-C(10)	1.418(6)
C(9)-H(9)	1.01(4)
C(11)-C(12)	1.364(5)
C(11)-C(20)	1.430(5)
C(12)-C(13)	1.423(6)
C(13)-C(14)	1.357(6)
C(13)-H(13)	0.98(3)
C(14)-C(15)	1.398(6)
C(14)-H(14)	0.99(4)
C(15)-C(20)	1.418(6)
C(15)-C(16)	1.428(6)
C(16)-C(17)	1.343(7)
C(16)-H(16)	1.10(5)
C(17)-C(18)	1.386(7)
C(17)-H(17)	1.05(4)
C(18)-C(19)	1.389(6)
C(18)-H(18)	1.00(4)
C(19)-C(20)	1.410(5)
C(19)-H(19)	0.96(4)
C(21)-C(22)	1.436(6)
C(21)-H(21)	0.96(4)
C(22)-C(23)	1.398(5)
C(22)-C(27)	1.405(6)
C(23)-C(24)	1.389(6)
C(24)-C(25)	1.362(8)
C(24)-H(24)	0.98(5)
C(25)-C(26)	1.374(8)
C(25)-H(25)	0.98(5)
C(26)-C(27)	1.364(7)
C(26)-H(26)	0.99(6)
C(27)-H(27)	1.00(4)
C(21)-N(1)-C(2)	122.8(4)

C(21)-N(1)-H(2)	104(2)
C(2)-N(1)-H(2)	133(2)
C(12)-O(1)-H(1)	119(4)
C(23)-O(2)-H(2)	109(3)
C(2)-C(1)-C(10)	118.6(4)
C(2)-C(1)-C(11)	120.8(4)
C(10)-C(1)-C(11)	120.6(4)
C(1)-C(2)-C(3)	121.2(4)
C(1)-C(2)-N(1)	117.1(4)
C(3)-C(2)-N(1)	121.7(4)
C(4)-C(3)-C(2)	119.6(5)
C(4)-C(3)-H(3)	122(2)
C(2)-C(3)-H(3)	119(2)
C(3)-C(4)-C(5)	121.6(5)
C(3)-C(4)-H(4)	113(3)
C(5)-C(4)-H(4)	126(3)
C(4)-C(5)-C(10)	119.2(4)
C(4)-C(5)-C(6)	122.3(5)
C(10)-C(5)-C(6)	118.5(5)
C(7)-C(6)-C(5)	120.8(5)
C(7)-C(6)-H(6)	125(2)
C(5)-C(6)-H(6)	114(2)
C(6)-C(7)-C(8)	120.7(6)
C(6)-C(7)-H(7)	122(3)
C(8)-C(7)-H(7)	117(3)
C(9)-C(8)-C(7)	120.1(6)
C(9)-C(8)-H(8)	123(3)
C(7)-C(8)-H(8)	117(3)
C(8)-C(9)-C(10)	121.3(5)
C(8)-C(9)-H(9)	120(2)
C(10)-C(9)-H(9)	118(2)
C(5)-C(10)-C(9)	118.6(4)
C(5)-C(10)-C(1)	119.6(4)
C(9)-C(10)-C(1)	121.8(4)
C(12)-C(11)-C(20)	119.3(4)
C(12)-C(11)-C(1)	120.2(4)
C(20)-C(11)-C(1)	120.5(4)
O(1)-C(12)-C(11)	118.5(4)
O(1)-C(12)-C(13)	120.4(4)
C(11)-C(12)-C(13)	121.1(4)
C(14)-C(13)-C(12)	120.0(4)
C(14)-C(13)-H(13)	120(2)
C(12)-C(13)-H(13)	120(2)
C(13)-C(14)-C(15)	120.8(5)
C(13)-C(14)-H(14)	118(2)
C(15)-C(14)-H(14)	121(2)
C(14)-C(15)-C(20)	119.9(4)
C(14)-C(15)-C(16)	121.6(5)
C(20)-C(15)-C(16)	118.5(5)
C(17)-C(16)-C(15)	121.0(5)
C(17)-C(16)-H(16)	128(3)
C(15)-C(16)-H(16)	112(3)
C(16)-C(17)-C(18)	121.1(5)
C(16)-C(17)-H(17)	126(2)
C(18)-C(17)-H(17)	113(2)
C(17)-C(18)-C(19)	120.1(5)
C(17)-C(18)-H(18)	125(3)
C(19)-C(18)-H(18)	115(3)
C(18)-C(19)-C(20)	120.4(5)
C(18)-C(19)-H(19)	119(2)

C(20)-C(19)-H(19)	121(2)
C(19)-C(20)-C(15)	118.8(4)
C(19)-C(20)-C(11)	122.3(4)
C(15)-C(20)-C(11)	118.9(4)
N(1)-C(21)-C(22)	121.5(5)
N(1)-C(21)-H(21)	124(2)
C(22)-C(21)-H(21)	115(2)
C(23)-C(22)-C(27)	118.4(5)
C(23)-C(22)-C(21)	120.5(5)
C(27)-C(22)-C(21)	121.1(5)
O(2)-C(23)-C(24)	120.5(5)
O(2)-C(23)-C(22)	120.3(4)
C(24)-C(23)-C(22)	119.2(5)
C(25)-C(24)-C(23)	120.2(6)
C(25)-C(24)-H(24)	125(3)
C(23)-C(24)-H(24)	115(3)
C(24)-C(25)-C(26)	122.0(6)
C(24)-C(25)-H(25)	121(3)
C(26)-C(25)-H(25)	117(3)
C(27)-C(26)-C(25)	118.4(6)
C(27)-C(26)-H(26)	119(3)
C(25)-C(26)-H(26)	123(3)
C(26)-C(27)-C(22)	121.7(6)
C(26)-C(27)-H(27)	123(3)
C(22)-C(27)-H(27)	116(3)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (A^2 x 10^3).
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	49(2)	49(2)	53(2)	-6(2)	-4(2)	0(2)
O(1)	40(2)	86(2)	59(2)	3(2)	6(2)	-4(2)
O(2)	74(2)	55(2)	87(3)	3(2)	-36(2)	-3(2)
C(1)	34(2)	53(3)	46(3)	3(2)	2(2)	-8(2)
C(2)	44(3)	48(3)	50(3)	2(2)	-2(2)	-3(2)
C(3)	69(3)	57(3)	61(3)	-8(3)	-16(3)	-9(3)
C(4)	63(3)	76(4)	56(3)	-2(3)	-21(3)	-10(3)
C(5)	44(3)	69(3)	49(3)	12(3)	-3(2)	-4(3)
C(6)	64(3)	85(4)	55(3)	15(4)	-10(3)	-3(3)
C(7)	74(4)	83(5)	76(4)	25(4)	-9(3)	17(4)
C(8)	92(4)	64(4)	80(4)	15(4)	-14(3)	8(4)
C(9)	60(3)	59(3)	60(3)	8(3)	-6(3)	-3(3)
C(10)	36(2)	54(3)	56(3)	9(2)	3(2)	-7(2)
C(11)	46(3)	36(2)	39(2)	0(2)	0(2)	2(2)
C(12)	38(3)	46(3)	54(3)	4(2)	-5(2)	-1(2)
C(13)	64(3)	62(3)	40(3)	-3(3)	1(3)	2(3)
C(14)	59(3)	64(3)	53(3)	-9(3)	-14(3)	-4(3)
C(15)	45(3)	48(3)	62(3)	4(3)	-9(3)	-1(2)
C(16)	44(3)	80(4)	87(4)	9(4)	-20(3)	-6(3)
C(17)	34(3)	82(4)	102(5)	17(4)	-8(3)	-5(3)
C(18)	46(3)	64(3)	84(4)	3(3)	11(3)	3(3)
C(19)	46(3)	55(3)	58(3)	4(3)	6(3)	0(2)
C(20)	34(2)	44(3)	53(3)	2(2)	-1(2)	1(2)
C(21)	63(3)	57(4)	57(3)	-7(3)	-10(3)	-9(3)
C(22)	54(3)	49(3)	58(3)	-3(3)	-1(2)	2(2)
C(23)	53(3)	58(3)	65(3)	5(3)	-1(3)	4(3)
C(24)	77(4)	75(4)	95(4)	12(4)	-29(3)	-2(3)
C(25)	86(5)	75(5)	97(5)	25(4)	-15(4)	10(4)
C(26)	100(4)	60(4)	90(4)	13(4)	-12(4)	-8(4)
C(27)	80(4)	61(4)	75(4)	1(3)	-11(3)	-7(3)

Observed and calculated structure factors

h	k	l	10Fo	10Fc	10σ	h	k	l	10Fo	10Fc	10σ	h	k	l	10Fo	10Fc	10σ	h	k	l	10Fo	10Fc	10σ	h	k	l	10Fo	10Fc	10σ
2	0	0	386	387	3	6	9	0	12	5	12	10	5	1	61	33	12	4	2	2	89	87	4	4	11	2	44	13	16
4	0	0	853	836	7	7	9	0	14	8	14	0	6	1	211	208	4	5	2	2	229	221	3	5	11	2	91	83	9
6	0	0	210	209	3	8	9	0	50	20	15	1	6	1	233	225	3	6	2	2	136	133	3	6	11	2	41	20	20
8	0	0	146	146	4	0	10	0	0	29	1	2	6	1	151	144	3	7	2	2	42	8	9	0	12	2	26	33	26
10	0	0	44	1	17	1	10	0	57	65	7	3	6	1	226	221	3	8	2	2	104	99	5	1	12	2	23	30	23
1	1	0	331	333	3	2	10	0	49	56	8	4	6	1	87	90	4	9	2	2	84	77	6	2	12	2	38	29	22
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8	2	0	86	81	5	1	13	0	44	12	17	2	8	1	43	46	8	5	4	2	153	153	3	0	1	3	342	348	3
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3	8	0	111	114	4	10	4	1	0	17	1	4	1	2	248	250	3	1	10	2	83	94	5	1	6	3	195	194	3
4	8	0	62	66	6	0	5	1	612	603	6	5	1	2	199	193	3	2	10	2	0	16	1	2	6	3	132	132	3
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6	8	0	81	75	6	2	5	1	0	13	1	7	1	2	50	44	7	4	10	2	55	60	8	4	6	3	236	241	3
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2	9	0	86	83	5	8	5	1	75	78	6	2	2	2	293	294	3	2	11	2	35	34	14	0	7	3	156	153	5
3	9	0	11	2	11	9	5	1	50	25	14	3	2	2	352	348	3	3	11	2	48	22	9	1	7	3	178	187	3

Observed and calculated structure factors

h	k	l	10Fo	10Fc	10s
2	7	3	61	64	5
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4	7	3	44	53	8
5	7	3	68	69	6
6	7	3	69	66	6
7	7	3	100	99	5
8	7	3	95	97	8
9	7	3	50	13	15
0	8	3	92	94	6
1	8	3	186	180	3
2	8	3	51	60	7
3	8	3	113	125	4
4	8	3	58	53	7
5	8	3	89	85	5
6	8	3	97	92	5
7	8	3	140	143	4
8	8	3	50	17	15
0	9	3	66	69	9
1	9	3	217	212	4
2	9	3	204	207	4
3	9	3	101	99	5
4	9	3	23	40	22
5	9	3	97	93	5
6	9	3	89	86	6
7	9	3	82	90	9
8	9	3	24	25	23
0	10	3	21	28	21
1	10	3	172	169	4
2	10	3	73	75	6
3	10	3	63	75	7
4	10	3	87	85	5
5	10	3	110	96	5
6	10	3	40	38	20
7	10	3	21	12	20
0	11	3	0	2	1
1	11	3	101	109	5
2	11	3	53	47	8
3	11	3	0	9	1
4	11	3	0	32	1
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6	11	3	37	23	25
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1	12	3	45	17	16
2	12	3	0	27	1
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4	12	3	57	53	13
0	13	3	39	18	38
1	13	3	0	17	1
2	13	3	41	19	20
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3	0	4	392	395	3
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6	0	4	64	58	5
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8	0	4	42	24	10
9	0	4	93	99	5
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9	1	4	50	10	8
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3	2	4	214	216	3
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5	2	4	220	218	3
6	2	4	135	137	3
7	2	4	89	90	5
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7	3	4	129	124	4
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7	4	4	116	116	4
8	4	4	87	98	5
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1	5	4	175	167	4
2	5	4	163	160	3
3	5	4	232	229	3
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1	6	4	85	96	6
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3	7	4	86	88	4
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9	7	4	71	64	11
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7	10	4	186	193	4
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9	10	4	56	62	7
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3	11	4	86	76	8
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6	11	4	47	48	10
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7	0	5	644	653	5
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9	0	5	216	211	3
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8	4	5	166	163	3
9	4	5	209	203	3
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2	5	5	177	179	4
3	5	5	80	79	6
4	5	5	0	34	1
5	5	5	58	52	13
6	5	5	91	88	5
7	5	5	551	534	5
8	5	5	210	203	3
9	5	5	170	163	3
10	5	5	63	53	5
0	6	5	94	91	4
1	6	5	154	148	4
2	6	5	74	71	6
3	6	5	84	71	6
4	6	5	81	39	9
5	6	5	319	317	4
6	6	5	141	142	3
7	6	5	102	100	4
8	6	5	45	58	7
9	6	5	125	129	4
10	6	5	92	98	5
0	7	5	110	98	4
1	7	5	81	67	6
2	7	5	54	41	8
3	7	5	48	29	16
4	7	5	32	40	19
5	7	5	270	272	3
6	7	5	127	124	4
7	7	5	0	5	1
8	7	5	144	149	4
9	7	5	159	163	4
10	7	5	186	186	4
0	8	5	59	51	7
1	8	5	75	83	10
2	8	5	35	56	34
3	8	5	0	14	1
4	8	5	89	90	4
5	8	5	62	69	6
6	8	5	191	188	4
7	8	5	21	44	21
8	8	5	163	172	4
9	8	5	100	99	5
10	8	5	78	73	9
0	9	5	41	26	20
1	9	5	148	153	6
2	9	5	243	243	4
3	0	6	53	51	6
4	0	6	73	76	6
5	0	6	551	534	5
6	0	6	210	203	3
7	0	6	141	142	3
8	0	6	102	100	4
9	0	6	45	58	7
10	0	6	125	129	4
0	1	6	92	98	5
1	1	6	110	98	4
2	1	6	81	67	6
3	1	6	54	41	8
4	1	6	48	29	16
5	1	6	32	40	19
6	1	6	270	272	3
7	1	6	127	124	4
8	1	6	0	5	1
9	1	6	144	149	4
10	1	6	159	163	4
0	2	6	186	186	4
1	2	6	59	51	7
2	2	6	75	83	10
3	2	6	0	14	1
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6	2	6	191	188	4
7	2	6	21	44	21
8	2	6	163	172	4
9	2	6	100	99	5
10	2	6	78	73	9
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2	3	6	243	243	4
3	4	6	226	223	3
4	4	6	269	268	3
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8	4	6	110	107	3
9	4	6	90	83	4
10	4	6	71	60	6
0	5	6	30	17	18
1	5	6	156	152	4
2	5	6	65	11	11
3	5	6	146	141	4
4	5	6	232	235	3
5	5	6	600	596	5
6	5	6	380	370	3
7	5	6	363	367	3
8	5	6	50	59	6
9	5	6	127	126	4
10	5	6	196	199	4
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1	6	6	82	83	6
2	6	6	62	56	12
3	6	6	27	22	26
4	6	6	78	82	4
5	6	6	228	228	3
6	6	6	241	238	3
7	6	6	175	169	3
8	6	6	108	111	4
9	6	6	138	144	4
10	6	6	48	28	8
0	7	6	94	94	5
1	7	6	40	32	12
2	7	6	41	51	20
3	7	6	249	255	4
4	7	6	115	119	3
5	7	6	146	152	3
6	7	6	264	261	3
7	7	6	118	112	3
8	7	6	84	88	4
9	7	6	70	66	5
10	7	6	134	137	4
0	8	6	29	18	20
1	8	6	58	50	12
2	8	6	58	5	13
3	8	6	183	179	4
4	8	6	142	144	3
5	8	6	377	373	4
6	8	6	174	169	3
7	8	6	67	69	5
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9	8	6	83	87	5
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0	9	6	4	30	4
1	9	6	45	22	18
2	9	6	61	65	7
3	9	6	118	113	3
4	9	6	86	81	4
5	9	6	72	63	5
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7	9	6	79	85	5
8	9	6	82	86	5
9	10	6	72	69	6
10	10	6	62	68	6
0	11	6	38	45	12
1	11	6	54	60	8
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4	11	6	191	192	4
5	11	6	57	43	7
6	11	6	57	55	7
7	11	6	60	62	7
8	11	6	21	36	20
9	11	6	31	36	31
10	11	6	31	22	30
0	12	6	152	154	6
1	12	6	44	52	10
2	12	6	37	36	13
3	12	6	39	26	12
4	12	6	28	14	28
5	12	6	64	40	11
6	12	6	21	45	20
7	12	6	68	65	10
8	12	6	23	36	23
9	12	6	35	22	31
10	12	6	29	26	29
0	13	6	18	16	17
1	13	6	49	33	16
2	13	6	41	38	21
3	0	7	178	177	3
4	0	7	351	343	3
5	0	7	278	283	3
6	0	7	152	158	3
7	0	7	39	33	9
8	0	7	348	348	4
9	0	7	65	53	7
10	0	7	82	74	6
0	1	7	51	18	14
1	1	7	71	70	6
2	1	7	311	313	3
3	1	7	342	338	3
4	1	7	330	329	3
5	1	7	161	169	3
6	1	7	60	57	6
7	1	7	169	174	3
8	1	7	129	136	4
9	1	7	121	104	4
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2	2	7	215	213	3
3	2	7	694	675	5
4	2	7	64	46	5
5	2	7	34	44	10
6	2	7	130	131	3
7	2	7	267	276	4
8	2	7	226	234	4
9	2	7	67	42	6
10	2	7	41	28	18

Observed and calculated structure factors

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
10	2	7	19	13	19	5	0	8	36	27	10	5	9	8	34	42	15	0	7	9	0	24	1	1	5	10	123	128	4
0	3	7	0	17	1	6	0	8	295	301	4	6	9	8	65	47	11	1	7	9	93	113	4	2	5	10	63	75	6
1	3	7	113	107	3	7	0	8	34	12	13	7	9	8	46	30	17	2	7	9	150	146	4	3	5	10	30	35	13
2	3	7	269	258	3	8	0	8	38	7	12	0	10	8	0	19	1	3	7	9	49	49	8	4	5	10	47	49	8
3	3	7	184	177	3	9	0	8	99	92	8	1	10	8	87	89	5	4	7	9	53	61	8	5	5	10	54	54	8
4	3	7	77	72	4	10	0	8	49	10	15	2	10	8	52	59	9	5	7	9	66	69	6	6	5	10	89	87	5
5	3	7	51	53	6	0	1	8	334	332	4	3	10	8	103	100	5	6	7	9	0	21	1	7	5	10	107	111	5
6	3	7	112	111	4	1	1	8	195	195	3	4	10	8	0	32	1	7	7	9	51	51	14	8	5	10	34	39	34
7	3	7	80	79	5	2	1	8	81	87	4	5	10	8	13	24	12	8	7	9	68	40	11	0	6	10	38	55	15
8	3	7	89	88	5	3	1	8	361	355	3	6	10	8	0	10	1	0	8	9	56	19	11	1	6	10	105	109	4
9	3	7	44	28	17	4	1	8	88	101	4	0	11	8	0	10	1	1	8	9	122	115	4	2	6	10	59	51	6
10	3	7	44	16	18	5	1	8	200	203	3	1	11	8	56	56	12	2	8	9	113	104	4	3	6	10	50	61	8
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3	4	7	205	200	3	9	1	8	28	16	27	5	11	8	43	32	19	6	8	9	42	37	17	7	6	10	52	58	13
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7	4	7	138	135	4	2	2	8	339	334	3	3	12	8	22	22	21	2	9	9	55	58	8	2	7	10	90	97	5
8	4	7	18	22	18	3	2	8	319	305	3	1	0	9	44	38	7	3	9	9	0	5	1	3	7	10	22	29	22
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0	5	7	0	4	1	5	2	8	52	56	7	3	0	9	0	22	1	5	9	9	19	24	18	5	7	10	112	114	5
1	5	7	179	171	3	6	2	8	299	310	4	4	0	9	65	62	5	6	9	9	39	50	22	6	7	10	84	73	6
2	5	7	119	119	3	7	2	8	282	286	4	5	0	9	67	72	5	0	10	9	67	57	10	7	7	10	46	61	17
3	5	7	130	120	3	8	2	8	64	46	7	6	0	9	124	124	4	1	10	9	60	60	7	8	7	10	39	37	24
4	5	7	64	65	5	9	2	8	41	25	19	7	0	9	169	175	4	2	10	9	0	21	1	0	8	10	17	21	16
5	5	7	41	53	9	10	2	8	0	34	1	8	0	9	33	9	15	3	10	9	50	51	9	1	8	10	151	147	4
6	5	7	142	138	4	0	3	8	96	90	5	9	0	9	79	73	9	4	10	9	0	20	1	2	8	10	0	13	1
7	5	7	27	49	26	1	3	8	169	165	3	10	0	9	21	9	21	5	10	9	29	21	28	3	8	10	169	169	4
8	5	7	18	19	18	2	3	8	244	236	3	0	1	9	385	376	4	6	10	9	44	12	17	4	8	10	100	106	5
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0	6	7	0	9	1	4	3	8	76	79	5	2	1	9	373	356	3	1	11	9	62	25	11	6	8	10	87	72	9
1	6	7	73	83	5	5	3	8	99	103	4	3	1	9	50	44	6	2	11	9	62	71	12	7	8	10	0	34	1
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7	6	7	125	121	4	1	4	8	60	39	5	9	1	9	41	34	19	0	0	10	140	138	4	5	9	10	52	32	14
8	6	7	72	56	10	2	4	8	181	177	3	10	1	9	34	15	34	1	0	10	31	34	10	6	9	10	54	53	13
9	6	7	38	39	22	3	4	8	143	140	3	0	2	9	62	52	7	2	0	10	114	110	3	0	10	10	69	76	10
0	7	7	97	91	6	4	4	8	74	72	5	1	2	9	56	48	5	3	0	10	0	12	1	1	10	10	0	23	1
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3	7	7	224	227	4	7	4	8	72	75	6	4	2	9	103	106	4	6	0	10	78	75	5	4	10	10	24	27	23
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7	7	7	36	17	13	1	5	8	130	129	3	8	2	9	81	80	6	0	1	10	190	189	4	2	11	10	68	53	11
8	7	7	0	17	1	2	5	8	50	52	6	9	2	9	0	15	1	1	1	10	140	142	3	3	11	10	54	27	14
0	8	7	133	137	6	3	5	8	131	125	3	0	3	9	78	86	6	2	1	10	81	83	4	4	11	10	38	39	25
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3	8	7	70	67	6	6	5	8	77	81	6	3	3	9	67	63	5	5	1	10	150	158	4	1	0	11	114	116	3
4	8	7	67	72	6	7	5	8	63	59	7	4	3	9	12	24	12	6	1	10	230	233	4	2	0	11	186	184	3
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6	8	7	26	33	26	9	5	8	0	12	1	6	3	9	160	166	4	8	1	10	67	66	7	4	0	11	0	31	1
7	8	7	35	17	30	0	6	8	136	138	5	7	3	9	238	247	4	9	1	10	0	0	1	5	0	11	93	95	5
8	8	7	46	33	17	1	6	8	67	66	5	8	3	9	64	62	7	0	2	10	170	170	4	6	0	11	29	26	19
0	9	7	56	49	11	2	6	8	196	190	3	9	3	9	40	40	21	1	2	10	301	293	3	7	0	11	50	50	8
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4	9	7	22	23	22	6	6	8	110	112	5	3	4	9	32	49	11	5	2	10	67	70	5	1	1	11	189	186	3
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7	9	7	6	21	5	9	6	8	47	35	16	6	4	9	35	38	13	8	2	10	50	58	9	4	1	11	93	99	4
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2	10	7	89	80	5	2	7	8	73	74	5	9	4	9	24	14	23	1	3	10	255	251	3	7	1	11	62	56	7
3	10	7	70	79	6	3	7	8	219	220	4	0	5	9	129	124	5	2	3	10	90	85	4	8	1	11	74	62	6
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5	10	7	0	15	1	5	7	8	0	16	1	2	5	9	204	199	3	4	3	10	117	122	4	0	2	11	213	206	4
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1	11	7	43	30	11	8	7	8	53	55	14	5	5	9	8	11	8	7	3	10	54	53	8	3	2	11	106	102	4
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3	11	7	17	41	17	1	8	8	88	93	5	7	5	9	104	98	5	9	3	10	42	47	19	5	2	11	257	255	4
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4	0	8	98	89	4	4	9	8	35	22	14	8	6	9	43	44	18	0	5	10	218	208	5	6	3	11	67	49	6

Observed and calculated structure

h	k	l	10Fo	10Fc	10σ	h	k	l	10Fo	10Fc	10σ	h	k	l	10Fo	10Fc	10σ	h	k	l	10Fo	10Fc	10σ	h	k	l	10Fo	10Fc	10σ
7	3	11	39	50	12	6	2	12	47	44	9	5	2	13	37	44	12	7	2	14	37	38	23	7	3	15	25	22	24
8	3	11	98	94	8	7	2	12	34	31	14	6	2	13	44	41	10	8	2	14	48	17	16	0	4	15	85	95	8
9	3	11	0	25	1	8	2	12	57	51	12	7	2	13	75	81	6	0	3	14	170	174	5	1	4	15	73	72	6
0	4	11	0	1	1	9	2	12	34	24	33	8	2	13	63	38	12	1	3	14	83	83	5	2	4	15	0	28	1
1	4	11	87	88	4	0	3	12	197	196	5	0	3	13	69	80	8	2	3	14	80	89	5	3	4	15	49	42	8
2	4	11	137	137	3	1	3	12	151	155	3	1	3	13	94	94	4	3	3	14	64	72	6	4	4	15	0	34	1
3	4	11	99	99	4	2	3	12	51	51	7	2	3	13	164	162	3	4	3	14	103	113	5	5	4	15	40	39	12
4	4	11	0	36	1	3	3	12	168	159	3	3	3	13	99	102	4	5	3	14	38	41	12	6	4	15	46	30	16
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6	4	11	79	91	6	5	3	12	29	29	18	5	3	13	48	62	9	7	3	14	49	32	15	0	5	15	67	52	9
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1	5	11	79	86	5	1	4	12	52	62	7	1	4	13	50	62	7	3	4	14	39	55	11	5	5	15	28	49	27
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1	6	11	120	123	4	1	5	12	41	40	9	1	5	13	180	173	4	4	5	14	67	78	6	6	6	15	52	26	14
2	6	11	69	77	6	2	5	12	120	116	4	2	5	13	77	78	5	5	5	14	38	53	12	0	7	15	20	5	19
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1	8	11	116	113	4	1	7	12	207	205	4	1	7	13	144	144	4	5	7	14	63	41	11	0	10	15	81	68	14
2	8	11	83	78	5	2	7	12	103	101	5	2	7	13	58	61	7	6	7	14	69	43	11	1	10	15	0	13	1
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2	9	11	125	120	5	2	8	12	104	102	5	3	8	13	47	41	10	1	9	14	68	50	10	7	0	16	0	15	1
3	9	11	43	33	11	3	8	12	76	89	6	4	8	13	34	42	33	2	9	14	16	19	16	0	1	16	121	119	6
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1	1	12	120	118	3	8	0	13	22	26	22	1	1	14	135	129	4	1	2	15	76	77	5	1	4	16	25	41	24
2	1	12	110	106	4	0	1	13	84	88	6	2	1	14	22	36	21	2	2	15	133	131	4	2	4	16	43	51	10
3	1	12	55	59	6	1	1	13	131	133	3	3	1	14	69	76	6	3	2	15	93	98	5	3	4	16	83	81	6
4	1	12	37	47	10	2	1	13	87	92	4	4	1	14	91	102	5	4	2	15	104	110	5	4	4	16	84	93	6
5	1	12	152	149	4	3	1	13	171	165	3	5	1	14	101	101	5	5	2	15	62	67	7	5	4	16	37	42	22
6	1	12	122	130	4	4	1	13	117	113	4	6	1	14	0	17	1	6	2	15	42	8	11	6	4	16	23	20	23
7	1	12	31	43	17	5	1	13	139	144	4	7	1	14	29	33	29	7	2	15	26	27	25	7	4	16	35	19	34
8	1	12	35	39	28	6	1	13	74	78	6	8	1	14	51	14	14	8	2	15	65	51	12	0	5	16	0	2	1
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2	2	12	49	52	7	1	2	13	77	72	5	3	2	14	188	186	4	3	3	15	84	83	5	4	5	16	29	45	22
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4	2	12	169	167	4	3	2	13	126	130	4	5	2	14	79	85	6	5	3	15	55	56	8	6	5	16	0	28	1
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Observed and calculated structure factors

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
1	6	16	57	66	8	4	3	17	31	42	17	1	2	18	98	98	5	0	2	19	194	181	6	1	3	20	0	22	1
2	6	16	40	49	12	5	3	17	46	63	16	2	2	18	69	74	7	1	2	19	12	25	12	2	3	20	0	45	1
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3	2	17	21	21	21	6	0	18	90	69	9	3	0	19	11	24	11	3	1	20	0	30	1	2	0	22	57	53	13
4	2	17	114	102	5	0	1	18	74	71	9	4	0	19	0	11	1	4	1	20	34	19	33	0	1	22	28	10	27
5	2	17	0	41	1	1	1	18	9	14	9	5	0	19	59	46	12	5	1	20	22	28	22	1	1	22	12	26	12
6	2	17	13	26	12	2	1	18	54	50	8	0	1	19	109	91	7	0	2	20	49	63	23	2	1	22	40	56	22
7	2	17	30	19	30	3	1	18	40	46	11	1	1	19	0	17	1	1	2	20	6	29	5	0	2	22	0	20	1
0	3	17	16	23	15	4	1	18	24	40	24	2	1	19	0	19	1	2	2	20	17	29	17	1	2	22	44	6	17
1	3	17	161	154	4	5	1	18	45	47	17	3	1	19	0	20	1	3	2	20	0	5	1	2	2	22	0	33	1
2	3	17	30	30	18	6	1	18	46	42	17	4	1	19	45	12	17	4	2	20	0	3	1	0	3	22	0	17	1
3	3	17	60	62	7	0	2	18	51	28	12	5	1	19	45	24	17	0	3	20	53	4	21	1	3	22	43	30	19

Experimental Section[34]

General Procedure for Formylation of Phenols[35]

Magnesium (3.60 g, 150 mmol) and magnesium methoxide (682 mg, 0.750 mmol) were placed in a 500 mL flask in 71 mL of anhydrous methanol and 30 mL of toluene to be heated to reflux for 1.5 h. To the white, cloudy solution was added the phenol (250 mmol) and heating was continued for another h. An additional 200 mL of toluene was added and the methanol-toluene azeotrope was then removed by distillation (bp = 63 °C) from the clear, yellow solution. Once the distillation temperature rose above 100 °C, heating was temporarily stopped and another 50 mL of toluene was added to the white suspension. Paraformaldehyde (23.0 g, 750 mmol) was then added in 3-5 g batches over 1 h with resumed heating. The thick, yellow solution was stirred at 110 °C and the low boiling materials were removed by distillation throughout the addition of the paraformaldehyde. After all the paraformaldehyde was added, heating was continued for another 2 h. The solution was then cooled to room temperature, and diluted with 250 mL of a 10% aqueous sulfuric acid solution. The mixture was stirred for 1.5 h at 60 °C. The organic layer was separated and the aqueous layer was extracted with another 50 mL of toluene. The combined organic layers were washed with 150 mL of a 10% aqueous solution of sulfuric acid and 100 mL of a saturated aqueous NaCl solution. After drying over anhydrous Na_2SO_4, the organic solution was concentrated. The salicylaldehyde was purified by flash chromatography on silica gel.

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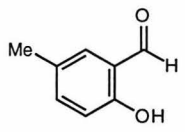
34. For general procedures, see chapter 2 experimental section.

35. Aldred, R.; Johnston, R.; Levin, D.; Neilan, J. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1823.



Isolated in 81% yield as a yellow, crystalline solid.[35]

mp: 55-56 °C

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 10.84 (1H, s), 9.82 (1H, s), 7.32 (1H, d, *J* = 9.2), 7.31 (1H, s), 6.88 (1H, d, *J* = 9.2), 2.32 (3H, s).

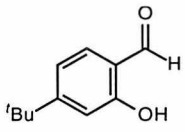
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 196.5, 159.4, 138.0, 133.3, 129.0, 120.2, 117.3, 20.2.

IR: (thin film)

3024, 2950, 2919, 2854, 2740, 1660, 1625, 1591, 1486, 1376, 1345, 1323, 1284, 1239, 1210, 1152, 1047, 1011, 932, 910, 894, 832, 770, 750, 725, 670 cm^{-1}.

TLC: R_f 0.63 (4:1 hexane/ethyl acetate)



Isolated in 70% yield as a clear, colorless oil.[35]

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 11.01 (1H, s), 9.82 (1H, s), 7.46 (1H, d, *J* = 8.0), 7.04 (1H, dd, *J* = 8.0, 1.6), 6.99 (1H, d, *J* = 1.6), 1.30 (9H, s).

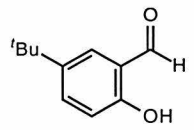
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 195.7, 161.7, 161.5, 133.2, 118.4, 117.5, 114.3, 35.4, 30.7.

IR: (thin film)

3167, 2966, 2906, 2869, 2745, 1654, 1629, 1566, 1503, 1477, 1459, 1377, 1345, 1323, 1285, 1245, 1216, 1197, 1144, 1088, 1025, 946, 876, 831, 813, 795, 747, 706, 663 cm^{-1}.

TLC: R_f 0.78 (4:1 hexane/ethyl acetate)



Isolated in 75% yield as a clear, colorless oil.[36]

^1H NMR: (300 MHz, C_6D_6)

δ 11.42 (1H, s), 9.22 (1H, s), 7.10 (1H, dd, *J* = 8.8, 2.5), 6.97 (1H, d, *J* = 2.5), 6.84 (1H, d, *J* = 8.8), 1.09 (9H, s).

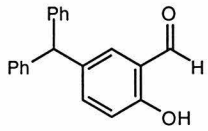
^{13}C NMR: (75 MHz, C_6D_6)

δ 196.8, 160.1, 142.3, 134.5, 129.8, 120.4, 117.5, 33.9, 31.2.

IR: (thin film)

3178, 3072, 2955, 2861, 1696, 1655, 1619, 1584, 1478, 1390, 1373, 1361, 1314, 1284, 1261, 1226, 1179, 926, 826, 773, 732, 650, 603 cm^{-1}.

TLC: R_f 0.68 (4:1 hexane/ethyl acetate)



Isolated in 80% yield as white powder.

mp: 104-105 °C

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36. Kerr, J. M.; Suckling, C. J.; Bamfield, P. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 887.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 10.95 (1H, s), 9.76 (1H, s), 7.36-7.21 (8H, m), 7.14-7.09 (4H, m), 6.94 (1H, d, J = 9.2), 5.54 (1H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 196.7, 160.2, 143.2, 138.3, 135.7, 133.8, 129.3, 128.5, 126.6, 120.2, 117.6, 55.6.

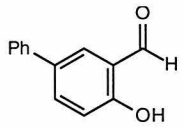
IR: (thin film)

3060, 3025, 2850, 1656, 1622, 1588, 1493, 1482, 1451, 1375, 1282, 1192, 1140, 1078, 1030, 953, 914, 847, 772, 741, 699 cm^{-1}.

HRMS: (FAB)

calcd for $C_{20}H_{17}O_2$ $(M+H)^+$ 289.1229, found 289.1228.

TLC: R_f 0.51 (4:1 hexane/ethyl acetate)



Isolated in 70% yield as yellow flakes after recrystallization from ethanol.

mp: 100-101 °C

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 11.04 (1H, s), 9.95 (1H, s), 7.80-7.73 (2H, m), 7.60-7.35 (5H, m), 7.09 (1H, d, J = 12).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 196.6, 160.8, 139.2, 135.6, 133.2, 131.8, 128.8, 127.3, 126.5, 120.6, 118.0.

IR: (thin film)

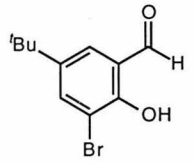
3094, 2853, 1651, 1621, 1588, 1510, 1473, 1376, 1299, 1260, 1178, 904, 892, 853, 768, 752, 716, 692, 674, 585 cm^{-1}.

HRMS: (EI)

calcd for $C_{13}H_{10}O_2$ $(M)^+$ 198.0681, found 198.0681.

TLC: R_f 0.75 (4:1 hexane/ethyl acetate)

3-Bromo-5-*t*butylsalicylaldehyde. To a 250 mL flask containing a solution of the crude 5-*t*butylsalicylaldehyde (as prepared above in the formylation procedure) (31.4 g, 176 mmol) in 90 mL of glacial acetic acid was added bromine (11.4 mL, 220 mmol) dropwise. The orange solution was allowed to stir for 24 h at 23 °C. The solution was then diluted with 100 mL of water to precipitate the product. The crystals were collected by suction filtration and washed with water (3 x 50 mL). The yellow solid was dissolved in hot 10:1 hexane/ethyl acetate and treated with charcoal. The impurities were removed passing the hot solution through filter paper. The solution was allowed to cool and gave yellow crystals in 42% yield (27.1 g).



mp: 81-82 °C

^{1}H NMR: (300 MHz, C_6D_6)

δ 11.77 (1H, s), 8.96 (1H, s), 7.65 (1H, d, J = 2.3), 6.79 (1H, d, J = 2.3), 0.98 (9H, s).

^{13}C NMR: (75 MHz, C_6D_6)

δ 196.1, 156.5, 143.6, 137.3, 129.3, 120.9, 111.3, 33.9, 30.9.

IR: (thin film)

3072, 3037, 2955, 2861, 2731, 1661, 1614, 1455, 1414, 1378, 1325, 1261, 1214, 1155, 1114, 1014, 938, 885, 850, 814, 732, 691, 626 cm^{-1}.

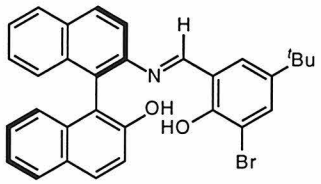
HRMS: (EI)

calcd for $C_{11}H_{13}{}^{79}BrO_2$ $(M)^+$ 256.0099, found 256.0092.

TLC: R_f 0.77 (4:1 hexane/ethyl acetate)

General Procedure for Schiff Base Formation

(*R*)-2-Amino-2'-hydroxy-1,1'-binaphthyl (0.100 g, 0.350 mmol, 1.0 equiv) and 1.2 equivalents of the salicylaldehyde (0.420 mmol) were taken up in 5 mL of absolute ethanol and heated to reflux for 24 h. The solvent was removed *in vacuo* and the product was isolated by flash chromatography on silica gel or by recrystallization. The isolated orange powder was dried under vacuum (2mm Hg) over 8 h.



27

Isolated in 85% yield as an orange powder after chromatography with 4:1 hexane/ethyl acetate as eluent.

mp: 164 °C

$[\alpha]_D^{19}$ +22.8° (*c* = 1.0, $CHCl_3$)

^{1}H NMR: (300 MHz, DMSO-d6)

δ 13.21 (1H, s), 9.59 (1H, s), 9.07 (1H, s), 8.16 (1H, d, *J* = 8.9), 8.04 (1H, d, *J* = 7.7), 7.93 (1H, d, *J* = 9.2), 7.90 (1H, d, *J* = 9.2), 7.87 (1H, d, *J* = 7.7), 7.61 (1H, s), 7.54 (1H, s), 7.48 (1H, dd, *J* = 7.7, 7.0), 7.37 (1H, d, *J* = 8.9), 7.31 (1H, dd, *J* = 7.7, 7.0), 7.22 (1H, dd, *J* = 7.7, 7.0), 7.13 (1H, dd, *J* = 8.4, 7.7), 7.10 (1H, d, *J* = 8.4), 6.79 (1H, d, *J* = 7.7), 1.22 (9H, s).

^{13}C NMR: (75 MHz, DMSO-d$_6$)

δ 162.8, 154.8, 152.8, 143.1, 142.3, 133.6, 133.1, 133.0, 132.4, 129.5, 129.3, 129.1, 129.0, 128.2, 128.1, 127.9, 126.8, 126.3, 126.1, 125.9, 123.8, 122.5, 119.5, 118.4, 117.8, 115.4, 109.5, 33.9, 31.0.

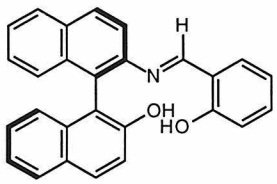
IR: (thin film)

3389, 3049, 2955, 2908, 2861, 1608, 1502, 1461, 1425, 1343, 1261, 1208, 1161, 1138, 1067, 973, 950, 926, 873, 808, 744, 714 cm^{-1}.

HRMS: (EI)

calcd for $C_{31}H_{26}{}^{79}BrNO_2$ $(M)^+$ 523.1147, found 523.1156.

TLC: R_f 0.39 (4:1 hexane/ethyl acetate)



Isolated in 91% yield as orange needles after recrystallization from toluene.

mp: 223-224 °C

$[\alpha]_D^{19}$ +111° (*c* = 0.55, $CHCl_3$)

^{1}H NMR: (300 MHz, DMSO-d$_6$)

δ 12.44 (1H, s), 9.49 (1H, s), 9.07 (1H, s), 8.15 (1H, d, *J* = 8.8), 8.04 (1H, d, *J* = 8.0), 7.92 (2H, d, *J* = 8.8), 7.87 (1H, d, *J* = 8.0), 7.50 (2H, dd, *J* = 8.0, 7.0), 7.34 (1H, d, *J* = 8.8), 7.30 (1H, d, *J* = 8.8), 7.24 (1H, dd, *J* = 8.0, 7.0), 7.22 (1H, dd, *J* = 8.0, 7.0), 7.14 (2H, d, *J* = 8.0), 6.85 (1H, dd, *J* = 8.0, 7.0), 6.82 (1H, d, *J* = 8.0), 6.63 (1H, d, *J* = 8.0).

^{13}C NMR: (75 MHz, DMSO-d_6)

δ 162.4, 160.1, 152.7, 143.3, 133.6, 133.1, 132.9, 132.6, 132.4, 129.4, 129.1, 128.2, 128.1, 127.9, 126.7, 126.3, 126.1, 125.8, 123.8, 122.4, 119.2, 118.7, 118.4, 117.4, 116.4, 115.8.

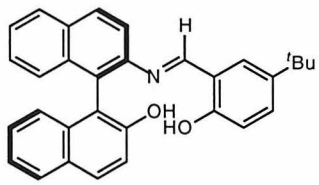
IR: (thin film)

3336, 3057, 1609, 1506, 1436, 1346, 1278, 1201, 1150, 979, 927, 815, 753 cm^{-1}.

HRMS: (EI)

calcd for $C_{27}H_{19}NO_2$ $(M)^+$ 389.1416, found 389.1419.

TLC: R_f = 0.21 in 4:1 hexane/ethyl acetate



Isolated as orange powder by chromatography using 6:1 hexane/ethyl acetate as eluent in 75% yield.

mp: 148-150 °C

$[\alpha]_D^{19}$ +83.2° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 12.21 (1H, s), 9.50 (1H, s), 9.07 (1H, s), 8.15 (1H, d, *J* = 8.8), 8.03 (1H, d, *J* = 8.0), 7.91 (2H, d, *J* = 8.8), 7.86 (1H, d, *J* = 8.0), 7.54 (1H, s), 7.47 (1H, dd, *J* = 8.0, 7.0), 7.36 (1H, d, *J* = 8.8), 7.30 (1H, dd, *J* = 8.0, 7.0), 7.29 (1H, d, *J* = 8.0), 7.21 (1H, dd, *J* = 8.0, 7.0), 7.16 (1H, d, *J* = 8.8), 7.12 (1H, dd, *J* = 8.0, 7.0), 6.84 (1H, d, *J* = 8.0), 6.58 (1H, d, *J* = 8.8), 1.22 (9H, s).

^{13}C NMR: (75 MHz, DMSO-d_6)

δ 162.9, 157.9, 152.7, 143.6, 140.9, 133.6, 133.1, 132.3, 130.2, 129.3, 129.1, 128.9, 128.9, 128.1, 128.1, 127.9, 126.6, 126.2, 126.1, 125.6, 123.9, 122.4, 118.5, 118.3, 117.5, 116.0, 115.9, 33.7, 31.2.

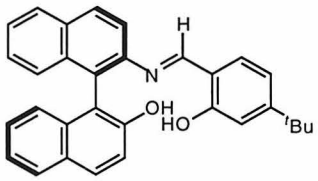
IR: (thin film)

3366, 3049, 2943, 2861, 2355, 1619, 1572, 1484, 1461, 1425, 1373, 1355, 1337, 1284, 1261, 1202, 1173, 1138, 1067, 1020, 973, 920, 867, 814, 744 cm^{-1}.

HRMS: (EI)

calcd for $C_{31}H_{27}NO_2$ $(M)^+$ 445.2042, found 445.2045.

TLC: R_f 0.60 (4:1 hexane/ethyl acetate)



Isolated in 70% yield by chromatography using 6:1 hexane/ethyl acetate as eluent.

mp: 128-130 °C

$[\alpha]_D^{19}$ +100° (*c* = 0.42, $CHCl_3$)

^1H NMR: (300 MHz, DMSO-d_6)

δ 12.2 (1H, s), 9.50 (1H, s), 9.07 (1H, s), 8.03 (1H, d, *J* = 8.8), 7.91 (2H, d, *J* = 8.8), 7.86 (1H, d, *J* = 8.0), 7.54 (1H, s), 7.47 (1H, dd, *J* = 8.0, 7.0), 7.36 (2H, d, *J* = 8.8), 7.30 (1H, dd, *J* = 8.0, 7.0), 7.29 (1H, d, *J* = 8.0), 7.21 (1H, dd, *J* = 8.0, 7.0), 7.16 (1H, d, *J* = 8.8), 7.12 (1H, dd, *J* = 8.0, 7.0), 6.84 (1H, d, *J* = 8.0), 6.58 (1H, d, *J* = 8.8), 1.22 (9H, s).

^{13}C NMR: (75 MHz, DMSO-d$_6$)

δ 162.9, 157.9, 152.7, 143.6, 140.9, 133.6, 133.1, 132.3, 130.2, 129.3, 129.1, 128.9, 128.9, 128.1, 128.1, 127.9, 126.6, 126.2, 126.1, 125.6, 123.9, 122.4, 118.5, 118.3, 117.5, 116.0, 115.9, 33.7, 31.2.

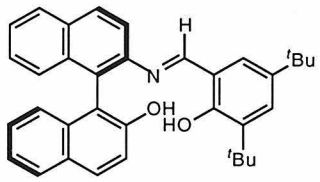
IR: (thin film)

3519, 3383, 3058, 2964, 1606, 1554, 1508, 1459, 1432, 1367, 1348, 1272, 1197, 1144, 1092, 977, 951, 865, 816, 749 cm^{-1}.

HRMS: (FAB)

calcd for $C_{31}H_{28}NO_2$ $(M+H)^+$ 446.2120, found 446.2120.

TLC: R_f 0.63 (4:1 hexane/ethyl acetate)



Isolated by chromatography using 8:1 hexane/ethyl acetate as eluent in 60% yield.

mp: 119-121 °C

$[\alpha]_D^{19}$ +139° (*c* = 0.43, $CHCl_3$)

^{1}H NMR: (300 MHz, DMSO-d$_6$)

δ 13.02 (1H, s), 9.46 (1H, s), 8.97 (1H, s), 8.14 (1H, d, *J* = 8.9), 8.04 (1H, d, *J* = 8.1), 7.89 (1H, d, *J* = 8.9), 7.87 (1H, d, *J* = 8.9), 7.85 (1H, d, *J* = 8.1), 7.48 (1H, t, *J* = 8.1), 7.36 (1H, d, *J* = 1.0), 7.32 (1H, d, *J* = 8.9), 7.22-7.18 (3H, m), 7.13 (1H, t, *J* = 8.3), 6.81 (1H, d, *J* = 8.3), 1.22 (9H, s), 1.13 (9H, s).

^{13}C NMR: (75 MHz, DMSO-d$_6$)

δ 163.3, 157.4, 152.6, 143.5, 139.4, 135.4, 133.6, 133.0, 132.1, 129.0, 129.0, 128.5, 128.1, 128.0, 127.8, 126.9, 126.7, 126.4, 126.0, 126.0, 125.4, 123.7, 122.1, 118.2, 118.1, 117.6, 115.7, 34.3, 33.7, 31.1, 28.9.

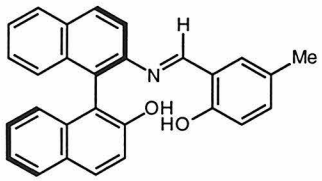
IR: (thin film)

3528, 3425, 3057, 2958, 2907, 2861, 1611, 1582, 1505, 1467, 1438, 1392, 1361, 1270, 1250, 1205, 1170, 1145, 1128, 975, 816, 773, 747 cm^{-1}.

HRMS: (EI)

calcd for $C_{35}H_{35}NO_2$ $(M)^+$ 501.2668, found 501.2670.

TLC: R_f 0.51 (4:1 hexane/ethyl acetate)



Isolated by recrystallization from toluene in 60% yield.

mp: 234-236 °C

$[\alpha]_D^{19}$ +88.3° (c = 0.33, $CHCl_3$)

^1H NMR: (300 MHz, DMSO-d_6)

δ 12.19 (1H, s), 9.52 (1H, s), 8.99 (1H, s), 8.14 (1H, d, J = 8.8), 8.03 (1H, d, J = 7.9), 7.92 (1H, d, J = 7.5), 7.89 (1H, d, J = 8.1), 7.87 (1H, d, J = 7.9), 7.47 (1H, t, J = 7.5), 7.36 (1H, d, J = 8.8), 7.33-7.10 (5H, m), 7.05 (1H, d, J = 8.1), 6.84 (1H, d, J = 8.1), 6.54 (1H, d, J = 8.3), 2.17 (3H, s).

^{13}C NMR: (75 MHz, DMSO-d_6)

δ 162.2, 157.9, 152.7, 143.5, 133.5, 133.1, 132.3, 132.2, 129.2, 129.0, 128.9, 128.8, 128.0, 128.0, 127.9, 127.1, 126.5, 126.1, 126.0, 125.6, 123.8, 122.3, 118.8, 118.3, 117.4, 116.2, 115.8, 19.8.

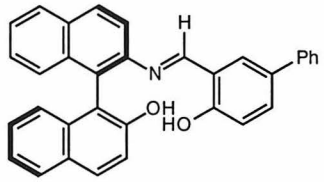
IR: (thin film)

3380, 3049, 2908, 1625, 1579, 1490, 1433, 1345, 1280, 1210, 1156, 979, 812, 748 cm^{-1}.

HRMS: (EI)

calcd for $C_{28}H_{21}NO_2$ $(M)^+$ 403.1572, found 403.1580.

TLC: R_f 0.32 (4:1 hexane/ethyl acetate)



Isolated by chromatography using 6:1 hexane/ethyl acetate as eluent in 84% yield.

mp: 130-132 °C

$[\alpha]_D^{19}$ +48.8° (*c* = 0.87, $CHCl_3$)

^{1}H NMR: (300 MHz, DMSO-d_6)

δ 12.49 (1H, s), 9.49 (1H, s), 9.15 (1H, s), 8.17 (1H, d, *J* = 8.9), 8.04 (1H, d, *J* = 8.1), 7.96-7.87 (4H, m), 7.59-7.12 (12H, m), 6.88 (1H, d, *J* = 8.3), 6.75 (1H, d, *J* = 8.5).

^{13}C NMR: (75 MHz, DMSO-d_6)

δ 162.3, 159.7, 152.7, 143.3, 139.1, 133.5, 133.1, 132.3, 131.0, 130.7, 130.5, 129.3, 129.1, 128.7, 128.0, 128.0, 127.9, 126.7, 126.5, 126.2, 126.1, 125.9, 125.6, 123.8, 122.4, 119.4, 118.3, 117.3, 116.9, 116.9, 115.8.

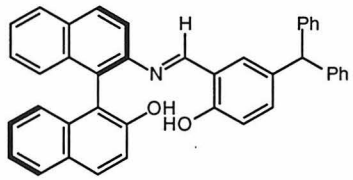
IR: (thin film)

3519, 3384, 3057, 2963, 1611, 1504, 1462, 1433, 1362, 1346, 1265, 1206, 1166, 1145, 1071, 1025, 980, 930, 863, 815, 775, 749, 718 cm^{-1}.

HRMS: (EI)

calcd for $C_{33}H_{23}NO_2$ $(M)^+$ 465.1729, found 465.1732.

TLC: R_f 0.38 (4:1 hexane/ethyl acetate)



Isolated by chromatography using 5:1 hexane/ethyl acetate as eluent in 67% yield.

mp: 120-122 °C

$[\alpha]_D^{19}$ +31.1° (*c* = 0.34, $CHCl_3$)

^1H NMR: (300 MHz, DMSO-d_6)

12.40 (1H, s), 9.49 (1H, s), 8.99 (1H, s), 8.10 (1H, d, *J* = 9.0), 8.02 (1H, d, *J* = 8.1), 7.91 (2H, d, *J* = 9.0), 7.86 (1H, d, *J* = 7.8), 7.46 (1H, t, *J* = 7.8), 7.35-7.06 (16H, m), 6.98 (1H, dd, *J* = 8.5, 2.1), 6.79 (1H, d, *J* = 8.3), 6.59 (1H, d, *J* = 8.5), 5.51 (1H, s).

^{13}C NMR: (75 MHz, DMSO-d_6)

δ 162.1, 158.6, 152.6, 143.7, 143.3, 134.0, 133.5, 133.0, 132.5, 132.3, 129.2, 129.0, 129.0, 128.8, 128.8, 128.2, 128.2, 128.0, 127.9, 127.9, 126.5, 126.1, 126.0, 125.6, 123.7, 122.3, 118.8, 118.3, 117.4, 116.3, 115.8, 54.8.

IR: (thin film)

3519, 3389, 3060, 3025, 2943, 2919, 1619, 1572, 1484, 1449, 1431, 1372, 1343, 1279, 1267, 1202, 1173, 1143, 1073, 1026, 979, 944, 926, 861, 808, 744, 697 cm^{-1}.

HRMS: (FAB)

calcd for $C_{40}H_{30}NO_2$ $(M+H)^+$ 556.2276, found 556.2282.

TLC: R_f 0.31 (4:1 hexane/ethyl acetate)

General Procedure for Preparation of Silyl Ketene Acetals[37]

To a solution of 11.2 mL of diisopropylamine (80 mmol, 1.1 equiv) in 50 mL of THF at 0 °C was added 50 mL of a 1.60 M solution of n-butyllithium in hexanes (80 mmol, 1.1 equiv) dropwise. After stirring the solution for 15 min at 0 °C the solution was cooled to -78 °C. To the solution was added the alkyl acetate (73 mmol, 1.0 equiv) dropwise. The solution was stirred at -78 °C for another 45 min and then 11.0 mL of trimethylsilyl chloride (87 mmol, 1.2 equiv) was added to quench to the enolate. The solution was kept at -78 °C for 30 min and then allowed to warm to 23 °C. The solution was diluted with 120 mL of pentane and allowed to stand for 15 min. The white suspension was then filtered with suction through a plug of sodium sulfate. The filtrate was concentrated *in vacuo* and taken back up in 30 mL of pentane to be filtered a second time through sodium sulfate. The filtrate was concentrated *in vacuo* and distilled. Obtained a 75/25 mixture of O- to C-silylated product in 70-95% yield.

O-Methyl, O-Trimethylsilyl ketene acetal (Adaptation of above procedure). To a solution of 11.2 mL of diisopropylamine (80 mmol, 1.1 equiv) in 50 mL of THF at 0 °C was added 50 mL of a 1.60 M solution of n-butyllithium in hexanes (80 mmol, 1.1 equiv) dropwise. After stirring the solution for 15 min at 0 °C the solution was cooled to -78 °C. To the solution was added 5.80 mL of methyl acetate (73 mmol, 1.0 equiv) dropwise. The solution was stirred at -78 °C for another 45 min and then 11.0 mL of trimethylsilyl chloride (87 mmol, 1.2 equiv) was added to quench to the enolate. The solution was kept at -78 °C for 30 min and then allowed to warm to 23 °C. The solution was diluted with 100 mL of pentane and allowed to stand for 15 min. The white suspension was then filtered with suction through a plug of sodium sulfate. The filtrate

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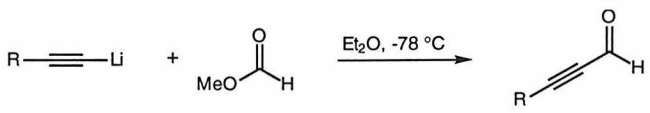
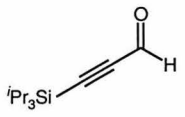
37. (a) Prepared according to procedure of Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y., *J. C. S. Perkin I*, **1982**, 1099. (b) Weber, W. P., *Silicon Reagents for Organic Synthesis*, Springer-Verlag, Berlin, **1983**, 100.

was concentrated *in vacuo* and taken back up in 250 mL of pentane and washed with (100 mL) 5% sodium bicarbonate, (2 x 75 mL) 1.0 M cupric sulfate and (100 mL) saturated sodium chloride. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was distilled under aspirator (Bp = 44-46 °C @ ~40 mm Hg). Obtained a 75/25 mixture of O- to C-silylated product in 52% yield, 5.50 g.



General Procedure for Preparation of Propargaldehydes

To a solution of the terminal acetylene (10 mmol) in 30 mL of Et_2O at 0 °C was added 6.88 mL of a 1.6 M solution of butyllithium in hexanes (11 mmol) dropwise. After stirring for 30 min at 0 °C, the solution was cooled to -78 °C. To the cooled solution was added 1.23 mL of methyl formate (20 mmol) rapidly. The solution was kept at -78 °C for 1 h and then was allowed to warm to 23 °C. The solution was diluted with 100 mL of Et_2O and washed with 50 mL of a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was isolated by chromatography on silica gel.



Isolated as a clear, colorless oil in 93% yield.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 9.21 (1H, s), 1.14-1.10 (3H, m), 1.11 (18H, d, J = 4.2).

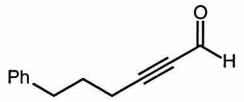
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 176.5, 104.4, 100.7, 18.4, 10.9.

IR: (thin film)

2946, 2893, 2868, 2149, 1668, 1464, 1385, 1368, 1240, 1073, 1000, 920, 883, 702, 679, 585 cm^{-1}.

TLC: R_f 0.65 (10:1 hexane/ethyl acetate)



Isolated as a clear, colorless oil in 80% yield.

^1H NMR: (300 MHz, $CDCl_3$)

δ 9.20 (1H, t, J = 0.6), 7.33-7.18 (5H, m), 2.75 (2H, t, J = 7.5), 2.42 (2H, ddd, J = 7.0, 7.0, 0.6), 1.93 (2H, ddd, J = 7.5, 7.0, 7.0).

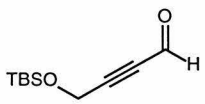
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 177.0, 140.6, 128.4, 128.4, 126.1, 98.5, 81.9, 34.5, 28.9, 18.3.

IR: (thin film)

3084, 3062, 3027, 2941, 2861, 2741, 2279, 2200, 1950, 1876, 1810, 1668, 1602, 1496, 1455, 1423, 1389, 1346, 1326, 1188, 1135, 1080, 1047, 1030, 966, 910, 863, 841, 814, 795, 747, 700 cm^{-1}.

TLC: R_f 0.58 (4:1 hexane/ethyl acetate)



Isolated as a clear, colorless oil in 86% yield.[38]

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38. Torisawa, Y.; Satoh, K.; Ikegami, S. *Heterocycles* **1989**, *28*, 729.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 9.21 (1H, s), 4.48 (2H, s), 0.89 (9H, s), 0.11 (6H, s).

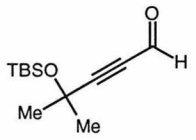
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 176.4, 94.8, 84.1, 51.4, 25.6, 18.2, -5.3.

IR: (thin film)

2956, 2931, 2886, 2858, 2258, 2187, 1675, 1472, 1447, 1389, 1364, 1257, 1124, 1091 cm^{-1}.

TLC: R_f 0.70 (4:1 hexane/ethyl acetate)



Isolated as a clear, colorless oil in 88% yield.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 9.23 (1H, s), 1.52 (6H, s), 0.86 (9H, s), 0.17 (6H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 176.5, 101.0, 82.3, 66.4, 32.0, 25.6, 17.9, -3.0.

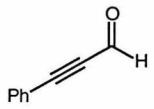
IR: (thin film)

2987, 2956, 2931, 2888, 2858, 2738, 2267, 2206, 1674, 1473, 1464, 1435, 1388, 1380, 1361, 1254, 1232, 1169, 1055, 1035, 1005, 939, 903, 839, 811, 778, 693, 648, 589, 560 cm^{-1}.

HRMS: (FAB)

calcd for $C_{12}H_{23}O_2Si$ $(M+H)^+$ 227.1467, found 227.1468.

TLC: R_f 0.72 (4:1 hexane/ethyl acetate)



Isolated as a clear, colorless oil in 75% yield.[39]

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 9.38 (1H, s), 7.57-7.33 (5H, m).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 176.5, 133.0, 131.1, 128.5, 119.2, 94.8, 88.2.

IR: (thin film)

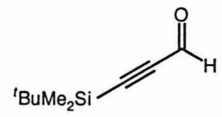
2961, 2849, 2189, 1660, 1489, 1443, 1365, 1260, 1178, 1087, 1028, 1002, 977, 757, 688 cm^{-1}.

TLC: R_f 0.54 (4:1 hexane/ethyl acetate)

^{t}Butyldimethylsilylpropargaldehyde. To a solution of 5.6 g of propargaldehyde diethyl acetal (44 mmol) in 60 mL of THF at 0 °C was added 30 mL of a 1.6 M solution of butyllithium in hexanes (48 mmol). After stirring the solution for 1 h, 7.9 g of TBSCl (52 mmol) was added via cannula in 30 mL of THF. The solution was stirred for another 15 min at 0 °C and then was warmed to 23 °C. The reaction mixture was poured onto 150 mL of a saturated aqueous NaCl solution and was extracted with 150 mL of pentane. The organic layer was dried over anhydrous Na_2SO_4 and was concentrated *in vacuo*. The residue was taken up in 60 mL of CH_2Cl_2 and 30 mL of formic acid, and stirred for 2 h at 23 °C. The biphase was diluted with 100 mL of water and the organic layer was separated. The aqueous layer was extracted with another 20 mL of CH_2Cl_2 and the combined organic extracts were washed with 100 mL of 1.0 M NaOH. The organic

39. Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *Tetrahedron: Asymmetry* **1991**, *2*, 635.

phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was distilled under vacuum and the product was isolated as clear, colorless oil (bp = 54 °C at 4 mm Hg) in 91% yield (6.73 g).



Isolated as a clear, colorless oil in 91% yield.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 9.18 (1H, s), 0.97 (9H, s), 0.20 (6H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 176.7, 102.9, 101.9, 25.9, 16.5, -5.3.

IR: (thin film)

3425, 3319, 2956, 2887, 2861, 2735, 2135, 1669, 1472, 1464, 1410, 1386, 1364, 1254, 1000, 940, 842, 826, 813, 780, 699, 672 cm^{-1}.

HRMS: (FAB)

calcd for $C_{19}H_{17}OSi$ $(M+H)^+$ 169.1049, found 169.1050.

TLC: R_f 0.51 (10:1 hexane/ethyl acetate)

General Procedure for Enantioselective Aldol Mediated by 12

To a 0.10 M solution of **11** (0.11 equiv) in toluene was added $Ti(O^iPr)_4$ (0.050 equiv). The resulting solution was stirred for 1 h at 23 °C and then was concentrated *in vacuo*. The residue was redissolved in the reaction solvent to give a 0.050 M solution (relative to Ti) and was cooled to 0 °C. To the solution were added the aldehyde (1.0 equiv) and the silyl ketene acetal (1.2 equiv) sequentially. The reactions were quenched after 4 h at 0 °C by pouring onto water. The mixture was diluted with a saturated solution of aqueous NaCl and Et_2O. The organic layer was separated, dried over anhydrous

Na_2SO_4 and concentrated *in vacuo*. The residue was treated with 10% trifluoroacetic acid (TFA) in THF to effect desilylation. Once complete, the solution was partitioned between Et_2O and water. The organic layer was separated and washed with a 1.0 M NaOH solution. The organics were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The adduct was isolated by flash chromatography on silica gel.

A portion of the aldol adduct was converted to the corresponding (*S*)-MTPA-ester.[40] To a solution of the alcohol (0.01 mmol, 1 equiv) and 15 mg 4-dimethylaminopyridine (DMAP) in 0.50 mL of CH_2Cl_2 was added (*R*)-MTPA-Cl (0.01 mmol, 1.1 equiv). Once conversion to the ester was complete, the reaction mixture transferred to a column of silica gel and eluted with 6:1 hexanes/EtOAc. The enantiomeric excess of the product was determined by integration of the ^1H NMR (300 MHz, $CDCl_3$ or C_6D_6) resonances of the methoxy signals between δ 3.4-3.6 ppm.

General Procedure for Enantioselective Mukaiyama Aldol Addition Reaction with 14.

Method A

To a 5.5 mM solution of **11** (0.044 equiv) in toluene was added Ti(^{i}PrO)$_4$ (0.020 equiv). The orange solution was stirred for 1 h at 23 °C before adding 3,5-di-*tert*-butylsalicylic acid (0.024 equiv) in toluene (12 mM). Stirring was continued for an additional h at 23 °C. The solvent was removed *in vacuo* and the solid orange residue was taken up in Et_2O to give a 5.0 mM solution (relative to Ti). After cooling the solution to 0 °C, 2,6-lutidine (0.20 equiv), the aldehyde (1.0 equiv) and silyl ketene acetal (1.2 equiv) were added sequentially. The flask was then kept at 0 °C for 4 h before it was quenched by pouring onto water. The mixture was extracted with Et_2O after diluting with a saturated aqueous NaCl solution. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was treated with 10% trifluoroacetic acid (TFA) in

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40. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

THF to effect desilylation. Once complete, the solution was partitioned between Et_2O and water. The organic layer was separated and washed with a 1.0 M NaOH solution. The organics were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The adduct was isolated by flash chromatography on silica gel.

Method B (No solvent removal *in vacuo*)

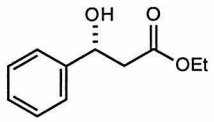
To a 5.5 mM solution of the chiral Schiff base ligand (0.044 equiv) in toluene at 23 °C was added $Ti(^iPrO)_4$ (0.020 equiv). The orange solution was stirred for 1 h at 23 °C. To the orange solution was added 3,5-di-^{t}butylsalicylic acid[41] (0.040 equiv) in toluene (0.010 M) via cannula. Stirring was continued for an additional h at 23 °C and then the solution was cooled to -20 °C. To the cooled solution was added trimethylsilyl chloride (0.20 equiv) followed by triethylamine (1.0 equiv) and the aldehyde (1.0 equiv). After stirring the resulting solution for 15 min, the silyl ketene acetal (2.0 equiv) was added. The solution was allowed to gradually warm to 23 °C over 6 h before it was quenched by pouring onto water. The mixture was diluted with Et_2O and a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in 10% TFA/THF to effect desilylation. Once complete, the solution was partitioned between Et_2O and water. The organic layer was washed with a 1.0 M NaOH solution. The separated organic layer was then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica gel was used to isolate the β-hydroxy ester adduct.

General Procedure for Assay by (*S*)-MTPA Derivatization

To a solution of the alcohol (0.01 mmol, 1 equiv) and 15 mg of 4-dimethylaminopyridine (DMAP) in 0.50 mL of CH_2Cl_2 was added (*R*)-MTPA-Cl (0.01

41. The salicylic acid is dried prior to usage by dissolving in toluene and concentrating *in vacuo*.

mmol, 1.1 equiv). Once conversion to the ester was complete, the reaction mixture transferred to a column of silica gel and eluted with 6:1 hexanes/EtOAc. The enantiomeric excess of the product was determined by integration of the ^{1}H NMR (300 MHz, $CDCl_3$ or C_6D_6) resonances of the methoxy signals between δ 3.4-3.6 ppm.



Isolated as a clear, colorless oil in 92% yield.[42]

$[\alpha]_{365}^{19}$ +63.1° (*c* = 2.7, $CHCl_3$)

$[\alpha]_D^{19}$ +35.4° (*c* = 1.6, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.40-7.28 (5H, m), 5.16-5.12 (1H, m), 4.19 (2H, q, *J* = 7.1), 3.27 (1H, d, *J* = 3.4), 2.78 (1H, dd, *J* = 16.5, 6.1), 2.70 (1H, dd, *J* = 16.5, 2.3), 1.27 (3H, t, *J* = 7.1).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.4, 142.4, 128.5, 127.8, 125.6, 70.3, 60.9, 43.3, 14.1.

IR: (thin film)

3436, 3060, 3025, 2978, 2919, 1719, 1490, 1448, 1396, 1366, 1296, 1260, 1190, 1155, 1079, 1055, 1025, 949, 908, 885, 844, 756, 697 cm^{-1}.

TLC: R_f 0.14 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) methoxy resonances at δ 3.52 and 3.42 ppm in ratio of 29.5:1 (93% ee).

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42. (a) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. (b) Cohen, S. G.; Weinstein, S. Y. *J. Am. Chem. Soc.* **1964**, *86*, 725.

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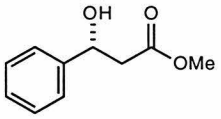


Isolated as a clear, colorless oil in 84% yield.[43]

$[\alpha]_D^{19}$ +33.2° (*c* = 1.2, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.40-7.27 (5H, m), 5.16-5.12 (1H, m), 3.73 (3H, s), 3.23 (1H, s), 2.78 (1H, dd, *J* = 16.4, 6.1), 2.71 (1H, dd, *J* = 16.4, 4.3).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.8, 142.4, 128.5, 127.8, 125.6, 70.3, 51.9, 43.1.

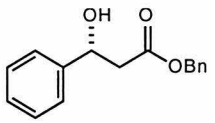
IR: (thin film)

3448, 3025, 2943, 1731, 1490, 1431, 1361, 1267, 1196, 1161, 1055, 1026, 985, 908, 879, 756, 697 cm^{-1}.

TLC: R_f 0.12 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.52 and 3.42 ppm in ratio of 48.0:1 (96% ee).

HPLC data: Using a flow rate of 0.50 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 17.3 min (major) and 13.0 min (minor) in a ratio of 53:1 (96% ee).



Isolated as a clear, colorless oil in 94% yield.

$[\alpha]_D^{25}$ +31.5° (*c* = 1.0, $CHCl_3$)

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43. Devant, R.; Braun, M. *Chem. Ber.* **1986**, *119*, 2191.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.41-7.29 (10H, m), 5.17 (2H, s), 5.19-5.14 (1H, m), 3.32 (1H, d, *J* = 3.6), 2.85 (1H, dd, *J* = 16.4, 8.7), 2.77 (1H, dd, *J* = 16.4, 4.2).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.0, 142.4, 135.4, 128.5, 128.5, 128.3, 128.2, 127.8, 125.6, 70.2, 66.6, 43.3.

IR: (thin film)

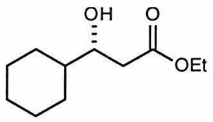
3452, 3064, 3033, 2955, 1732, 1497, 1455, 1382, 1268, 1159, 1082, 1060, 1023, 914, 753, 699 cm^{-1}.

HRMS: (FAB)

calcd for $C_{16}H_{16}O_3$ $(M+H)^+$ 257.1178, found 257.1175.

TLC: R_f 0.17 (4:1 hexane/ethyl acetate)

HPLC data: Using a flow rate of 0.50 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 18.3 min (major) and 14.9 min (minor) in a ratio of 55:1 (96% ee).



Isolated as a clear colorless oil in 86% yield.[44]

$[\alpha]_{365}^{19}$ +20.8° (*c* = 1.7, $CHCl_3$)

$[\alpha]_D^{19}$ +27.8° (*c* = 0.66, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 4.16 (2H, q, *J* = 7.1), 3.82-3.77 (1H, m), 2.84 (1H, s), 2.53 (1H, dd, *J* = 16.3, 3.0), 2.45 (1H, dd, *J* = 16.3, 9.3), 1.94-1.66 (6H, m), 1.5-1.0 (5H, m), 1.29 (3H, t, *J* = 7.1).

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44. Bernardi, A.; Colombo, L.; Gennari, C.; Prati, L. *Tetrahedron* **1984**, *40*, 3769.

^{13}C NMR: (75 MHz, $CDCl_3$)

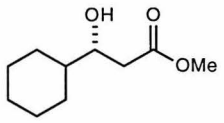
δ 173.5, 72.1, 60.6, 43.0, 38.5, 28.7, 28.2, 26.4, 26.1, 26.0, 14.1.

IR: (thin film)

3495, 2919, 2849, 1725, 1713, 1443, 1367, 1179, 1032, 891 cm^{-1}.

TLC: R_f 0.30 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.55 and 3.52 ppm in ratio of 31.2:1 (94% ee).



Isolated as a clear colorless oil in 81% yield.[45]

$[\alpha]_D^{19}$ +25.1° (*c* = 1.1, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 3.77 (1H, m), 3.70 (3H, s), 2.83 (1H, d, *J* = 4.0), 2.52 (1H, dd, *J* = 16.3, 3.0), 2.41 (1H, dd, *J* = 16.3, 9.4), 1.87-1.63 (5H, m), 1.38-0.97 (6H, m).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 173.9, 72.1, 51.7, 43.0, 38.3, 28.7, 28.2, 26.4, 26.1, 26.0.

IR: (thin film)

3460, 2919, 2837, 1725, 1437, 1308, 1279, 1167, 1102, 1038, 991, 885, 838 cm^{-1}.

TLC: R_f 0.23 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.65 and 3.59 ppm in ratio of 39.1:1 (95% ee).

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45. Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437.

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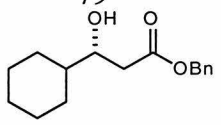


Isolated as a clear, colorless oil in 95% yield.

$[\alpha]_D^{25}$ +23.5° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.41-7.33 (5H, m), 5.15 (2H, s), 3.84-3.76 (1H, m), 2.87 (1H, d, *J* = 3.6), 2.585 (1H, dd, *J* = 16.3, 3.2), 2.48 (1H, dd, *J* = 16.3, 9.2), 1.88-1.84 (1H, m), 1.76-1.75 (2H, m), 1.68-1.63 (2H, m), 1.42-1.32 (1H, m), 1.29-1.14 (3H, m), 1.11-0.96 (2H, m).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 173.3, 135.6, 128.6, 128.3, 128.2, 72.1, 66.4, 43.0, 38.6, 28.7, 28.2, 26.3, 26.1, 26.0.

IR: (thin film)

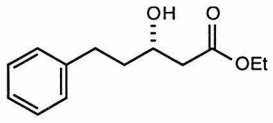
3467, 3034, 2926, 2853, 1732, 1498, 1451, 1404, 1382, 1311, 1280, 1261, 1215, 1164, 1104, 1044, 1029, 994, 893, 750, 698 cm^{-1}.

HRMS: (FAB)

calcd for $C_{16}H_{23}O_3$ $(M+H)^+$ 263.1647, found 263.1645.

TLC: R_f 0.34 (4:1 hexane/ethyl acetate)

HPLC data: Using a flow rate of 0.80 ml/min with 90/10 hexane/ethyl acetate eluent, the enantiomers elute at 11.3 min (major) and 8.0 min (minor) in a ratio of 20:1 (90% ee).



Isolated as a clear, colorless oil in 98% yield.[46]

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46. Kuwajima, I.; Minami, N.; Sato, T. *Tetrahedron Lett.* **1976**, 2253.

$[\alpha]_{365}^{19}$ -3.14° (*c* = 0.88, $CHCl_3$)

$[\alpha]_D^{19}$ +1.88° (*c* = 1.4, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.36-7.16 (5H, m), 4.17 (2H, q, *J* = 7.1), 4.04-4.00 (1H, m), 3.10 (1H, s), 2.88-2.80 (1H, m), 2.78-2.65 (1H, m), 2.52 (1H, dd, *J* = 16.5, 3.7), 2.44 (1H, dd, *J* = 16.5, 8.4), 1.91-1.81 (1H, m), 1.79-1.68 (1H, m), 1.27 (3H, t, *J* = 7.1).

^{13}C NMR: (75 MHz, $CDCl_3$)

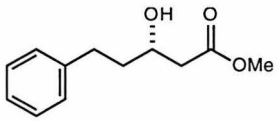
δ 173.0, 141.7, 128.4, 128.4, 125.9, 67.2, 60.7, 41.2, 38.1, 31.7, 14.1.

IR: (thin film)

3436, 3025, 2966, 2919, 2860, 1725, 1495, 1448, 1372, 1302, 1255, 1184, 1155, 1084, 1025, 931, 743, 696 cm^{-1}.

TLC: R_f 0.17 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.57 and 3.54 ppm in ratio of 17.9:1 (89% ee).



Isolated as a clear colorless oil in 98% yield.[47]

$[\alpha]_D^{19}$ +1.8° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.31-7.17 (5H, m), 4.05-4.01 (1H, m), 3.71 (3H, s), 3.10 (1H, s), 2.83-2.68 (2H, m), 2.53 (1H, dd, *J* = 16.5, 4.2), 2.45 (1H, dd, *J* = 16.5, 8.7), 1.87-1.73 (2H, m).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 173.3, 141.6, 128.4, 128.4, 125.8, 67.1, 51.7, 41.1, 38.1, 31.7.

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47. Fujisawa, T.; Fujimura, A.; Sato, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1273.

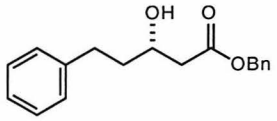
IR: (thin film)

3436, 3013, 2933, 2849, 1731, 1596, 1490, 1455, 1431, 1361, 1302, 1255, 1196, 1173, 1155, 1085, 1055, 997, 932, 873, 750, 697 cm^{-1}.

TLC: R_f 0.14 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.68 and 3.61 ppm in ratio of 34.0:1 (94% ee).

HPLC data: Using a flow rate of 0.50 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 13.4 min (major) and 15.3 min (minor) in a ratio of 26:1 (93% ee).



Isolated as a clear colorless oil in 95% yield.

$[\alpha]_D^{25}$ +1.4° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.48-7.25 (10H, m), 5.23 (2H, s), 4.16-4.09 (1H, m), 3.15 (1H, d, *J* = 3.9), 2.95-2.85 (1H, m), 2.82-2.72 (1H, m), 2.65 (1H, dd, *J* = 16.6, 4.0), 2.58 (1H, dd, *J* = 16.6, 8.1), 1.99-1.80 (2H, m).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.7, 141.6, 135.4, 128.6, 128.4, 128.3, 128.2, 125.8, 67.1, 66.5, 41.3, 38.0, 31.7.

IR: (thin film)

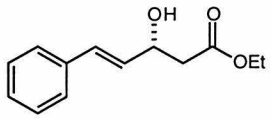
3421, 3028, 2928, 1729, 1496, 1454, 1378, 1349, 1255, 1173, 1081, 1055, 1026, 997, 967, 747, 698 cm^{-1}.

HRMS: (FAB)

calcd for $C_{18}H_{21}O_3$ $(M+H)^+$ 285.1491, found 285.1485.

TLC: R_f 0.18 (4:1 hexane/ethyl acetate)

HPLC data: After transesterifying to the methyl ester (stirred 24 h with 10% K_2CO_3 in MeOH) the product was assayed by HPLC. Using a flow rate of 0.50 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 13.4 min (major) and 15.3 min (minor) in a ratio of 20.3:1 (91% ee).



Isolated as a clear, colorless oil in 92% yield.[48]

$[\alpha]_{365}^{19}$ +27.6° (*c* = 0.94, $CHCl_3$)

$[\alpha]_D^{19}$ +13.6° (*c* = 1.2, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.42-7.25 (5H, m), 6.68 (1H, d, *J* = 16.0), 6.23 (1H, dd, *J* = 16.0, 6.1), 4.77-4.73 (1H, m), 4.21 (2H, q, *J* = 7.1), 3.10 (1H, d, *J* = 4.2), 2.69 (1H, dd, *J* = 16.3, 4.1), 2.61 (1H, dd, *J* = 16.3, 5.9), 1.30 (3H, t, *J* = 7.1).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.2, 136.6, 130.7, 130.2, 128.7, 127.9, 126.6, 69.0, 60.9, 41.8, 14.3.

IR: (thin film)

3424, 2978, 1954, 1883, 1725, 1713, 1601, 1578, 1496, 1449, 1373, 1155, 1102, 1032, 967, 750, 691 cm^{-1}.

TLC: R_f 0.14 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.58 and 3.52 ppm in ratio of 26.0:1 (93% ee).

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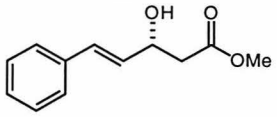
48. Araki, S.; Ito, H.; Butsugan, Y. *Syn. Commun.* **1988**, 453.

83



Isolated as a clear, colorless oil in 99% yield.[49]

$[\alpha]_D^{19}$ +11.9° (*c* = 0.99, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.40-7.23 (5H, m), 6.66 (1H, d, *J* = 15.9), 6.23 (1H, dd, *J* = 15.9, 6.2), 4.76-4.72 (1H, m), 3.73 (3H, s), 3.13 (1H, s), 2.69 (1H, dd, *J* = 16.1, 4.6), 2.61 (1H, dd, *J* = 16.1, 3.4).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.5, 136.3, 130.8, 129.9, 128.5, 127.8, 126.5, 68.8, 51.8, 41.3.

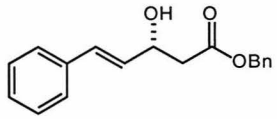
IR: (thin film)

3448, 3025, 2943, 1725, 1490, 1431, 1402, 1355, 1284, 1202, 1161, 1102, 1032, 967, 750, 691 cm^{-1}.

TLC: R_f 0.12 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.69 and 3.61 ppm in ratio of 80.0:1 (98% ee).

HPLC data: Using a flow rate of 0.50 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 16.3 min (major) and 21.3 min (minor) in a ratio of 98:1 (98% ee).



Isolated as a clear, colorless oil in 98% yield.

$[\alpha]_D^{25}$ +4.6° (*c* = 1.0, $CHCl_3$)

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49. Meyer, H. H. *Liebigs Ann. Chem.* **1979**, 484.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.40-7.23 (5H, m), 6.66 (1H, dd, *J* = 16.0, 1.1), 6.23 (1H, dd, *J* = 16.0, 6.1), 5.18 (2H, s), 4.78-4.75 (1H, m), 3.08 (1H, d, *J* = 4.4), 2.75 (1H, dd, *J* = 16.2, 2.1), 2.68 (1H, d, *J* = 16.2).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 171.9, 136.3, 135.4, 130.8, 129.8, 128.6, 128.5, 128.3, 128.2, 127.8, 126.5, 68.8, 66.6, 41.5.

IR: (thin film)

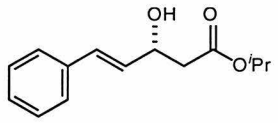
3398, 3062, 3031, 2952, 1733, 1496, 1455, 1382, 1279, 1162, 1104, 1025, 968, 750, 696 cm^{-1}.

HRMS: (EI)

calcd for $C_{18}H_{18}O_3$ $(M)^+$ 282.1256, found 282.1260.

TLC: R_f 0.15 (4:1 hexane/ethyl acetate)

HPLC data: Using a flow rate of 0.80 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 40.4 min (major) and 31.1 min (minor) in a ratio of 50:1 (96% ee).



Isolated as a clear, colorless oil in 84% yield.[50]

$[\alpha]_D^{25}$ +7.8° (*c* = 1.0, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.40-7.22 (5H, m), 6.65 (1H, dd, *J* = 16.0, 1.1), 6.21 (1H, dd, *J* = 16.0, 6.0), 5.06 (1H, m, *J* = 6.3, 6.3, 6.3, 6.3, 6.3, 6.3), 4.73-4.69 (1H, m,), 3.17 (1H, d, *J* = 4.3,), 2.64 (1H, dd, *J* = 16.2, 4.6), 2.58 (1H, dd, *J* = 16.2, 7.7), 1.24 (6H, d, *J* = 6.3).

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50. Inomata, K.; Kawahara, T.; Mukaiyama, T. *Chem. Lett.* **1974**, 245.

^{13}C NMR: (75 MHz, $CDCl_3$)

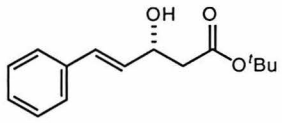
δ 171.8, 130.7, 129.9, 128.5, 127.7, 126.5, 68.9, 68.4, 41.7, 21.8.

IR: (thin film)

3436, 3026, 2980, 2936, 1727, 1494, 1467, 1449, 1374, 1282, 1170, 1107, 1046, 966, 818, 750, 693 cm^{-1}.

TLC: R_f 0.15 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.57 and 3.52 ppm in ratio of 23:1 (92% ee).



Isolated as a clear, colorless oil in 9% yield.[51]

$[\alpha]_D^{19}$ +7.7° (*c* = 1.0, $CHCl_3$)

IR: (thin film)

3434, 2978, 2931, 1725, 1494, 1450, 1393, 1368, 1291, 1256, 1150, 1103, 1030, 966, 844, 749, 693 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.39-7.22 (5H, m), 6.65 (1H, dd, *J* = 16.0, 1.1), 6.21 (1H, dd, *J* = 16.0, 6.0), 4.70-4.66 (1H, m,), 3.24 (1H, d, *J* = 4.2), 2.59 (1H, dd, *J* = 16.1, 4.7), 2.52 (1H, dd, *J* = 16.1, 7.7), 1.47 (9H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 171.6, 136.6, 130.5, 130.2, 128.5, 127.6, 126.5, 81.4, 68.9, 42.5, 28.1.

TLC: R_f 0.18 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.58 and 3.52 ppm in ratio of 4.6:1 (64% ee).

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51. Meyer, H. H. *Justus Liebigs Ann. Chem.* **1978**, 337.

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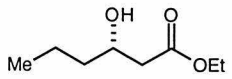


Isolated as a clear, colorless oil in 95% yield.[52]

$[\alpha]_{365}^{19}$ +10.5° (*c* = 0.58, $CHCl_3$)

$[\alpha]_D^{19}$ +9.46° (*c* = 0.83, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 4.17 (2H, q, *J* = 7.1), 4.02 (1H, m), 2.94 (1H, d, *J* = 4.0), 2.50 (1H, dd, *J* = 16.5, 3.2), 2.39 (1H, dd, *J* = 16.5, 8.9), 1.55-1.34 (4H, m), 1.27 (3H, t, *J* = 7.1), 0.93 (3H, t, *J* = 7.1).

^{13}C NMR: (75 MHz, $CDCl_3$)

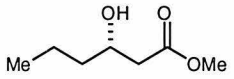
δ 173.1, 67.7, 60.6, 41.3, 38.6, 18.7, 14.2, 13.9.

IR: (thin film)

3483, 2955, 2919, 2861, 1725, 1708, 1449, 1367, 1302, 1290, 1179, 1138, 1079, 1014, 955, 850, 720, 685 cm^{-1}

TLC: R_f 0.22 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR (C_6D_6) methoxy resonances at δ 3.50 and 3.43 ppm in ratio of 15.4:1 (88% ee).



Isolated as a clear, colorless oil in 76% yield.[53]

$[\alpha]_D^{19}$ +11.0° (*c* = 0.90, $CHCl_3$)

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52. Crump, D. R. *Aus. J. Chem.* **1982**, 1945.

53. Devant, R.; Braun, M. *Chem. Ber.* **1986**, *119*, 2191.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 4.01 (1H, m), 3.70 (3H, s), 2.89 (1H, s), 2.51 (1H, dd, *J* = 16.4, 3.3), 2.40 (1H, dd, *J* = 16.4, 8.9), 1.54-1.31 (4H, m), 0.92 (3H, t, *J* = 7.0).

^{13}C NMR: (75 MHz, $CDCl_3$)

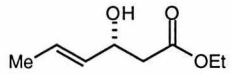
δ 173.5, 67.7, 51.7, 41.1, 38.6, 18.6, 13.9.

IR: (thin film)

3448, 2943, 2919, 2861, 1731, 1431, 1361, 1302, 1261, 1167, 1119, 1073, 1020, 991, 844 cm^{-1}.

TLC: R_f 0.18 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^{1}H NMR (C_6D_6) methoxy resonances at δ 3.27 and 3.21 ppm in ratio of 40.5:1 (95% ee).



Isolated as a clear, colorless oil in 77% yield.[54]

$[\alpha]_{365}^{19}$ +26.5° (*c* = 1.0, $CHCl_3$)

$[\alpha]_D^{19}$ +11.3° (*c* = 1.0, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 5.73 (1H, m), 5.51 (1H, m), 4.48 (1H, m), 4.17 (2H, q, *J* = 7.1), 2.86 (1H, d, *J* = 4.0), 2.55 (1H, d, *J* = 16.4, 4.1), 2.48 (1H, dd, *J* = 16.4, 2.4), 1.69 (3H, dd, *J* = 6.3, 0.8), 1.27 (3H, t, *J* = 7.1).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.4, 131.7, 127.5, 68.9, 60.7, 41.5, 17.7, 14.2.

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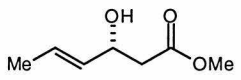
54. Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717.

IR: (thin film)

3436, 2978, 2919, 1713, 1443, 1366, 1302, 1278, 1249, 1167, 1114, 1091, 1026, 961 cm^{-1}.

TLC: R_f 0.15 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR (C_6D_6) methoxy resonances at δ 3.50 and 3.44 ppm in ratio of 23.7:1 (92% ee).



Isolated as a clear, colorless oil in 82% yield.[55]

$[\alpha]_D^{19}$ +19.4° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 5.73 (1H, m), 5.50 (1H, m), 4.48 (1H, m), 3.70 (3H, s), 2.82 (1H, d, *J* = 4.0), 2.53 (2H, m), 1.69 (3H, d, *J* = 6.3).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.8, 131.7, 127.6, 68.9, 51.8, 41.3, 17.7.

IR: (thin film)

3436, 2942, 2919, 1731, 1437, 1355, 1284, 1250, 1167, 1120, 1044, 1014, 967, 879 cm^{-1}.

TLC: R_f 0.15 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR (C_6D_6) methoxy resonances at δ 3.25 and 3.20 ppm in ratio of 80.0:1 (98% ee).

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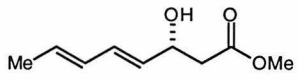
55. Chamberlin, R. A.; Dezube, M.; Dussault, P. *Tetrahedron Lett.* **1981**, *22*, 4611.



Isolated as a clear, colorless oil in 83% yield.

$[\alpha]_D^{19}$ +1.0° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 6.22 (1H, dd, *J* = 15.2, 10.4), 6.02 (1H, t, *J* = 10.4), 5.70 (1H, dd, *J* = 15.2, 6.5), 5.54 (1H, dd, *J* = 15.2, 6.5), 4.56-4.52 (1H, m), 3.69 (3H, s), 2.95 (1H, d, *J* = 4.2), 2.59-2.53 (2H, m), 1.73 (3H, d, *J* = 6.5).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.5, 131.2, 130.6, 130.5, 130.4, 68.5, 51.7, 41.3, 41.3.

IR: (thin film)

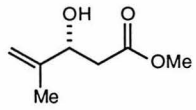
3439, 3019, 2954, 2915, 2853, 1737, 1438, 1410, 1356, 1273, 1214, 1172, 1104, 1075, 1028, 989 cm^{-1}.

HRMS: (EI)

calcd for $C_9H_{14}O_3$ $(M)^+$ 170.0943, found 170.0947.

TLC: R_f 0.18 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.67 and 3.58 ppm in ratio of 203:1 (99% ee).



Isolated as a clear, colorless oil in 74% yield.

$[\alpha]_D^{19}$ +24.9° (*c* = 0.99, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 5.02 (1H, s), 4.87 (1H, s), 4.47 (1H, t, *J* = 6.0), 3.71 (3H, s), 2.94 (1H, s), 2.57 (2H, dd, *J* = 11.3, 6.0), 1.74 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.9, 145.5, 111.4, 71.5, 51.8, 39.9, 18.1.

IR: (thin film)

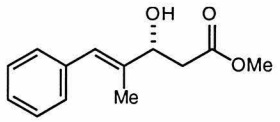
3448, 2954, 1736, 1654, 1439, 1356, 1278, 1165, 1048, 995, 903 cm^{-1}.

HRMS: (EI)

calcd for $C_7H_{12}O_3$ $(M)^+$ 144.0786, found 144.0791.

TLC: R_f 0.15 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) methoxy resonances at δ 3.67 and 3.60 ppm in ratio of 36:1 (95% ee).



Isolated as a clear, colorless oil in 92% yield.

$[\alpha]_D^{19}$ +4.9° (*c* = 1.0, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.35-7.20 (5H, m), 6.58 (1H, s), 4.60 (1H, t, *J* = 6.5), 3.72 (3H, s), 3.00 (1H, s), 2.64 (2H, d, *J* = 6.5), 1.87 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.9, 138.1, 137.2, 128.9, 128.1, 126.5, 126.0, 73.5, 51.9, 40.1, 13.7.

IR: (thin film)

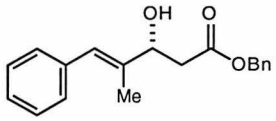
3448, 3013, 2954, 1731, 1490, 1437, 1343, 1273, 1167, 1073, 1044, 1014, 985, 920, 867, 750, 697 cm^{-1}.

HRMS: (EI)

calcd for $C_{13}H_{16}O_3$ $(M)^+$ 220.1100, found 220.1094.

TLC: R_f 0.15 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.70 and 3.63 ppm in ratio of 60:1 (97% ee).



Isolated as a clear, colorless oil in 91% yield.

$[\alpha]_D^{25}$ +2.3° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.43-7.22 (10H, m), 6.61 (1H, s), 5.20 (2H, s), 4.71-4.64 (1H, m), 3.12 (1H, d, *J* = 3.6), 2.78 (1H, dd, *J* = 15.9, 2.5), 2.71 (1H, d, *J* = 15.9), 1.90 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.2, 138.0, 137.1. 135.4, 128.9, 128.5, 128.3, 128.2, 128.0, 126.5, 73.5, 66.6, 40.3, 13.7.

IR: (thin film)

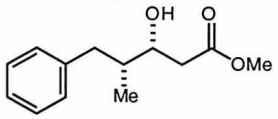
3447, 3060, 3031, 2954, 1733, 1621, 1600, 1496, 1455, 1381, 1272, 1156, 1023, 920, 870, 820, 750, 697 cm^{-1}.

HRMS: (FAB)

calcd for $C_{19}H_{20}O_3$ $(M)^+$ 296.1412, found 296.1421.

TLC: R_f 0.16 (4:1 hexane/ethyl acetate)

HPLC data: Using a flow rate of 0.50 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 19.9 min (major) and 16.5 min (minor) in a ratio of 67:1 (97% ee).



Isolated as a clear, colorless oil in 91% yield.

$[\alpha]_D^{19}$ +4.4° (*c* = 1.3, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.38-7.17 (5H, m), 4.00-3.96 (1H, m), 3.70 (3H, s), 3.00 (1H, bs), 2.89-2.85 (2H, m), 2.60-2.39 (3H, m), 0.90 (3H, d, *J* = 6.8).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 173.8, 140.7, 129.1, 128.3, 125.9, 69.9, 51.8, 40.1, 39.4, 38.7, 13.5.

IR: (thin film)

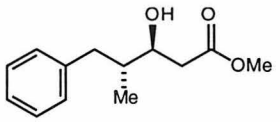
3468, 3061, 3026, 2955, 1732, 1602, 1495, 1454, 1438, 1379, 1292, 1264, 1198, 1173, 1060, 991, 880, 748, 701 cm^{-1}.

HRMS: (EI)

calcd for $C_{13}H_{18}O_3$ $(M)^+$ 222.1256, found 222.1253.

TLC: R_f 0.23 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.66 and 3.59 ppm in ratio of 37:1 (95% ee).



Isolated as a clear, colorless oil in 88% yield.

$[\alpha]_D^{19}$ -13.3° (*c* = 1.2, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.38-7.17 (5H, m), 3.92-3.88 (1H, m), 3.72 (3H, s), 3.00 (1H, bs), 2.93-2.90 (2H, m), 2.60-2.39 (3H, m), 0.84 (3H, d, *J* = 6.8).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 173.8, 140.5, 129.2, 128.2, 125.8, 71.4, 51.8, 40.2, 38.6, 38.0, 14.9.

IR: (thin film)

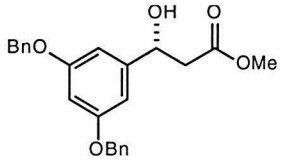
3457, 3061, 3026, 2956, 1735, 1602, 1495, 1454, 1438, 1290, 1199, 1170, 1089, 1056, 991, 748, 701 cm^{-1}.

HRMS: (EI)

calcd for $C_{13}H_{18}O_3$ $(M)^+$ 222.1256, found 222.1253.

TLC: R_f 0.23 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) methoxy resonances at δ 3.60 and 3.66 ppm in ratio of 16.3:1 (88% ee).



Isolated as a white, crystalline solid in 85% yield.

mp: 82-83 °C

$[\alpha]_D^{25}$ +18.8° (*c* = 1.0, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.46-7.32 (10H, m), 6.67 (2H, d, *J* = 2.2), 6.57 (1H, d, *J* = 2.2), 5.11-5.07 (1H, m), 5.04 (4H, s), 3.74 (3H, s), 3.35 (1H, bs), 2.77 (1H, dd, *J* = 16.3, 6.2), 2.70 (1H, dd, *J* = 16.3, 2.3).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.7, 160.0, 145.0, 136.6, 128.5, 127.9, 127.5, 104.6, 101.2, 70.2, 70.0, 51.9, 43.0.

IR: (thin film)

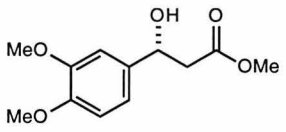
3487, 3033, 2951, 1734, 1596, 1452, 1377, 1348, 1291, 1215, 1159, 1054, 1028, 838, 738, 697 cm^{-1}.

HRMS: (FAB)

calcd for $C_{24}H_{24}O_5$ $(M)^+$ 392.1624, found 392.1613.

TLC: R_f 0.07 (4:1 hexane/ethyl acetate)

HPLC data: Using a flow rate of 0.50 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 31.6 min (major) and 29.8 min (minor) in a ratio of 25:1 (92% ee).



Isolated as a clear, colorless oil in 93% yield.

$[\alpha]_D^{25}$ +37.1° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 6.88 (1H, d, *J* = 1.8), 6.82 (1H, dd, *J* = 8.2, 1.8), 6.76 (1H, d, *J* = 8.2), 5.24-4.99 (1H, m), 3.82 (3H, s), 3.80 (3H, s), 3.65 (3H, s), 3.39 (1H, d, *J* = 3.2), 2.71 (1H, dd, *J* = 16.1, 9.1), 2.61 (1H, dd, *J* = 16.1, 4.0).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.2, 149.8, 149.3, 136.0, 118.2, 112.5, 110.4, 70.2, 56.2, 56.2, 51.4, 43.4.

IR: (thin film)

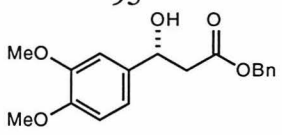
3501, 3001, 2953, 2837, 1735, 1607, 1594, 1528, 1464, 1439, 1420, 1360, 1263, 1236, 1139, 1068, 1026, 862, 813, 764, 733, 694, 648, 566 cm^{-1}.

HRMS: (FAB)

calcd for $C_{12}H_{16}O_5$ $(M)^+$ 240.0998, found 240.1011.

TLC: R_f 0.11 (2:1 hexane/ethyl acetate)

HPLC data: Using a flow rate of 0.50 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 21.7 min (major) and 20.1 min (minor) in a ratio of 61:1 (97% ee).



Isolated as a white, crystalline solid in 92% yield.

mp: 49-50 °C

$[\alpha]_D^{25}$ +24.8° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.37-7.30(5H, m), 6.91 (1H, s), 6.87 (1H, d, *J* = 8.2), 6.80 (1H, d, *J* = 8.2), 5.15 (2H, s), 5.12-5.07 (1H, m), 3.85 (2H, s), 3.29 (1H, bs), 2.83 (1H, dd, *J* = 16.2, 9.0), 2.73 (1H, dd, *J* = 16.2, 4.0).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.0, 148.9, 135.4, 135.0, 128.5, 128.3, 128.1, 117.8, 110.9, 108.7, 70.1, 66.5, 55.8, 55.7, 43.4.

IR: (thin film)

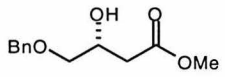
3507, 3065, 3033, 3002, 2937, 2836, 1732, 1607, 1594, 1517, 1456, 1420, 1382, 1264, 1237, 1156, 1067, 1027, 860, 812, 754, 699 cm^{-1}.

HRMS: (FAB)

calcd for $C_{18}H_{20}O_5$ $(M)^+$ 316.1311, found 316.1308.

TLC: R_f 0.12 (2:1 hexane/ethyl acetate)

HPLC data: Using a flow rate of 0.80 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 21.9 min (major) and 18.4 min (minor) in a ratio of 53:1 (96% ee).



Isolated as a clear, colorless oil in 86% yield.[56]

$[\alpha]_D^{25}$ +8.6° (*c* = 1.0, $CHCl_3$)

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56. Walkup, R. D.; Cunningham, R. T. *Tetrahedron Lett.* **1987**, *28*, 4019.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.39-7.29 (5H, m), 4.56 (2H, s), 4.28-4.21 (1H, m), 3.69 (3H, s), 3.51 (1H, dd, *J* = 9.6, 4.5), 3.46 (1H, dd, *J* = 9.6, 5.9), 3.11 (1H, d, *J* = 4.5), 2.55 (2H. d, *J* = 6.3).

^{13}C NMR: (75 MHz, $CDCl_3$)

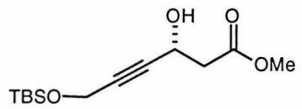
δ 172.4, 137.7, 128.3, 127.7, 127.6, 73.2, 73.0, 67.0, 51.7, 37.9.

IR: (thin film)

3458, 3064, 3031, 2953, 2921, 2863, 1736, 1497, 1454, 1439, 1362, 1260, 1207, 1171, 1104, 1006, 952, 914, 886, 740, 700 cm^{-1}.

TLC: R_f 0.31 (2:1 hexane/ethyl acetate)

HPLC data: Using a flow rate of 0.50 ml/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 17.6 min (major) and 14.9 min (minor) in a ratio of 9.7:1 (81% ee).



Isolated as a clear, colorless oil in 91% yield.

$[\alpha]_D^{19}$ +17.1° (*c* = 1.1, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 4.79 (1H, q, *J* = 6.0), 4.31 (1H, d, *J* = 1.7), 3.71 (3H, s), 3.19 (1H, d, *J* = 6.0), 2.73 (2H, d, *J* = 6.0), 0.88 (9H, s), 0.09 (6H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 171.6, 83.7, 83.7, 58.6, 51.9, 51.6, 41.5, 25.7, 18.2, -5.2.

IR: (thin film)

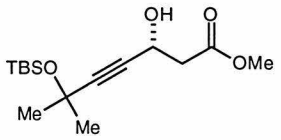
3422, 2954, 2930, 2887, 2858, 1741, 1472, 1463, 1439, 1409, 1390, 1362, 1255, 1166, 1131, 1085, 1026, 1006, 837, 815, 779, 722, 666 cm^{-1}.

HRMS: (FAB)

calcd for $C_{13}H_{25}O_4Si$ $(M+H)^+$ 273.1522, found 273.1530.

TLC: R_f 0.18 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR (C_6D_6) methoxy resonances at δ 3.15 and 3.12 ppm in ratio of 250:1 (99% ee).



Isolated as a clear, colorless oil in 88% yield.

$[\alpha]_D^{19}$ +20.6° (*c* = 1.1, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 4.78 (1H, q, *J* = 6.0), 3.73 (3H, s), 3.03 (1H, d, *J* = 6.0), 2.73 (2H, d, *J* = 6.0), 1.43 (6H, s), 0.85 (9H,s), 0.14 (6H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 171.7, 90.5, 81.2, 66.1, 58.7, 51.9, 41.6, 32.8, 25.6, 17.9, -3.0.

IR: (thin film)

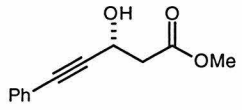
3378, 2978, 1731, 1643, 1437, 1361, 1279, 1226, 1161, 1049, 1014, 950, 850 cm^{-1}.

HRMS: (FAB)

calcd for $C_{15}H_{28}O_4SiNa$ $(M+Na)^+$ 323.1654, found 323.1650.

TLC: R_f 0.09 (10:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.69 and 3.60 ppm in ratio of 53:1 (96% ee).



Isolated as a clear, colorless oil in 96% yield.

$[\alpha]_D^{19}$ +19.2° (*c* = 1.1, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.44-7.27 (5H, m), 5.01 (1H, q, *J* = 6.0), 3.74 (3H, s), 3.37 (1H, d, *J* = 6.0), 2.85 (2H, dd, *J* = 11.3, 6.0).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 171.6, 131.7, 128.5, 128.2, 122.1, 87.9, 85.0, 59.1, 52.0, 41.8.

IR: (thin film)

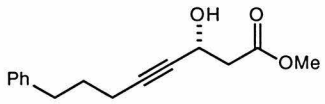
3435, 3057, 3022, 2953, 2849, 2233, 1958, 1889, 1732, 1598, 1572, 1490, 1441, 1403, 1360, 1279, 1215, 1168, 1044, 992, 918, 876, 852, 758, 692 cm^{-1}.

HRMS: (EI)

calcd for $C_{12}H_{12}O_3$ $(M)^+$ 204.0786, found 204.0780.

TLC: R_f 0.16 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.71 and 3.63 ppm in ratio of 32:1 (94% ee).



Isolated as a clear, colorless oil in 84% yield.

$[\alpha]_D^{19}$ +19.3° (*c* = 1.0, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.37-7.17 (5H, m), 4.77 (1H, q, *J* = 6.1), 3.73 (3H, s), 3.08 (1H, d, *J* = 6.1), 2.75 (2H, d, *J* = 6.1), 2.70 (2H, t, *J* = 7.4), 2.22 (2H, t, *J* = 7.0), 1.82 (2H, ddd, *J* = 7.4, 7.0, 7.0).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 171.8, 141.4, 128.4, 128.3, 125.8, 85.4, 79.8, 58.9, 51.9, 42.1, 34.6, 29.9, 18.0.

IR: (thin film)

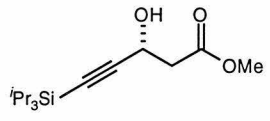
3448, 3026, 2948, 2860, 1739, 1602, 1496, 1454, 1438, 1356, 1278, 1167, 1055, 1028, 749, 701 cm^{-1}.

HRMS: (EI)

calcd for $C_{15}H_{18}O_3$ $(M)^+$ 246.1256, found 246.1243.

TLC: R_f 0.17 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) methoxy resonances at δ 3.69 and 3.60 ppm in ratio of 52:1 (96% ee).



Isolated as a clear, colorless oil in 88% yield.

$[\alpha]_D^{19}$ +20.4° (*c* = 0.93, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 4.75 (1H, dd, *J* = 6.7, 6.0), 3.70 (3H, s), 3.15 (1H, d, *J* = 6.7), 2.75 (2H, d, *J* = 6.0), 1.04 (18H, d, *J* = 1.3), 1.06-1.02 (3H, m).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 171.6, 106.5, 86.0, 59.2, 51.9, 42.1, 18.4, 11.0.

IR: (thin film)

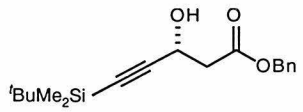
3447, 2944, 2866, 1741, 1464, 1438, 1363, 1274, 1168, 1061, 998, 883 cm^{-1}.

HRMS: (FAB)

calcd for $C_{15}H_{29}O_3Si$ $(M+H)^+$ 285.1886, found 285.1880.

TLC: R_f 0.11 (10:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.69 and 3.60 ppm in ratio of 76:1 (97% ee).



Isolated as a clear, colorless oil in 99% yield.

$[\alpha]_D^{25}$ +11.7° (*c* = 2.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.38-7.33 (5H, m), 5.17 (2H, s), 4.78 (1H, dd, *J* = 6.3, 6.0), 2.99 (1H, d, *J* = 6.3), 2.81 (2H, d, *J* = 6.0), 0.91 (9H, s), 0.09 (6H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 171.0, 135.3, 128.6, 128.4, 128.2, 108.9, 88.3, 66.7, 59.2, 42.1, 26.0, 16.4, -4.8.

IR: (thin film)

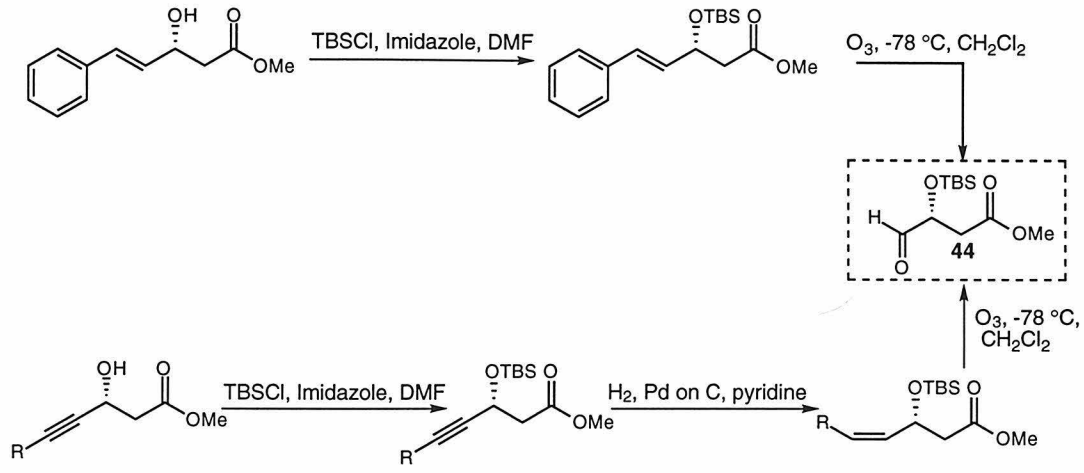
3455, 2954, 2930, 2887, 2857, 2175, 1738, 1499, 1463, 1387, 1362, 1250, 1164, 1057, 1005, 839, 826, 811, 777, 748, 697, 682 cm^{-1}.

HRMS: (FAB)

calcd for $C_{18}H_{27}O_3Si$ $(M+H)^+$ 319.1729, found 319.1733.

TLC: R_f 0.07 (10:1 hexane/ethyl acetate)

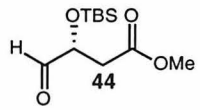
(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) methoxy resonances at δ 3.44 and 3.54 ppm in ratio of 161:1 (99% ee).



General Procedure for Correlation of Absolute Stereochemistry of Propargaldehyde Aldol Adducts to Fragment Derived from Cinnamaldehyde Adduct

A 0.30 M solution of the β-hydroxyester (1.0 equiv) and imidazole (1.5 equiv) in DMF was treated with TBSCl added via cannula in DMF. The solution was stirred for 3 h and then was partitioned between Et_2O and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in pyridine (to give a 0.15 M solution) with 10 mol% of 5% palladium on carbon. The system was placed under hydrogen with a balloon and stirred for about 1.5 h (reactions were monitorred by TLC). Once the hydrogenolysis was complete, the solution was diluted with Et_2O and passed through a plug of celite. The organics were washed with 2.0 M HCl, 5% $NaHCO_3$ and a saturated aqueous solution of NaCl. The organics were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The olefin was redissolved in CH_2Cl_2 and cooled to -78 °C for treatment with a dilute stream of ozone. Once the olefin was consumed, as monitored by TLC, the system was flushed with nitrogen and treated with 2.5 equiv of PPh_3. The solution was allowed to gradually warm to 23 °C and was concentrated *in*

vacuo. Aldehyde **43** was isolated by flash chromatogaphy on silica gel using 8:1 hexane/ethyl acetate as eluent. The products were all correlated by optical rotation.



44

$[\alpha]_D^{19}$ +41.6° (*c* = 1.0, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 9.68 (1H, s), 4.39-4.35 (1H, m), 3.68 (3H, s), 2.73 (1H, dd, *J* = 15.6, 4.7), 2.63 (1H, dd, *J* = 15.6, 6.9), 0.89 (9H, s), 0.11 (3H, s), 0.07 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.8, 170.6, 74.2, 51.9, 38.3, 25.5, 18.0, -4.8, -5.2.

IR: (thin film)

2954, 2931, 2887, 2858, 1741, 1473, 1464, 1438, 1410, 1362, 1256, 1193, 1175, 1122, 1080, 1006, 957, 839, 813, 780, 670 cm^{-1}.

TLC: R_f 0.30 (4:1 hexane/ethyl acetate)

HRMS: (FAB)

calcd for $C_{11}H_{23}O_4Si$ $(M+H)^+$ 247.1366, found 247.1362.

Chapter 4

Application of Acetate Aldol: Enantioselective Synthesis of (*R*)-(-)-Epinephrine

Recently, β-adrenoreceptor agonists or β-blockers have been the focus of drug design because of their high specificity in biological action.[57] β-Amino arylethanols with the (*R*)-(-) configuration at the hydroxyl center have a high affinity for β-receptors. Both naturally occurring and industrially produced β-blockers are shown below in Figure 5. Albuterol (**47**), terbutaline (**50**), isoproterenol (**46**) and sotalol (**49**) have been used to treat asthma, glaucoma and cardiovascular disease.[57,58] Alkyl substitution on the amine, and phenols at the 3 and 5 positions are structural features attributed to recognition of the β-receptors, while aminoethanol derivatives with unsubstituted amines and a phenol at the 4 position have high affinity for α-adrenoreceptors.[59] For example, isoproterenol (**46**) has a high affinity for β-receptors while epinephrine (**45**) is nonselective in recognition of α– and β-receptors.

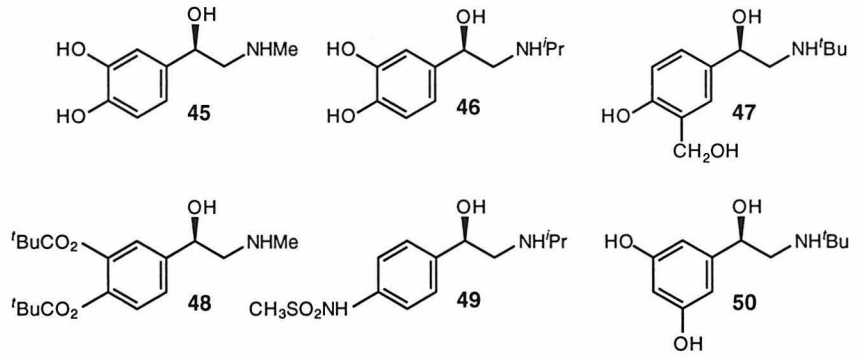


Figure 5. β-Adrenoreceptor agonists or blockers.

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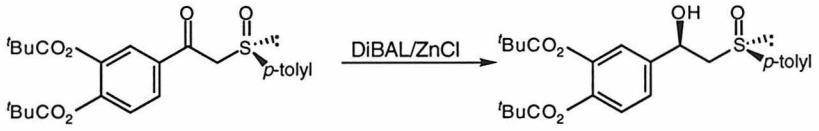
57. (a) Main, B. G.; Tucker, H. In *Medicinal Chemistry*, 2nd Ed.; Genellin, C. R.; Roberts, S. M., Ed.; Academic Press: London, **1993**, 187-208. (b) Lunts, L. H. C. *ibid.* 210-226.

58. Brittain, R. T.; Farmer, J. B.; Marshall, R. J. *Br. J. Pharmac.* **1973**, *48*, 144.

59. Lullman, H.; Mohr, K.; Ziegler, A.; Bieger, D. In *Pocket Atlas of Pharmacology*, Thieme Medical Publishers: New York, **1993**, 79-95.

Typically the β-blocker drugs are produced as the racemate in spite of the fact that only the (*R*) enantiomer is biologically active.[57b] The few enantioselective syntheses of β-amino arylethanol derivatives have typically focused on asymmetric reduction of α-amino-acetophenone derivatives. Although the various approaches have been successful at installing the desired stereochemistry, the reagents employed are typically used on a stoichiometric level or at high catalyst loads. Solladie-Cavallo and co-workers stereoselectively reduced an arylketone precursor to **48** with diisobutylaluminum hydride (DIBAL) in 98% diastereoselectivity (eq 20) by incorporating an optically pure chiral sulfoxide into the substrate.[60]



(20)

Corey and Link demonstrated that α-chloro-acetophenone derivatives could be reduced with 10 mol% of the CBS-catalyst[61] (Figure 6) in 97% ee (eq 21).[62] Gao and co-workers[63] employed the CBS-catalyst stoichiometrically to enantioselectively reduce a

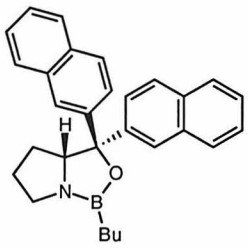


Figure 6. CBS catalyst.

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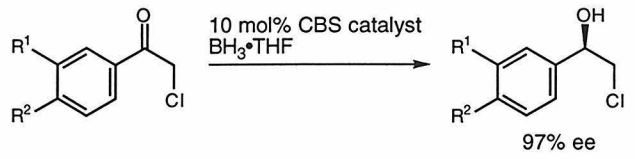
60. Solladie-Cavallo, A.; Simon-Wermeister, M.-C.; Farkhami, D. *Helv. Chim. Acta* **1991**, *74*, 390.

61. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861.

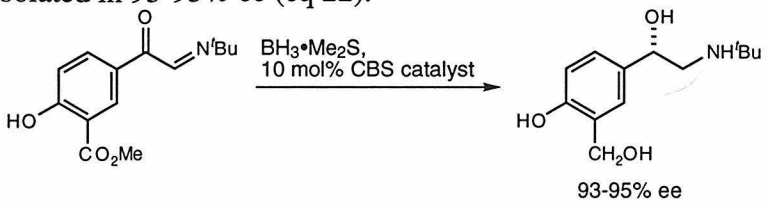
62. (a) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442. (b) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1990**, *31*, 601.

63. Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 5551.



(21)

ketoimine precursor of (*S*)-albuterol in 97% ee. When utilizing 10 mol% of the CBS catalyst, and carrying out a slow addition of the ketoimine and borane to the catalyst, (*S*)-albuterol was isolated in 93-95% ee (eq 22).

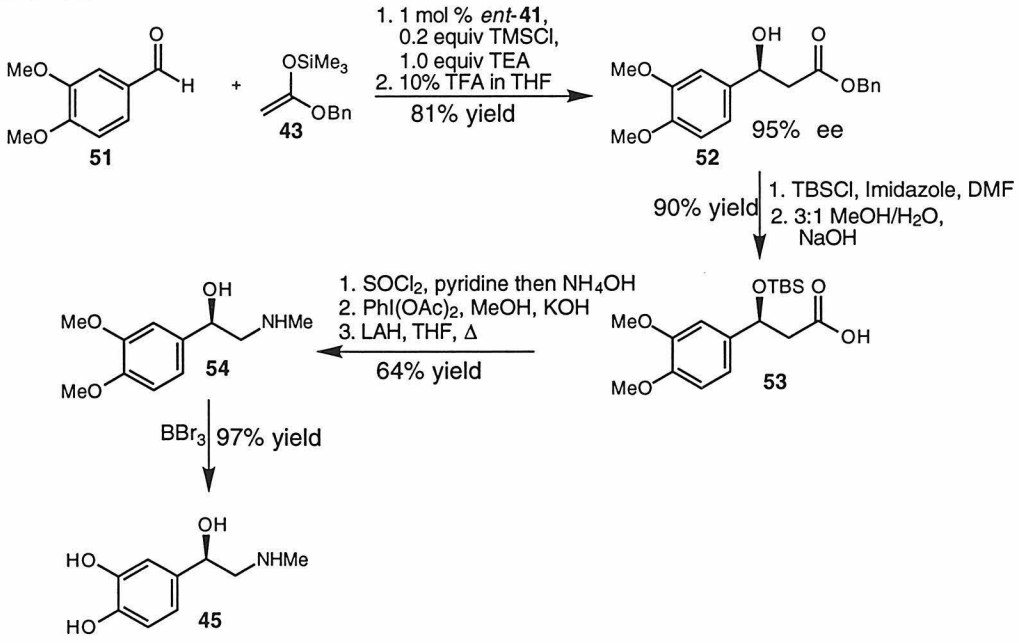


(22)

The synthesis of (*R*)-epinephrine (**45**) was undertaken to demonstrate the utility of the catalytic, enantioselective acetate aldol and to extend the scope of products available to include β-amino arylethanols. The plan was to carry out an acetate aldol on a benzaldehyde derivative and convert the carboxylate to the desired substituted amine via a Curtius or Hoffman rearrangement.

The route (Scheme 15) began with an enantioselective acetate aldol addition to 3,4-dimethoxybenzaldehyde (**51**). This reaction was carried out on a 2.0 g scale in toluene

Scheme 15



without removing volatiles in the catalyst preparation. The crystalline benzyl ester was isolated after desilylation with trifluoroacetic acid (TFA) in tetrahydrofuran (THF) in 81% yield. Analysis by chiral HPLC revealed that the product had been formed in 95% ee. The addition could also be carried out with the methyl acetate derived silyl ketene acetal (**42**) to afford the corresponding methyl ester in 97% ee.

The β-hydroxy was protected as the silyl ether with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide (DMF). The crude ester was then saponified in alkaline 3:1 methanol/water. Acid **53** was isolated in 90% yield for the two steps. To form the primary amide in preparation for the Hoffman rearrangement, the acid was first converted to the acyl chloride with thionyl chloride in dichloromethane. The acid chloride was then quenched in situ upon treatment with an aqueous solution of ammonium hydroxide. The crude amide was then dissolved in methanol with potassium hydroxide at 0 °C to be treated with diacetoxy iodosobenzene to effect rearrangement to the methyl carbamate.[64] After a work-up, the unpurified carbamate was exhaustively reduced to the corresponding methylamine, **54**, by heating in THF with lithium aluminum hydride. The amino-alcohol, **54**, was isolated in 64% yield for the three step sequence (**53** → **54**).

In preparation for the final deprotection with boron tribromide, the solution of amino-alcohol **54** in dichloromethane was deoxygenated by the freeze-pump-thaw method. When neglecting to deoxygenate prior to revealing the catechol, this product would rapidly oxidize to the corresponding *ortho*-quinone. The aryl-methylethers were successfully cleaved with BBr_3 by starting the reaction at -78 °C and gradually warming to 0 °C.[65] The boron was removed as trimethyl borate by repetitively treating the catechol with HCl and methanol followed by concentrating *in vacuo*. (*R*)-Epinephrine hydrochloride was obtained in 97% yield. For the overall synthesis, epineprine was obtained in 48% yield,

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64. Moriarty, R. M.; Chany, C. J.; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem. 1993*, **58**, 2478.

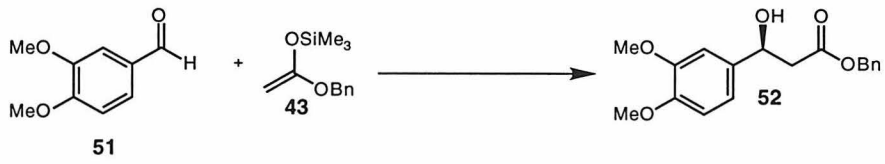
65. McOmie, J. F. W.; West, D. E. In *Organic Syntheses, Coll. Vol. 5*, Wiley: New York, **1973**, 413-414.

starting from commercially available **51**.[66] To confirm the assignment, the product was compared to authentic material by ^{1}H and ^{13}C NMR as well as by optical rotation and was found to match all data identically.

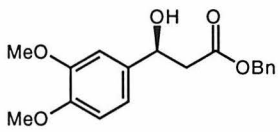
Aside from demonstrating the ability to access amino-alcohols, the two benzaldehyde derivatives screened in the asymmetric aldol show the tolerance of the catalyst to the ether functionality. In addition, the use of the benzyl acetate derived silyl ketene acetal (**43**) affords an aldol adduct in comparable enantioselectivity to the addition with the methyl acetate derived silyl ketene acetal (**42**), highlighting the utility of the more easily prepared **43**. Furthermore, the benzyl ester adduct of the dimethoxybenzaldehyde is crystalline while the methyl ester is not. The judicious selection of an ester to promote crystallinity of the adduct could be exploited for other substrates as well.

66. Purchased from Aldrich Chemical Company.

Experimental Section



52. To a solution of 120 mg of *ent*-**27** in 40 mL of toluene at 23 °C was added 29 μL of $Ti(O^iPr)_4$. After stirring the resulting orange solution for 1 h at 23 °C, **40** was added via cannula in 20 mL of toluene. The solution was stirred for an additional h at 23 °C and then was cooled to -20 °C. To the cooled solution was added 253 μL of TMSCl followed by 1.39 mL of TEA and 1.66 g of **51** (added via cannula in 5 mL of toluene). After the solution had stirred for another 15 min, **43** was added dropwise. The reaction mixture was allowed to gradually warm to 23 °C over 6 h. After this time the solution was quenched by pouring onto 60 mL of a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was treated with 10 mL of a 10% solution of TFA in THF to effect desilylation. After 5 min desilylation was complete and the solution was partitioned between 50 mL of water and 50 mL of Et_2O. The organic layer was washed with 50 mL of a 1.0 M NaOH solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product, **52**, was isolated as a white crystalline solid in 81% yield (2.56 g) by chromatography on 60 mL of silica (3 cm diameter column) using 2:1 hexane/ethyl acetate as eluent.



mp: 49-50 °C

$[\alpha]_D^{19}$ -24.8° (*c* = 1.0, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.37-7.30 (5H, m), 6.91 (1H, s), 6.87 (1H, d, *J* = 8.2), 6.80 (1H, d, *J* = 8.2), 5.15 (2H, s), 5.12-5.07 (1H, m), 3.85 (2H, s), 3.29 (1H, bs), 2.83 (1H, dd, *J* = 16.2, 9.0), 2.73 (1H, dd, *J* = 16.2, 4.0).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 172.0, 148.9, 135.4, 135.0, 128.5, 128.3, 128.1, 117.8, 110.9, 108.7, 70.1, 66.5, 55.8, 55.7, 43.4.

IR: (thin film)

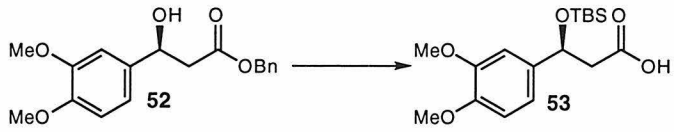
3507, 3065, 3033, 3002, 2937, 2836, 1732, 1607, 1594, 1517, 1456, 1420, 1382, 1264, 1237, 1156, 1067, 1027, 860, 812, 754, 699 cm^{-1}.

HRMS: (FAB)

calcd for $C_{18}H_{20}O_5$ $(M)^+$ 316.1311, found 316.1308.

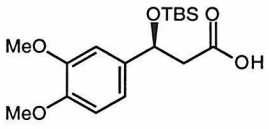
TLC: R_f 0.12 (2:1 hexane/ethyl acetate)

HPLC data: Using a flow rate of 0.80 mL/min with 80/20 hexane/ethyl acetate eluent, the enantiomers elute at 21.9 min (major) and 18.4 min (minor) in a ratio of 38:1 (95% ee).



53. To a solution of 384 mg of **52** (1.60 mmol) and 163 mg of imidazole (2.40 mmol) in 2 mL of dimethylformamide (DMF) was added 289 mg of *tert*-butyldimethylsilyl chloride (1.92 mmol) in 1 mL of DMF via cannula. The solution was stirred at 23 °C for 3 h. The solution was then partitioned between 30 mL of water and 20 mL of Et_2O. The aqueous layer was extracted with another 10 mL of Et_2O and the combined organic layers were dried over anhydrous Na_2SO_4. After concentrating the organics *in vacuo*, the crude material was taken up in 30 mL of 2:1 MeOH/H_2O with 1.0 g of NaOH. The solution was stirred for 2 h at 23 °C and then was diluted with 50 mL of water and 50 mL of CH_2Cl_2.

The mixture was acidified with 15 mL of 2.0 M HCl, and then the organic layer was separated. The aqueous layer was extracted twice more with 25 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and were concentrated *in vacuo*. The product, **53**, was isolated by chromatography on silica gel using 4:1 hexane/ethyl acetate as eluent in 90% yield (480 mg) as a clear, colorless oil.



$[\alpha]_D^{19}$ -41.3° (*c* = 1.1, $CHCl_3$)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 6.96 (1H, d, *J* = 1.8), 6.88 (1H, dd, *J* = 8.3, 1.8), 6.81 (1H, d, *J* = 8.3), 5.17-5.13 (1H, m), 3.88 (3H, s), 3.87 (3H, s), 2.79 (1H, dd, *J* = 14.8, 9.2), 2.63 (1H, dd, *J* = 14.8, 4.0), 0.89 (9H, s), -0.08 (3H, s), -0.10 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 177.0, 149.0, 148.4, 136.4, 117.9, 110.9, 108.9, 71.7, 55.7, 55.7, 46.1, 25.6, 18.0, -4.8, -5.4.

IR: (thin film)

2955, 2856, 2678, 1714, 1607, 1595, 1515, 1464, 1442, 1389, 1362, 1326, 1299, 1260, 1154, 1138, 1089, 1029, 1006, 957, 914, 835, 813, 777, 733, 668, 649, 584 cm^{-1}.

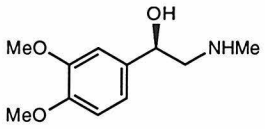
HRMS: (FAB)

calcd for $C_{17}H_{28}O_5Si$ $(M)^+$ 312.1937, found 312.1926.

TLC: R_f 0.30 (2:1 hexane/ethyl acetate)

54. To a solution of 480 mg of **53** (1.41 mmol) and 125 μL of pyridine with 2 drops of DMF in 5 mL of CH_2Cl_2 at 0 °C was added 206 μL of thionyl chloride dropwise. The solution was stirred at 0 °C for 30 min and then was allowed to warm to 23 °C to stir for an additional h. After this time the solution was added dropwise to a stirring solution of 30 mL of 38% NH_4OH at 0 °C. A white precipitate formed which was allowed to stir for another 10 min after completing addition. The organics were extracted three times with 15 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and were concentrated *in vacuo* to give a white crystalline solid. The amide was dissolved in 5 mL of anhydrous MeOH with 198 mg of KOH (3.53 mmol). The solution was cooled to 0 °C and 545 mg of diacetoxy iodosobenzene (1.69 mmol) was added.[64] The solution was allowed to gradually warm to 23 °C over 1.5 h. The solution was partitioned between 25 mL of CH_2Cl_2 and 25 mL of water. The aqueous layer was extracted twice more with 15 mL of CH_2Cl_2 each time. The combined organic layers were dried over anhydrous Na_2SO_4 and were concentrated *in vacuo*. The carbamate was dissolved in 5 mL of THF and was treated with 161 mg of lithium aluminum hydride (4.23 mmol). The solution was heated to reflux for 1.5 h. The solution was then cooled to 0 °C and quenched with 5 mL of water. The mixture was diluted with 50 mL of CH_2Cl_2, 50 mL of water and 5 mL of HCl. After stirring the mixture to hydrolyze the aluminum from the amine, the mixture was made alkaline with NaOH. The mixture developed a suspension after stirring and was filtered through a plug of celite. The aqueous layer was extracted five more times with 15 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and were concentrated *in vacuo*. The product was isolated by chromatography on silica gel by first eluting impurities with 2:1 THF/MeOH and then by switching to 9:1 MeOH/AcOH to elute the product. The product was free based with 5 mL of 1.0 M NaOH and extracted 5 times with 15 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous

Na_2SO_4 and were concentrated *in vacuo*. The product, **54**, was isolated as a clear, colorless oil in 64% (200 mg).



$[\alpha]_D^{19}$ -35.8° (*c* = 2.2, $CHCl_3$)

^1H NMR: (300 MHz, $CDCl_3$)

δ 6.86 (1H, d, *J* = 1.7), 6.79 (1H, dd, *J* = 8.2, 1.7), 6.75 (1H, d, *J* = 8.2), 4.63 (1H, dd, *J* = 7.8, 5.0), 3.80 (3H, s), 3.79 (3H, s), 3.25 (2H, bs), 2.64 (1H, dd, *J* = 15.0, 7.8), 2.63 (1H, dd, *J* = 15.0, 5.0), 2.32 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 148.8, 148.1, 135.6, 117.8, 110.8, 108.8, 71.3, 59.1, 55.7, 55.6, 35.7.

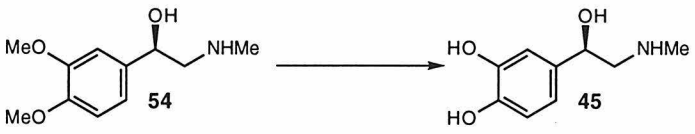
IR: (thin film)

3318, 2939, 2836, 2801, 1644, 1607, 1594, 1515, 1463, 1455, 1417, 1318, 1264, 1235, 1140, 1112, 1064, 1027, 865, 812, 764, 742, 645, 619 cm^{-1}.

HRMS: (FAB)

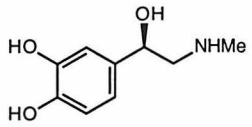
calcd for $C_{11}H_{18}NO_3$ $(M+H)^+$ 212.1287, found 212.1287.

TLC: R_f 0.05 (2:1 THF/MeOH)



45. The amino-alcohol, **54**, (30 mg, 0.136 mmol) was dissolved in 2 mL of CH_2Cl_2 and deoxygenated with 3 cycles of the freeze-pump-thaw method. The solution was cooled to -78 °C and treated with 50 μL of BBr_3.[65] The solution was allowed to gradually warm to 0 °C over 2 h. To the solution was added 2 mL of anhydrous MeOH. After stirring for 5 min, 4 drops of 12 M HCl was added and the solution was concentrated

in vacuo. The residue was taken back up in 4 mL of MeOH with 4 drops of 12 M HCl to be concentrated *in vacuo* and this process was repeated 5 times. After drying the solid under vacuum, the hydrochloride salt of epinephrine was isolated as an off-white solid in 97% yield (29 mg).



$[\alpha]_D^{19}$ -56.0° (*c* = 2.5, MeOH)

$[\alpha]_D^{19}$ -52.5° (*c* = 2.2, 1 N HCl)[67]

^{1}H NMR: (300 MHz, CD_3CN)

δ 8.07 (4H, bs), 7.03 (1H, s), 6.88 (1H, d, *J* = 7.7), 6.87 (1H, d, *J* = 7.7), 5.53 (1H, dd, *J* = 8.0, 7.3), 3.81 (1H, d, *J* = 7.3), 3.78-3.50 (2H, m), 2.61 (3H, t, *J* = 5.6).

^{13}C NMR: (75 MHz, CD_3CN)

δ 146.9, 145.9, 129.5, 121.0, 116.7, 115.9, 55.7, 48.5, 33.8.

IR: (thin film)

3209, 2796, 1706, 1606, 1518, 1449, 1362, 1283, 1233, 1198, 1114, 1072, 1020, 872, 816 cm^{-1}.

TLC: R_f 0.73 (9:1 MeOH/AcOH)

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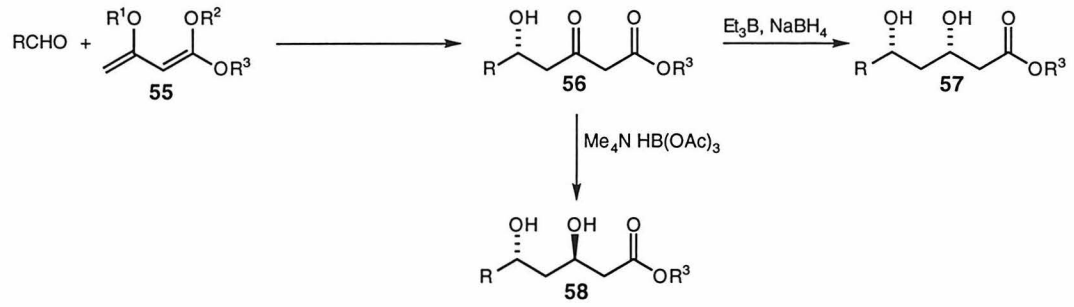
67. Literature: $[\alpha]_D^{25}$ -51.8° (1 N HCl) Merck Index

Chapter 5

Enantioselective Dienolate Additions with Acetoacetate Derivatives

In an effort to extend the asymmetric methodology beyond acetate additions, it was hoped that a dienolate derived from acetoacetate could be designed that would be compatible with aldol catalyst **41**. Acetoacetate derived dienolates,[68] such as **55**, would lead to δ-hydroxy-β-ketoester products (**56**). Such additions would be more efficient at installing 1,3-diol functionality since syn- and anti-diols are accessible from directed reductions of hydroxyketones (Scheme 16).[69,70]

Scheme 16



The first dienolates screened were derived from acetoacetates, crotonates or crotonamides. None of these substrates exhibited levels of reactivity or selectivity comparable to the silyl ketene acetals (entries 1-6, Table 12). The reactions with the crotonamide derived dienolates (entries 3-5) showed very slow turning over of the catalyst. The reactions for entries 3-5 never produced product in better than 35% yield, even after

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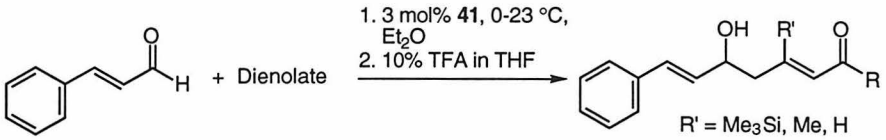
68. (a) Chan, T.–H.; Brownbridge, P. *J. Chem. Soc. Chem. Comm.* **1979**, 578. (b) Chan, T.–H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688. (c) Chu, D. T. W.; Huchin, S. N. *Can. J. Chem.* **1980**, *58*, 138.

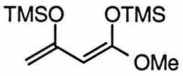
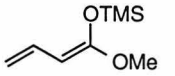
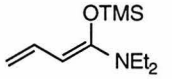
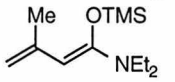
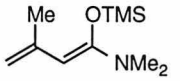
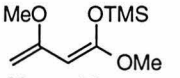
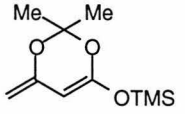
69. Syn reduction: Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419, and references therein.

70. Anti reduction: Evans, D.A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447, and references therein.



(23)

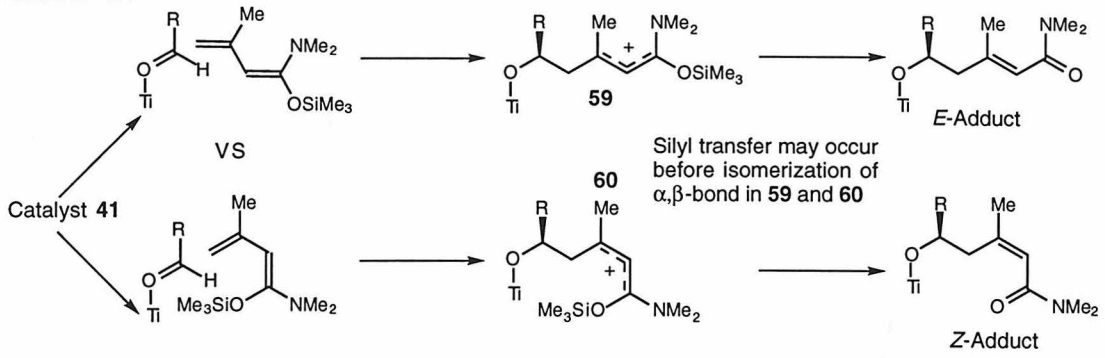
Table 12. Dienolates Screened for Enantioselective Aldol Addition

Entry	Dienolate	% ee[a]
1		NR
2		NR
3		0%
4		33%
5		64%
6		64%
7		92%

[a] Optical purity determined by conversion to the (S)-MTPA ester and analysis by ^{1}H NMR spectroscopy.

allowing the reactions to stir for 16 hours at 23 °C. This was likely due to the amide products binding competitively with aldehydes to the catalyst because amides are more nucleophilic than esters. For entries 3-5, the products isolated had both *E*- and *Z*-olefin isomers present. Moreover the isomers were of slightly different optical purity for entry 5. The *Z*-adduct was isolated in 64% ee (4.5:1 enantiomeric ratio) while the *E*-adduct was isolated in 50% ee (3:1 enantiomeric ratio). This suggests that the dienolates may react from different conformations. The transfer of the silyl group from the amide product may be faster than bond rotation about the α,β-bond in the intermediates (**59** and **60**) to the final amide product (Scheme 17).

Scheme 17



To solve the problem with reactivity, a dioxinone derived dienolate **61** was prepared.[71,72,73] By locking the two π-systems in plane, we speculated that the dioxinone derived dienolate would have superior nucleophilicity at the δ-carbon. For the other dienolates, the conjugated π-systems may rotate out of plane due to A_{1-3} steric interactions. Indeed, it was found that the dioxinone derived dienolate had reactivity similar to the silyl ketene acetals (4 h at 0 °C in Et_2O or toluene), though the selectivity was slightly lower (Table 13). Using 1 to 3 mol% of Ti complex **41**, unbranched, unsaturated aldehyde adducts were obtained in 90-94% ee, while α-branched and saturated aldehydes were isolated in 80-84% ee.[74] Although the enantioselectivities are lower than in the acetate adducts, many of the dioxinone products are crystalline, allowing for enhancement of optical purity through recrystallization.

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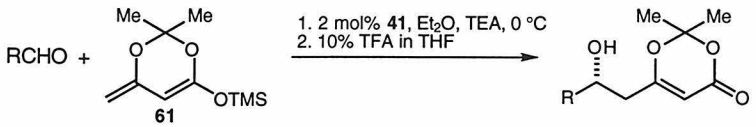
71. Grunwell, J. R.; Karapides, A.; Wigal, C. T.; Hinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91.

72. Chiral dioxionones have been used as precursors to dienolates to carry out diastereoselective additions to aldehydes, see Seebach, D.; Gysel, U.; Kinkel, J. N. *Chimia* **1991**, *45*, 114.

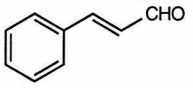
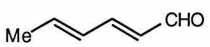
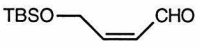
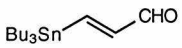
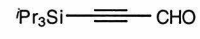
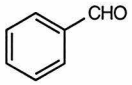
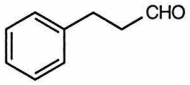
73. Dioxinone derived dienolates have been used to carry out enantioselective additions to aldehydes with a Ti(IV)-2,2'-dihydroxy-1,1'-binaphthyl complex, see: (a) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435. (b) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 839.

74. Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360.



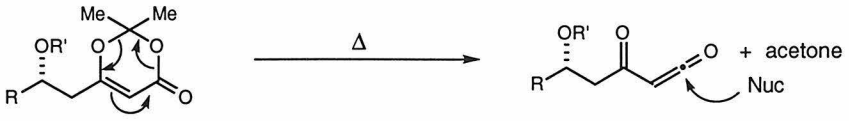
(24)

Table 13. Substrates Screened in Asymmetric Dienolate Addition

Entry	Aldehyde	Yield	ee[a]
1		88%	92% (99%)[b]
2		95%	92%
3		97%	94%
4		80%	92%
5		86%	91%
6		83%	84% (96%)[b]
7		97%	80%

[a] Optical purity determined by conversion to the (S)-MTPA ester and analysis by ^{1}H NMR spectroscopy. [b] Optical purity after recrystallization from 6:1 hexane/ethyl acetate.

An advantage of the dioxinone products was in their flexibility of being easily converted to other useful intermediates. The dioxinone products were derivatized by heating in toluene to extrude acetone and form an acyl ketene intermediate (eq 25).

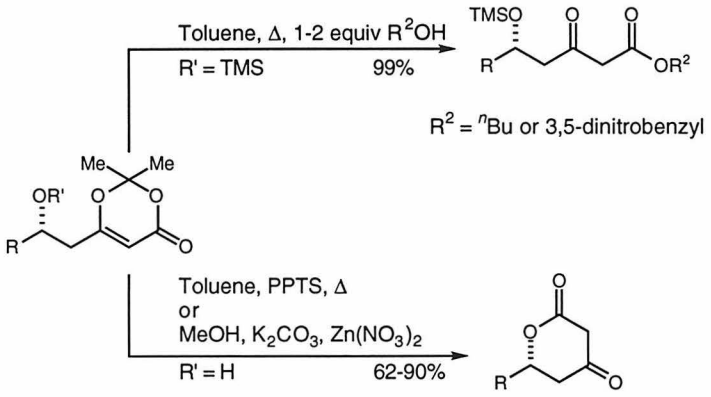


(25)

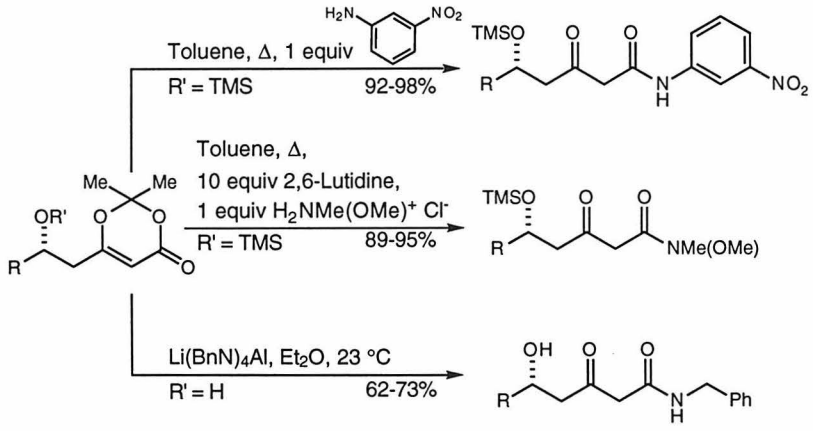
Nucleophiles such as alcohols or amines attack the ketene to produce the corresponding β-ketoester (Scheme 18) or β-ketoamide (Scheme 19). Carrying out the transformations to obtain the corresponding ketoester with the δ-hydroxy group protected provided the

products in quantitative yield. Leaving the δ-hydroxyl group unprotected in the dioxinone adducts while heating in the presence of mild acid (pyridinium *p*-toluenesulfonate (PPTS)) or stirring with base (potassium carbonate) led to δ-lactones.[75] The zinc nitrate was added to the lactonization protocol to minimize formation of elimination side-products.[76] It was discovered that Weinreb amide derivatives were equally accessible, which allow for the direct reduction of the amide to the aldehyde. Alternatively, the dioxinone could be opened to amides using the Solladie-Cavallo method (lithium aluminumtetrabenzylamide) (Scheme 19).

Scheme 18



Scheme 19



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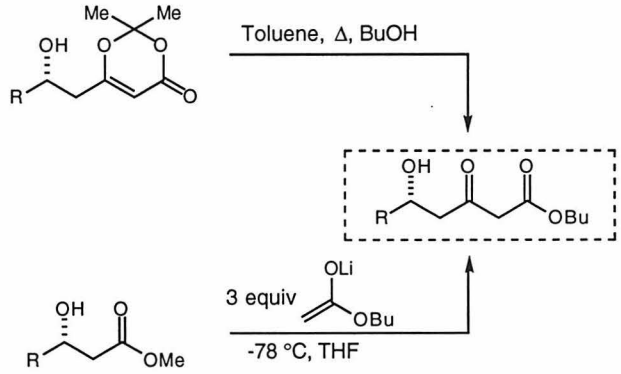
75. The stereochemical integrity of the stereocenter in lactone products was determined by opening the lactone with benzyl amine to the corresponding β–keto–amide and comparison to authentic material prepared via an independent route.

76. Buonora, P. T.; Rosauer, K. G.; Dai, L. *Tetrahedron Lett.* **1995**, *36*, 4009.

The absolute configuration of the dioxinone adducts was determined by correlation to compounds prepared by the acetate aldol (Scheme 20). The dioxinone products were opened to the corresponding δ-hydroxy-β-ketoesters to be compared by optical rotation to the identical product prepared by a Claisen addition to the known optical active β-hydroxyester. The β-hydroxy esters were directly converted to the δ-hydroxy-β-ketoesters by a Claisen addition of the lithium enolate of butyl acetate.[77] To carry out the addition, three equivalents of the nucleophile were required. The first equivalent deprotonated the free hydroxyl group, the second equivalent added to the ester and the final equivalent deprotonated the α-carbon. All the products contained absolute stereochemistry which was identical to the sense of induction observed in the acetate aldol additions.

Scheme 20



77. Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385.

Experimental Section[78]

General Procedure for Enantioselective Dienolate Aldol Addition Reaction

To a 5.5 mM solution of the chiral Schiff base ligand (0.044 equiv) in toluene was added $Ti(^iPrO)_4$ (0.020 equiv). The orange solution was stirred for 1 h at 23 °C and a solution of 3,5-di-*tert*-butylsalicylic acid (0.040 equiv; 20 mM in toluene) was added. Stirring was continued for an additional h at 23 °C. The solvent was removed *in vacuo* and the orange solid was dissolved in Et_2O to give a 5.5 mM solution (relative to chiral ligand). After cooling the solution to 0 °C, triethylamine (0.40 equiv) was added to the solution, followed by the sequential addition of the aldehyde (1.0 equiv) and the dienolate (1.5 equiv). After stirring the reaction for 4 h at 0 °C, it was quenched by pouring onto water. The mixture was extracted with Et_2O. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was treated with 10% TFA in THF. After desilylation was complete the solution was partitioned between Et_2O and water. The organic layer was washed twice with a 5% aqueous $NaHCO_3$ solution, was dried over anhydrous Na_2SO_4 and was concentrated *in vacuo*. Purification by chromatography on silica gel using 2:1 hexane/EtOAc afforded the aldol adduct.

A portion of the aldol adduct was converted to the corresponding (*S*)-MTPA-ester[79] as follows. To a solution of the alcohol (0.010 mmol, 1 equiv) and 15 mg of dimethylaminopyridine (DMAP) in 0.50 mL of CH_2Cl_2 was added (*R*)-MTPA-Cl (0.011 mmol, 1.1 equiv). The MTPA-ester was purified by chromatography on silica gel, using 4:1 hexane/EtOAc as eluent. The enantiomeric excess of the product was determined by integration of the ^1H NMR (300 MHz, $CDCl_3$) spectrum.

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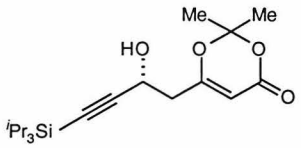
78. For a description of general purification and analytical procedures, see chapter 2.

79. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.



Isolated in 86% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +10.2° (*c* = 1.1, $CHCl_3$)

IR: (thin film)

3416, 2172, 1714 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 5.36 (1H, s), 4.66 (1H, t, *J* = 6.7), 2.63 (2H, m), 2.51 (1H, bs), 1.67 (6H, s), 1.04 (18H, d, *J* = 1.3), 1.0 (3H, m).

^{13}C NMR: (75 MHz, $CDCl_3$)

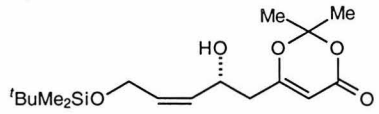
δ 167.1, 160.9, 106.7, 106.4, 95.8, 87.2, 59.6, 42.1, 25.1, 24.9, 18.5, 11.0.

HRMS: (FAB)

calcd for $C_{19}H_{33}O_4Si$ $(M+H)^+$ 353.2148, found 353.2151.

TLC: R_f 0.18 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) vinyl resonances at δ 5.30 and 5.19 ppm in ratio of 22.0:1 (91% ee).



Isolated in 97% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +10.5° (*c* = 0.95, $CHCl_3$).

IR: (thin film)

3448, 1719 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 5.84-5.68 (2H, m), 5.30 (1H, s), 4.43 (1H, q, *J* = 6.2), 4.15 (2H, d, *J* = 3.9), 2.43 (2H, d, *J* = 6.6), 2.30 (1H, bs), 1.67 (3H, s), 1.66 (3H, s), 0.88 (9H, s), 0.04 (6H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

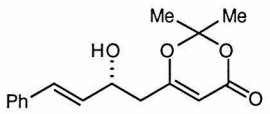
δ 168.5, 161.1, 131.4, 130.5, 106.6, 95.2, 69.0, 62.6, 41.4, 25.8, 25.3, 24.8, 18.3, -5.3.

HRMS: (FAB)

calcd for $C_{17}H_{31}O_5Si$ $(M+H)^+$ 343.1941, found 343.1943.

TLC: R_f 0.08 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) vinyl resonances at δ 5.30 and 5.19 ppm in ratio of 31.8:1 (94% ee).



Isolated in 88% yield as a white crystalline solid.[6]

mp: 85-86 °C

$[\alpha]_D^{19}$ +6.2° (*c* = 1.0, $CHCl_3$)

IR: (thin film)

3420, 1728 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.38-7.27 (5H, m), 6.63 (1H, d, *J* = 15.9), 6.20 (1H, dd, *J* = 15.9, 6.6), 5.36 (1H, s), 4.59 (1H, q, *J* = 6.6), 2.54 (2H, m), 2.24 (1H, bs), 1.68 (3H, s), 1.68 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

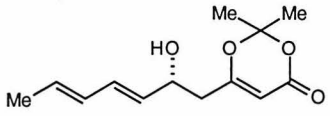
δ 168.3, 161.1, 136.0, 131.4, 130.2, 128.6, 128.1, 126.5, 106.7, 95.3, 69.7, 41.5, 25.3, 24.8.

HRMS: (FAB)

calcd for $C_{16}H_{19}O_4$ $(M+H)^+$ 275.1283, found 275.1285.

TLC: R_f 0.10 (2:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) vinyl resonances at δ 5.30 and 5.19 ppm in ratio of 24.4:1 (92% ee). After recrystallizing 90 mg of the dioxinone adduct from 6:1 hexane/EtOAc, 55 mg (61% yield) of white needle crystals (mp = 88-89 °C) were obtained which were found to be 99% ee by integration of the ^{1}H NMR of the (*S*)-MTPA-ester.



Isolated in 95% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +13.4° (*c* = 1.0, $CHCl_3$)

IR: (thin film)

3418, 1714 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 6.19 (1H, dd, *J* = 15.2, 10.5), 5.99 (1H, m), 5.71 (1H, dd, *J* = 14.9, 6.7), 5.52 (1H, dt, *J* = 7.0, 7.0, 0.48), 5.29 (1H, s), 4.39 (1H, q, *J* = 6.6), 2.46 (1H, dd, *J* = 14.2, 7.3), 2.39 (1H, dd, *J* = 14.2, 5.3), 2.23 (1H, bs), 1.74 (3H, dd, *J* = 6.7, 1.0), 1.66 (3H, s), 1.65 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

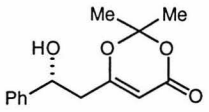
δ 168.5, 161.2, 131.9, 131.1, 130.8, 130.2, 106.6, 95.1, 69.4, 41.5, 25.2, 24.8, 18.1.

HRMS: (FAB)

calcd for $C_{13}H_{19}O_4$ $(M+H)^+$ 239.1283, found 239.1284.

TLC: R_f 0.16 (2:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) vinyl resonances at δ 5.26 and 5.14 ppm in ratio of 26.0:1 (93% ee).



Isolated in 83% yield as a white crystalline solid.[80]

mp: 63-64 °C

$[\alpha]_D^{19}$ +35.9° (c = 1.0, $CHCl_3$)

IR: (thin film)

3426, 1714 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.36-7.29 (5H, m), 5.27 (1H, s), 4.95 (1H, dd, J = 8.6, 4.9), 2.71 (1H, dd, J = 14.6, 8.6), 2.60 (1H, bs), 2.54 (1H, dd, J = 14.6, 4.8), 1.64 (3H, s), 1.63 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

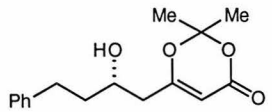
δ 168.5, 161.2, 142.8, 128.6, 128.1, 125.7, 106.6, 95.2, 71.0, 43.1, 25.3, 24.6.

HRMS: (EI)

calcd for $C_{14}H_{17}O_4$ $(M+H)^+$ 249.1127, found 249.1126.

TLC: R_f 0.18 (4:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) vinyl resonances at δ 5.30 and 5.19 ppm in ratio of 11.9:1 (84% ee). After recrystallizing 150 mg of the dioxinone adduct from 6:1 hexane/EtOAc, 110 mg (73% yield) of white needle crystals (mp = 74 °C) were obtained which were found to be 96% ee by integration of the ^1H NMR of the (*S*)-MTPA-ester.



Isolated in 97% yield as a white crystalline solid.

mp: 51 °C

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80. (a) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435. (b) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 839.

$[\alpha]_D^{19}$ +2.5° (*c* = 1.1, $CHCl_3$)

IR: (thin film)

3448, 1718 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.32-7.17 (5H, m), 5.31 (1H, s), 3.92 (1H, m), 2.79 (1H, m), 2.71 (1H, m), 2.40 (1H, m), 2.38 (1H, m), 2.28 (1H, bs), 1.82 (2H, m), 1.67 (3H, s), 1.66 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

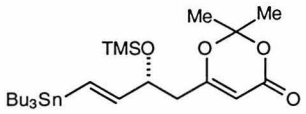
δ 168.8, 161.1, 141.4, 128.5, 128.4, 126.1, 106.6, 95.2, 68.4, 41.8, 38.9, 31.8, 25.3, 25.0.

HRMS: (EI)

calcd for $C_{16}H_{21}O_4$ $(M+H)^+$ 277.1440, found 277.1445.

TLC: R_f 0.11 (2:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^1H NMR ($CDCl_3$) vinyl resonances at δ 5.22 and 5.14 ppm in ratio of 8.9:1 (80% ee).



Isolated in 79% yield as a colorless oil.

$[\alpha]_D^{19}$ +21.9° (*c* = 1.0, $CHCl_3$)

IR: (thin film)

2956, 2926, 2872, 2852, 1735, 1637, 1464, 1388, 1375, 1271, 1250, 1206, 1071, 1012, 946, 899, 842, 806, 744 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 6.16 (1H, dd, *J* = 19.0, 1.0), 5.92 (1H, dd, *J* = 19.0, 5.9), 5.25 (1H, s), 4.34-4.30 (1H, m), 2.40 (1H, dd, *J* = 11.4, 4.9), 2.35 (1H, dd, *J* = 11.4, 2.9), 1.68 (3H, s), 1.67 (3H, s), 1.47 (6H, m), 1.31 (6H, m), 0.88 (9H, t, *J* = 7.2), 0.89 (6H, t, *J* = 8.2), 0.09 (9H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 168.7, 161.0, 149.4, 129.4, 106.3, 95.2, 73.5, 42.7, 29.1, 27.2, 25.4, 24.9, 13.6, 9.5, 0.3.

HRMS: (FAB)

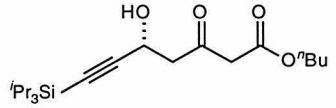
calcd for $C_{25}H_{48}O_4SiSn$ $(M)^+$ 560.2343, found 560.2335.

TLC: R_f 0.24 (10:1 hexane/ethyl acetate)

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) vinyl resonances at δ 5.25 and 5.14 ppm in ratio of 24:1 (92% ee).

General Procedure for Conversion of Acetonide Protected Aldol Products to Ketoesters.

The protected aldol product was dissolved in anhydrous n-butanol and heated at reflux for 2 h. The solvent was then removed *in vacuo* and the ketoester was isolated by chromatography on silica gel using 4:1 hexane/EtOAc as eluent.



Isolated in 91% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +18.7° (*c* = 0.97, $CHCl_3$).

IR: (thin film)

3425, 1741, 1718 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 4.83 (1H, m), 4.13 (2H, t, *J* = 6.7), 3.49 (2H, s), 3.04 (1H, dd, *J* = 17.3, 7.7), 2.93 (1H, bs), 2.92 (1H, dd, *J* = 17.3, 4.1), 1.61 (2H, m), 1.36 (2H, m), 1.04 (18H, d, *J* = 2.8), 1.0 (3H, m), 0.92 (3H, t, *J* = 7.3).

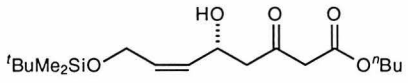
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 201.3, 166.7, 106.4, 86.2, 65.4, 58.6, 49.9, 49.8, 30.4, 19.0, 18.5, 13.6, 11.0.

HRMS: (EI)

calcd for $C_{20}H_{37}O_4Si$ $(M+H)^+$ 369.2461, found 369.2474.

TLC: R_f 0.32 (4:1 hexane/ethyl acetate)



Isolated in 71% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +15.3° (*c* = 0.93, $CHCl_3$)

IR: (thin film)

3434, 1742, 1714 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 5.85-5.67 (2H, m), 4.63 (1H, q, *J* = 5.4) 4.18-4.10 (4H, m), 3.48 (2H, s), 2.77 (2H, d, *J* = 6.1), 2.73 (1H, bs), 1.62 (2H, m), 1.38 (2H, m), 0.92 (3H, t, *J* = 7.3), 0.90 (9H, s), 0.06 (6H, s).

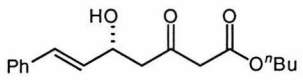
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.6, 166.9, 130.8, 130.1, 67.9, 65.4, 62.9, 50.0, 49.6, 30.5, 25.9, 19.0, 18.4, 13.6, -5.3.

HRMS: (FAB)

calcd for $C_{18}H_{34}O_5NaSi$ $(M+Na)^+$ 381.2074, found 381.2064.

TLC: R_f 0.27 (4:1 hexane/ethyl acetate)



Isolated in 81% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +18.6° (*c* = 0.94, $CHCl_3$)

IR: (thin film)

3480, 1738, 1714 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.38-7.24 (5H, m), 6.64 (1H, d, *J* = 19.5), 6.20 (1H, dd, *J* = 15.9, 6.1), 4.79 (1H, q, *J* = 6.0), 4.14 (2H, t, *J* = 6.7), 3.51 (2H, s), 2.90 (1H, bs), 2.86 (2H, d, *J* = 6.0), 1.62 (2H, m), 1.36 (2H, m), 0.92 (3H, t, *J* = 7.3).

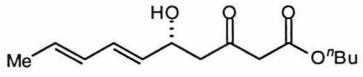
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.7, 166.9, 136.3, 130.6, 129.8, 128.5, 127.8, 126.5, 68.3, 65.4, 49.9, 49.6, 30.4, 19.0, 13.6.

HRMS: (EI)

calcd for $C_{17}H_{22}O_4$ $(M)^+$ 290.1518, found 290.1513.

TLC: R_f 0.17 (4:1 hexane/ethyl acetate)



Isolated in 67% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +17.2° (*c* = 1.2, $CHCl_3$)

IR: (thin film)

3448, 1736, 1718 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 6.21 (1H, dd, *J* = 15.0, 10.5), 6.00 (1H, dt, *J* = 10.5, 1.4, 1.4), 5.71 (1H, m, *J* = 15.0, 6.8, 6.8, 6.8), 5.53 (1H, dd, *J* = 15.1, 6.3), 4.60 (1H, q, *J* = 6.3), 4.12 (2H, t, *J* = 6.7), 3.47 (2H, s), 2.80 (1H, bs), 2.76 (2H, m), 1.74 (3H, d, *J* = 6.8), 1.61 (2H, m), 1.36 (2H, m), 0.92 (3H, t, *J* = 7.3).

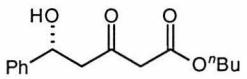
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.7, 166.9, 131.2, 130.6, 130.5, 130.4, 68.2, 65.4, 49.9, 49.6, 30.4, 19.0, 18.1, 13.6.

HRMS: (EI)

calcd for $C_{14}H_{22}O_4$ $(M)^+$ 254.1518, found 254.1527.

TLC: R_f 0.17 (4:1 hexane/ethyl acetate)



Isolated in 68% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +43.0° (*c* = 1.2, $CHCl_3$)

IR: (thin film)

3482, 1739, 1713 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.37-7.27 (5H, m), 5.19 (1H, dd, *J* = 8.9, 3.5), 4.13 (2H, t, *J* = 6.7), 3.48 (2H, s), 3.09 (1H, bs), 3.00 (1H, dd, *J* = 17.4, 8.9), 2.91 (1H, dd, *J* = 17.2, 3.5), 1.62 (2H, m), 1.37 (2H, m), 0.93 (3H, t, *J* = 7.3)

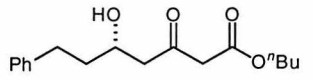
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.9, 166.9, 142.5, 128.6, 127.8, 125.6, 69.8, 65.4, 51.6, 49.9, 30.4, 19.0, 13.6.

HRMS: (EI)

calcd for $C_{15}H_{20}O_4$ $(M)^+$ 264.1362, found 264.1367.

TLC: R_f 0.20 (4:1 hexane/ethyl acetate)



Isolated in 67% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +5.2° (c = 0.90, $CHCl_3$)

IR: (thin film)

3403, 1738, 1713 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.36- 7.16 (5H, m), 4.14 (2H, t, J = 6.7), 4.10 (1H, m), 3.46 (2H, s), 2.84-2.66 (5H, m), 1.85-1.67 (2H, m), 1.62 (2H, m), 1.37 (2H, m), 0.93 (3H, t, J = 7.3).

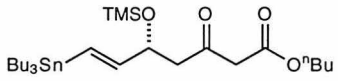
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 203.7, 166.9, 141.6, 128.4, 128.3, 125.9, 66.7, 65.4, 49.8, 49.6, 37.9, 31.7, 30.4, 19.0, 13.6.

HRMS: (FAB)

calcd for $C_{17}H_{24}O_4Na$ $(M+Na)^+$ 315.1573, found 315.1563.

TLC: R_f 0.31 (4:1 hexane/ethyl acetate)



Isolated in 99% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +26.0° (c = 1.0, $CHCl_3$)

IR: (thin film)

2957, 2927, 2872, 2853, 1747, 1721, 1651, 1633, 1464, 1417, 1376, 1338, 1312, 1250, 1175, 1148, 1071, 1023, 990, 974, 843, 750, 689, 597, 312 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 6.15 (1H, dd, J = 19.0, 1.0), 5.92 (1H, dd, J = 19.0, 5.4), 4.54 (1H, m), 4.12 (2H, t, J = 6.7), 3.47 (2H, s), 2.77 (1H, dd, J = 14.7, 8.8), 2.54 (1H, dd, J = 14.7, 3.9), 1.62 (2H, m), 1.46 (6H, m), 1.36 (2H, m), 1.28 (6H, m), 0.92 (3H, t, J = 7.4), 0.87 (15H, t, J = 7.4).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 201.5, 167.1, 149.4, 128.4, 73.0, 65.1, 50.9, 50.7, 30.5, 29.1, 27.2, 19.0, 13.7, 13.6, 9.4, 0.1.

HRMS: (FAB)

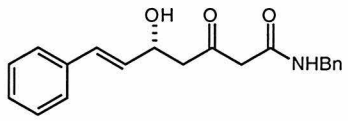
calcd for $C_{26}H_{52}O_4Si^{120}Sn$ $(M)^+$ 576.2657, found 576.2645.

TLC: R_f 0.46 (10:1 hexane/ethyl acetate)

Conversion of cinnamaldehyde adduct to benzylamide. The protected aldol adduct was converted to the benzylamide according to the procedure of Solladie-Cavallo and Benchegroun[81] for 200 mg of cinnamaldehyde adduct. Lithium aluminum hydride (83 mg, 2.2 mmol) was heated at reflux for 2 h in 8.0 mL of Et_2O. The solution was then cooled to 23 °C and benzylamine (1.2 mL, 11 mmol) was added dropwise. The resulting solution was stirred at 23 °C for 30 min and thickened. The suspension was diluted with 8.0 mL of Et_2O and the cinnamaldehyde-derived dioxinone adduct (200 mg, 0.73 mmol) was added via cannula in 4.0 mL of Et_2O and 2.0 mL of toluene. Stirring was continued for 72 h and then was quenched with dropwise addition of 5 mL of water. The reaction mixture was diluted with 30 mL of CH_2Cl_2, 15 mL of water and 5.0 mL of 2.0 M HCl. The aqueous layer was extracted with another 15 mL of CH_2Cl_2. The combined organic layers were washed with 10 mL of 5.0% $NaHCO_3$ and were dried over anhydrous

81. Solladie–Cavallo, A.; Benchegroun, M. *J. Org. Chem.* **1992**, *57*, 5831.

Na_2SO_4. After concentrating *in vacuo*, the product was isolated by chromatography on silica gel using 1.5:1 EtOAc/CH_2Cl_2. The amide was obtained as a white solid in 73% yield (171 mg).



mp: 86-87 °C

$[\alpha]_D^{19}$ +11.5° (*c* = 1.1, $CHCl_3$)

IR: (thin film)

3324, 3084, 3063, 3029, 2925, 1718, 1651, 1551, 1496, 1454, 1424, 1361, 1330, 1158, 1072, 1029, 969, 913, 748, 696, 608 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.41 (1H, m), 7.35-7.20 (10H, m), 6.59 (1H, dd, *J* = 16.0, 0.9), 6.16 (1H, dd, *J* = 16.0, 6.2), 4.73 (1H, m), 4.39 (2H, m), 3.44 (2H, s), 2.80 (1H, dd, *J* = 16.5, 8.4), 2.71 (1H, dd, *J* = 16.5, 4.1), 3.55 (1H, bs).

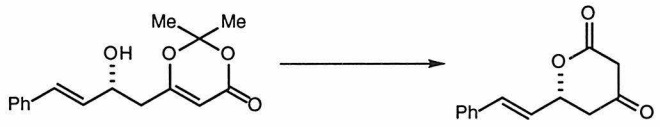
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 205.4, 165.7, 137.7, 136.2, 130.5, 130.0, 128.6, 128.5, 127.7, 127.6, 127.4, 126.4, 68.4, 50.3, 50.0, 43.5.

HRMS: (FAB)

calcd for $C_{20}H_{21}NO_3$ $(M)^+$ 323.1521, found 323.1510.

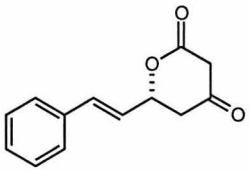
TLC: R_f 0.48 (2:1 ethyl acetate/CH_2Cl_2)



Conversion of cinnamaldehyde adduct to δ-lactone. The dioxinone (100 mg, 0.37 mmol), potassium carbonate (50 mg, 0.37 mmol) and zinc nitrate[82] (28 mg,

82. Buonora, P. T.; Rosauer, K. G.; Dai, L. *Tetrahedron Lett.* **1995**, *36*, 4009.

0.073 mmol) were stirred at 23 °C in 2 mL of anhydrous methanol for 8 h. The solution was then partitioned between 20 mL of CH_2Cl_2 and 10 mL of 0.5 M HCl. The aqueous layer was extracted with another 10 mL of CH_2Cl_2 and the combined organic layers were washed with 10 mL of a saturated aqueous NaCl solution. The organic solution was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was purified by chromatography on silica gel using 2:1 CH_2Cl_2/EtOAc to give the lactone as a white solid in 79% yield (62 mg).



mp: 129-130 °C

$[\alpha]_D^{19}$ +56.6° (*c* = 0.82, $CHCl_3$)

IR: (thin film)

2910, 2676, 1697, 1579, 1386, 1286, 1245, 1230, 1197, 1037, 962, 863, 832, 749, 694 cm^{-1}.

^1H NMR: (300 MHz, CD_3CN)

δ 7.50-7.28 (5H, m), 6.77 (1H, d, *J* = 15.9), 6.35 (1H, dd, *J* = 15.9, 6.6), 5.38 (1H, m), 3.75 (1H, d, *J* = 18.7), 3.29 (1H, d, *J* = 18.7), 2.77 (1H, dd, *J* = 18.3, 3.6), 2.65 (1H, dd, *J* = 18.3, 10.3).

^{13}C NMR: (75 MHz, CD_3CN)

δ 201.4, 168.4, 136.7, 134.1, 129.6, 129.3, 127.7, 126.1, 76.4, 48.2, 43.7.

HRMS: (FAB)

calcd for $C_{13}H_{13}O_3$ $(M+H)^+$ 217.0865, found 217.0868.

TLC: R_f 0.05 (2:1 hexane/ethyl acetate)

Chapter 6

Applications of Dienolate Additions: Synthesis of HMG-Coenzyme Reductase Inhibitors and Macrolactin A

Synthesis of HMG-Coenzyme Reductase Inhibitors

HMG-coenzyme reductase inhibitors are a large class of compounds produced by the pharmaceutical industry for lowering cholesterol in the bloodstream (Figure 7).[83] These drugs mimic 3-hydroxy-3-methylglutaratyl-coenzyme A (HMG-CoA) through a syn-1,3-diol side chain and bind competitively to prevent the production of cholesterol at an early rate-determining step in the biosynthesis. The absolute and relative stereochemistry of the 1,3-diol is critical for the drug to be recognized by the enzyme. As a result, the inhibitors must be prepared asymmetrically or resolved to be effective.

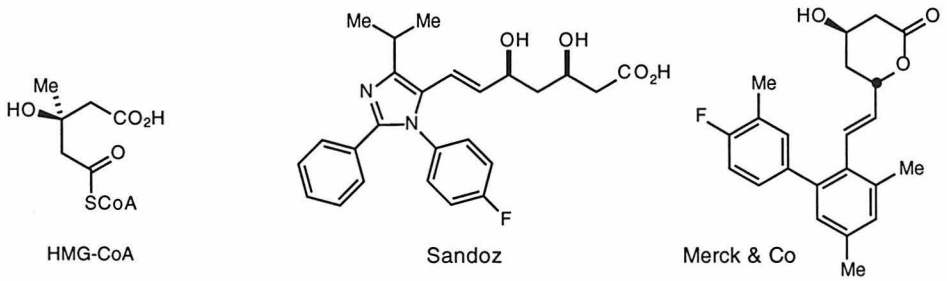


Figure 7. HMG-CoA and industrially produced HMG-coenzyme reductase inhibitors.

The standard pharmacophore for the design of HMG-coenzyme reductase inhibitors is shown in Figure 8.[84] Various HMG-coenzyme reductase inhibitors could be prepared

---

83. Lee, T.–J. *Trends in Biochem. Sci.* **1987**, *8*, 442.

84. Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.

by a dienolate addition to an unsaturated aldehyde with the desired functionality already incorporated in the aldehyde. The ketone revealed after opening the dioxinone could be reduced to afford the syn-diol through a directing effect of the existing β-stereocenter. This strategy would be viable but not necessarily efficient since it would require the execution of a different enantioselective dienolate addition for every aldehyde evaluated.

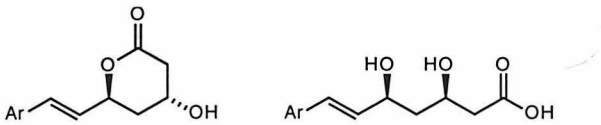
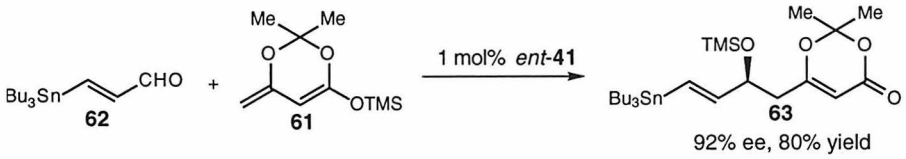


Figure 8. Pharmacophore for HMG-coenzyme reductase inhibitors.

A more convergent approach to constructing HMG-coenzyme reductase inhibitors would be to perform a single dienolate addition to β-stannylpropenal (**62**, Scheme 21). This dioxinone adduct has the flexibility of facile incorporation of any aryl group desired for screening and drug development by carrying out a palladium coupling with the corresponding arylhalide. With such a strategy, a library of compounds could be assembled from a common chiral building block.

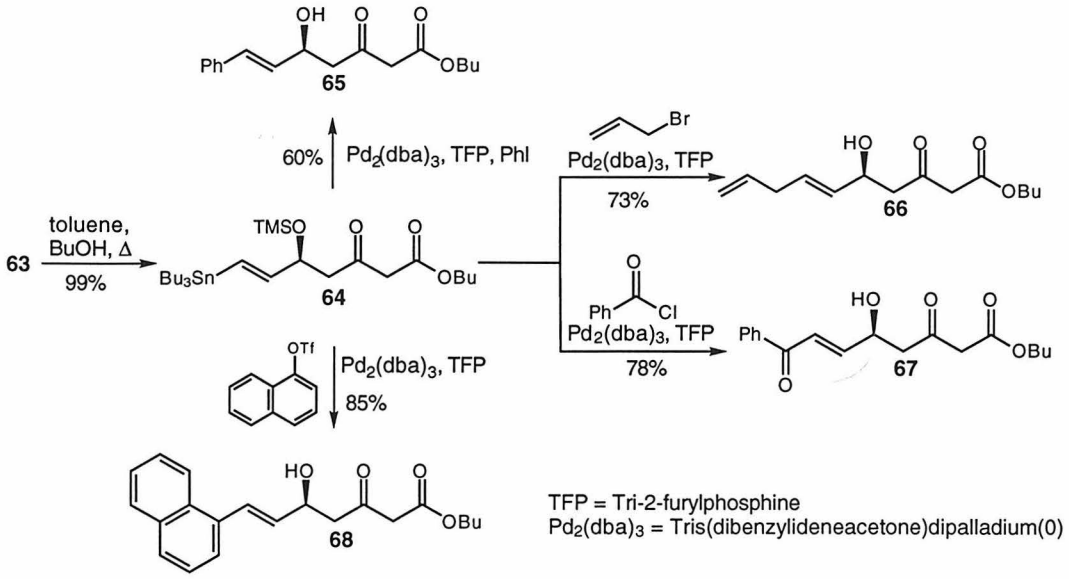
Scheme 21



This tactic was demonstrated by carrying out an aldol addition with *ent*-**41** on β-stannylpropenal (**62**) which afforded the dioxinone adduct in 92% ee and 80% yield. The dioxinone adduct was opened to ketoester **64** in 99% yield and a variety of palladium couplings were carried out successfully (Scheme 22).[85] Both aryl iodides and triflates

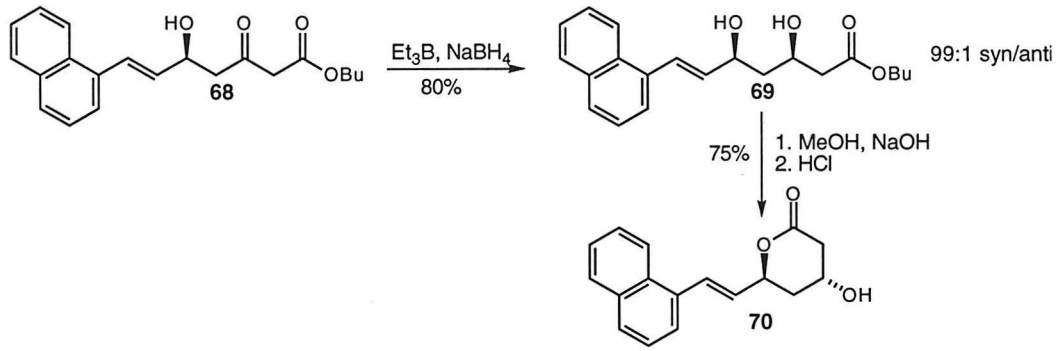
85. Farina, V.; Krishman, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

Scheme 22



smoothly coupled with the synthon in 60 and 85% respectively, proving its worth as a precursor for HMG-CoA reductase inhibitors. To further illustrate the scope of synthon **64**, palladium couplings with allyl bromide and benzoyl chloride were executed in good yield. The product derived from naphthyl triflate, **68**, was carried on to obtain a known reductase inhibitor **70** (Scheme 23).[86] Ketoester **68** was reduced to the syn-diol (**69**) in >98% diastereoselectivity and 75% yield.[86] The diol was cyclized to lactone **70** with base and treated with acid to precipitate the product, completing the synthesis of the inhibitor.

Scheme 23



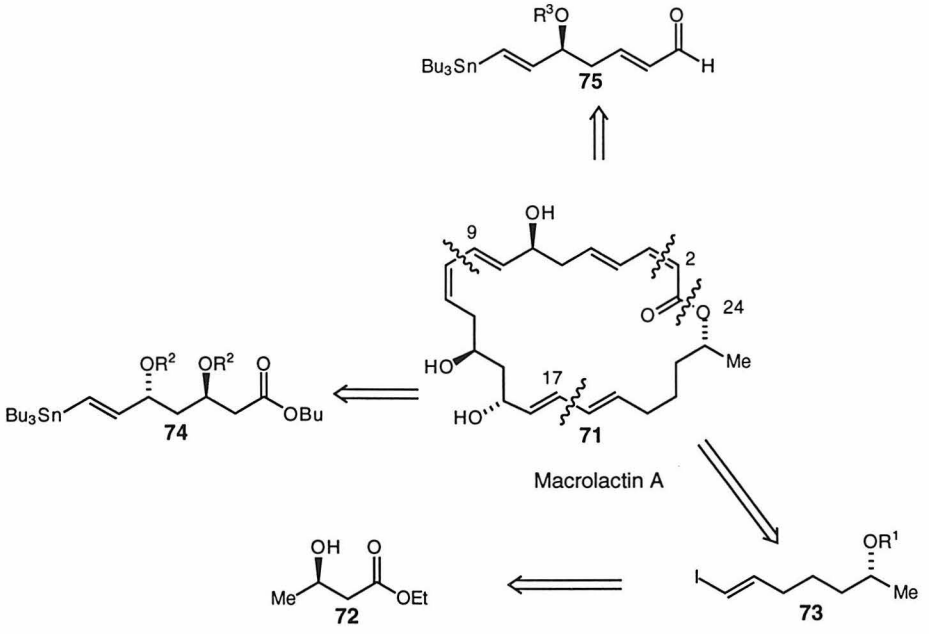
86. Chen, K-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923.

Synthesis of Macrolactin A

To further demonstrate the utility of the β-stannylpropenal-derived dioxinone (**63**), the synthesis of macrolactin A was undertaken.[87] This dienolate adduct was going to be employed as a precursor to two of three key fragments. Macrolactin A (**71**) is a 24-membered polyene macrolide isolated from a taxonomically-undefined deep sea bacterium. Interest in this class of biologically active macrocyclic lactones stems from their ability to protect T-lymphoblast cells against HIV replication. Further studies have not been possible due to the lack of natural abundance of macrolactin A. Using the aldol methodology, we have undertaken the synthesis to develop an efficient route that would allow for further clinical evaluation.

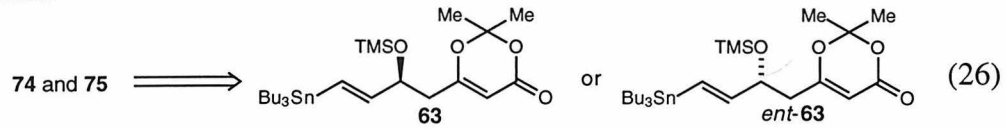
The retrosynthetic plan involved disconnecting three key fragments at the lactone, C1, the C2-C3 cis-olefin, and two of the dienes at C9-C10 and C17-C18 (Scheme 21).

Scheme 24



87. Gustafson, K.; Roman, R.; Fennical, W. *J. Am. Chem. Soc.* **1989**, *111*, 7519.

This would require preparation of three fragments, **73**, **74**, **75**.[88] The stannylated dioxinone product, **63**, would be used to construct two of the fragments. An added benefit to using **63** would be that the pieces could be stitched together via palladium couplings. The macrocycle could be assembled by a lactonization at C1, a Still-modified Horner-Emmons olefination[89] at C2-C3 and by a Stille couplings at the C9-C10 and C17-C18 diene bonds.[90]



(26)

Assembly of the first fragment (Scheme 25) began with a dienolate addition to β-stannylpropenal (**62**) mediated by the (*R*)-Ti catalyst (**41**) to afford *ent*-**63** in 92% ee and 80% yield. The dioxinone was opened to the butyl ketoester (*ent*-**64**) in quantitative yield by refluxing in butanol for 2.5 hours. The δ-hydroxy was deprotected with HF•pyridine to provide **76** in 96% yield.[91] The ketone in **76** was reduced with tetramethylammonium triacetoxyborohydride in 1:1 acetonitrile/acetic acid to afford the anti-1,3-diol (**77**) in 14:1 (anti/syn) diastereoselectivity.[92] The diol, **77**, was then protected as the acetonide in 89% yield to produce **78** by treatment with 2-methoxypropene and pyridinium *p*-toluenesulfonate (PPTS) in dimethylformamide (DMF).[93]

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88. Fragment previously prepared, see: Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657.

89. Still, C. W.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

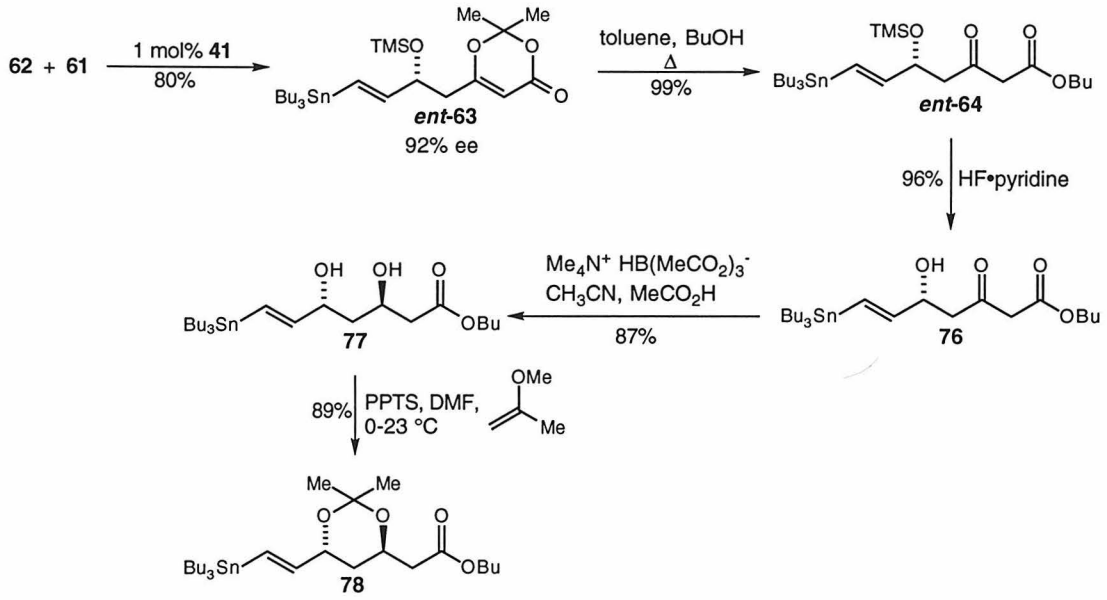
90. Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

91. (a) Trost, B. M.; Caldwell, C. G.; Murayana, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252. (b) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523.

92. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

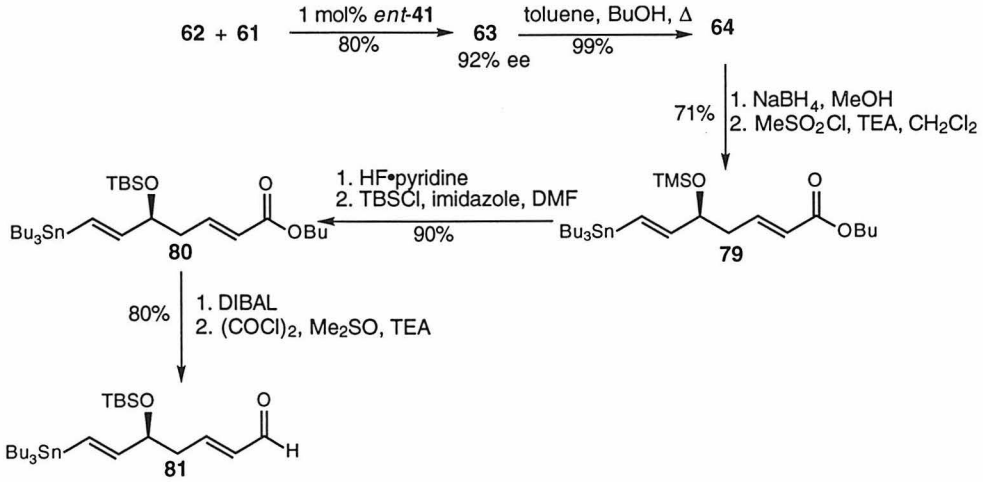
93. (a) Corey, E. J.; Kim, S.; Yoo, S.; Nicolau, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620. (b) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.

Scheme 25



The other fragment was also prepared by a dienolate addition to β-stannylpropenal (**62**) but with the use of the (*S*)-Ti catalyst (*ent*-**41**) (Scheme 26). The dioxinone, **63**, was obtained in 92% ee and converted to the butyl ketoester **64** in quantitative yield with heating in butanol. The ketone was stereorandomly reduced with $NaBH_4$ in methanol at 0 °C to the 1,3-diol. The crude material was converted to the β-mesylate with methanesulfonylchloride and triethylamine. The mesylate was eliminated *in situ* to **79** with the addition of excess triethylamine and heating at reflux in CH_2Cl_2 for 12 hours. The

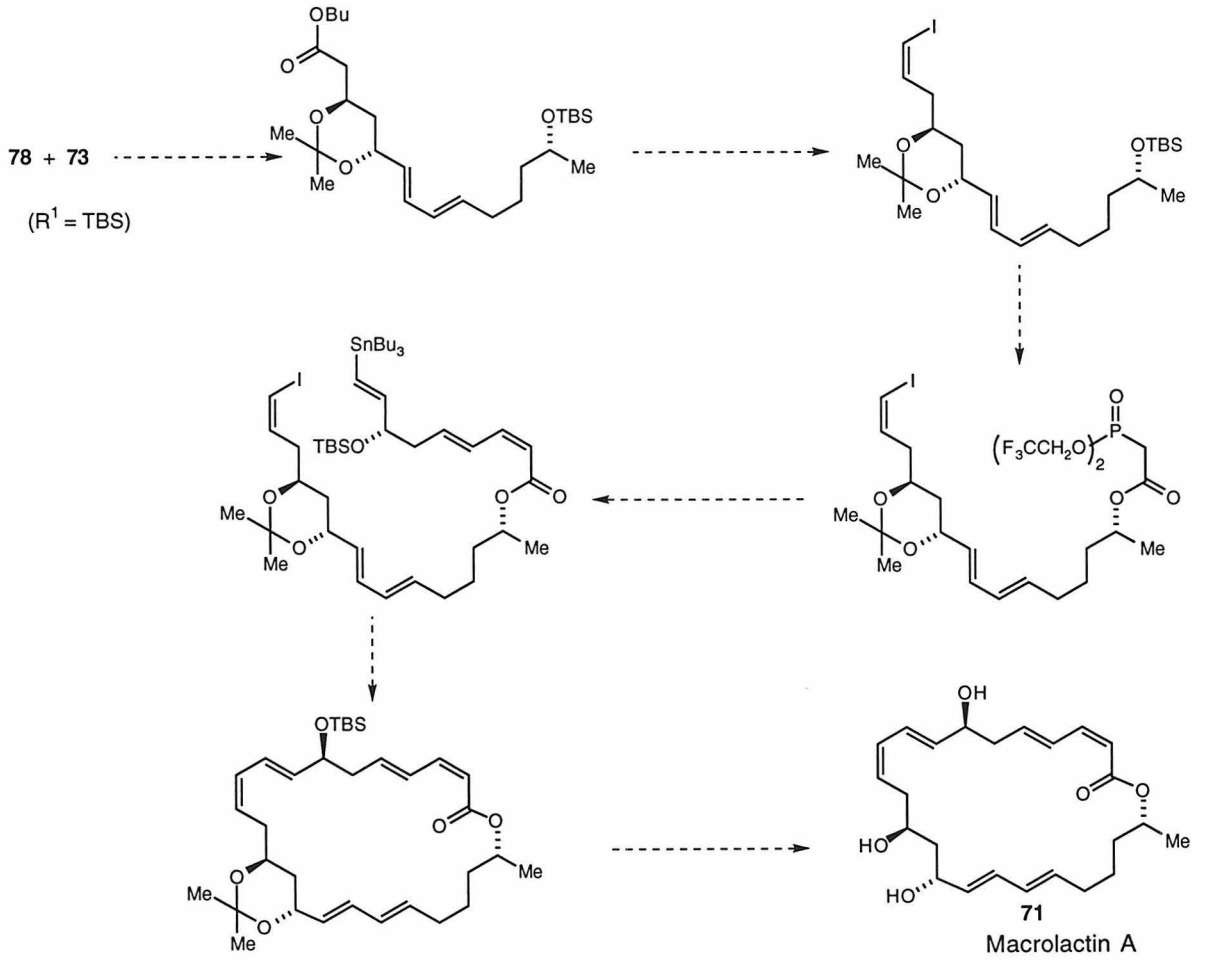
Scheme 26



trimethylsilyl ether of **79** was converted to the more robust *tert*-butyldimethylsilyl ether (**80**) in 90% yield by a deprotection with HF•pyridine, and subsequent treatment with *tert*-butyldimethylsilyl chloride and imidazole in DMF at 0 °C. The oxidation state of the ester was adjusted by reduction to the corresponding alcohol with diisobutylaluminum hydride (DIBAL). The primary alcohol was oxidized with oxalyl chloride, dimethylsulfoxide (DMSO) and triethylamine to afford aldehyde **81** in 80% yield for the two steps.

It was the responsibility of Dr. Yuntae Kim to prepare fragment **73** from **72** and link the three fragments to form the macrocycle. Our current approach to completing the synthesis is shown in Scheme 27. The first two fragments could be connected by a Stille

Scheme 27



coupling. After adjusting the oxidation state of the ester to an aldehyde, a Wittig olefination could be carried out to afford the vinyl iodide. Deprotection of the alcohol at C23 and esterification with a phosphonoacetate would provide a suitable precursor for the olefination at C2-C3. The third fragment could be incorporated into the carbon skeleton by the Still-modified Horner-Emmons olefination.[89] After cyclization of the macrocycle with an intramolecular Stille coupling, the hydroxyl groups could be deprotected to afford macrolactin A (**71**).

Fragments such as **78** and **81** should be useful synthons for the construction of other polyol macrolide natural products and analogs. A few other biologically active polyene macrolides are represented below in Figure 9.

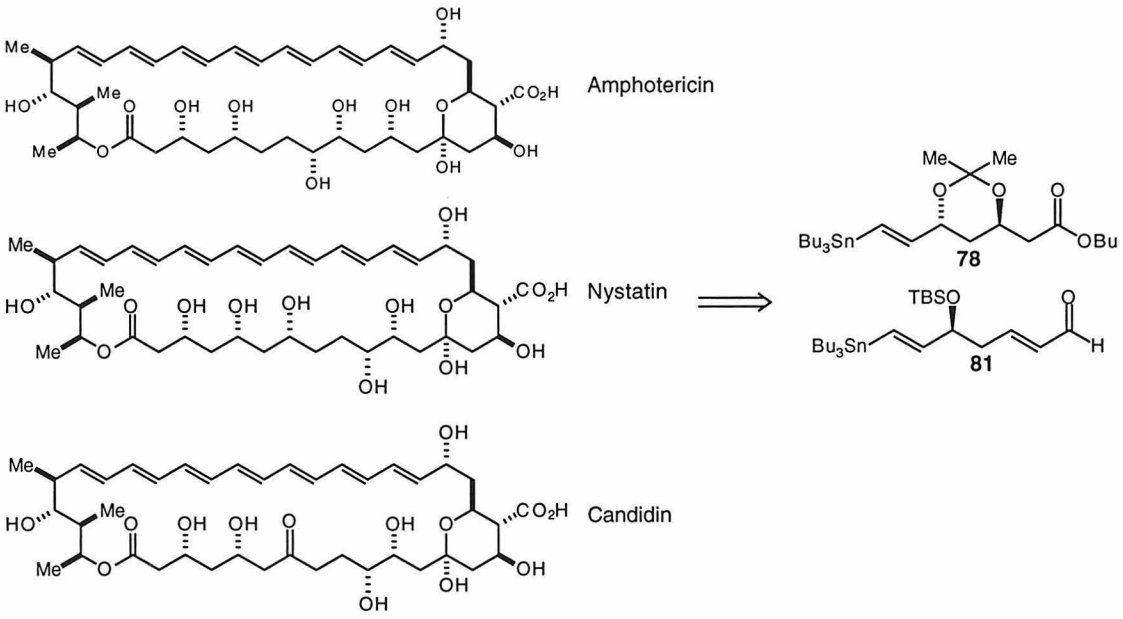
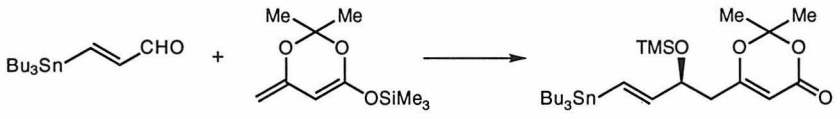


Figure 9. Representative polyene macrolides.

Experimental Section[94]

Preparation of aldehyde 62.[95] To a suspension of 1.79 g of cuprous cyanide (20 mmol) in 50 mL of THF at -50 °C was added 25 mL of a 1.6 M solution of butyllithium (40 mmol) in hexanes. The solution was stirred for 10 min at -50 °C and was then cooled to -78 °C. To the solution was added 10.8 mL of tributyltin hydride (40 mmol) dropwise. After addition was complete, the solution was stirred for another 15 min and then 2.39 mL of propargaldehyde diethyl acetal (17 mmol) was added. The solution was stirred for 2 h at -78 °C and then was quenched by adding 5 mL of anhydrous MeOH. The red solution was allowed to gradually warm to 0 °C and then was further quenched with the addition of 100 mL of a saturated aqueous NH_4Cl solution. The mixture was diluted with 150 mL of Et_2O and 100 mL of a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in 80 mL of CH_2Cl_2 and treated with 40 mL of 88% formic acid. The mixture was stirred rapidly for 30 min and then was diluted with 100 mL of water and 50 mL of CH_2Cl_2. The separated organic layer was washed with 100 mL of 1.0 M NaOH, was dried over anhydrous Na_2SO_4 and was concentrated *in vacuo*. The product was isolated as a clear, colorless oil in 70% yield (4.11 g) by chromatography on 120 mL of silica gel (4 cm diameter column) using 40:1 hexane/Et_2O as eluent.



Enantioselective dienolate addition at 0.5 mol% of *ent*-41 to afford 63. To a solution of 35 mg of *ent*-**27** (.066 mmol) in 9 mL of toluene at 23 °C was added

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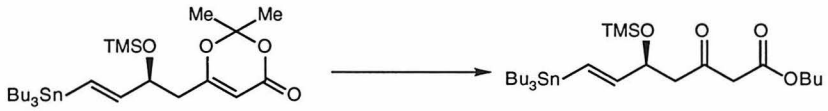
94. For general procedures and purification methods see chapter 2.

95. Ostwald, R.; Chavant, P-Y.; Stadtmuller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143.

8.53 mg of $Ti(O^iPr)_4$ (.030 mmol). After stirring the solution for 1 h at 23 °C, 30 mg of **40** (0.12 mmol) was added via cannula in 3 mL of toluene. Stirring was continued for an additional h and then the volatiles were removed *in vacuo*. The residue was redissolved in 8 mL of Et_2O and cooled to 0 °C. To the solution was added 70 mL of 2,6-lutidine (0.60 mmol) followed by **62** and **61**. The reaction was stirred at 0 °C for 24 h and then was quenched by pouring onto 30 mL of a saturated aqueous solution of NaCl. The organics were extracted with 50 mL of Et_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The adduct **63** was purified by chromatography on silica gel using 15:1 hexane/ethyl acetate initially and then switching the eluent to 10:1 hexane/ethyl acetate. The dioxinone adduct **63** was isolated in 80% yield (2.70 g) as a clear, colorless oil.



Opening of dioxinone 63 to ketoester 64. The dioxinone **63** (2.70 g, 4.83 mmol) was dissolved in 2 mL of butanol and 10 mL of toluene to be heated to reflux. Heating was continued for 2.5 h. The solution was then cooled to 23 °C and concentrated *in vacuo*. The ketoester **64** was isolated in 99% yield (2.78 g) by chromatography on silica gel using 15:1 hexane/ethyl acetate as eluent.

Stille Couplings of 3-tributylstannyl-2-propenal adduct (64). Couplings were carried out according to the literature procedure for analogous additions with vinyltributyltin and the appropriate coupling partner.[96] Each Stille coupling was followed by a desilylation with 5% TFA in THF with a workup using 5% NaHCO3 and the usual purification by chromatography.

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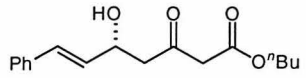
96. Farina, V.; Krishman, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.



Isolated in 60% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ -18.6° (*c* = 0.94, $CHCl_3$)

IR: (thin film)

3480, 1738, 1714 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.38-7.24 (5H, m), 6.64 (1H, d, *J* = 19.5), 6.20 (1H, dd, *J* = 15.9, 6.1), 4.79 (1H, q, *J* = 6.0), 4.14 (2H, t, *J* = 6.7), 3.51 (2H, s), 2.90 (1H, bs), 2.86 (2H, d, *J* = 6.0), 1.62 (2H, m), 1.36 (2H, m), 0.92 (3H, t, *J* = 7.3).

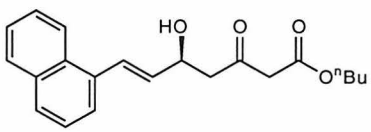
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.7, 166.9, 136.3, 130.6, 129.8, 128.5, 127.8, 126.5, 68.3, 65.4, 49.9, 49.6, 30.4, 19.0, 13.6.

HRMS: (EI)

calcd for $C_{17}H_{22}O_4$ $(M)^+$ 290.1518, found 290.1513.

TLC: R_f 0.17 (4:1 hexane/ethyl acetate)



Isolated in 85% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ -7.9° (*c* = 1.0, $CHCl_3$).

IR: (thin film)

3446, 2960, 2873, 1738, 1715, 1654, 1508, 1458, 1396, 1317, 1149, 1061, 969, 797, 777 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 8.10 (1H, dd, *J* = 7.7, 1.7), 7.81 (2H, m), 7.58-7.40 (5H, m), 6.23 (1H, dd, *J* = 15.6, 5.9), 4.91 (1H, m), 4.15 (2H, t, *J* = 6.6), 3.53 (2H, s), 3.08 (1H, d, *J* = 3.6), 2.93 (2H, d, *J* = 6.0), 1.62 (2H, m), 1.37 (2H, m), 0.92 (3H, t, *J* = 7.3).

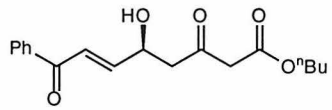
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.6, 166.9, 134.2, 133.6, 133.2, 131.1, 128.5, 128.1, 127.8, 126.0, 125.8, 125.5, 123.8, 123.7, 68.5, 65.4, 50.0, 49.7, 30.4, 19.0, 13.6.

HRMS: (FAB)

calcd for $C_{21}H_{24}O_4$ $(M)^+$ 340.1675, found 340.1657.

TLC: R_f 0.10 (6:1 hexane/ethyl acetate)



Isolated in 78% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ -10.9° (*c* = 1.0, $CHCl_3$)

IR: (thin film)

3458, 2960, 2933, 2873, 1738, 1732, 1714, 1668, 1651, 1626, 1598, 1579, 1448, 1408, 1285, 1204, 1150, 1064, 1017, 982, 840, 773, 699 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.95 (2H, d, *J* = 7.2), 7.54 (1H, t, *J* = 7.3), 7.45 (2H, dd, *J* = 7.3, 7.2), 7.25 (1H, dd, *J* = 15.3, 1.7), 6.96 (1H, dd, *J* = 15.3, 3.92), 4.91 (1H, m), 4.13 (2H, t, *J* = 6.7), 3.50 (2H, s), 3.40 (1H, bs), 2.93 (1H, dd, *J* = 17.7, 3.4), 2.82 (1H, dd, *J* = 17.7, 8.7), 1.61 (2H, m), 1.35 (2H, m), 0.90 (3H, t, *J* = 7.3).

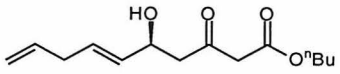
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.2, 190.2, 166.8, 147.3, 137.5, 133.0, 128.6, 128.6, 124.5, 67.0, 65.6, 49.7, 48.5, 30.4, 19.0, 13.6.

HRMS: (FAB)

calcd for $C_{18}H_{22}O_5$ $(M)^+$ 318.1467, found 318.1455.

TLC: R_f 0.31 (1:1 hexane/ethyl acetate)



Isolated in 73% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ -19.4° (*c* = 1.1, $CHCl_3$)

IR: (thin film)

3446, 2961, 1735, 1715, 1637, 1410, 1316, 972, 915 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 5.83-5.68 (2H, m), 5.50 (1H, dd, *J* = 15.4, 6.4), 5.04 (1H, d, *J* = 7.1), 4.99 (1H, d, *J* = 2.4), 4.57 (1H, m), 4.13 (2H, t, *J* = 6.7), 3.47 (2H, s), 2.77 (2H, d, *J* = 2.4), 2.74 (2H, s), 2.70 (1H, bs), 1.62 (2H, m), 1.36 (2H, m), 0.92 (3H, t, *J* = 7.3).

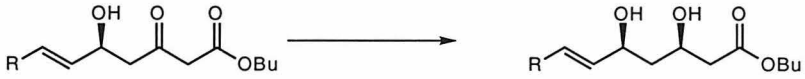
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.8, 166.9, 136.0, 131.6, 129.9, 115.7, 68.3, 65.4, 50.0, 49.6, 36.1, 30.5, 19.0, 13.6.

HRMS: (FAB)

calcd for $C_{14}H_{23}O_4$ $(M+H)^+$ 255.1596, found 255.1579.

TLC: R_f 0.18 (6:1 hexane/ethyl acetate)



General Procedure for the Syn Reduction of a 1,3-Diol.[97]

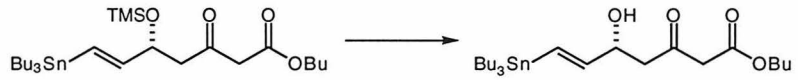
To a mixture of 2 mL of THF and 0.50 mL of anhydrous MeOH was added 311 μL of a 1.0 M solution of triethylborane (0.311 mmol) in THF. The solution was allowed to stir for 1 h at 23 °C. The solution was then cooled to -78 °C and the 1,3-hydroxyketone was added (0.194 mmol) via cannula in THF. The solution was stirred for 30 min and then $NaBH_4$ was added. After 3 h at -78 °C, the reaction was quenched with the addition

97. Chen, K-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923.

of 100 mL of acetic acid. After allowing the solution to warm to 23 °C, it was diluted with ethyl acetate, washed twice with a saturated solution of $NaHCO_3$, and dried over Na_2SO_4. The organic solution was concentrated *in vacuo*. The 1,3-diol was purified by chromatography on silica gel.

General Procedure for the Lactonization of β,δ-Dihydroxyester.[98]

The dihydroxyester was dissolved in 4:1 EtOH/1.0 N NaOH and stirred for 1 h. The solution was acidified with 12 N HCl, diluted with water, and the lactone was extracted three times with CH_2Cl_2. The combined extracts were washed once with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was isolated by chromatography on silica gel.



Desilylation of *ent*-64 to afford 76. The neat silyl ether *ent*-**64** (1.43 g, 2.48 mmol) was treated with 2.0 mL of an HF•pyridine solution in THF.[99] After 30 min desilylation was complete, as monitorred by TLC. The solution was diluted with 60 mL of Et_2O and was washed with 20 mL of 2.0 M HCl, 30 mL of 5% $NaHCO_3$, and 20 mL of a saturated aqueous solution of NaCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The hydroxyketoester **76** was isolated in 96% yield (1.20 g) as

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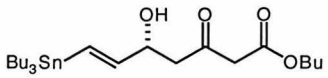
98. Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.

99. (a) Trost, B. M.; Caldwell, C. G.; Murayana, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252. (b) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523.

a clear, colorless oil by chromatography on silica gel using 8:1 hexane/ethyl acetate as eluent.



$[\alpha]_D^{19}$ +15.0° (c = 0.92, $CHCl_3$)

IR: (thin film)

3448, 2958, 2927, 2872, 1741, 1717, 1654, 1464, 1418, 1376, 1314, 1227, 1148, 1070, 990, 873 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 6.22 (1H, dd, J = 19.1, 1.3), 5.98 (1H, dd, J = 19.1, 4.9), 4.58-4.54 (1H, m), 4.13 (2H, t, J = 6.7), 3.49 (2H, s), 2.77 (1H, dd, J = 14.7, 3.3), 2.74 (1H, dd, J = 14.7, 3.8), 2.74 (1H, d, J = 1.6), 1.68-1.58 (2H, m), 1.50-1.40 (6H, m), 1.40-1.20 (8H, m), 0.92 (3H, t, J = 7.4), 0.87 (15H, t, J = 7.2).

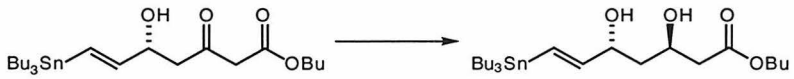
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 202.9, 167.0, 148.0, 128.9, 70.6, 65.4, 50.0, 49.4, 30.4, 29.0, 27.2, 19.0, 13.7, 13.7, 9.4.

HRMS: (FAB)

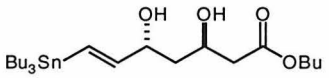
calcd for $C_{23}H_{44}O_4NaSn$ $(M+Na)^+$ 527.2159, found 527.2156.

TLC: R_f 0.37 (4:1 hexane/ethyl acetate)



Reduction of 76 with triacetoxyborohydride to afford 77. A solution of 3.70 g of tetramethylammonium triacetoxyborohydride (14.1 mmol) in 25 mL of anhydrous acetic acid and 20 mL of acetonitrile was stirred at 23 °C for 30 min. The solution was cooled to 0 °C and 1.18 g of **76** (2.34 mmol) was added via cannula in 5 mL of acetonitrile. After stirring for 1.5 h at 0 °C the reaction was quenched by pouring onto 300 mL of sodium-potassium tartrate and diluting with 300 mL of CH_2Cl_2. The mixture

was made alkaline with NaOH and the aqueous layer was extracted four times with 80 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The diol **77** was isolated in 87% yield (1.03 g) and 13.6:1 (anti/syn) diastereoselectivity as a clear, colorless oil by chromatography on silica gel using 4:1 hexane/ethyl acetate as eluent.



$[\alpha]_D^{19}$ -1.7° (*c* = 0.76, $CHCl_3$)

IR: (thin film)

3422, 2957, 2927, 2872, 2853, 1735, 1464, 1418, 1376, 1292, 1250, 1177, 1070, 991, 960, 874, 840 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 6.22 (1H, dd, *J* = 19.1, 1.2), 6.04 (1H, dd, *J* = 19.1, 4.7), 4.44-4.38 (1H, m), 4.38-4.30 (1H, m), 4.10 (2H, t, *J* = 6.7), 3.57 (1H, bs), 2.80 (1H, bs), 2.54 (1H, dd, *J* = 16.4, 8.0), 2.48 (1H, dd, *J* = 16.4, 4.3), 1.80 (1H, ddd, *J* = 14.3, 9.0, 3.3), 1.68-1.58 (2H, m), 1.50-1.40 (6H, m), 1.40-1.20 (8H, m), 0.93 (3H, t, *J* = 7.3), 0.88 (15H, t, *J* = 7.1).

^{13}C NMR: (75 MHz, $CDCl_3$)

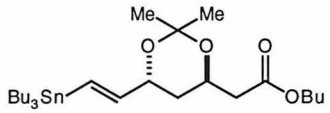
δ 172.8, 150.1, 127.3, 72.1, 65.5, 64.6, 41.8, 41.3, 30.5, 29.0, 27.2, 19.0, 13.7, 13.7, 9.4.

HRMS: (FAB)

calcd for $C_{23}H_{46}O_4NaSn$ $(M+Na)^+$ 529.2316, found 529.2309.

TLC: R_f 0.12 (4:1 hexane/ethyl acetate)

Protection of diol 77 as acetonide 78. To a solution of 1.00 g of **77** (1.98 mmol) in 10 mL of DMF with 40 mg of PPTS at 0 °C was added 758 μL of 2-methoxypropene (7.92 mmol). The solution was allowed to gradually warm to 23 °C over two h and continue stirring at 23 °C for another h. The reaction mixture was poured onto 40 mL of water and was extracted with 40 mL of Et_2O. The organic layer was washed with another 20 mL of water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The acetonide **78** was isolated in 89% yield (959 mg) as a clear, colorless oil by chromatography on silica gel using 20:1 hexane/ethyl acetate.



$[\alpha]_D^{19}$ +25.7° (*c* = 0.82, $CHCl_3$)

IR: (thin film)

2957, 2927, 2872, 2854, 1739, 1654, 1605, 1464, 1378, 1313, 1272, 1224, 1186, 1164, 1078, 1017, 986, 960, 874, 798 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 6.13 (1H, dd, *J* = 19.2, 0.5), 6.01 (1H, dd, *J* = 19.2, 4.8), 4.34-4.26 (2H, m), 4.08 (2H, t, *J* = 6.6), 2.53 (1H, dd, *J* = 15.4, 8.0), 2.43 (1H, dd, *J* = 15.4, 5.5), 1.87-1.82 (1H, m), 1.78-1.68 (1H, m), 1.59-1.57 (2H, m), 1.47-1.44 (6H, m), 1.38 (3H, s), 1.35 (3H, s), 1.33-1.20 (8H, m), 0.91 (3H, t, *J* = 7.3), 0.87 (15H, t, *J* = 7.1).

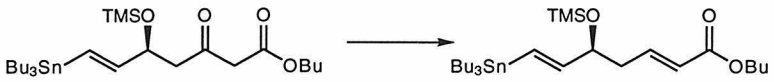
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 170.9, 148.0, 128.9, 100.5, 70.2, 64.3, 63.3, 41.0, 36.7, 30.6, 29.0, 27.2, 25.5, 24.6, 19.1, 13.6, 13.6, 9.4.

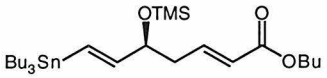
HRMS: (FAB)

calcd for $C_{26}H_{49}O_4Sn$ $(M-2H+H)^+$ 545.2653, found 545.2671.

TLC: R_f 0.67 (4:1 hexane/ethyl acetate)



Reduction and elimination of 64 to 79. To a solution of 1.22 g of **64** (2.13 mmol) in 15 mL of absolute ethanol at 0 °C was added 161 mg of $NaBH_4$ (4.25 mmol). The solution was stirred for 30 min and then was quenched by pouring onto 40 mL of 5% $NaHCO_3$. The organics were extracted three times with 20 mL of CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in 10 mL of CH_2Cl_2 with 589 μL of triethylamine (4.25 mmol) and cooled to 0 °C. To the solution was added 247 μL of mesitylsulfonyl chloride (3.20 mmol). After stirring the resulting solution for 30 min at 0 °C, an additional 2.95 mL of triethylamine (21.3 mmol) was added. The solution was then heated to relflux to effect elimination. Heating was continued for 12 h and then the solution was partitioned between 20 mL water and another 20 mL of CH_2Cl_2. The mixture was acidified with 6 mL of 2.0 M HCl. The separated organic layer was washed with 20 mL of 5% $NaHCO_3$ and 20 mL of a saturated aqueous solution of NaCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The olefin **79** was isolated in 71% yield (846 mg) as a clear colorless oil by chromatography on silica gel using 20:1 hexane/ethyl acetate as eluent.



$[\alpha]_D^{19}$ -3.0° (*c* = 1.0, $CHCl_3$)

IR: (thin film)

2957, 2928, 2872, 2854, 1724, 1657, 1464, 1313, 1251, 1216, 1178, 1071, 988, 842, 749, 690 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 6.92 (1H, ddd, *J* = 15.7, 7.5, 7.5), 6.10 (1H, d, *J* = 19.0), 5.90 (1H, dd, *J* = 19.0, 5.4), 5.84 (1H, dd, *J* = 15.7, 0.6), 4.18-4.06 (1H, m), 4.12 (2H, t, *J* = 6.7), 2.38 (2H, t, *J* = 6.9), 1.70-1.57 (2H, m), 1.56-1.40 (6H, m), 1.40-1.20 (8H, m), 0.93 (3H, t, *J* = 7.4), 0.88 (15H, t, *J* = 7.4), 0.10 (9H, s).

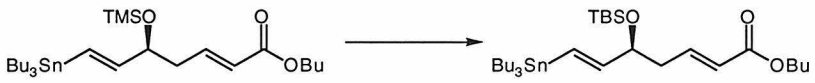
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 166.5, 150.0, 145.6, 128.1, 123.3, 75.2, 64.0, 40.9, 30.7, 29.1, 27.2, 19.2, 13.7, 13.7, 9.4, 0.2.

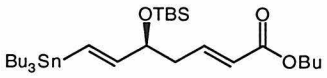
HRMS: (FAB)

calcd for $C_{26}H_{51}O_3SiSn$ $(M\text{-}2H+H)^+$ 559.2629, found 559.2625.

TLC: R_f 0.46 (10:1 hexane/ethyl acetate)



Switching silyl ether protecing group to afford 80. The silyl ether **79** (765 mg, 1.57 mmol) was treated with 1.0 mL of a HF•pyridine solution in THF. Desilylation was complete in 30 min and the solution was diluted with 30 mL of Et_2O and was washed with 10 mL of 2.0 M HCl, 20 mL of 5% $NaHCO_3$ and 10 mL of a saturated aqueous solution of NaCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in 5 mL of DMF with 214 mg of imidazole (3.14 mmol) and 355 mg of TBSCl (2.36 mmol). Formation of the silyl ether was complete in 1 h. The solution was diluted with 30 mL of Et_2O and 20 mL of water. The organic layer was washed with 10 mL of 2.0 M HCl, 20 mL of 5% $NaHCO_3$ and 10 mL of a saturated aqueous solution of NaCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The silyl ether **80** was isolated as a clear, colorless oil in 90% yield (850 mg) by chromatography on silica gel using 20:1 hexane/ethyl acetate as eluent.



$[\alpha]_D^{19}$ -5.7° (c = 0.89, $CHCl_3$)

IR: (thin film)

2957, 2929, 2872, 2856, 1724, 1655, 1464, 1377, 1360, 1312, 1256, 1216, 1179, 1071, 988, 836, 776, 670 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 6.93 (1H, ddd, J = 15.7, 7.5, 7.5), 6.10 (1H, dd, J = 19.0, 0.9), 5.91 (1H, dd, J = 19.0, 5.5), 5.82 (1H, d, J = 15.7), 4.20-4.08 (1H, m), 4.12 (2H, t, J = 6.6), 2.37 (2H, t, J = 6.3), 1.70-1.57 (2H, m), 1.56-1.40 (6H, m), 1.40-1.20 (8H, m), 0.93 (3H, t, J = 7.3), 0.88 (9H, s), 0.88 (15H, t, J = 7.4), 0.03 (3H, s), 0.02 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 166.4, 150.3, 145.7, 127.9, 123.3, 75.4, 64.0, 41.2, 30.7, 29.1, 27.2, 25.8, 19.2, 18.3, 13.7, 13.7, 9.5, -4.4, -4.9.

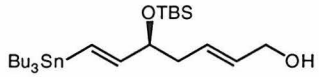
HRMS: (FAB)

calcd for $C_{29}H_{57}O_3SiSn$ $(M-2H+H)^+$ 601.3099, found 601.3085.

TLC: R_f 0.47 (10:1 hexane/ethyl acetate)

Reduction of 80. To a solution of ester **80** (850 mg, 1.41 mmol) in 10 mL of toluene at -78 °C was added 2.36 mL of a solution of diisobutylaluminum hydride (3.53 mmol) in toluene. The solution was maintained at -78 °C for 2 h and then quenched by adding 5 mL of MeOH. The solution was allowed to warm to 0 °C and was poured onto 20 mL of water. After acidifying the mixture with 8 mL of 2.0 M HCl, the organics were extracted with 30 mL of Et_2O. The organic layer was washed with 20 mL of 5% $NaHCO_3$, and 20 mL of a saturated aqueous solution of NaCl. The organic layer was

dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The alcohol was isolated as a clear, colorless oil in 94% yield (704 mg) by chromatography on silica gel using 8:1 hexane/ethyl acetate as eluent.



$[\alpha]_D^{19}$ -5.1° (c = 0.99, $CHCl_3$)

IR: (thin film)

3338, 2956, 2927, 2855, 1464, 1419, 1361, 1253, 1074, 989, 970, 835, 775 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 6.05 (1H, dd, J = 19.0, 0.6), 5.91 (1H, dd, J = 19.0, 5.3), 5.69-5.66 (2H, m), 4.10-4.05 (3H, m), 2.80 (1H, bs), 2.26-2.22 (2H, m), 1.54-1.42 (6H, m), 1.38-1.20 (6H, m), 0.89 (9H, s), 0.88 (9H, t, J = 7.2), 0.87 (6H, t, J = 7.9), 0.03 (3H, s), 0.02 (3H, s).

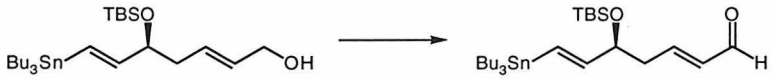
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 150.9, 131.2, 129.6, 127.0, 76.2, 63.8, 41.2, 29.1, 27.2, 25.9, 25.9, 18.3, 13.7, 9.5, -4.4, -4.8.

HRMS: (FAB)

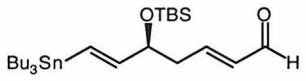
calcd for $C_{25}H_{52}O_2NaSiSn$ $(M+Na)^+$ 555.2656, found 555.2662.

TLC: R_f 0.27 (10:1 hexane/ethyl acetate)



Oxidation to afford aldehyde 81. To a solution of 65 μL of oxalyl chloride (0.751 mmol) in 4 mL of CH_2Cl_2 at -78 °C was added 107 μL of DMSO (1.50 mmol). After stirring the solution for 5 min 133 mg (0.250 mmol) of the alcohol (from reduction of **80**) was added via cannula in 1.5 mL of CH_2Cl_2. The solution was stirred at -78 °C for 30 min and then 278 μL of triethylamine (2.00 mmol) was added. The solution was allowed

to gradually warm to 0 °C over 1 h. The solution was then poured onto 10 mL of water and acidified with 2 mL of 2.0 M HCl. The organics were extracted with 20 mL of 2:1 Et_2O/hexane, washed with 10 mL of 5% $NaHCO_3$, washed with 10 mL of a saturated aqueous solution of NaCl and dried over anhydrous Na_2SO_4. After concentrating the organic extracts in vacuo, the aldehyde **81** was isolated as a clear, colorless oil in 85% yield (112 mg) by chromatography on silica gel.



$[\alpha]_D^{19}$ -6.5° (*c* = 1.0, $CHCl_3$)

IR: (thin film)

2956, 2928, 2855, 1698, 1464, 1376, 1362, 1340, 1253, 1131, 990, 974, 836, 776 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 9.48 (1H, d, *J* = 8.0), 6.83 (1H, ddd, *J* = 15.7, 7.3, 7.3), 6.13 (1H, d, *J* = 19.1), 6.12 (1H, dd, *J* = 15.7, 8.0), 5.91 (1H, dd, *J* = 19.1, 5.6), 4.24-4.22 (1H, m), 2.53 (2H, t, *J* = 6.6), 1.54-1.42 (6H, m), 1.38-1.20 (6H, m), 0.88 (9H, s), 0.87 (15H, t, *J* = 7.2), 0.03 (3H, s), 0.03 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 193.9, 155.3, 149.8, 134.7, 128.6, 75.0, 41.4, 29.1, 27.2, 25.8, 18.2, 13.7, 9.4, -4.3, -4.9.

HRMS: (FAB)

calcd for $C_{25}H_{50}O_2NaSiSn$ $(M+Na)^+$ 553.2500, found 553.2497.

TLC: R_f 0.45 (10:1 hexane/ethyl acetate)

Chapter 7

Structural Studies on the Titanium Schiff Base Complexes

^{1}H NMR Studies

In order to gain insight into the solution structure of the various titanium complexes developed in our work, ^{1}H NMR spectroscopy was used to follow the various ligand exchange processes. The resonances of the ^{t}butyl moiety on the salicylimine were used as NMR tags.

The formation of the Schiff base complex **39** was examined and it was found that whether 1 or 2 equivalents of **27** were combined with Ti(O^{i}Pr)$_4$ in toluene, once the volatiles were removed only **39** was present with two distinct resonances at 0.93 and 0.98 ppm (Scheme 28). No resonances corresponding to isopropanol or isopropoxide were present, suggesting that the isopropoxides were replaced by two Schiff base ligands on the Ti(IV) complex. Apparently the action of removing the volatiles drives the formation of **39** to completion and any excess Ti(O^{i}Pr)$_4$ is lost *in vacuo*. When 2 equivalents of **27** with 1 equivalent of Ti(O^{i}Pr)$_4$ in toluene without removing volatiles *in vacuo*, resonances corresponding to equal amounts of **39** and free ligand **27** (resonance at 1.03 ppm) were present. In addition, a new complex was present with a single ^{t}butyl resonance at 0.92 ppm (Scheme 28) in a quantity equal to **39**. This new complex could possibly be the intermediate in ligand exchange, possessing a single Schiff base ligand bound to Ti(IV). If excess **27** (i.e. 3 equiv **27**) was added to Ti(O^{i}Pr)$_4$ in toluene, after concentrating in vacuo, **39** was observed along with free ligand **27**.

Confirmation of the composition of complex **39** was obtained by vapor pressure osmometry (VPO).[100] Complex **39** was prepared by combining two equivalents of

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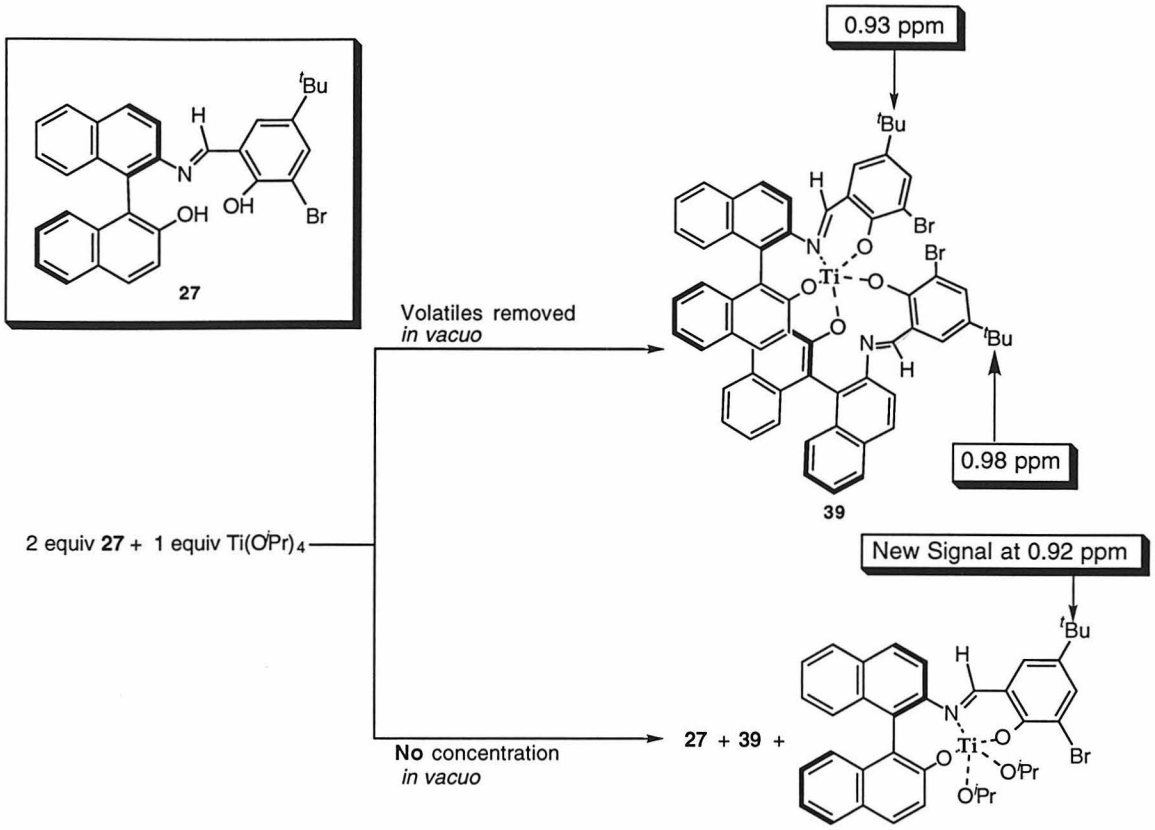
100. Signer method used as described by: Burger, B. J.; Bercaw, J. E. In *Experimental Organometallic Chemistry, A Practicum in Synthesis and Characterization* (Wayda, A. L. and Darensbourg, M. Y. ed.), American Chemical Society: **1987**, 94-96.

Scheme 28



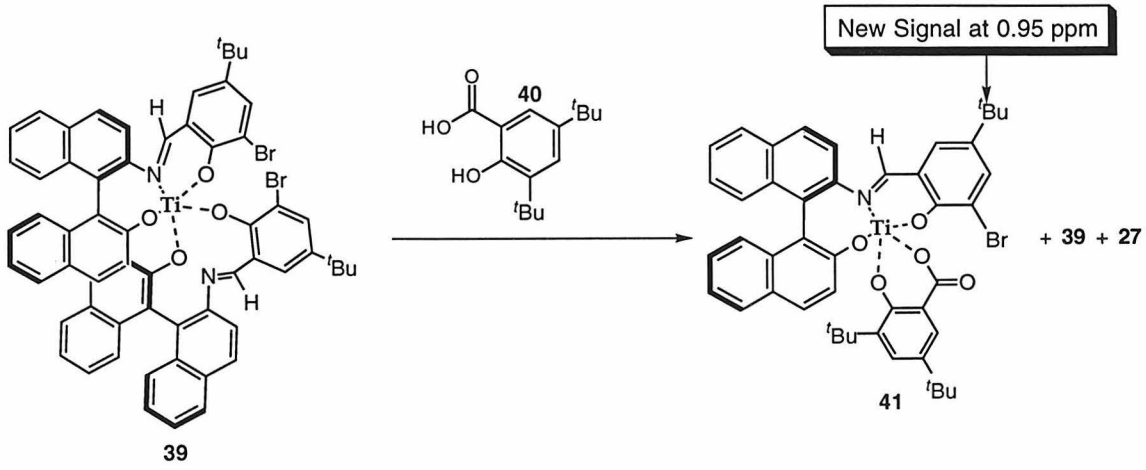
27 with 1 equivalent of $Ti(O^iPr)_4$ in toluene. After stirring the solution for 30 minutes, the volatiles were removed *in vacuo*. The residue was redissolved in CH_2Cl_2 and was transferred via cannula to an apparatus for carrying out VPO. For the four experiments carried out, ligand **27** and 2,2'-ethylidenebis(4,6-di-*t*butylphenol) were used as standards, each for two trials. The system was degassed by cooling to -78 °C and evacuating (at ~2 mm Hg). Then, the system was sealed to remain under vacuum. The apparatus was allowed to stand for two to three weeks to allow for equilibration. The experimental molecular weight of the Ti(IV) complex was correlated to the standard (eq 27) by measuring the final volumes of the solvent in the two bulbs. Using the two different standards for molecular weight correlation, the average experimental weight of 1096 was found to be in agreement with the 2:1 model (**39**), which was calculated to have a molecular weight of 1093.

$$MW_x = (mg_x)\bullet(MW_s)\bullet(mL_s)/[(mg_s)\bullet(mL_x)] \quad (27)$$

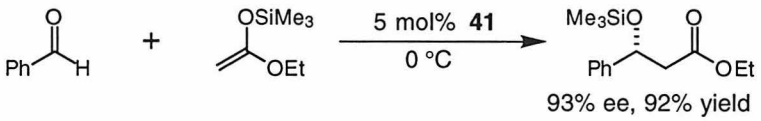
MW_x = MW of **39**, mg_x = weight of **39**, MW_s = MW of standard, mL_s = final volume of standard, mg_s = weight of standard, mL_x = final volume of **39**

The preparation of the titanium complex **41** with the salicylate was also examined by ^{1}H NMR spectroscopy. The catalyst was prepared by combining two equivalents of **27** with 1 equivalent of Ti(O^{i}Pr)$_4$ in toluene. After stirring the solution for 1 hour, 2.4 equivalents of salicylic acid **40** were added. The resulting solution was stirred for an additional hour. During this time a signal corresponding to free ligand (**27**) grew into the spectrum and a single new complex (resonance at 0.95 ppm) was gradually formed over the course of one hour (Scheme 29), and stopped at partial conversion. We speculated that this new complex was **41** because the observations were consistent with the desired ligand exchange, the salicylic acid, **40**, replacing one of the Schiff base ligands bound to Ti(IV) to form **41**. To complete the preparation of the catalyst, the volatiles were removed *in vacuo*. After redissolving the residue in C_6D_6 for analysis by ^{1}H NMR spectroscopy, it was observed that 50% of the Ti was still present as complex **39** (Scheme 29).

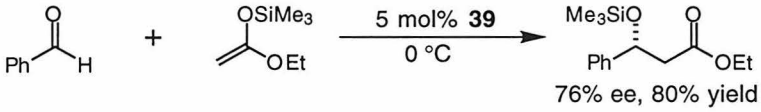
Scheme 29



The remaining Ti was bound as complex **41**. Since this was the catalyst preparation originally employed to carry out the enantioselective aldol additions, this suggests that the success of the enantioselective aldol reactions (eq 28) relies on the inherent higher reactivity of **41** compared to **39**, since **39** provides products in much poorer enantioselectivity (eq 29). It was later discovered that the desired complex **41** could be prepared exclusively by isolating **39** (concentrating *in vacuo*), adding 2 equivalents of salicylic acid **40** in toluene, and concentrating *in vacuo* a second time.



(28)



(29)

The free Schiff base ligand liberated from the exchange process described above (**39** + **40** → **41** + **27**) was shown to be only a spectator in the aldol reactions. One equivalent of the opposite enantiomer of ligand (*ent*-**27**) was combined with a freshly prepared solution of catalyst **41** (Figure 10). The reaction of cinnamaldehyde and *O*-methyl-*O*-trimethylsilyl ketene acetal proceeded uneventfully after adding the opposite enantiomer of free ligand (complete in 2 hours at 0 °C). Assay of the aldol adduct by conversion to the (*S*)-MTPA ester revealed by ^{1}H NMR spectroscopy that the product had been formed in 96% ee. *The addition of the excess ligand did not erode the selectivity even slightly, demonstrating that exchange of the tridentate ligand is slow or inoperative relative to the reaction time scale.*

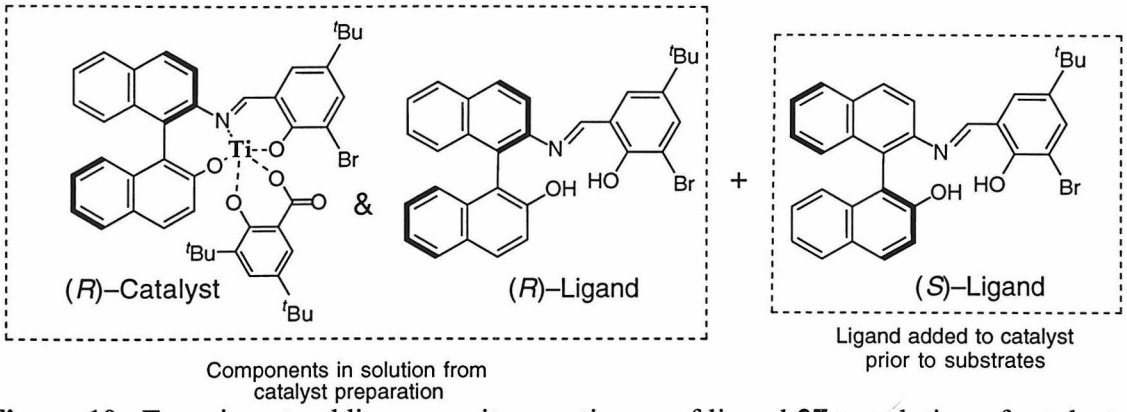


Figure 10. Experiment, adding opposite enantiomer of ligand **27** to solution of catalyst prior to initiating aldol reaction between cinnamaldehyde and a silyl ketene acetal.

Studies in Concentration and Nonlinear Effects of Reactions

Changing the concentration of the substrates, over the range 0.017 M to 0.33 M (200 fold range), and the catalyst, over the range 0.50 mM to 10 mM (200 fold range), had no substantial effect on the enantioselectivity of the products. Consequently, it was assumed that the active catalyst was not in a dynamic equilibrium of different aggregation states since concentration should affect the equilibrium.

Evidence suggesting that there may be competing dynamic processes in solution was discovered in studies correlating the optical purity of the catalyst to the optical purity of the products. It was found that in preparing catalyst of lower optical purity, the products showed a level of optical purity higher than that of the catalyst employed (Figure 11). The catalyst was prepared by the original preparation which entailed stirring a solution of **27** and *ent*-**27** (2 equiv total) and $Ti(O^iPr)_4$ (1 equiv) in toluene for 1 hour and then adding **40** (2 equiv). After stirring the solution for an additional hour, it was concentrated *in vacuo*. The residue was redissolved in Et_2O and cooled to 0 °C. Cinnamaldehyde and *O*-methyl-*O*-trimethylsilyl ketene acetal were added to the catalyst solution and after 4 hours the reaction was worked-up. Desilylation of the adduct and conversion to the (*S*)-MTPA ester allowed the extent of asymmetric induction to be assayed by ^1H NMR spectroscopy. For example, preparing the catalyst as described above from a 2.3:1 ratio of **27** to *ent*-**27** (40%

ee ligand), afforded product in a ratio of 4.5:1, 64% ee (Figure 11). These nonlinear effects may be attributed to the heterodimer (of **41** and *ent*-**41**) forming preferentially to the homodimer. This results in a pool of active, monomeric catalyst and an inactive μ-bridged dimer of **41** and *ent*-**41**. However, it should be noted that under these conditions of preparation, the catalyst is not purely **41**. In addition to **41**, an equal amount of complex **39** is present. Therefore, it is also possible that the nonlinear effects observed result from aggregation of **41** with **39**. An additional possibility is that the nonlinear effects arise from a slow ligand exchange between salicylic acid **40** and the hetero-2:1 complex (**27** and *ent*-**27** bound to Ti in **39**).

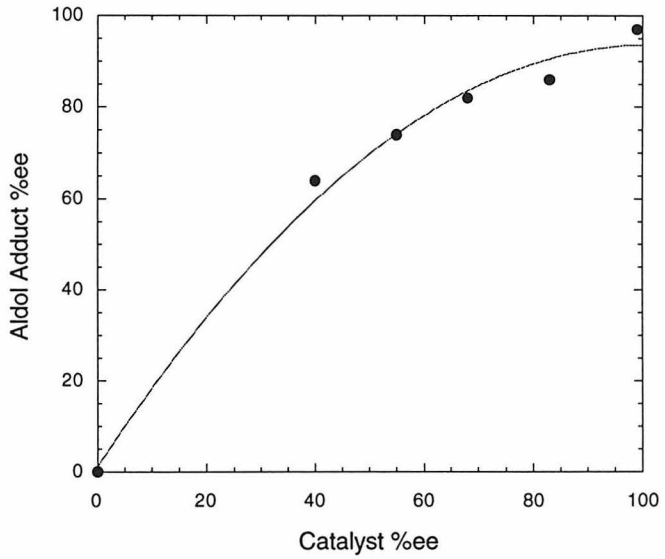
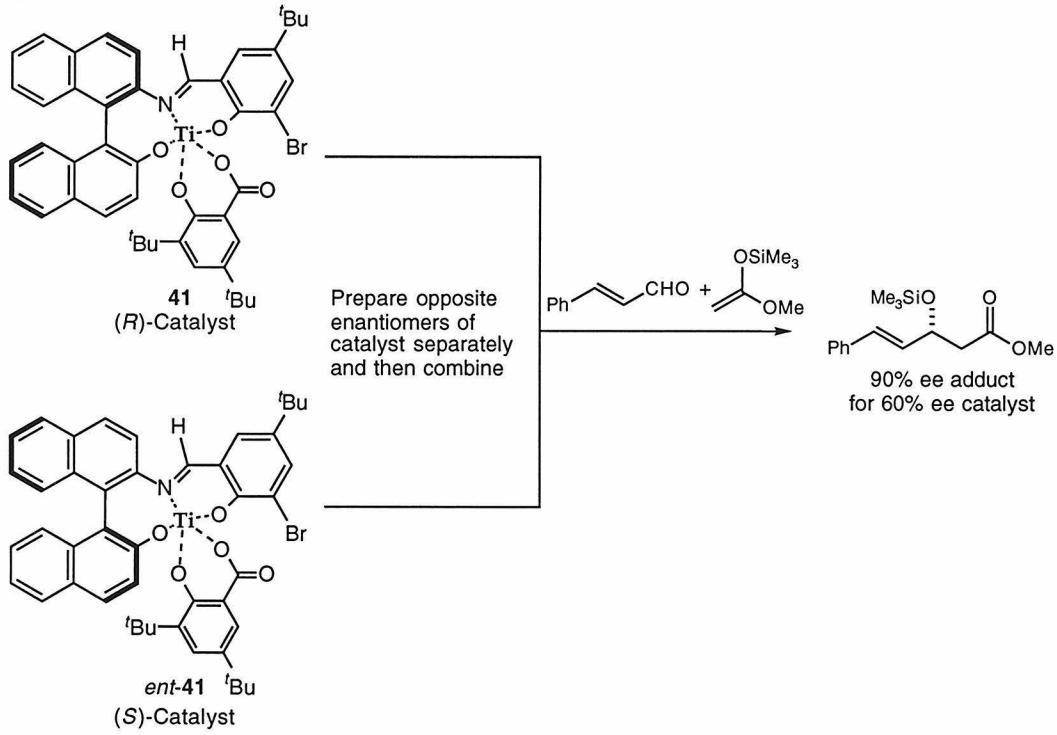


Figure 11. Correlation of optical purity of catalyst to optical purity of adduct derived from cinnamaldehyde and *O*-methyl-*O*-trimethylsilyl ketene acetal.

To dismiss the possibility of slow ligand exchange causing the nonlinear effects, a different set of data was obtained using the standard catalyst preparation (leading to a mixture of **41** and **39**). The reactions were executed by separately preparing **41** and *ent*-**41**, and then combining them in various ratios just prior to adding the substrates (Scheme 30). When combining the (*R*)- and (*S*)-catalysts (**41** and *ent*-**41**) in a 2:1 ratio (33% ee

catalyst), the cinnamaldehyde adduct was isolated in 52% ee, while employing 60% ee catalyst, afforded product in 90% ee. *These experiments rule out attributing the nonlinear effects to slower ligand exchange between salicylic acid* ***40*** *and the hetero-2:1 complex (i.e.,* ***27*** *and ent -****27*** *bound to Ti in* ***39****) in the formation of the active catalyst* ***41***, since the nonlinear effects are still present when preparing the catalyst optically pure and then combining **41** and *ent*-**41**.

Scheme 30



Experiments were conducted correlating optical purity of the catalyst to the adduct (Figure 12) by using a modified version of the standard protocol that provides pure catalyst **41**. Ligands **27** and *ent*-**27** (2 equiv total) were added to a solution of $Ti(O^iPr)_4$ (1 equiv) in toluene. After stirring for 30 minutes, the solutions were concentrated *in vacuo*. To the residue was added salicylic acid **40** in toluene. The resulting solution was stirred for an hour and then was concentrated *in vacuo*. The orange solid was redissolved in Et_2O and was cooled to 0 °C. After adding triethylamine to the catalyst solution followed by cinnamaldehyde and *O*-methyl-*O*-trimethylsilyl ketene acetal the reactions proceeded at the

usual rates (complete in 2 hours at 0 °C). Following work-up, the adduct was desilylated for analysis of the optical purity by chiral HPLC. The data in Figure 12 shows a linear relationship between the optical purity of the ligand (**27**) employed and the adduct. *This implies that the origin of the nonlinear effects may have been due to interactions between complexes **39** and **41** in solution.* More importantly, these results are consistent with the active catalyst, **41**, existing as a monomer in solution.

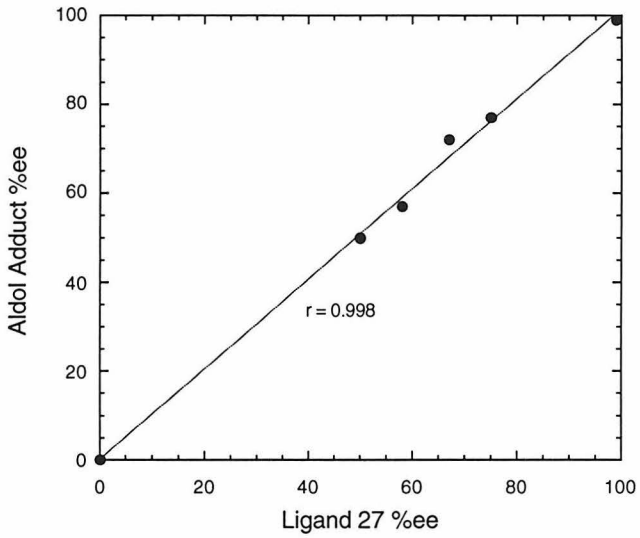


Figure 12. Correlation between optical purity of ligand and aldol adduct using pure catalyst **41**.

Experimental Section[101]

Molecular weight determination of complex 39 by vapor pressure osmometry.[100] First complex **39** was prepared as usual: To a solution of 21 mg of **27** in 4 mL of toluene at 23 °C was added 5.69 mg of $Ti(O^iPr)_4$. The solution was stirred at 23 °C for 1 hour and then was concentrated *in vacuo*. The complex was redissolved in 2 mL of CH_2Cl_2. The complex was transferred via cannula to one of the bulbs in the apparatus for vapor pressure osmometry. In the other bulb was placed a known compound, 21 mg of **27** or 17.5 mg of 2,2'-ethylidenebis(4,6-di-^{t}butylphenol), in 2 mL of CH_2Cl_2. The system was cooled to -78 °C and evacuated for 10 minutes (at 2 mm Hg). The system was then sealed and allowed to equilibrate at 23 °C. Equilibration usually required 2-3 weeks. The relative volumes of the two bulbs were used to correlate the molecular weight of the unknown complex by the equation:

$$MW_X = (mg_X)\bullet(MW_S)\bullet(mL_S)/[(mg_S)\bullet(mL_X)]$$

where MW_X is the molecular weight of the unknown, mg_X is the weight of the unknown, MW_S is the molecular weight of the standard, mL_S is the volume of the standard in the bulb, mg_S is the weight of the standard, mL_X is the volume of the unknown in the bulb. After taking four measurements the average molecular weight was found to be 1096 and the calculated weight is 1093. Data:

using **27** as a standard

Trial 1: MW = 1123, Trial 2: MW = 958.

using 2,2'-ethylidenebis(4,6-di-^{t}butylphenol) as a standard

Trial 1: MW = 1183, Trial 2: MW = 1119.

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101. For general purification and analytical methods, see chapter 2.

General Procedure of Enantioselective, Catalytic Aldol with Preparation of Pure 14

To a 0.022 M solution[102] of **27** (0.044 equiv) in toluene at 23 °C was added $Ti(O^iPr)_4$ (0.020 equiv). The orange solution was stirred for 15 minutes at 23 °C and then was concentrated *in vacuo*. To the orange solid was added **40** (0.040 equiv) in toluene (0.020 M)[103] via cannula. Stirring was continued for two hours at 23 °C. The solvent was removed *in vacuo* and the solid orange residue was taken up in Et_2O and cooled to -20 °C to give a 0.0055 M solution (relative to chiral ligand). To the solution were added trimethylsilyl chloride (0.20 equiv), triethylamine (1.0 equiv), and the aldehyde (1.0 equiv). After 15 minutes the silyl ketene acetal (2.0 equiv) was added dropwise to the catalyst solution. The solution was allowed to gradually warm to 23 °C over 6 hours before it was quenched by pouring onto a saturated aqueous solution of NaCl. The mixture was extracted with Et_2O, and dried over anhydrous Na_2SO_4. The organic extracts were concentrated *in vacuo*. The residue was taken up in 10% TFA/THF to effect desilylation. Once complete, the solution was partitioned between Et_2O and water. The organic layer was washed with a 1.0 M NaOH solution. The separated organic layer was then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica gel was used to isolate the β-hydroxyester adduct.

Data for optical purity correlation experiments:

Trial 1:	50% ee ligand gave 50% ee cinnamaldehyde adduct
Trial 2:	58% ee ligand gave 57% ee cinnamaldehyde adduct
Trial 3:	67% ee ligand gave 72% ee cinnamaldehyde adduct
Trial 4:	75% ee ligand gave 77% ee cinnamaldehyde adduct
Trial 5:	99% ee ligand gave 98% ee cinnamaldehyde adduct

102. Concentrations over the range of .011 to .11 M work equally well.
103. Concentrations over the range of .010 to .10 M work equally well.

General Procedures for Aldol Reactions Correlating Optical Purity of Catalyst to Product

Method A

The ligand **27** and *ent*-**27** were combined in various ratios and then used to prepare the catalyst as described in chapter 3 experimental section (preparation of **41**). Results of experiments:

Trial	ratio of **27**/*ent*-**27**	(% ee ligand)	(% ee product)
Trial 1:	2.3:1	40% ee	64% ee
Trial 2:	3.4:1	55% ee	74% ee
Trial 3:	5.3:1	68% ee	82% ee
Trial 4:	10.5:1	83% ee	86% ee
Trial 5:	>200:1	99% ee	97% ee

Method B

The ligands **27** and *ent*-**27** were used separately to prepare optically pure catalyst as described in chapter 3 (preparation of **41**) and then the prepared catalyst batches of opposite optical purity were combined in varying ratios just prior to adding the substrates at 0 °C. Results of experiments:

Trial	ratio of **41**/*ent*-**41**	(% ee catalyst)	(% ee product)
Trial 1:	2:1	33% ee	52% ee
Trial 2:	4:1	60% ee	90% ee

Chapter 8

Catalytic, Enantioselective Additions with 2-Methoxypropene

Ketone and ester *O*-silyl enol ether derivatives have been utilized widely in stereoselective aldol addition reactions.[104] Although *O*-silyl enol ether derivatives of simpler ketones (cyclohexanone, acetone) are commercially available, in general, the corresponding ester derivatives (silyl ketene acetals) must be prepared in the laboratory prior to use. In some instances the preparative methods require the use of additives such as HMPA and can provide mixtures of *C*- and *O*- silylated products.[105] Thus, the development of stereoselective aldol addition processes employing commercially available enolates or enolate equivalents would be advantageous.[106]

Work by Deaton and Ciufolini[107] had shown that aldol type additions to aldehydes could be accomplished using 2-methoxypropene as a nucleophile in the presence of $Yb(OTf)_3$ and acid catalyst. To adapt this methodology to an asymmetric reaction, Dr. Wheeseong Lee found that the chiral Schiff base-Ti(IV) complex **39** (Figure 13) could

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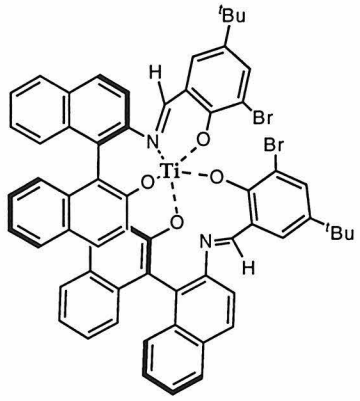
104. (a) Franklin, A. S.; Patterson, I. *Contemp. Org. Synt.* **1994**, 317. (b) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 989. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (d) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnutte, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026. (e) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537. (f) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (g) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (h) Braun, M.; Sacha, H. *J. Prakt. Chem.* **1993**, *335*, 653.

105. (a) Colvin, E. W., *Silicon in Organic Synthesis*, Butterworths: London, **1981**. (b) Weber, W. P., *Silicon Reagents for Organic Synthesis*, Springer-Verlag: Berlin, **1983**.

106. Two aldehyde addition processes have been described which employ commercially available enolate precursors: (1) the Au(I)-ferrocenylphosphine-catalyzed (1 mol%) aldol addition of a-isocyanoacetates to aldehydes affording 5-alkyl-2-oxazoline-4-carboxylate products, see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215. (2) the Ln(III)-Binol-catalyzed (10 mol%) Henry reaction with nitromethane, see (a) Sasai, H.; Suzuki, T.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571.

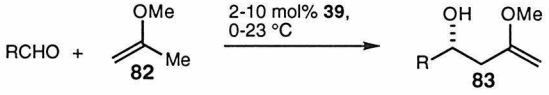
107. Deaton, M. V.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34*, 2409.

effectively catalyze the same process (eq 30).[108] It was unnecessary to use the salicylic acid (**40**) for turnover in this reaction since the reaction appeared to proceed analogously to an ene reaction (proton transfer as shown in Figure 14). The product isolated from the addition under neutral work-up conditions was the free alcohol, (**83**), containing a terminal methoxy vinyl ether moiety rather than a methyl ketone. The vinyl ether most likely arose from the terminal carbon of the adduct transferring a proton to the alkoxide bound to the titanium catalyst.



39

Figure 13. Aldol catalyst for mediating enantioselective 2-methoxypropene additions to aldehydes.



(30)

Under optimal conditions, the aldol addition reaction is conducted by dissolution of **39** (2-10 mol%) in 2-methoxypropene at 0 °C followed by the addition of 2,6-di-*tert*-butylpyridine (0.4 equiv) and the aldehyde (1.0 equiv).[109] After being stirred for 1.5-22

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108. Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649.

109. We have conducted the addition reactions in the absence of added base in good yields and selectivities. However, because of the sensitivity of the solvent 2-methoxypropene and the reaction products to decomposition in the presence of adventitious H^+, we have found it convenient to employ a hindered base as an H^+ scavenger. The addition of Et_3N, $^iPr_2NEt$, or 2,6-lutidine leads to diminution of the reaction rate.

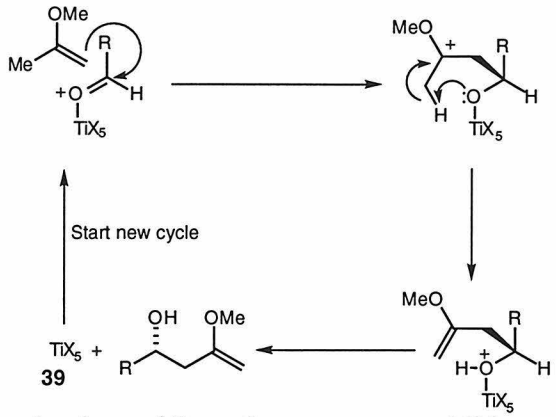

Figure 14. Possible mechanism of 2-methoxypropene addition to an aldehyde mediated by **39**.

hours at 0-23 °C, the reaction mixture was concentrated *in vacuo* and the residue was treated with a biphasic mixture of Et_2O and aqueous 2 N HCl solution to afford the corresponding β-hydroxyketone adduct after work-up and chromatography on silica gel. As shown in Table 14, a variety of aldehydes serve as substrates in the addition reaction and yield, upon work-up, acetone-aldol adducts in 79-99% yields.[110,111] In addition, for each adduct shown, preparation of the derived (*S*)-MTPA esters allowed the extent of asymmetric induction (66-98% ee's) to be assayed by ^1H NMR spectroscopy. The absolute configuration of the products was established unambiguously by comparison with the known optically active β-hydroxyketones.[112] It is interesting to note that the catalyst

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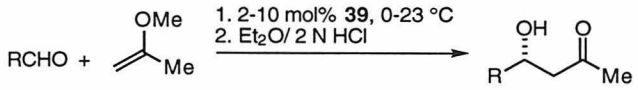
110. Stoichiometric quantities of $Ti(O^iPr)_4$ by itself does not catalyze the addition of 2-methoxypropene to aldehydes. Moreover, the catalytic addition employing **39** can be conducted with excess $Ti(O^iPr)_4$ in the presence of 10 mol% **39** in equally good enantioselectivities and yields.

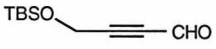
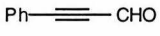
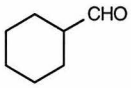
111. Additions of α,β-enals, such as cinnamaldehyde and sorbaldehyde, furnish adducts with good enantioselectivities albeit in low yields. For these substrates, we speculate that the first formed vinyl ether adducts undergo a Cope rearrangement and subsequent decomposition.

112. The absolute configuration was correlated to known compounds for entries 4-6: (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (b) Narasaka, K.; Miwa, T. Hayashi, H.; Ohta, M. *Chem. Lett.* **1984**, *1399*. (c) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C.; Annunziata, R.; Mauro, C.; Cozzi, F. J. *Chem. Commun.* **1983**, 403.



(31)

Table 14. Catalytic, Enantioselective Additions of 2-Methoxypropene to Aldehydes

Entry	Aldehyde	Temp.	Yield	ee[a]
1		0 °C	99%	98%
2		0 °C	85%	93%
3		0 °C	99%	91%
4		0-23 °C	98%	90%
5	PhCHO	0-23 °C	83%	66%
6		0-23 °C	79%	75%

[a] Optical purity determined by conversion to the (*S*)-MTPA ester and analysis by ^{1}H NMR spectroscopy.

system affords the highest enantioselectivities with the less sterically demanding aldehydes (entries 1-3, Table 4), while with branched aldehydes (entries 5 and 6), reduced levels of absolute induction are observed. Despite their versatility as synthetic precursors, α,β-ynals have been examined as substrates in enantioselective, catalytic aldol additions in only one other study where they were shown to react with silyl thioketene acetals to give carbinol products in 79-88% ee's.[113] The catalytic process described herein employing acetylenic aldehydes, 2-methoxypropene and **39** provides a useful method for the preparation of optically active propargylic alcohols.[114,115]

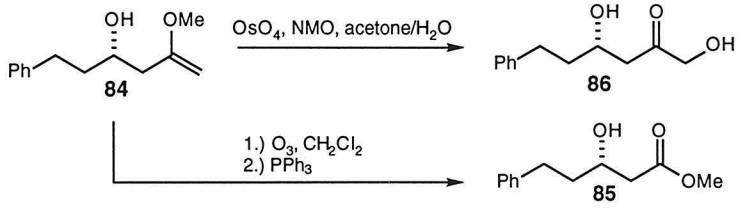
113. Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *Tetrahedron: Asymmetry* **1991**, *2*, 635.

114. Reduction of ynones with optically active boranes provides optically active propargylic alcohols: (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.;

We have conducted the addition reactions in the absence of added base in good yields and selectivities. However, because of the sensitivity of the solvent 2-methoxypropene and the reaction products to decomposition in the presence of adventitious H^+, we have found it convenient to employ a hindered base as an H^+ scavenger. The addition of Et_3N, $^iPr_2NEt$, or 2,6-lutidine leads to diminution of the reaction rate.

In the absence of an acidic work-up the enol ether product can be isolated from the reactions making available additional subsequent transformations (Scheme 31). The enol ether **84** was treated with a dilute stream of ozone in dichloromethane at -78 °C and was quenched with triphenylphosphine to afford the β-hydroxy ester **85**. Treatment of **84** with catalytic osmium tetroxide and *N*-methylmorpholine provided the α-hydroxyketone **86**. Thus, in addition to providing access to acetone aldol adducts, this methodology can also be used to obtain optically active acetate aldol adducts as well as more highly functionalized α-hydroxyacetone adducts.

Scheme 31



To ensure successful reactions it was found that it was necessary to take care in purifying the 2-methoxypropene by passage through a column of basic alumina followed by fractional distillation. Impurities in the 2-methoxypropene often led to incomplete reactions and less than optimal selectivities in the products. This was not surprising since

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Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16.

115. The alkynylation of aldehydes promoted by chiral oxazaborilidines also affords optically active propargylic alcohols, see: Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.

the 2-methoxypropene was being used in excess (200 equivalents) to carry out the reactions. The large excess of 2-methoxypropene required to run the reactions does not prohibit the use of this methodology since 2-methoxypropene is an inexpensive commodity chemical.

Overall, this methodology is efficient for constructing optically pure propargyl alcohols from a commercially available enol ether and affords β-hydroxyketone adducts in good yields and useful levels of enantioselectivity. This reactions provides an alternative to the well-established Mukaiyama aldol additions with silyl enol ether derivatives. The salient features of 2-methoxypropene as an enolate equivalent include the following: (1) 2-methoxypropene is readily available from commercial sources at a nominal price and (2) its use obviates the need for laboratory preparation of the derived silyl enol ethers for aldol addition reactions.

Experimental Section[116]

General Procedure for Catalytic, Enantioselective Acetone-Aldol Addition Reaction

To a 0.010 M solution of **27** (0.20 equiv) in toluene was added $Ti(^iPrO)_4$ (0.1 equiv) and the orange solution was stirred for 1 h at 23 °C. The solvent was removed *in vacuo* and the solid orange residue was taken up in 2-methoxypropene (200 equiv) at 0 °C. 2,6-Di-*tert*-butyl-4-methylpyridine (0.40 equiv) and aldehyde (1.0 equiv) were added sequentially. The reaction was allowed to gradually warm to 23 °C and continue stirring until complete as monitored by TLC. The reaction was concentrated *in vacuo* and the resulting residue was treated with a biphasic mixture of Et_2O and aqueous 2.0 N HCl. It was extracted with Et_2O, and the combined organic extracts were dried over anhydrous Na_2SO_4. The organic extracts were concentrated *in vacuo*. Purification by chromatography on silica gel using 4:1 hexanes/EtOAc to elute the ligand followed by 1:1 hexanes/EtOAc afforded the β-hydroxyketone adduct.

A portion of the aldol adduct was converted to the corresponding (*S*)-MTPA-ester.[117] To a solution of the alcohol (0.01 mmol, 1 equiv) and 15 mg of 4-dimethylaminopyrindine in 1 mL of CH_2Cl_2 was added (*R*)-MTPA-Cl (0.01 mmol, 1.1 equiv). The reaction mixture transferred to a column of silica gel with CH_2Cl_2 and eluted with 10:1 hexanes/EtOAc. The enantiomeric excess of the product was determined by integration of the ^1H NMR (300 MHz, $CDCl_3$ or C_6D_6) resonances of the methyl signals.

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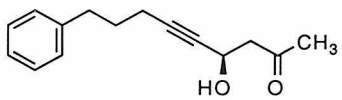
116. For general purification and analytical procedures, see chapter 2.

117. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.



Isolated in 99% yield as a clear, colorless oil.

$[\alpha]_D^{19}$ +28.5° (*c* = 1.0, $CHCl_3$)

IR: (thin film)

3418, 3084, 3061, 3026, 2940, 2861, 1714, 1602, 1496, 1454, 1428, 1361, 1265, 1164, 1063 cm^{-1}.

^1H NMR: (300 MHz, $CDCl_3$)

δ 7.19-7.33 (5H, m), 4.81 (1H, m), 3.16 (1H, d, *J* = 3.2), 2.92 (1H, dd, *J* = 17.4, 7.6), 2.81 (1H, dd, *J* = 17.5, 4.1), 2.71 (2H, t, *J* = 7.8), 2.23 (2H, ddd, *J* = 7.1, 7.1, 2.0), 2.21 (3H, s), 1.84 (2H, q, *J* = 7.7).

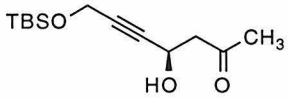
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 207.9, 141.4, 128.4, 128.3, 125.8, 85.1, 80.0, 58.4, 50.4, 34.7, 30.6, 30.0, 18.1.

HRMS: (EI)

calcd for $C_{15}H_{17}O_2$ $(M-H)^+$ 229.1228, found 229.1230

(*S*)-MTPA ester data: ^1H NMR (C_6D_6) methoxy resonances at δ 1.35 and 1.31 ppm in ratio of 27.6:1 (98% ee).



Isolated as a clear, colorless oil in 85% yield.

$[\alpha]_D^{19}$ +28.7° (*c* = 1.0, $CHCl_3$)

IR: (thin film)

3422, 2928, 2857, 1718, 1618, 1508, 1459, 1363, 1253, 1130, 1082, 913, 835, 777, 744 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 4.81 (1H, m), 4.33 (2H, d, *J* = 1.7), 3.07 (1H, d, *J* = 5.4), 2.91 (1H, dd, *J* = 17.7, 6.7), 2.81 (1H, dd, *J* = 17.6, 4.1), 2.20 (3H, s), 0.90 (9H, s), 0.11 (6H, s).

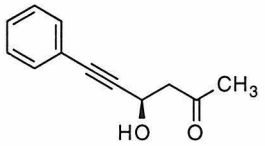
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 207.7, 83.9, 83.6, 58.3, 51.6, 49.8, 30.7, 25.8, 18.3, -5.2.

HRMS: (EI)

calcd for $C_9H_{15}O_3Si$ $(M\text{-}C_4H_9)^+$ 199.0790, found 199.0794

(*S*)-MTPA ester data: ^{1}H NMR (C_6D_6) methyl resonances at δ 1.35 and 1.31 ppm in ratio of 27.6:1 (93% ee).



Isolated as a clear, colorless oil in 99% yield.

$[\alpha]_D^{19}$ +37.2° (*c* = 1.4, $CHCl_3$)

IR: (thin film)

3410, 3058, 2908, 2364, 2231, 1711, 1598, 1571, 1490, 1442, 1363, 1256, 1163, 1070, 1026, 972, 918, 758, 692 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.43-7.27 (5H, m), 5.04-5.00 (1H, m), 3.38 (1H, d, *J* = 5.3), 3.02 (1H, dd, *J* = 17.5, 7.8), 2.90 (1H, dd, *J* = 17.5, 4.1), 2.21 (3H, s).

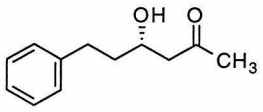
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 207.7, 131.6, 128.4, 128.2, 122.2, 88.3, 84.8, 58.7, 50.0, 30.6.

HRMS: (EI)

calcd for $C_{12}H_{11}O_2$ $(M\text{-}H)^+$ 187.0759, found 187.0757

(*S*)-MTPA ester data: ^{1}H NMR (C_6D_6) methyl resonances at δ 1.38 and 1.35 ppm in ratio of 20.4:1 (91% ee).



Isolated as a clear, colorless oil in 98% yield.

$[\alpha]_D^{19}$ +20.6° (*c* = 1.0, $CHCl_3$)[118]

IR: (thin film)

3448, 3025, 2925, 1702, 1602, 1496, 1364, 1166, 1092, 700 cm^{-1}.

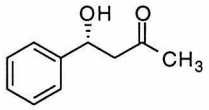
^1H NMR: (300 MHz, $CDCl_3$)

δ 7.36-7.21 (5H, m), 4.12-4.08 (1H, m), 3.26 (1H, d, *J* = 3.3), 2.91-2.82 (1H, m), 2.78-2.68 (1H, m), 2.65 (1H, d, *J* = 0.9), 2.63 (1H, d, *J* = 4.9), 2.20 (3H, s), 1.93-1.80 (1H, m), 1.79-1.70 (1H, m).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 209.8, 141.7, 128.3, 128.3, 125.8, 66.6, 49.9, 37.9, 31.6, 30.7.

(*S*)-MTPA ester data: ^1H NMR ($C6D_6$) methyl resonances at δ 1.50 and 1.45 ppm in ratio of 19.1:1 (90% ee).



Isolated as a clear, colorless oil in 83% yield.

$[\alpha]_D^{19}$ +62.1° (*c* = 1.2, $CHCl_3$)[119]

IR: (thin film)

3424, 3086, 3062, 3031, 3004, 2961, 2901, 1956, 1890, 1712, 1604, 1494, 1454, 1416, 1361, 1164, 1086, 1062, 1027, 949, 917, 819, 755, 701 cm^{-1}.

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118. Narasaka, K.; Miwa, T.; Hayashi, H.; Ohta, M. *Chem. Lett.* 1984, 1399.

119. Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

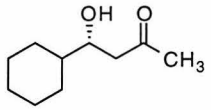
^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.34-7.26 (5H, m), 5.14-5.10 (1H, m), 3.47 (1H, d, *J* = 3.1), 2.87 (1H, dd, *J* = 17.5, 9.0), 2.77 (1H, dd, *J* = 17.5, 3.2), 2.16 (3H, s).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 209.0, 142.7, 128.4, 127.5, 125.5, 69.7, 51.9, 30.7.

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) methyl resonances at δ 2.15 and 2.05 ppm in ratio of 4.9:1 (66% ee).



Isolated as a clear, colorless oil in 79% yield.

$[\alpha]_D^{19}$ +43.1° (*c* = 0.5, $CHCl_3$)[8]

IR: (thin film)

3434, 2925, 2853, 1710, 1450, 1418, 1360, 1308, 1275, 1166, 1106, 1063, 1050, 969, 931, 893 cm^{-1}.

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 3.82-3.78 (1H, m), 2.63 (1H, dd, *J* = 17.5, 3.1), 2.54 (1H, dd, *J* = 17.5, 9.0), 2.18 (3H, s), 1.86-1.63 (5H, m), 1.35-1.15 (4H, m), 1.10-0.96 (2H, m).

^{13}C NMR: (75 MHz, $CDCl_3$)

δ 210.5, 71.6, 47.0, 42.9, 28.8, 26.4, 26.1, 26.0.

(*S*)-MTPA ester data: ^{1}H NMR ($CDCl_3$) methyl resonances at δ 2.14 and 2.05 ppm in ratio of 6.9:1 (75% ee).

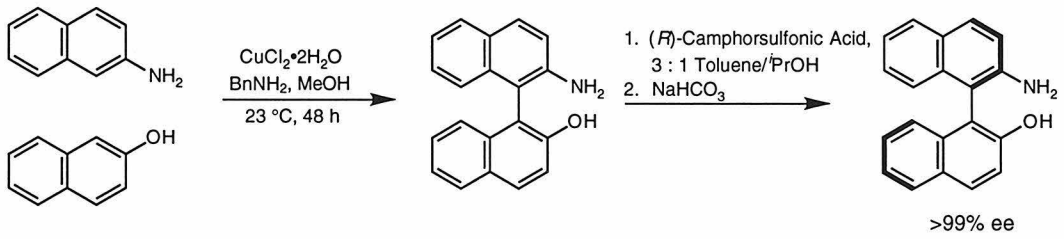
Chapter 9

Resolution of 2-Amino-2'-Hydroxy-1,1'-Binaphthyl

The main impediment to using the chiral Schiff base complex **41** for aldol reactions was the difficulty involved in obtaining optically pure 2-amino-2'-hydroxy-1,1'-binaphthyl (**25**), which is the precursor to Schiff base ligand **27**. The original procedure developed by Smrcina and Kocovsky required an oxidative coupling between 2-naphthylamine and 2-naphthol in the presence of cupric chloride and α-methylbenzylamine.[120] The product was obtained from the coupling in 46% ee and was enhanced to >98% ee by multiple recrystallizations (4-5 times). This process was not only unreliable but also low yielding.

To improve upon this route, a resolution was developed using (*R*)- or (*S*)-10-camphorsulfonic acid (CSA) to form diastereomers as salts (Scheme 32). One of the

Scheme 32



diastereomers selectively crystallized at elevated temperature from solution in 3:1 toluene/isopropanol. The isolated salt was free based with 5% $NaHCO_3$ and the crude material was recrystallized once from benzene. A small sample of the solid was converted to the corresponding (*S*)–MTPA ester of the phenol (cat. DMAP, triethylamine, (*R*)–MTPACl, CH_2Cl_2).[121] Analysis by ^1H NMR spectroscopy revealed that it had been formed in 99% ee. (Ratio of diastereomers determined from integration of methoxy peaks

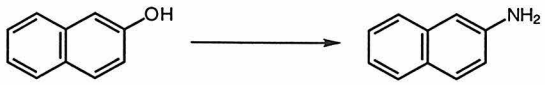
120. Smrcina, M.; Lorenc, M.; Hanus, V.; Sedmera, P.; Kocovsky, P. *J. Org. Chem.*, **1992**, *57*, 1917.

on ^{1}H NMR (300 MHz, $CDCl_3$): major δ 2.95 ppm, minor δ 2.81 ppm). The optical purity of **25** was also assayed by HPLC using the chiralcel OD column which confirmed the optical purity was 99% ee. For a flow rate of 0.5 mL/min and eluent composition of 4:1 hexane/isopropanol, **25** eluted at 22.7 minutes and *ent*-**25** eluted at 20.8 minutes.

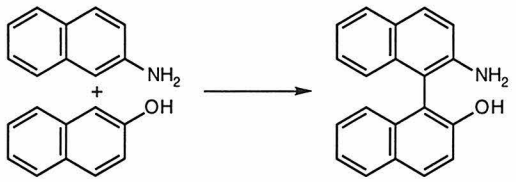
The remaining material in the mother liquor could be free based with sodium hydroxide and kinetically recrystallized as described by Smrcina to obtain optically pure material. As an alternative, the recovered material from the mother liquor could be resubjected to the resolution conditions using the opposite enantiomer of CSA that was previously employed.

Utilizing this resolution procedure, multiple gram quantities of optically pure 2-amino-2'-hydroxy-1,1'-binaphthyl (**25**) have been prepared. With improved access to this compound, additional derivatives will surely be constructed.

Experimental Section[121]



2–Naphthylamine.[122] In a 450 mL stainless steel high pressure vessel were placed 2-naphthol (15.7 g, 109 mmol) and ammoniumsulfite monohydrate (70.5 g, 526 mmol) in 120 mL of a 30% aqueous NH_4OH solution. The contents were heated to 160 °C and stirred for 48 hours. Upon cooling the reaction mixture, the contents were transferred to a 4 L flask and large clumps of solid were broken up. The suspension was diluted with 3.5 L water and the pH of the solution was adjusted to 14 with sodium hydroxide. 2-Naphthylamine was recrystallized from the aqueous solution as a flaky, tan solid (11.1 g, 71%).[123]



(±)-2–Amino–2'–hydroxy–1,1'–binaphthyl (±25). Methanol (1.4 L) was deoxygenated in a 2 L flask by bubbling through nitrogen for 1.5 hours. In a separate 1 L flask were put 2-naphthol (5.00 g, 34.7 mmol) and 2-naphthylamine (5.00 g, 34.7 mmol) in 400 mL of the deoxygenated methanol. Benzylamine (37.2 g, 347 mmol) was placed in a 500 mL flask and dissolved in 200 mL of deoxygenated methanol. To the remaining deoxygenated methanol was added $CuCl_2 \cdot 2H_2O$ (14.8 g, 86.8 mmol). Once all the copper (II) chloride was dissolved by stirring, the solution of benzylamine was added

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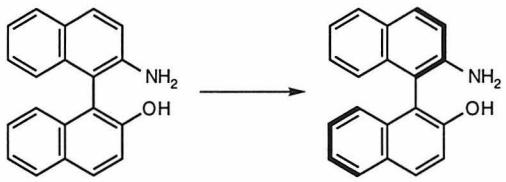
121. For general purification methods and analytical procedures, see chapter 2.

122. Drake, N. L. in *The Bucherer Reaction*; (Adams, R., Ed.);*Organic Reactions*, Wiley, New York, **1942**, *Vol. 1*, 105.

123. 2-Naphthylamine is known to be a potent carcinogen and should be handled with caution.

via cannula. After stirring the copper and benzylamine solution for 10 minutes at room temperature, the solution of 2-naphthol and 2-naphthylamine was added via cannula. The solution was stirred at 23 °C for 48 hours. The precipitate which formed was collected with a fritted funnel and washed three times with 75 mL of methanol. The filter cake was stirred with 100 mL of 37% aqueous HCl and 100 mL of water for 15 minutes. Then 150 mL of a 30% aqueous NH_4OH solution was added slowly followed by 500 mL of water. The precipitate was isolated by filtration after allowing the solution to cool to 23 °C and was washed three times with 75 mL of water. To ensure complete removal of the copper, the solid was washed once again in the following manner: first the solid was stirred with 50 mL of 37% aqueous HCl and 100 mL water for 10 minutes; next a 30% aqueous solution of NH_4OH (70 mL) was slowly added to the solution and was then diluted with 300 mL of water; after cooling to 23 °C, the precipitate was collected by filtration and washed three times with 75 mL of water. After the washings and filtrations, the filter cake was recrystallized from 1.2 L of isopropanol and dried *in vacuo* to give a 48% yield (4.8 g).



(*R*)–(+)–2-Amino-2'-hydroxy-1,1'-binaphthyl (25). In a 250 mL flask with a magnetic stir bar was put (±)–2-amino-2'-hydroxy-1,1'-binaphthyl (2.00 g, 7.01 mmol) in 120 mL of toluene and 40 mL of isopropanol.[124] The suspension was heated to 60 °C with rapid stirring and (*R*)-camphor-10-sulfonic acid[125] (1.71 g, 7.36 mmol) was added. The light brown mixture became homogeneous within 1 minute following addition of the (*R*)–camphorsulfonic acid. Stirring was continued and heating was maintained at 60

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124. Toluene and isopropanol were distilled from calcium hydride or dried over 3 Å sieves prior to use.

125. The camphorsulfonic acid was recrystallized from ethyl acetate prior to use.

to 65 °C for 20 minutes, during which time a white precipitate began to form. The well stirred solution was then allowed to gradually cool to room temperature over 1 hour and was allowed to stand overnight. The precipitate which forms was isolated by filtration and washed twice with 4 mL of toluene. The filter cake was suspended in a mixture of 50 mL of dichloromethane and 50 mL of a 5% aqueous $NaHCO_3$ solution. The mixture was stirred rapidly for 15 minutes over which time the organic phase became homogeneous. The mixture was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with another 20 mL of dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 0.88 g (88%) crude product.

Recrystallization of the product from 9 mL of benzene (10 mL of benzene/ 1.0 g binaphthyl) afforded 0.64 g (64%) of **25** with an optical purity of 99% ee,[126] mp 169 °C, $[\alpha]_D^{19}$ +122° (c 1.04, THF).[127]

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126. A small sample of the solid was converted to the corresponding (*S*)–MTPA ester of the phenol (cat. DMAP, triethylamine, (*R*)–MTPACl, CH_2Cl_2).[126] Analysis by ^1H NMR spectroscopy revealed that it had been formed in 99% ee. (Ratio of diastereomers determined from integration of methoxy peaks on ^1H NMR (300 MHz, $CDCl_3$): major δ 2.95 ppm, minor δ 2.81 ppm). The optical purity of **25** was also assayed by HPLC using the chiralcel OD column. For a flow rate of 0.5 mL/min and eluent composition of 4:1 hexane/isopropanol, **25** eluted at 22.7 minutes and *ent*-**25** eluted at 20.8 minutes.

127. For (*R*)-2-amino-2'-hydroxy-1,1'-binaphthyl the literature[1] reports mp 171-3 °C; $[\alpha]_D^{19}$ +116°, for 97% ee.