Geminal Dicarboxylates as Carbonyl Surrogates for Asymmetric Synthesis. Part II. Scope and Applications

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Abstract: An enantioselective synthesis of allylic esters has been achieved by a novel asymmetric alkylation of allylic *gem*-dicarboxylates. The catalyst derived from palladium(0) and *R,R*-1,2-di(2′-diphenylphosphinobenzamido)cyclohexene efficiently induced the alkylation process with a variety of nucleophiles to provide allylic esters as products in good yield. High regio- and enantioselectivities were observed in the alkylation with most nucleophiles derived from malonate, whereas a modest level of ee's was obtained in the reactions with less reactive nucleophiles such as bis(phenylsulfonyl)ethane. In the latter case, a slow addition procedure proved effective, leading to significantly improved ee's. The utility of the alkylation products was demonstrated by several synthetically useful transformations including allylic isomerizations, allylic alkylations, and Claisen rearrangements. Using these reactions, the chirality of the initial allylic carbon−oxygen bond could be transferred to new carbon−oxygen, carbon−carbon, or carbon−nitrogen bonds in a predictable fashion with high stereochemical fidelity. The conversion of *gem*-diesters to chiral esters by the substitution reaction is the equivalent of an asymmetric carbonyl addition by stabilized nucleophiles. In conjunction with the subsequent reactions that occur with high stereospecificity, allylic *gem*-dicarboxylates serve as synthons for a double allylic transformation.

Introduction

Allylic esters are exceptionally versatile synthetic building blocks in organic chemistry. This feature originates from the steric and electronic properties of the allylic setting which allows for easy introduction of a new bond and provides strong diastereofacial guidance to the addition reactions of the adjacent alkene. Thus, allylic esters are useful in a variety of reactions exemplified by metal-catalyzed allylic alkylations,[1] allylic transpositions,[2] Claisen rearrangements,[3] cycloaddition reactions,[4] epoxidations,[5] and dihydroxylations.[6] These processes generally proceed with high stereochemical fidelity, thereby transferring or propagating the chirality of the allylic center to other location(s) within the molecule. Therefore, the enantioselective preparation of allylic esters constitutes an important transformation in asymmetric synthesis. In particular, catalytic methods for performing such transformations would be a more desirable solution for accessing allylic systems.

A classical approach to the construction of chiral allylic systems involves an enzymatic[7] or chemical[8] resolution of racemic allylic alcohols. Although these methods have found a number of applications, they suffer from the limitation of a 50% theoretical yield. A recent deracemization strategy using a Pd-catalyzed asymmetric *O*-alkylation reaction is free of this limitation at least for symmetrically substituted allylic systems.[9] The more widely adopted strategies utilize carbonyl addition reactions such as the asymmetric reduction[10] or alkylation of α,β-unsaturated systems. In particular, the asymmetric addition of dialkylzinc provides more synthetic flexibility as the allylic stereogenic center is created through an alkylation process.[11] However, this process is critically dependent on the nature of the nucleophile and, thus far, not feasible with stabilized nucleophiles. A simple nucleophilic addition to α,β-unsaturated aldehydes which would create such an allylic system is complicated by various issues of selectivity. In addition to

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(7) For reviews, see: (a) Faber, K. *Biotransformations in Organic Chemistry*, 3rd ed.; Springer-Verlag: Berlin, 1997. (b) Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994; pp 41−130. (c) Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1608. (d) Theil, F. *Chem. Rev.* **1995**, *95*, 2203.

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(10) Corey, E. J.; Heldal, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987 and references therein.

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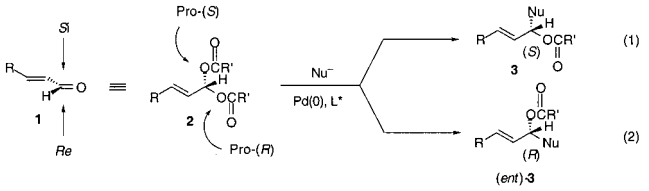
differentiation of the two prochiral faces of the carbonyl group, stabilized nucleophiles are prone to undergo a conjugate addition due to the reversibility and unfavorable equilibrium of a carbonyl addition. For these reasons, chiral induction by the carbonyl addition of a stabilized nucleophile has not been developed, in contrast to the well-documented examples utilizing unstabilized nucleophiles.

An alternative strategy to the carbonyl addition evolves from the recognition of a carbonyl group as the sum of two C−O bonds.[12] In this approach, the problem of differentiating the two enantiotopic π-faces of a carbonyl group becomes that of asymmetric substitution of either of the enantiotopic C−O bonds of the acetal. While this concept has proved successful in the chiral auxiliary-based approaches, such a transformation can also be performed in a catalytic fashion by the asymmetric allylic alkylation (AAA) using *gem*-dicarboxylates **2** (eqs 1 and 2). In

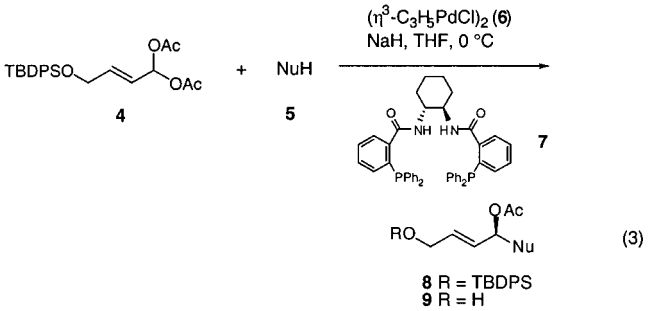


(1) (2)

the Pd-catalyzed alkylation with malonate esters, the readily available acylals serve as an "activated form" of a carbonyl group for stabilized nucleophiles, giving rise to allylic ester **3** as the product in high ee.[13,14] The chemoselectivity issue of the carbonyl versus Michael additions now becomes a question of regiocontrol in the nucleophilic addition to the π-allyl intermediate. Thus, the Pd-catalyzed allylic substitution of *gem*-dicarboxylates represents a novel method for the asymmetric synthesis of allylic esters in which chiral induction in the carbonyl addition of a stabilized nucleophile is achieved. Herein, we report our investigation on the scope and limitation of the alkylation process and the synthetic utility of the alkylation products.

Results

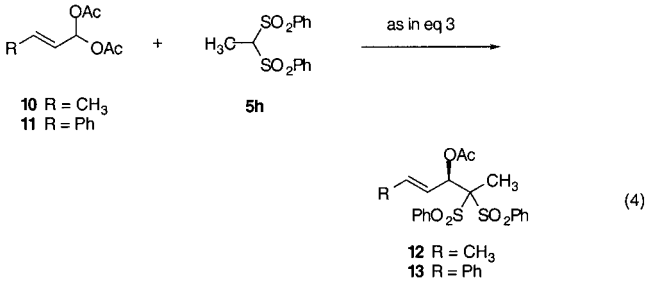
Asymmetric Alkylation. Testing the efficacy of various nucleophiles began with the reactions of the straight-chain derivative (**4**), which had also been used as a model substrate in the previous study[14] (eq 3). As established in our initial



(3)

studies, the best set of conditions employed *gem*-diacetate rather than dipropionate or diisobutyrate as the substrate, sodium hydride as the base, and THF as the solvent. Thus, employing these conditions, diacetate **4** was reacted at 0 °C in THF in the presence of 1 mol % π-allylpalladium chloride (**6**) and 3 mol % *R*,*R*-ligand **7**. The nucleophiles were generated from a mixture of 2.0−2.5 equiv of pronucleophile (**5**) and 1.5−2.0 equiv of sodium hydride. As summarized in Table 1, the alkylations of **4** with a variety of nucleophiles furnished allylic esters **8** as a single regioisomer in good yields with high ee's. All of the alkylation products were stable, easily handled, and readily purified by simple chromatography. The ee was determined by chiral shift studies on the corresponding desilylated alcohols **9** or chiral HPLC analysis. It is worthy of note that the alkyne, acetal, carbamate, cyano, and phenylsulfonyl functionalities did not interfere with the asymmetric process (entries 4−8). By contrast, attempts to use di-*tert*-butyl methylmalonate as the nucleophile failed to produce the alkylation product but rather resulted in the recovery of unreacted **4** under various conditions. Interestingly, strong dependence of the ee on the alkylation procedure was noted (entry 8). The initial result of the alkylation with sulfone derivative **5h** was disappointing as only 80% ee was obtained under the standard conditions. On the other hand, performing the same reaction using a slow addition procedure significantly improved the ee to 92%.

The results of the alkylation with the sulfone derivative led us to examine the reactions of **5h** with other substrates. Methyl- and phenyl-substituted *gem*-diacetates **10** and **11** were subjected to alkylation with **5h** under the standard conditions (eq 4).



(4)

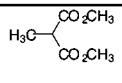
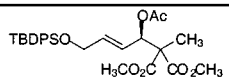
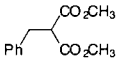
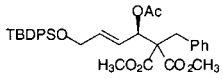
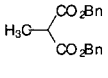
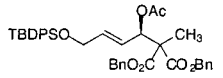
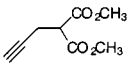
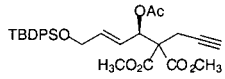
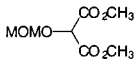
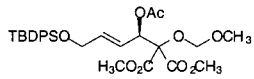
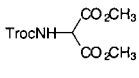
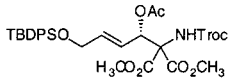
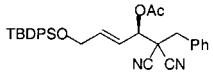
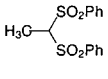
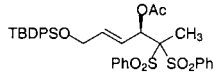
Although both substrates provided **12** and **13** as single regioisomers in 52% (99% based upon recovered starting material, brsm) and 90% yields, respectively, chiral shift studies on the alkylation products revealed modest ee's of 67% for **12** and 85% for **13**. Considering the excellent level of ee's that these substrates afforded in alkylations with **5a** and **5b**, these results seemed rather suprising. In particular, the ee of phenyl derivative **13** appeared even more puzzling since the alkylation of **11** invariably exhibited ee's greater than 95% regardless of the nucleophile.[13,14] The factors affecting the ee in this case were probed by using different sets of conditions. In the standard procedure, the nucleophile was generated at 25 °C and added to the mixture containing the substrate and catalyst at 0 °C. However, this procedure resulted in immediate precipitation of the nucleophile from the reaction mixture. Although increasing the solubility of the nucleophile by using tetraalkylammonium as the counterion or DBU as the base led to a homogeneous reaction, these modifications resulted in even slower reactions and large deterioration in ee. It was hoped at this point that a homogeneous reaction still employing sodium as counterion would give an efficient alkylation. Thus, after the nucleophile was generated, the alkylation was immediately carried out using a slow addition procedure, thereby taking advantage of the kinetic solubility that keeps the reaction mixture homogeneous.

(12) For use of chiral acetals as chiral auxiliaries, see: Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279. Johnson, W. S.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188. For leading references, see: Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998. Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10695. For a review, see: Alexakis, A.; Mangeney, P. *Tetrahedron*: *Asymmetry* **1990**, *1*, 477.

(13) Trost, B. M.; Lee, C. B.; Weiss, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 7247.

(14) See the preceding paper: Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3671−3686.

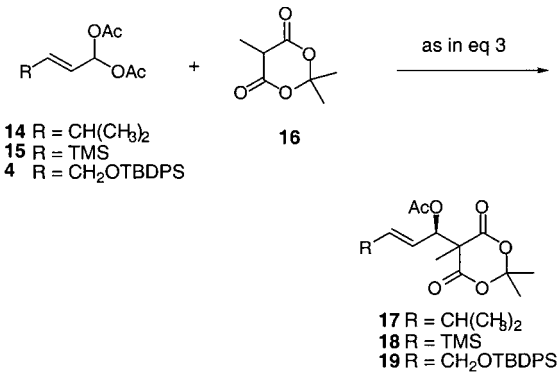
Table 1. Alkylations of **4** with Various Nucleophiles[a]

Entry	Nucleophile	Time (h)	Product	% Yield[b]	% *ee*
1[c]	 **5a**	2	 **8a**	85 87[f]	91[d] 93[f]
2[c]	 **5b**	3	 **8b**	98	90[d]
3	 **5c**	5	 **8c**	76	87[d]
4	 **5d**	6	 **8d**	86	91[e]
5	 **5e**	4	 **8e**	79	93[e]
6	 **5f**	6	 **ent-8f**	92	89[d,g]
7	 **5g**	1.5	 **8g**	80	90[d]
8	 **5h**	6	 **8h**	58[f] (80[h]) 88	92[d,f] 80[d]

[a] All reactions were carried out with 1% **6** and 3% **7** in THF (0.2−0.5 M) at 0 °C unless otherwise noted. [b] Isolated yields. [c] Reference 14, the preceding paper. [d] Determined by chiral shift studies on the corresponding desilylated alcohol **9** using (+)-Eu(hfc)$_3$ in $CDCl_3$. [e] Determined by chiral HPLC using Chiralel OD or Chiralpak AD column with a 2-propanol-heptane mixture as eluent. [f] Slow addition procedure was applied. [g] Reaction performed with *S,S*-ligand, *ent*-**7**. [h] Based upon the recovered starting material.

Indeed, this procedure increased the ee to 95%, albeit with a moderate isolated yield of 54% mainly due to lower conversion (80% brsm).

A cyclic nucleophile such as Meldrum's acid derivative **16** was also tested for the alkylation (eq 5). The alkylation of the

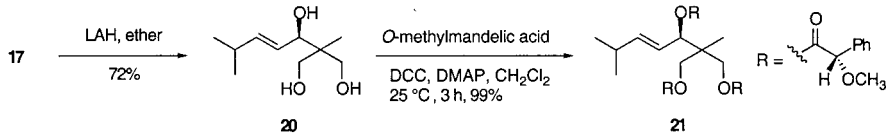


(5)

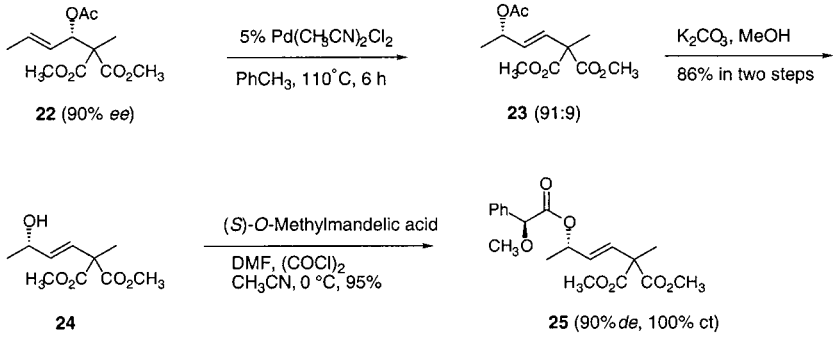
isopropyl-substituted substrate **14**, which gave 95% ee in the reaction with dimethyl methylmalonate (**5a**), provided **17** in 58% yield with a somewhat decreased 90% ee. Similarly, TMS derivative **18** was obtained in 83% yield with 85% ee from the reaction of **15**. It is of interest to note that no alkylation occurred when **15** was subjected to the reaction with **5a** in our previous studies. The generally lower enantioselectivities using **16** as nucleophile are typified by the alkylation of **4** that gave **19** in 86% yield with a much lower ee of 56%. This result, in particular, provides a striking contrast to those obtained with a variety of acyclic nucleophiles **5**, in which a high level of ee (87−93%) was uniformly observed (see Table 1).

While the ee was easily determined by chiral shift studies on these alkylation products, derivatization of **17** to *O*-methylmandelate **21** was carried out for further analysis (Scheme 1). The two-step sequence involving LAH reduction and esterification provided tris-*O*-methylmandelate **21** uneventfully. The signals from the two vinyl protons and the quaternary methyl group of the (*R*)- and (*S*)-mandelates were completely resolved in the ^{1}H NMR spectrum, and integration of those signals confirmed the measurement of 90% ee as determined by chiral shift studies. Furthermore, the pattern of their chemical shifts was in full agreement with the reported trend and thus established the absolute stereochemistry as depicted.[15]

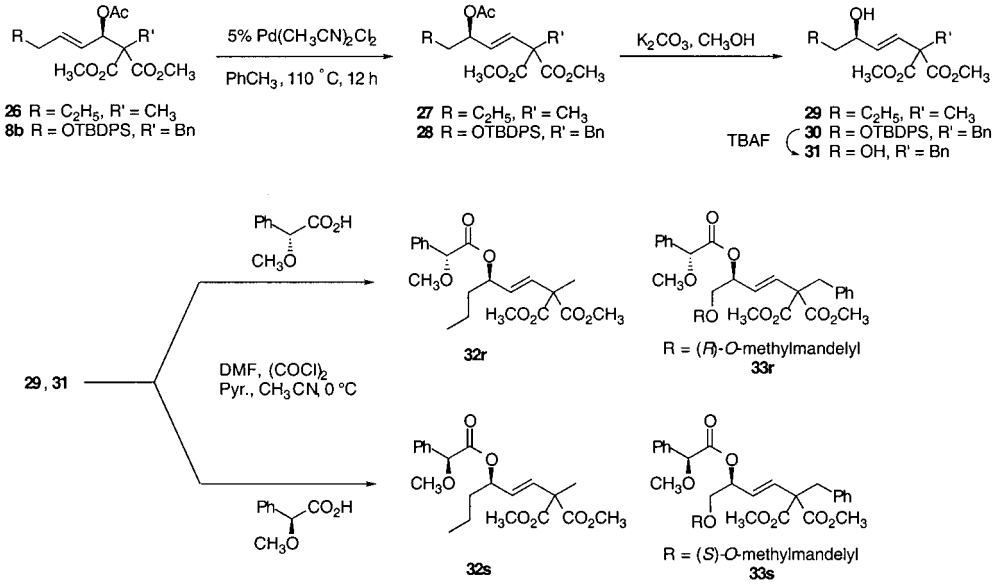
Scheme 1. Determination of Enantioselectivity and Absolute Configuration



Scheme 2. Palladium-Catalyzed Allylic Transposition of **22**



Scheme 3. Palladium-Catalyzed Allylic Transposition and Derivatization to Mandelates



Allylic Transposition. With the alkylation products in hand, their allylic isomerization reactions were next investigated. The equilibration reaction of allylic acetate **22** was performed using $PdCl_2(CH_3CN)_2$ as catalyst (Scheme 2).[16] Toluene proved to be the most efficient solvent as reactions in other solvents such as benzene and THF required longer reaction times and failed to achieve complete equilibrium. Thus, treatment of **22** (90% ee) with 5% catalyst in refluxing toluene for 6 h generated an inseparable mixture of **22** and **23** in a 9:91 ratio. As monitored by GC, the ratio of the transposed acetate **23** rapidly increased and slowly reached a constant value, at which point the reaction was stopped. Separation was readily accomplished by hydrolysis of the mixture to afford allylic alcohol **24** in 86% yield, while starting acetate **22** was degraded to crotonaldehyde and dimethyl methylmalonate (**5a**) by a retro-aldol process. Converting alcohol **24** into *O*-methylmandelate ester **25** provided unambiguous determination of the ee and the absolute configuration. Both the ee of 90% (corresponding to 100% chirality transfer, ct) and the (*S*) configuration of the allylic center indicated that the transposition reaction proceeded in a highly stereospecific manner with conformity to suprafacial topology.

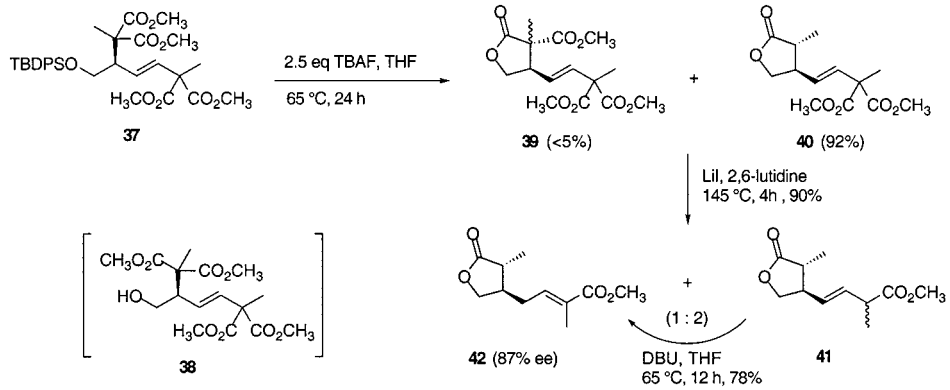
Following the same protocol, the *n*-propyl substituted **26** and TBDPS derivative **8b** were subjected to the transpostion reaction (Scheme 3). The reaction of **26** (92% ee) led to the formation of an 11:89 isomeric mixture of allylic acetates **26** and **27**. Cleavage of the acetyl group by treatment with methanolic potassium carbonate provided allylic alcohol **29** in 87% yield for two steps. On the other hand, isomerization of allylic acetate **8b** (90% ee) under the same palladium catalysis conditions went to completion. No starting material remained after 12 h reflux in toluene, and only the transposed acetate **28** was isolated in 85% yield. Hydrolysis of the acetyl group followed by removal of the silyl group with TBAF afforded diol **31** in 83% yield. For analysis of the stereochemical outcome, alcohol **29** and diol **31** were converted to both (*R*)- and (*S*)-*O*-methylmandelate esters in good yield.[17] Determination of the de's of the esters by ^{1}H NMR and chiral HPLC analyses gave 91−92% ee for **32** and 89−90% ee for **33** corresponding to 99−100% ct.

(15) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(16) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321.

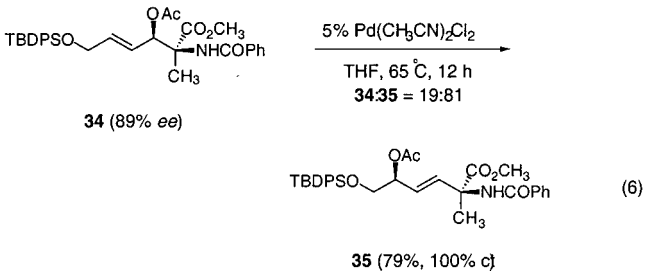
(17) Stadler, P. A. *Helv. Chim. Acta* **1978**, *61*, 1675.

Scheme 4. Derivatization of Bismalonate **37** to Lactone **42**



Analysis of the chemical shifts in the ^{1}H NMR spectra of these mandelate esters verified the absolute configuration.

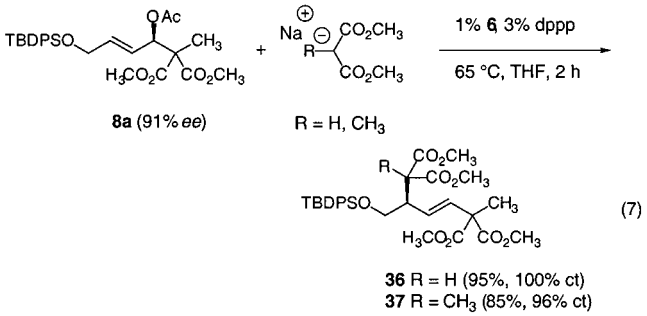
The α-alkyl-α-amino acid derivative **34**, which was available from our total synthesis of sphingofungin F through the alkylation of **4** with an azlactone nucleophile in 89% ee,[18] was also subjected to the transposition reaction in THF (eq 6).



(6)

Although the reaction gave a somewhat diminished 81:19 isomeric ratio, the rearranged acetate **35** could still be isolated in a fairly good yield (79%). The 89% ee determined by chiral shift studies demonstrated again the high stereospecificity achieved in this process.

Allylic Alkylations. While the allylic transposition reaction successfully achieved chirality transfer between the two allylic C−O bonds, the Pd-catalyzed allylic substitution allowed for the introduction of other types of carbon−carbon and carbon−heteroatom bonds. Due to the highly stereospecific nature of this process, a simple achiral ligand was sufficient for the stereoselctive formation of a new bond.[19] Allylic acetate **8a** (91% ee) was reacted with malonate-derived nucleophiles (eq 7). The reactions were performed by treating **8a** with the sodium

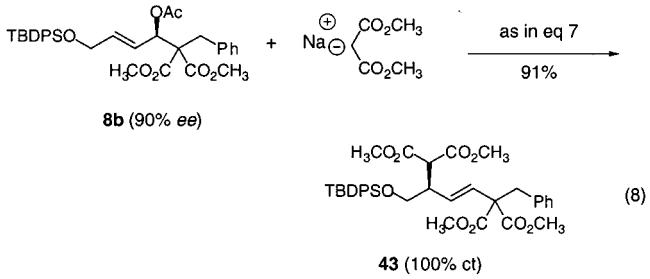


(7)

salt of malonate esters in refluxing THF in the presence of 1% **6** and 3% dppp. Alkylations with both unsubstituted or methyl-substituted malonate dimethyl esters proceeded cleanly to give the corresponding bis-malonate derivatives **36** and **37** as single regioisomers in good yields. While the use of either dppe or dppp ligand gave satisfactory yields of the desired products, no reaction was observed when triphenylphosphine was employed as ligand. Interestingly, the chiral ligand (*S*,*S*)-**7**, which would be the matched ligand for this second ionization, was found to be ineffective for the alkylation.

The complete sterochemical fidelity accompanied in the substitution reaction was verified by chiral shift studies on **36** that revealed 91% ee (100% ct). However, various efforts to determine the ee of the methyl analogue **37** did not provide unambiguous values. Thus, the bis-alkylated product **37** was further derivatized according to the sequence shown in Scheme 4. Bis-malonate **37** was treated with TBAF in refluxing THF to give a mixture of γ-lactones **39** and **40**. The formation of these γ-lactones was readily noted by two carbonyl stretches at 1775 and 1736 cm^{-1} in the IR spectra. The major lactone **40** arose from dealkylative decarboxylation of **39** which was initially generated from desilylated alcohol **38** followed by lactonization. The relative stereochemistry of lactone **40** was assigned as trans based on the large coupling constant (J = 11.4 Hz) between the two methine protons. The mixture of lactones **39** and **40** was further dealkylated with lithium iodide in refluxing 2,6-lutidine to provide an inseparable mixture of the unconjugated (**41**) and conjugated (**42**) methyl esters in 2:1 ratio.[20] Upon treatment with DBU, the β,γ-unsaturated ester **41** cleanly isomerized to α,β-unsaturated ester **42** as a single diastereomer. Chiral HPLC analysis of **42** gave 87% ee, corroborating the good degree of stereospecificity observed in the second alkylation (at least 96% ct). It is worth noting that the γ-lactone, a ubiquitous structural motif in various natural products, could be prepared by this three-step sequence in a highly enantio- and diastereoselective fashion.

The allylic acetate **8b** (90% ee) was similarly alkylated with dimethyl malonate to give bis-malonate **43** as a single product in 91% yield (eq 8). Both the chiral shift experiments and chiral

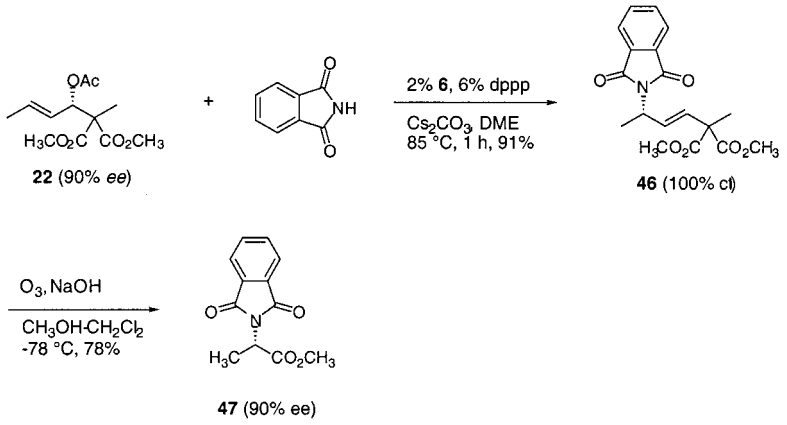


(8)

HPLC analysis on the alkylation product uniformly afforded

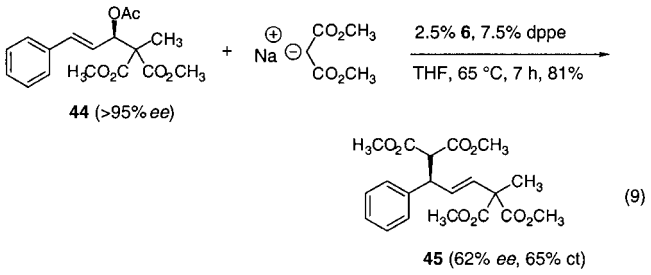
(18) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818.
(19) (a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (b) References 1c and 1d.
(20) Elsinger, F. *Organic Syntheses*; Wiley & Sons, New York, 1973; Collect. Vol. V, p 76.

Scheme 5. Allylic Alkylation with Phthalimide and Derivatization



90% ee. This stereochemical outcome, again, clearly demonstrated the efficiency of chirality transfer from a C−O bond to a new C−C bond by these Pd-catalyzed second allylic alkylations.

In contrast to the excellent results obtained from the alkylations of the TBDPS derived **8**, similar alkylations of the phenyl-substituted **44** gave rather poor stereochemical outcomes (eq 9). While the reaction of **44** (>95% ee) with dimethyl malonate



(9)

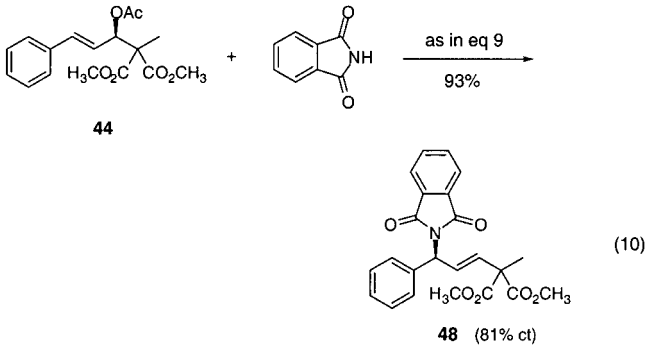
using dppe as ligand gave an 81% yield of the desired alkylation product **45**, it required much longer reaction time and suffered from severe loss of stereochemical integrity. The ee of **45** was only 62% (65% ct) as determined by chiral shift experiments. Various attempts to improve the stereospecificity by employing different ligands, solvents, and bases were not fruitful.

The allylic alkylation was extended to include the introduction of nitrogen nucleophiles. The reaction of allylic acetate **22** (90% ee) with the cesium salt of phthalimide using dppp as ligand and DME as solvent led to the formation of allylic phthalimide **46** as a single product in 91% yield (Scheme 5). The use of THF as solvent or triphenylphosphine as ligand did not induce the substitution process. Chiral HPLC analysis and chiral shift experiments on **46** afforded ee's of 89−90%, thereby attesting to the complete chirality transfer from a C−O bond to a C−N bond. To determine the absolute stereochemistry of the newly formed C−N bond, allylic phthalimide **46** was converted to (*S*)-*N*-phthaloyl alanine methyl ester (**47**). Ozonolysis of **46** according to the known protocol[21] directly generated α-amino acid derivative **47** in 78% yield and 90% ee. Comparison of the reported value for **47** (lit.[22] $[\alpha]_D = -21.8$) and the obtained optical rotation, $[\alpha]_D = -20.2$ (*c* 1.00, $CHCl_3$), corroborated the stereochemical assignment of both the initial asymmetric and second alkylations.

(21) (a) Marshall, J. A.; Garafalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675. (b) Jumnah, R.; Williams, J. M.; Williams, A. C. *Tetrahedron Lett.* **1993**, *34*, 6619.

(22) (a) Kashima, C.; Okada, R.; Arao, H. *J. Heterocycl. Chem.* **1991**, *28*, 1241. (b) Shoda, S.; Mukaiyama, T. *Chem. Lett.* **1980**, 391.

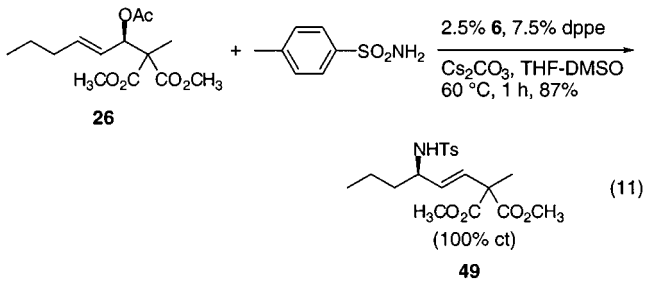
As was encountered in the alkylation with dimethyl malonate (**5a**), the phenyl-substituted **44** (>95% ee) showed similar aberration of optical purity in the phthalimidation (eq 10).



(10)

Despite the excellent yield of the reaction, the ee of allylic phthalimide **48** was only 77% (81% ct). Variation of ligands, counterions, catalyst concentrations, and solvents gave little improvement. Given that other substrates could be alkylated with high stereospecificity, the leakage of optical purity appears to be only endemic to the phenyl-substituted substrate **44**.

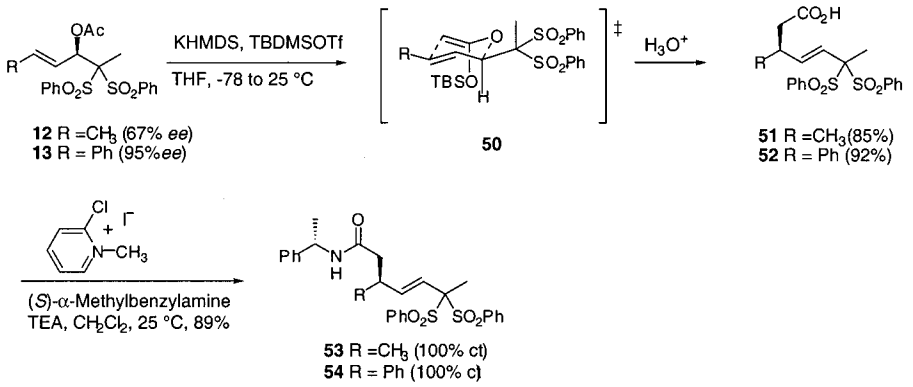
The introduction of a nitrogen functionality could also be carried out using an alternative nucleophile such as sulfonamides (eq 11). The Pd-catalyzed allylic amination of **26** (91% ee) with



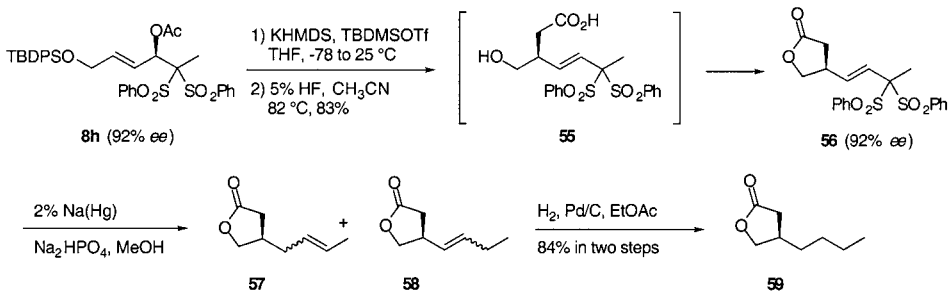
(11)

the sodium salt of *p*-toluenesulfonamide was performed. The initial reaction employing dppp as ligand and DME as solvent proceeded sluggishly to provide allylic sulfonamide **49** in 85% yield with 88% ee. The small loss of enantiopurity was ascribed to the long reaction time which was due to the poor solubility of the nucleophile in the reaction medium. Thus, the reaction conditions were modified by employing cesium carbonate as base, dppe as ligand, and a 1:1 THF−DMSO mixture as solvent. Indeed, these modifications led to a rapid alkylation and increased the yield to 87% and the ee to 91%.

Scheme 6. Claisen Rearrangement of Sulfones and Derivatization



Scheme 7. Claisen Rearrangement of **8h** and Derivatization to Lactone **59**



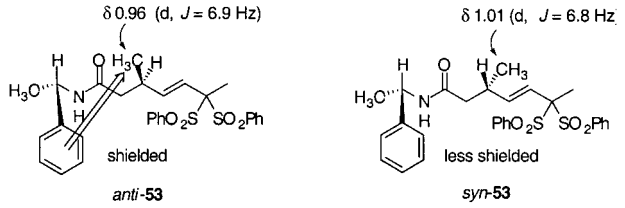


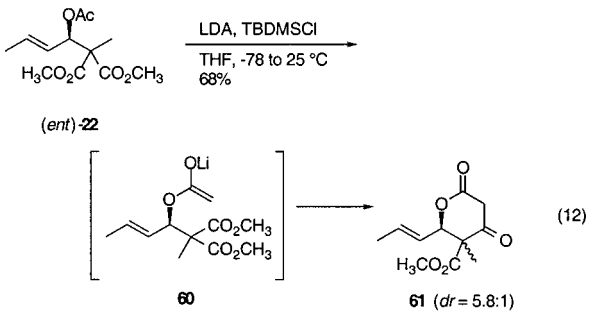
Figure 1. H NMR shielding effect in *syn*- and *anti*-(*S*)-α-methylbenzylamide **53**.

Claisen Rearrangement. Studies on the Claisen rearrangements were carried out using the substrates derived from the alkylations of bis(phenylsulfonyl)ethane (**5h**) (Scheme 6). Allylic acetates **12** (67% ee) and **13** (95% ee) were treated with LDA or KHMDS and TBDMSOTf in THF at −78 °C. Upon warming to room temperature, the generated silylketene acetals **50** rearranged smoothly to the silylesters, which were then hydrolyzed to γ,δ-unsaturated acids **51** and **52** in 85% and 92%, respectively. For analysis of the stereochemical outcome, these acids were condensed with (*S*)-α-methylbenzylamine to give **53** and **54** both in 89% yields. ^{1}H NMR integration of appropriate signals readily revealed the dr of the amides and thus the ee of acids **51** and **52**. A 67% ee for **51** and a 95% ee for **52**, which were identical with those of the corresponding starting acetate, were indicative of complete transfer of chirality from C−O bonds to C−C bonds via the Claisen rearrangement.

Analysis of the ^{1}H NMR spectra of amide **53** also provided the establishment of the absolute configuration. A recent NMR-based method has suggested a working model in which the shielding of C-3 substituents by the aromatic ring in the chiral amine moiety are different within a diastereomeric pair due to the conformation of α-alkylbenzylamides (Figure 1).[23] As a result of this anisotropic effect, the C-3 methyl group in the *anti*-isomer experiences an enhanced shielding effect and shows up at higher field than in the *syn*-isomer. The C-3 methyl chemical shift of the major amide, *anti*-**53** (R = CH_3), appeared at δ 0.96, whereas the minor amide, *syn*-**53**, had the corresponding signal at δ 1.01. The difference of the chemical shifts was quite large in magnitude ($\Delta\delta = \delta_{syn} - \delta_{anti} = +0.05$ ppm), and the shielding pattern clearly followed the proposed working model, indicating an (*S*)-configuration for the C-3 methyl group as depicted. Analysis of **54** was not possible due to the incomplete resolution of the corresponding signals in the ^{1}H NMR spectrum.

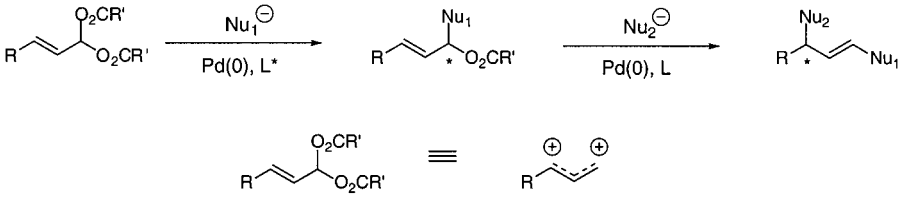
When the TBDPS-substituted **8h** was subjected to the rearrangement and subsequent desilylation, γ-lactone **56** was generated in good yield presumably via hydroxyacid **55** (Scheme 7). Chiral shift studies on **56** using (+)-Eu(hfc)$_3$ in C_6D_6 determined the ee to be 92%. Removal of the two phenylsulfonyl groups with 2% sodium amalgam gave an inseparable mixture of four alkene isomers in a 48:26:19:7 ratio. Subsequent hydrogenation of **57** and **58** afforded β-butyl-γ-butyrolactone (**59**) in 84% yield. As compared to the reported value, lit.[24] $[\alpha]_D = +5.7$ (*c* 1.73, $CHCl_3$), the measured optical rotation of **59**, $[\alpha]_D = +4.6$. (*c* 0.30, $CHCl_3$), confirmed the absolute configuration. Therefore, this correlation study verified the absolute stereochemistry of both the initial asymmetric alkylation product and the stereochemical course of the subsequent Claisen rearrangement.

In contrast to the sulfone-derived compounds, the malonate derived *ent*-**22** took rather a different course of reaction (eq 12).



(23) Hoye, T. R.; Koltun, D. O. *J. Am. Chem. Soc.* **1998**, *120*, 4638.

Scheme 8. Consecutive Allylic Alkylation of *gem*-Dicarboxylate



Subjection to the same conditions did not induce the rearrangement but rather led to a complex mixture of products. When LDA was employed as base in place of KHMDS, the lithium enolate underwent carbonyl addition to give β-keto-δ-lactone **61** in 68% yield as a 5.8:1 diastereomeric mixture.

Discussion

The results of the present investigation demonstrate the feasibility of constructing chiral allylic esters by the asymmetric allylic alkylation (AAA) reaction. The ready availability and considerable stability of the *gem*-dicarboxylates make this strategy appealing in accessing an allylic system in enantiomerically pure form. In particular, the various issues involved in the addition of stabilized nucleophiles to α,β-unsaturated aldehydes is efficiently resolved by the substitution process that produces aldol-like adducts. In our early investigation, a range of *gem*-diesters could be successfully employed as substrates, although highly substituted systems exhibited some degree of limitation.[14] On the other hand, as shown in the present study, the choice of nucleophile seems to be less restrictive. A variety of nucleophiles serve well in the alkylation to provide the desired product in good yields with high ee. Many functional groups in the nucleophiles are compatible with the alkylation process and may prove useful for further elaboration. Pertinent to this result is our work on the use of azlactones and phenylsulfinate nucleophiles that have been reported elsewhere.[25,26]

The lower ee that initially resulted from the alkylations of bis(phenylsulfonyl)ethane (**5h**) appears to be the consequence of its diminished reactivity as compared to that of the malonate-derived nucleophiles. The fact that the enantiodiscriminating event lies in the ionization step excludes the effect of the nucleophile on the ee. However, when the ionization occurs reversibly, this premise may not be valid. For example, when the nucleophiles are slow to add to the π-allylpalladium intermediate, the reversibility of ionization allows a mismatched ionization to be competitive, thereby leading to erosion of ee. In this case, the alkylation requires more efficient capture of the kinetic intermediate. This demand is met by the use of a slow addition procedure which allows the π-allylpalladium complex to experience excess nucleophile. The significantly higher ee's obtained through the slow addition procedure are consistent with the results of the previous study in which the less reactive **5b**, as compared to **5a**, often required a slow addition procedure for high enantioselectivity.[14] These results suggest the kinetic importance of the fast nucleophilic addition as well as good chiral recognition in the ionization. Although the ee was not optimized in the case of **10**, it should be noted that unlike **5a** or **5b** that gave a mixture of regioisomers, the increased steric hindrance of **5h** exhibited complete regioselectivity.

The distinctive value of the alkylation of *gem*-dicarboxylates is more clearly manifested by the synthetic versatility of the resulting allylic esters which permits various subsequent transformations with a high degree of stereospecificity. The palladium(II)-catalyzed allylic isomerization transfers the chirality of a C−O bond to a different location of the molecule. The good regioselectivities obtained from these allylic transposition reactions appear to be reflective of the large steric differences between the two allylic substituents. The *neo*-pentyl-like substituent at one allylic terminus provides a strong steric bias by which the equilibration between the two allylic acetates under palladium catalysis favors the transposed allylic acetates in a high ratio. In the case of **8b**, such steric differences between the two allylic substitutents leads to exclusive formation of only one regioisomer **28** in good yield. All rearrangements took place with high suprafacial stereospecificity,[27] as verified by the analysis of derivatized *O*-methylmandelate esters. The regiopreference of the second allylic alkylation that introduces a nucleophile at the allylic carbon distal to the initially introduced nucleophile moiety is in accord with that observed in the allylic transposition reactions. It is worthwhile to note that simple achiral ligands are sufficient to effect such transformations due to the mechanism of the palladium(0)-catalyzed allylic substitution which leads to overall retention of stereochemistry.[28] The successful results from both carbon and nitrogen nucleophiles invites the possibility of performing this second alkylation with other types of nucleophiles. Through the overall transformation to dialkylated products, *gem*-dicarboxylates become synthons for a double allylic cation (Scheme 8).

The ability of allylic esters to undergo Claisen rearrangements imparts more significance to the enantioselective method providing such compounds. As evident from the comparison of optical purity between the starting acetate and the rearranged product, the [3,3]-sigmatropic process proceeds with complete chirality transfer. The stereochemical course is best accounted for by the six-membered transition state **50** in which the bulky substituent is placed in an equatorial position. Of particular interest is the sequence shown in Scheme 7 where the phenylsulfonyl groups were easily removed after the desired transformation. The formation of **61** suggests that the lithium enolate undergoes carbonyl addition faster than silylation. Thus, the malonate moiety participated in a potentially useful, rare condensation process to give a β-keto-δ-lactone structure.[29]

Conclusions

In summary, a novel approach for the synthesis of chiral allylic esters has been developed using palladium-catalyzed asymmetric allylic alkylation of *gem*-diesters. High enantio- and regioselectivities have been obtained from the alkylation of readily available *gem*-diesters with a variety of nucleophiles by

(24) Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 935.
(25) (a) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635. (b) ref18.
(26) Trost, B. M.; Crawley, M. L.; Lee, C. B. *J. Am. Chem. Soc.* **2000**, *122*, 6120.
(27) Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. *J. Am. Chem. Soc.* **1980**, *102*, 7587.
(28) Reference 19.
(29) (a) Brandaenge, S.; Flodman, L.; Norberg, A. *J. Org. Chem.* **1984**, *49*, 927. (b) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. *Synlett* **1998**, 869.

a simple procedure. The unusual chiral induction process achieves an equivalent of asymmetric carbonyl addition with stabilized nucleophiles. The problems involved in addtion to α,β-unsaturated aldehydes are effectively resolved through the allylic substitution reaction that differentiates between two geminal sp^3-sp^3 carbon−oxygen bonds. The present asymmetric process in conjunction with the efficient transformations of the obtained allylic esters provides a useful approach for asymmetric synthesis.

Experimental Section

Dimethyl (2′*E*,1′*S*)-2-(1′-Acetoxy-4′-*tert*-butyldiphenylsilyloxy-2′-butenyl)-2-(2′,2′,2′-trichloroethoxycarbonylamino)malonate, (*ent*-8f). To a suspension of sodium hydride (95% powder, 54.5 mg, 2.16 mmol) in THF (2.5 mL) was added amidomalonate **5f** (0.926 g, 2.83 mmol). The resulting mixture was stirred at ambient temperature until hydrogen gas evolution ceased. To this solution was added a mixture of π-allylpalladium chloride dimer (**6**) (5.3 mg, 0.014 mmol), ligand *S*,*S*-**7** (30.0 mg, 0.0434 mmol), and geminal diacetate **4** (0.610 g, 1.44 mmol) in THF (2.5 mL) via cannula at 0°. After stirring at 0° for 6 h, the reaction mixture was poured into 10% aqueous $NaHSO_4$ (20 mL) and extracted with ether (15 mL × 3). The combined organic extracts were washed with 10% aqueous $NaHCO_3$ (15 mL) and brine, dried over anhydrous $MgSO_4$, and concentrated. Purification on a silica gel column (hexanes/ethyl acetate 10:1) yielded *ent*-**8f** as a colorless, sticky oil (0.908 g, 92%). The ee was 90% as determined by chiral shift studies using (+)-Eu(hfc)$_3$ in $CDCl_3$: $[\alpha]_D$ +6.4 (*c* 1.30, $CHCl_3$); IR (film) 1752, 1497, 1432, 1254, 1223, 1112, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.69−7.65 (m, 4H), 7.47−7.36 (m, 6H), 6.28 (s,1H), 6.23 (d, *J* = 5.2 Hz, 1H), 6.00−5.84 (m, 2H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.20 (d, *J* = 2.0 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.07 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 165.8, 165.4, 152.7, 135.4, 134.7, 133.3, 133.2, 129.7, 128.2, 127.6, 121.9, 95.2, 74.5, 73.8, 68.5, 63.3, 53.6, 53.5, 26.7, 20.8, 19.2. HRMS calcd for $C_{26}H_{27}NO_9Si^{37}Cl_3$ ($M^+ - t$-C_4H_9): 636.0432. Found: 636.0441. Anal. Calcd for $C_{30}H_{36}Cl_3NO_9Si$: C, 52.29; H, 5.27; N, 2.03. Found: C, 52.43; H, 5.18; N, 1.89.

(2′*E*,1′*R*)-2,2,5-Trimethyl-5-(1′-acetoxy-3′-trimethylsilyl-2′-propenyl)-1,3-dioxane-4,6-dione, (18). Following the procedure for *ent*-**8f**, the reaction of **15** (0.1078 g, 0.468 mmol) with a mixture of **16** (0.150 g, 0.948 mmol) and sodium hydride (60% dispersion, 30 mg, 0.75 mmol) was carried out in the presence of **6** (1.7 mg, 0.0046 mmol) and (*R*,*R*)-**7** (10.0 mg, 0.0145 mmol) in THF (0.5 mL) at room temperature for 5 h. Purification by silica gel chromatography (hexanes/ethyl acetate 10:1) gave of **18** as a colorless oil (0.128 g, 83%), which became crystalline upon storage in a refrigerator. The ee of **18** was 85% as determined by chiral shift studies using (+)-Eu(hfc)$_3$ in $CDCl_3$: mp 79−80 °C (recryst. from pentane); $[\alpha]_D$ −14.9 (*c* 1.63, $CHCl_3$); IR (film) 2957, 1754, 1454, 1381, 1291, 1249, 1217, 1092, 1056, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.14−5.99 (m, 2H), 5.64 (d, *J* = 6.0 Hz, 1H), 2.05 (s, 3H), 1.79 (s, 3H), 1.74 (s, 3H), 1.53 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 168.5, 167.3, 139.3, 137.0, 105.3, 81.0, 52.4, 29.7, 28.6, 21.1, 20.8, −1.5. Anal. Calcd for $C_{15}H_{24}O_6Si$: C, 54.86; H, 7.37. Found: C, 55.01; H, 7.20.

Dimethyl (1′*E*,3′*S*)-2-(3′-hydroxy-but-1′-enyl)-2-methylmalonate, (24). To a solution of $Pd(CH_3CN)_2Cl_2$ (15 mg, 0.058 mmol) in toluene (45 mL) was added a solution of **22** (90% ee, 0.301 g, 1.16 mmol) in toluene (5 mL). The resulting yellow solution was heated under reflux for 12 h, at which point the GC isomeric ratio (t_R (**22**) = 6.82 min and t_R (**23**) = 7.13 min) reached a constant value (8.7:91.3 = **22**:**23**). The reaction mixture was then cooled to room temperature, filtered through a short pad of silica gel, and concentrated to give a mixture of the two isomeric acetates (0.301 g). The isomeric mixture was dissolved in methanol (5 mL) and treated with K_2CO_3 (0.242 g, 1.75 mmol) at room temperature for 0.5 h. The reaction mixture was poured into 10% $NaHSO_4$ (5 mL) and extracted with ether (5 mL × 3). The combined organic layers were washed with 10% $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated. Purification on a silica gel column (hexanes/ethyl acetate 15:1) afforded **24** as a colorless, sticky oil (0.217 g, 86%). The ee of **24** was determined by integration of appropriate signals in the ^1H NMR spectrum of the corresponding *O*-methylmandelate **25**: t_R = 6.51 min (GC); $[\alpha]_D$ −0.11 (*c* 2.00, $CHCl_3$); IR (film) 3430, 1732, 1665, 1454, 1440, 1376, 1258, 1112, 1066, 975, 947 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.05 (dd, *J* = 15.9, 1.2 Hz, 1H), 5.62 (dd, *J* = 15.9, 6.1 Hz, 1H), 4.37−4.28 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 2.28 (br s, 1H), 1.52 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 171.6, 135.8, 127.5, 68.1, 55.1, 52.7 (2), 22.9, 20.0. HRMS Calcd for $C_9H_{13}O_5$ ($M^+ - CH_3$): 201.0762. Found: 201.0753.

Dimethyl (*E*,*S*)-2,6-Bis(methoxycarbonyl)-2-methyl-5-*t*-butyldiphenylsilyloxy-3-heptenedioate, (36). To a test tube charged with sodium hydride (95% powder, 10.0 mg, 0.417 mmol) and THF (0.5 mL) was added dimethyl malonate (65.2 mg, 0.493 mmol). After stirring for 0.5 h, a solution of **6** (0.72 mg, 0.0020 mmol), dppp (2.44 mg, 0.0059 mmol), and **8a** (0.101 g, 0.197 mmol, 91% ee) in THF (1 mL) was added via cannula. The resulting mixture was heated under reflux for 0.5 h, cooled to room temperature, poured into 10% $NaHSO_4$ (30 mL), and extracted with ether (20 mL × 3). The combined organic layers were washed with 10% $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated. Purification on a silica gel column (hexanes/ethyl acetate 10:1) yielded **36** as a colorless, sticky oil (0.109 g, 95%). The ee was 91% as determined by ^1H NMR chiral shift study using (+)-Eu(hfc)$_3$ in $CDCl_3$: $[\alpha]_D$ +16.8 (*c* 1.45, $CHCl_3$); IR (film) 1738 (br), 1434, 1263, 1112, 975 824, 743, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62−7.59 (m, 4H), 7.45−7.34 (m, 6H), 6.05 (d, *J* = 15.9 Hz, 1H), 5.73 (dd, *J* = 15.9, 9.4 Hz, 1H), 3.83 (d, *J* = 8.9 Hz, 1H), 3.75−3.65 (m, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 3.67 (s, 6H), 3.32−3.02 (m, 1H), 1.52 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5 (2), 168.8, 168.5, 135.6 (2), 135.3, 133.2, 131.6, 129.8, 129.0, 127.8, 64.5, 55.5, 52.6 (2), 52.4, 52.2, 45.1, 26.6, 20.2, 19.1. HRMS Calcd for $C_{30}H_{37}O_8Si$ ($M^+ - CH_3O$): 553.2258. Found: 553.2248. Anal. Calcd for $C_{31}H_{40}O_9Si$: C, 63.68; H, 6.90. Found: C, 63.97; H, 6.81.

Methyl (*E*,*S*)-2-methyl-2-methoxycarbonyl-5-phthalimido-3-hexenoate, (46). To a suspension of phthalimide (16.8 mg, 0.114 mmol) and Cs_2CO_3 (27.9 mg, 0.0856 mmol) in DME (0.25 mL) was added a mixture of acetate **22** (14.7 mg, 0.0570 mmol, 90% ee), **6** (0.40 mg, 0.0011 mmol), and dppp (1.4 mg, 0.0034 mmol) in DME (0.25 mL) at room temperature. The resulting mixture was heated under reflux for 1 h, diluted with ethyl acetate (10 mL), and washed with 2 N NaOH (5 mL), water, and brine. The organic layer was then dried over anhydrous $MgSO_4$ and concentrated. Purification by flash chromatography on a silica gel column (hexanes/ethyl acetate 3:1) afforded allylic phthalimide **46** as a colorless, sticky liquid (18.0 mg, 91%). The ee of **46** was determined to be 90% by chiral shift studies using (+)-Eu(hfc)$_3$ in $CDCl_3$ and 89% by chiral HPLC analysis: $[\alpha]_D$ +12.4 (*c* 1.20, $CHCl_3$); IR (film) 1737, 1711, 1613, 1459, 1441, 1385, 1256, 1112, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79−7.74 (m, 2H), 7.70−7.65 (m, 2H), 6.14 (d, *J* = 16.0 Hz, 1H), 6.02 (dd, *J* = 16.0, 7.1 Hz, 1H), 4.98−4.88 (m, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 1.52 (d, *J* = 7.0 Hz, 3H) 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 171.1, 167.6, 133.8, 131.9, 130.3, 130.2, 123.1, 55.2, 52.8, 48.2, 20.0, 18.8. HRMS Calcd for $C_{18}H_{19}NO_6$ (M^+): 345.1212. Found: 345.1211. Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.49; H, 5.45; N, 4.05.

(*E*,*S*)-3-Phenyl-6,6-bis(phenylsulfonyl)-4-heptenoic acid, (52). To a mixture of KHMDS (0.5 M in toluene, 0.53 mL, 0.27 mmol) and THF (2.0 mL) was added dropwise a solution of acetate **13** (95% ee, 0.107 g, 0.220 mmol) in THF (2.0 mL) at −78 °C. After 20 min, TBDMSOTf (0.066 mL, 0.29 mmol) was added to the mixture via a microliter syringe, and the resulting mixture was allowed to warm to room temperature over for 2 h. The mixture was then heated at 65 °C for 10 h, poured into 3 N H_2SO_4 (3 mL), stirred for 2 h, and extracted with ethyl acetate (10 mL × 3). The combined organic phases were dried over anhydrous $MgSO_4$, concentrated, and purified on a silica gel column (hexanes/ethyl acetate/acetic acid 50:50:0.5) to yield acid **52** as a white solid (0.098 g, 92%): mp 163−164 °C (recryst. ether); $[\alpha]_D$ +14.1 (*c* 1.25, $CHCl_3$); IR (film) 3380, 1711, 1651, 1584, 1512, 1334, 1067, 982, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.90 (br

s, 1H), 7.90−7.87 (m, 2H), 7.71−7.65 (m, 3H), 7.58−7.50 (m, 3H), 7.36−7.23 (m, 5H), 7.04−7.00 (m, 2H), 5.90 (d, J = 15.8 Hz, 1H), 5.80 (dd, J = 15.8, 6.8 Hz, 1H), 3.87 (q, J = 7.3 Hz, 1H), 2.71 (d, J = 7.9 Hz, 2H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 142.4, 140.6, 136.7, 136.3, 134.5, 134.3, 131.1, 130.8, 128.9, 128.6, 128.5, 127.4, 127.2, 121.3, 87.3, 44.6, 39.3, 15.2. HRMS Calcd for $C_{19}H_{19}O_4S$ ($M^+ - C_6H_5O_2S$): 343.1004. Found 343.1017.

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Supporting Information Available: Experimental procedures for the preparation of all new compounds as well as characterization data are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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