Efficient syntheses of four stable-isotope labeled (1*R*)-menthyl (1*S*,2*S*)-(+)-2-phenylcyclopropanecarboxylates†

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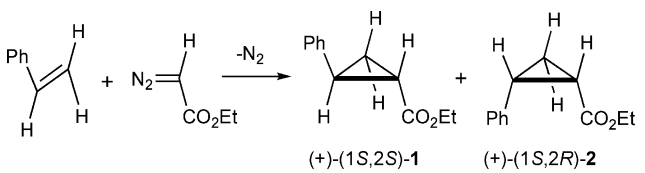
Many carbenoid cyclopropanation reactions promoted by chiral catalysts give product mixtures reflecting impressive diastereo- and enantioselectivities. Few provide a single chiral product efficiently. This limitation has been overcome in cyclopropanations of styrene and isotopically labeled styrenes with α-diazoacetates. Convenient syntheses on a 20 g scale of each of four chiral isotopically labeled (1*R*)-menthyl (1*S*,2*S*)-2-phenylcyclopropanecarboxylates (the 1-*d*-3-^{13}C, 1,(3*S*)-d_2, 1,2,(3*S*)-d_3, and 1,3,3-d_3 isotopomers) of better than 99% ee have been realized.

Introduction

The condensation of styrene with ethyl diazoacetate to give *cis* and *trans* isomers of ethyl 2-phenylcyclopropanecarboxylate has long been known.[1,2] It has received fresh attention since 1966 when it served to exemplify asymmetric catalysis by a soluble transition metal complex.[3] Heating styrene and the diazoacetate in 3 : 1 proportions in the presence of less than 1 mole percent of bis[*N*-(*R*)-α-phenylethylsalicylaldiminato]copper(II) gave in 72% yield an optically active mixture of esters (+)-(1*S*,2*S*)-**1** and (+)-(1*S*,2*R*)-**2** (Scheme 1). Isolation and purification of each diastereomer and of the related carboxylic acids followed by determinations of specific rotations demonstrated that the (+)-(1*S*,2*S*) *trans* ester had been formed with some 6% optical purity.[3,4]



Scheme 1 Stereoselective condensations of styrene with ethyl α-diazoacetate.

The (+)-(1*S*,2*R*) enantiomer was favored in the *cis* ester.[3,5] The same reaction employing the complex derived from (*S*)-(−)-α-methylbenzylamine gave *trans* ester of 6% optical purity favoring the (−)-(1*R*,2*R*) enantiomer.[3]

This demonstration of asymmetric catalysis was developed impressively with related catalysts based on copper(II).[6–8] Catalysts having sterically demanding substituents and diazoacetates having larger alkoxy groups, such as (1*R*)-menthyloxy ((1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methylcyclohexyloxy), were found to give higher degrees of enantioselectivity in this and related cyclopropanation reactions. Systematic searches for optimal copper(II) catalysts and diazoacetates led to an industrially valuable synthesis of (+)-*trans*-chrysanthemic acid: a bulky catalyst derived from D-alanine, 2,5-dimethylhexa-2,4-diene, and ethyl, (1*R*)-menthyl, (1*S*)-menthyl, and racemic menthyl diazoacetates provided *trans*-chrysanthemates with 68, 94, 90, and 90% ee, respectively. No substantial double asymmetric induction effect was in evidence.[7] That the absolute stereochemistry of the menthyl diazoacetate makes little contribution to the asymmetric catalysis has been confirmed repeatedly. (1*R*)-Menthyl diazoacetate and styrene with a catalytic amount of copper(I) chloride in homogeneous solution gives *trans* product of only 0.33% optical purity.[9] Again, a C_2-symmetric catalyst from (1*S*,2*S*)-*N*,*N*′-di(mesitylmethyl)-1,2-diphenyl-1,2-ethanediamine and Cu(OTf)$_2$ together with styrene and alkyl diazoacetate esters derived from 2,4-dimethylpentanol, (1*R*)-menthol, and (1*S*)-menthol gave product mixtures with comparable *trans* : *cis* ratios (89–93% *trans*) and ee values for the major *trans* diastereomer of 86–96%.[10] The chiral catalyst and the bulk, not the chiral nature, of the alkoxy group favor a high degree of asymmetric induction. Additional examples showing similar insensitivities of ee values for products from cyclopropanations of styrene employing (1*R*)- or (1*S*)-menthyl diazoacetates using different transition metal catalysts may be cited.[11,12] From an analytical viewpoint, of course, running a reaction with a (1*R*)- or (1*S*)-menthyl function rather than racemic menthyl diazoacetate is advantageous, for both de and ee values of the cyclopropanation products can be determined easily through capillary GC.

The majority of papers in recent years concerned with the efficacy of various chiral catalysts for condensations of styrene with diazoacetates have reported investigations with small-scale

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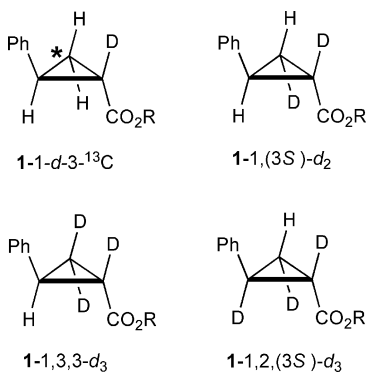
reactions and powerful GC and HPLC methods for determining yields and de and ee values. They have not provided practical guidance for multi-gram preparations of a single stereoisomer of a *trans*-2-phenylcyclopropanecarboxylate.

Commercially available racemic *trans*-2-phenylcyclopropanecarboxylic acid can be resolved completely and then serve as a convenient synthetic intermediate for securing other chiral cyclopropanes of known absolute configuration.[13,14] Utilizing chiral catalysts for asymmetric condensations of isotopically labeled styrenes with menthyl diazoacetates gives optically active labeled *trans*-2-phenylcyclopropanecarboxylates, intermediates providing ready access to a variety of hydrocarbons well suited for informative stereochemical and mechanistic investigations.[14–18] The product mixtures obtained through the cyclopropanations favor *trans* isomers with high stereoselectivities, but going further, to secure one stereochemically distinct product, has proved to be tedious and uneconomical.

Typically, a crude product mixture from a reaction employing racemic menthyl diazoacetate is Kugelrohr distilled (150 °C, 0.1 Torr) to afford the 2-phenylcyclopropanecarboxylates contaminated with fumarate and maleate esters. Hydrolysis with NaOH in aqueous methanol and acidification gives a mixture of acids. Separating *cis* and *trans* acids and achieving full optical resolution of the desired *trans* product can then be achieved through repeated recrystallizations of quinine salts.[13] A *trans* product of essentially 100% ee can be secured, but only with a serious concomitant loss of material sustained during the steps following the asymmetric cyclopropanation reaction.

A projected mechanistic investigation required on the order of 20 g of each of four *trans*-2-phenylcyclopropanecarboxylates embellished stereoselectively with deuterium or with deuterium and carbon-13, structures **1**-1-*d*-3-^{13}C, **1**-1,(3*S*)-d_2, **1**-1,3,3-d_3, and **1**-1,2,(3*S*)-d_3 (Scheme 2). In consideration of the synthetic and material requirements associated with preparing the requisite labeled styrenes, the existing cyclopropanation and full resolution protocols seemed less than satisfactory. The present work describes



Scheme 2 Crystalline *trans*-2-phenylcyclopropanecarboxylates prepared efficiently.

a modified isolation and full resolution approach that afforded the desired isotopically labeled cyclopropanes efficiently.

Strategic plan

A stored sample of a distilled but otherwise unprocessed product mixture from a catalyzed reaction of racemic menthyl diazoacetate with styrene was found to have partially crystallized. Small samples of the crystalline material and the liquid phase were hydrolyzed, and the 2-phenylcyclopropanecarboxylic acids obtained were converted to methyl esters. Analyses by GC on a "chiral" column demonstrated that the *trans* methyl ester from the crystalline material was more fully resolved than the ester from the non-crystalline phase. The menthyl ester which preferentially crystallized proved to be the (1*R*)-menthyl (1*S*,2*S*) *trans* ester. This determination raised the possibility that using (1*R*)-menthyl α-diazoacetate in asymmetrically catalyzed cyclopropanations of styrenes leading primarily to (1*S*,2*S*) products, or (1*S*)-menthyl diazoacetates in reactions favoring (1*R*,2*R*) products, could lead to single stereoisomers through simple recrystallization(s) of product mixtures. The alkoxy function would not contribute importantly to the asymmetric induction, but could facilitate the following purification and resolution requirements.

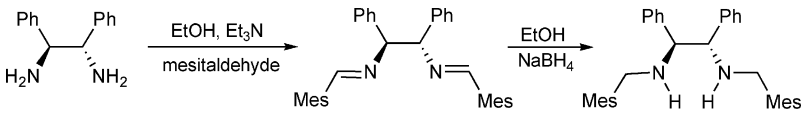
Results

Chiral copper(II) catalyst

Among the many chiral catalysts known to be effective for condensations of styrene with diazoacetates, the dissymmetric catalyst from (1*S*,2*S*)-*N*,*N*′-di(mesitylmethyl)-1,2-diphenyl-1,2-ethanediamine (**5**) and Cu(OTf)$_2$ was selected, for it provides very good diastereomeric and enantiomeric selectivities in the reaction and is relatively easy to synthesize. It was prepared as outlined in the literature,[19,20] through the condensation of commercial (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (**3**) with mesitaldehyde to give **4**, which on reduction with NaBH$_4$ provided **5** (Scheme 3).

This ligand and Cu(OTf)$_2$ in 1,2-dichloroethane catalyzed the reaction of (1*R*)-menthyl α-diazoacetate with styrene under the conditions detailed in the Experimental section to give a crude product mixture containing all four possible stereoisomeric cyclopropanation products. The (1*S*,2*S*) product accounted for some 85% of the mixture (Fig. 1).

α-Diazoacetates. Unlabeled (1*R*)-menthyl α-diazoacetate, used in preliminary experiments, and (1*R*)-menthyl α-deuteriodiazoacetate, needed for making the four isotopically labeled cyclopropane derivatives sought in the present work, were prepared using established methods.[15,21–23] Column chromatography of the crude unlabeled diazoacetate, an orange oil, afforded the material as a bright yellow solid. Three deuterium exchanges gave the (1*R*)-menthyl α-deuteriodiazoacetate as a yellow solid. This ester lacked



Scheme 3 Preparation of chiral ligand for Cu(II)-catalyzed condensations.

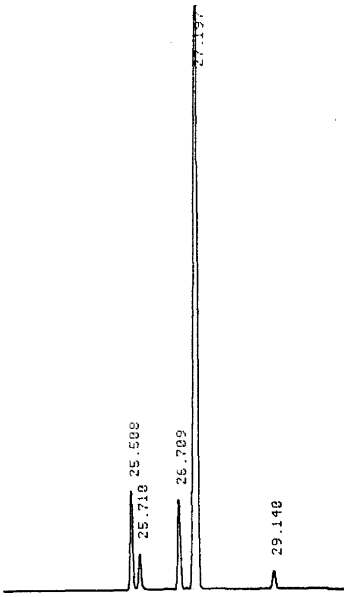
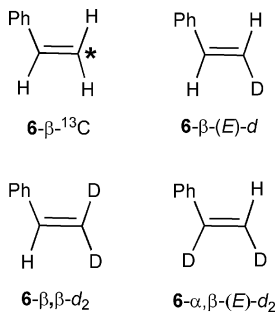


Fig. 1 Capillary GC analysis of a cyclopropanation product mixture from styrene and (1*R*)-menthyl α-deuteriodiazoacetate. From left to right, the (1*R*)-menthyl esters (with a deuterium at C1 of the cyclopropane moiety) are the (1*S*,2*R*) and (1*R*,2*S*) *cis* isomers followed by the (1*R*,2*R*) and (1*S*,2*S*) *trans* isomers, trailed on the right by a side product.

a singlet absorption at δ 4.70 in its ^{1}H NMR spectrum, consistent with essentially complete incorporation of deuterium at the α-carbon atom.

Labeled styrenes. All four isotopically labeled styrenes required to make the desired cyclopropane derivatives, **6**-β-^{13}C, **6**-β-(*E*)-*d*, **6**-β,β-d_2, and **6**-α,β-(*E*)-d_2 (Scheme 4) have been synthesized many times, for a variety of applications.[24] Preparations of **6**-β-(*E*)-*d* and **6**-α,β-(*E*)-d_2 present the most substantial challenges, for both high incorporation of label and high stereochemical integrity of the β-*d* labels are required.



Scheme 4 Stable-isotope labeled styrenes prepared as synthetic intemediates.

The first labeled styrene, **6**-β-^{13}C, was made from ^{13}C-labeled methyl iodide by way of $Ph_3P{=}{*}CH_2$ and a Wittig condensation with benzaldehyde.[25,26]

To make the second styrene, **6**-β-(*E*)-*d*, triphenyltin hydride[27] was prepared and added to phenylacetylene to give (*E*)-β-triphenylstannylstyrene.[28,29] Transmetalation using phenyllithium at −78 °C followed by treatment of the (*E*)-β-lithiostyrene with CH_3OD at −20 °C provided the β-(*E*)-*d* labeled styrene.[30–32] It was carefully purified and freed from residual tin by-products through distillation. (Failure to rid the labeled styrene of all traces of tin compounds led to completely ineffective asymmetric catalysis in the subsequent cyclopropanation reaction.) Integration of the ^{1}H NMR spectrum revealed relative intensities of the vinylic proton adsorptions of 1.00 to 1.00 to 0.01.

The third required styrene, **6**-β,β-d_2,[30,33–36] was secured through a reduction of methyl phenylacetate with $LiAlD_4$ followed by conversion of the intermediate 1,1-d_2-2-phenylethanol to 1,1-d_2-2-phenylethyl bromide with CBr_4 and PPh_3 in ether. Elimination of HBr with NaOEt in ethanol gave **6**-β,β-d_2 in 89% yield.

Finally, **6**-α,β-(*E*)-d_2 was obtained following the reaction sequence used for making **6**-β-(*E*)-*d*, substituting triphenyltin deuteride for triphenyltin hydride in the addition to phenylacetylene. The distilled labeled styrene was 99% pure by GC (73% yield).

Cyclopropanation reactions. More than a dozen small-scale runs led to a preferred reaction protocol. About 1 mol % of the copper(II) catalyst in 1,2-dichloroethane was diluted with a labeled styrene or a solution of the styrene in pentane, and then a twofold excess of (1*R*)-menthyl α-deuteriodiazoacetate was added slowly with the aid of a syringe pump. One stereoisomer was formed as 80–86% of the cyclopropanation product mixture. Simple column chromatography separated the maleate and fumarate esters. The mixture of 2-phenylcyclopropanecarboxylates was recrystallized from absolute ethanol. In some cases the ester which crystallized was still contaminated with a few percent of other diastereomers, and in others a single diastereomer was obtained. The analytical GC traces of Fig. 2 illustrate these two similar but distinct outcomes. When crystalline products from a single recrystallization were of less than 99.9% homogeneity, they were recrystallized a second time to give a pure (1*S*,2*S*) product. The overall yield of a single homogeneous product, which depended on the yield, the diastereselectivity, and the enantioselectivity of the cyclopropanation reaction, and on the losses incurred through

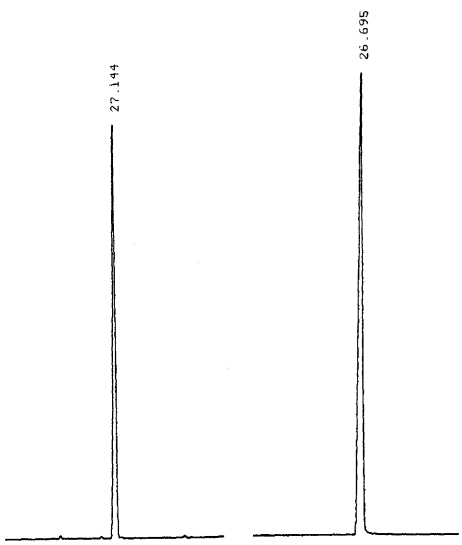


Fig. 2 (1*R*)-Menthyl esters after recrystallization. At left, a nearly homogeneous solid obtained after one recrystallization of crude unlabeled (1*R*)-menthyl esters; at right, the crystalline material obtained through one recrystallization of a cyclopropanation product mixture rich in **1**-1,2,(3*S*)-d_3.

one or at most two recrystallizations required to obtain a single stereoisomer, was as high as 74%.

This yield could be improved through further effort. Additional crystalline (1*S*,2*S*) product of better than 99.9% homogeneity could be obtained by concentrations of mother liquors, collecting second crops, and recrystallizing them (Fig. 3). These procedures could be followed conveniently through GC analyses of both crystalline materials collected and mother liquors. Recrystallization of second crop crystals always gave pure (1*S*,2*S*) products, as judged by GC analyses.

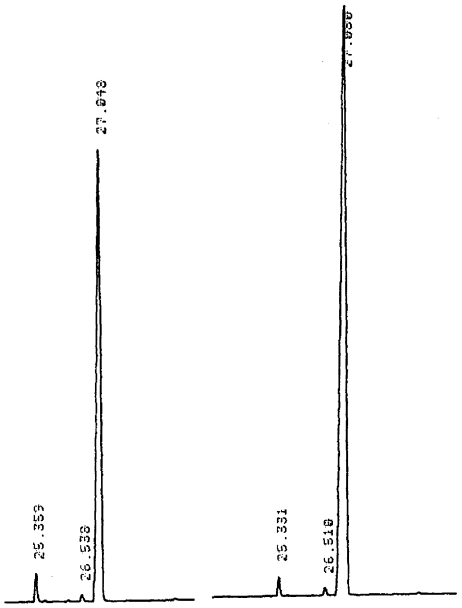


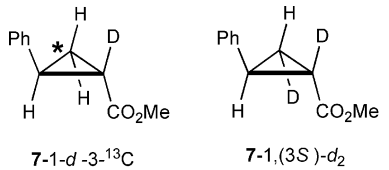
Fig. 3 Analytical GC traces for second crop solids. At left, crystals rich in **1**-1-*d*-3-^{13}C; at right, a second crop of solids from another cyclopropanation reaction providing **1**-1-*d*-3-^{13}C and related isomers.

The cyclopropanation reactions were typically run investing 2.5 g of an isotopically labeled styrene, a scale reflecting caution in view of the value of these starting materials and on the syringes and syringe-pump equipment immediately available. Larger scale asymmetric cyclopropanations following the protocol used in this work should be equally efficient.

Samples of the recrystallized (1*R*)-menthyl esters **1**-1-*d*-3-^{13}C, **1**-1,(3*S*)-d_2, **1**-1,3,3-d_3, and **1**-1,2,(3*S*)-d_3 were converted to the corresponding methyl esters **7**-1-*d*-3-^{13}C, **7**-1,(3*S*)-d_2, **7**-1,3,3-d_3, and **7**-1,2,(3*S*)-d_3 (Scheme 5) to check on ee values and to provide more convenient visual readings of the quality of isotopic labeling through ^{1}H NMR spectroscopy.

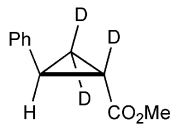
Upfield ^{1}H NMR spectra of methyl esters **7**-1,(3*S*)-d_2 and **7**-1,2,(3*S*)-d_3 are displayed in Fig. 4. Both the very high degree of deuterium incorporation at each relevant position and the specific stereochemical disposition of deuterium at C3 in the esters **7**-1,(3*S*)-d_2 and **7**-1,2,(3*S*)-d_3 are apparent. The resonances for residual protons at C1 and at C3 (*cis* to phenyl) at δ 1.92 and 2.52, respectively, are very minor.

Analyses by capillary GC using a column having a chiral stationary phase, one known to separate the enantiomeric forms of the *trans* methyl esters, failed to detect (1*R*,2*R*) esters. Only a single GC peak was observed (Fig. 5). Thus the ee values of the (1*R*)-menthol used to make the α-deuteriodiazoacetates and

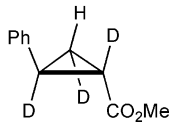


7-1-*d* -3-^{13}C

7-1,(3*S*)-d_2



7-1,3,3-d_3



7-1,2,(3*S*)-d_3

Scheme 5 Methyl *trans*-2-phenylcyclopropanecarboxylates of high stereochemical integrity.

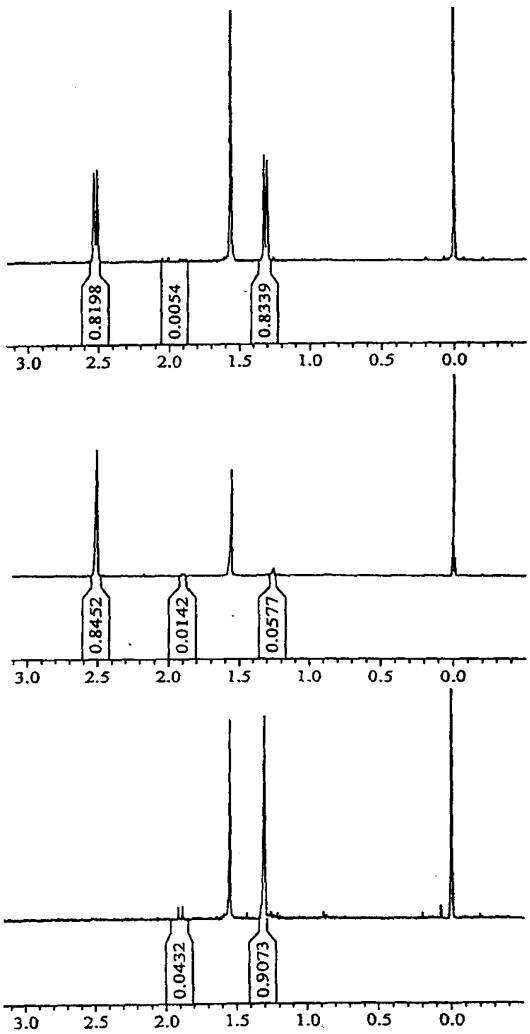


Fig. 4 ^{1}H NMR spectra for **7**-1,(3*S*)-d_2 (top), **7**-1,3,3-d_3 (middle), and **7**-1,2,(3*S*)-d_3 (bottom), from 0 to 3 ppm. All three spectra include a singlet at δ 1.55 from adventitious water.

of the recrystallized labeled (1*R*)-menthyl ester cyclopropanation products were very high, consistent with the given ee of 99% for the commercial (1*R*,2*S*,5*R*)-(−)-menthol employed.

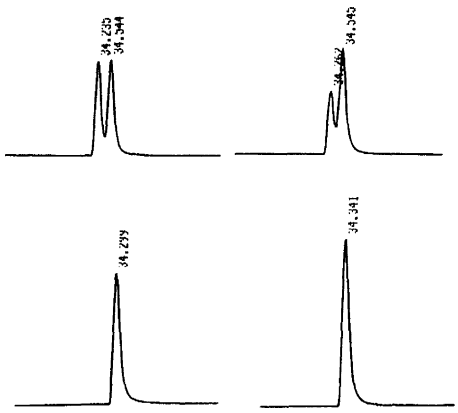


Fig. 5 Analyses of methyl *trans*-2-phenylcyclopropanecarboxylates using a Chiradex G-TA γ-cyclodextrin capillary column. Upper left trace: racemic unlabeled ester; upper right trace: racemic unlabeled ester plus resolved **7**-1-*d*-3-^{13}C; lower traces, left and right: fully resolved esters **7**-1-*d*-3-^{13}C and **7**-1,(3*S*)-d_2 derived from crystalline (1*R*)-menthyl esters.

Conclusions

The condensations of (1*R*)-menthyl diazoacetate with isotopically labeled styrenes in the presence of a chiral Cu(II) catalyst favoring (1*S*,2*S*) *trans*-2-phenylcyclopropanecarboxylates give product mixtures rich in the one diastereomer, and this diastereomer may be secured efficiently in pure crystalline form through one or at most two recrystallizations. The single enantiomer of the diazoester does not contribute importantly to the diastereoselectivity or enantioselectivity of the cyclopropanation reaction, but it greatly facilitates securing a single pure diastereomer from the reaction product mixture. Synthetically useful applications of this new variant of a cyclopropanation promoted by an asymmetric catalyst, pioneered by Noyori and Aratani, have provided multigram quantities of isotopically labeled cyclopropanes with convenience and fair efficiency. The functional groups at C1 and C2 in these structures may be transformed into other useful substituents through further synthetic steps, enhancing the practical utility of this specific exploitation of the improved process. Others are likely to follow.

Experimental

General

Proton and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DPX-300 spectrometer. Capillary GC analyses were obtained using a 25 m × 2 mm 0.33 μm HP Ultra 2 column at 100 °C for 10 min, then at 15 °C min^{-1} to 220 °C, then for 20 min at 220 °C.

(1*S*,2*S*)-(−)-1,2-Di(2,4,6-trimethylbenzylideneamino)-1,2-diphenylethane (4)[19,20]. This was prepared from (1*S*,2*S*)-(−)-1,2-diamino-1,2-diphenylethane (1.5 g, 7.1 mmol) and mesitaldehyde (2.4 g, 2.4 mL, 16.2 mmol), and was recrystallized twice from absolute ethanol. The white product (3.5 g, 93.7%) had mp 145.5–146.0 °C (lit.[20] mp 150.5–151.0 °C); ^{1}H NMR δ 2.24 (s, 6 H); 2.28 (s, 12 H); 4.70 (s, 2 H); 6.77 (s, 4 H); 7.08–7.29 (m, 10 H); 8.59 (s, 2 H) (compare ref. 20).

(1*S*,2*S*)-(−)-1,2-Di(2,4,6-trimethylbenzylamino)-1,2-diphenylethane (5). Reduction of **4** (3.5 g, 7.4 mmol) with $NaBH_4$ (2.0 g, 53.3 mmol)[19,20] and recrystallization from absolute ethanol provided **5** (3.4 g, 96.6%) as a white solid, mp 135–136 °C (lit.[20] mp 131–132 °C): ^{1}H NMR δ 2.07 (s, 12 H); 2.23 (s, 6 H); 3.37–3.56 (m, 4 H); 3.66 (s, 2 H); 6.77 (s, 4 H); 7.18 (s, 10 H) (compare ref. 20).

(1*R*)-Menthyl diazoacetate[15,21,22]. To a 2 L round-bottomed flask were added glycine (50.0 g, 0.67 mol), (1*R*)-(−)-menthol (123 g, 0.79 mol), *p*-toluenesulfonic acid (150 g, 0.79 mol), and benzene (1 L). The solution was heated to reflux until the theoretical amount of water was collected (26 mL, 5 days) in a Dean–Stark trap. The reaction mixture was cooled, filtered, and concentrated at reduced pressure. The viscous oil that remained was dissolved in ether (1.5 L), washed with saturated aqueous $NaHCO_3$ (10 × 300 mL), dried ($MgSO_4$), filtered, and concentrated to yield 158 g of crude glycinate product.

To a 2 L round-bottomed flask were added the crude glycinate (158 g), benzene (1 L), isoamyl nitrite (90.8 g, 0.78 mol), and acetic acid (12.7 g, 0.21 mol). The solution was stirred for 6 h at reflux. At that time a ninhydrin test was negative. The mixture was cooled to rt, washed with ice-cold 10% H_2SO_4 (250 mL), ice-cold water (250 mL), ice-cold saturated $NaHCO_3$ (250 mL), ice-cold water (250 mL), and finally ice-cold brine (250 mL). The organic solution was dried (Na_2SO_4), filtered, and concentrated to yield 155 g of an orange oil. The oil was chromatographed (silica, 9 : 1 hexanes–ethyl acetate) to give 96.1 g (64.4% for the two steps) of (1*R*)-menthyl diazoacetate as a bright yellow solid: ^{1}H NMR, see spectrum in ESI file†, and compare ref. 15.

(1*R*)-Menthyl α-deuteriodiazoacetate[15,23]. To a 500 mL flame-dried Morton flask were added CH_2Cl_2 (100 mL), (1*R*)-menthyl diazoacetate (51.7 g, 230 mmol), D_2O (12 mL, 99.9% D), 10% NaOD in D_2O (12 drops), and tetrabutylammonium bromide (30 mg). The solution was stirred vigorously under argon for 24 h. After that time, 10% NaOD in D_2O (12 drops) was added and the mixture was stirred for another 24 h. The mixture was transferred to a separatory funnel and the aqueous layer was removed. The organic layer was put back into the Morton flask and the exchange procedure was repeated two more times. After the third deuterium exchange, the organic solution was dried ($MgSO_4$), filtered, and concentrated to give 45.0 g (87.0%) of the α-deuteriodiazoester as a yellow solid: ^{1}H NMR, see spectrum in ESI file†, and compare ref. 15.

Styrene-β-^{13}C (6-β-^{13}C)[25,26]. To a 250 mL round-bottomed flask were added potassium *tert*-butoxide (3.9 g, 34.9 mmol), dry ether (100 mL) and $^{13}CH_3PPh_3I$ (13.0 g, 32.2 mmol; prepared[37] from ^{13}C-labeled iodomethane (5.0 g, 35.5 mmol, 99% ^{13}C)). The mixture was heated to reflux for 1 h under argon. At that time benzaldehyde (3.4 g, 32.2 mmol) was added and the solution was heated to reflux for 1 h. The reaction mixture was cooled to rt and water (10 mL) was added with vigorous stirring. The organic solution was removed and the aqueous layer was extracted with pentane (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated by distillation to give 2.1 g (63.4%) of styrene-β-^{13}C (**6**-β-^{13}C) as a 65% solution in pentane. A small sample was purified by preparative GC (1.5-m, 10% SE-30,

85 °C): ^{1}H NMR δ 4.96 and 5.49 (ddd, J = 160.3, 10.9, 0.7 Hz, 1 H), 5.47 and 5.99 (ddd, J = 154.3, 17.6, 0.7 Hz, 1 H), 6.69 (dd, J = 17.6, 10.9 Hz, 1 H), 7.18–7.47 (m, 5 H) (compare ref. 17); ^{13}C NMR δ 113.8; MS m/z (rel. intensity) 105 (100, M$^+$), 104 (74), 74 (55), 78 (81), 51 (45), 39 (19).

Triphenyltin hydride. This was prepared by reducing triphenyltin chloride (70.0 g, 182 mmol) with $LiAlH_4$ (3.4 g, 90.5 mmol) in ether (350 mL).[27] The product (53.5 g, 84.1%), bp 163–166 °C (2 mm) (lit.[27] bp 162–168 °C (0.5 mm)), was obtained as a clear oil.

***trans*-β-Triphenylstannylstyrene[28,29].** To a 500 mL round-bottomed flask were added triphenyltin hydride (53.5 g, 153 mmol), dry toluene (400 mL), BEt_3 (15.3 mL, 15.3 mmol, 1 M solution in hexanes) and phenylacetylene (15.6 g, 153 mmol).[38] The mixture was stirred for 1 h at rt under argon. At that time the reaction mixture was quenched with water (100 mL). The organic solution was removed and the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The organic layers were combined, washed with brine (2 × 80 mL), dried ($MgSO_4$), filtered and concentrated to give a yellow solid. The yellow solid was pulverized and washed with pentane (15 × 100 mL). The off-white solid was dried under vacuum to give 50.9 g (73.4%) of *trans*-β-triphenylstannylstyrene: ^{1}H NMR δ 7.09 (s, 2 H), 7.20–7.74 (m, 20 H) (compare ref. 28); mp 118–122 °C (lit.[29] 119–120 °C).

(*E*)-β-Deuteriostyrene (6-β-(*E*)-*d*)[30–32]. In a 500-mL round-bottomed flask *trans*-β-triphenylstannylstyrene (17.0 g, 37.5 mmol) was suspended in freshly distilled ether (150 mL). The flask was fitted with a 60 mL graduated addition funnel and cooled to −78 °C. Phenyllithium (27.0 mL, 1.8 M in 70 : 30 cyclohexane–ether) was cannulated into the addition funnel and then added to the reaction over 15 min. The solution was stirred for 50 min at −78 °C under argon. After that time the temperature was raised to −20 °C and CH_3OD (2.6 mL, 63.4 mmol, 99.5% D) was added. The reaction was slowly warmed to rt over 45 min. The white suspension was suction-filtered using a Büchner funnel fitted with coarse filter paper. The white precipitate in the Büchner funnel was rinsed with pentane (125 mL). The resulting solution was filtered a second time through a 7 : 1 Celite–$MgSO_4$ (5.5 cm × 8.0 cm) using pressure. The pad of Celite–$MgSO_4$ was rinsed with pentane (125 mL) and the organic solutions were combined and partially concentrated by distillation using a 9 cm Vigreux column. The resultant solution was stored at 0 °C for 24 h. The white precipitate that formed was removed by filtering the solution through a plug of cotton. The clear filtrate was distilled under reduced pressure using a 3 cm column packed with glass beads. Fraction 1 was mostly solvent (bp 65 °C (760–200 mm)); fraction 2 (bp 65 °C (200–135 mm)) gave 2.7 g (69.1%) of (*E*)-β-deuteriostyrene (**6**-β-(*E*)-*d*) as an 86% solution in pentane. A small sample of **6**-β-(*E*)-*d* was purified by preparative GC (1.5 m, 10% SE-30, 75 °C): ^{1}H-NMR δ 5.20–5.28 (dd, J = 11.3, 3.8 Hz, 1.1% of 1 H), 5.74 (d, J = 17.6 Hz, 1 H), 6.72 (d, J = 17.6 Hz, 1 H), 7.20–7.45 (m, 5 H) (compare ref. 30–32); MS m/z (rel. intensity) 105 (100, M$^+$), 104 (52), 79 (61), 78 (55), 51 (48), 39 (19).

1,1-d_2-2-Phenylethanol. This was prepared by reducing methyl phenylacetate (15.0 g, 100 mmol) with $LiAlD_4$ (2.7 g, 65.0 mmol, 98% D) in THF (40 mL).[33,34] There was obtained 10.6 g (85.5%) of 1,1-d_2-2-phenylethanol as a clear oil: bp 65–67 °C (2 mm) (lit.[39] bp 99.5 °C (10 mm) for the unlabeled compound); ^{1}H NMR δ 1.54–1.63 (m, 1 H), 2.84 (s, 2 H), 7.16–7.38 (m, 5 H) (compare ref. 33 and 34); MS m/z (rel. intensity) 124 (31, M$^+$), 92 (80), 91 (100), 65 (30), 51 (11), 39 (17).

β,β-Dideuteriostyrene (6-β,β-d_2)[30,33,35]. To a 500 mL round-bottomed flask were added 1,1-d_2-2-phenylethanol (10.6 g, 85.5 mmol), CBr_4 (31.1 g, 93.8 mmol) and Et_2O (250 mL).[36] When all of the CBr_4 had dissolved, PPh_3 (24.6 g, 93.8 mmol) was added and the solution was stirred under nitrogen at rt for 2 h. At that time the solution was filtered, the filtrate was concentrated, and the concentrate was passed through a plug of silica (hexanes). Concentration of the organic solution followed by vacuum distillation gave 15.0 g (93.8%) of 1,1-d_2-2-phenylethyl bromide as a clear oil (bp 52 °C (2.0 mm), lit.[40] bp 93–94 (13 mm) for the unlabeled compound); ^{1}H NMR δ 3.15 (s, 2 H), 7.15–7.37 (m, 5 H); MS m/z (rel. intensity) 188:186 (21:21, M$^+$), 107 (74), 91 (100), 51 (15), 39 (9).

Small pieces of sodium metal (5.0 g, 217 mmol) were added slowly with vigorous stirring to a 250 mL round-bottomed flask containing 75 mL of absolute ethanol at 0 °C. When all of the sodium was consumed the solution was warmed to rt and 1,1-d_2-2-phenylethyl bromide (15.8 g, 84.5 mmol) was added. The mixture was stirred for 3 h at rt under nitrogen. After that time the solution was diluted with water (100 mL) and the aqueous layer was extracted with pentane (3 × 100 mL). The organic layers were combined, washed with water (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated by distillation to give 8.0 g (89.3%) of β,β-dideuteriostyrene (**6**-β,β-d_2) as a 28% solution in pentane. A small sample was purified by preparative GC (1.5 m, 10% SE-30, 52 °C): ^{1}H NMR δ 6.71 (br s, 1 H), 7.21–7.45 (m, 5 H) (compare refs. 30, 33 and 35); MS m/z (rel. intensity) 106 (100, M$^+$), 105 (39), 80 (22), 79 (32), 51 (29), 39 (7).

Triphenyltin deuteride. This was prepared from triphenyltin chloride (45.0 g, 117 mmol) and $LiAlD_4$ (1.9 g, 45.2 mmol), and was obtained as a clear oil of bp 158–162 °C (1 mm) in 89% yield.

(*E*)-α-Deuterio-β-triphenylstannylstyrene. This was made from triphenyltin deuteride (36.4 g, 104 mmol) and phenylacetylene (10.6 g, 104 mmol) following the procedure used to make *trans*-β-triphenylstannylstyrene. There was obtained 29.5 g (62.5%) of (*E*)-α-deuterio-β-triphenylstannylstyrene, mp 119–122 °C: ^{1}H NMR δ 7.08 (t, J = 2.5 Hz, 1 H), 7.20–7.74 (m, 20 H) (compare ref. 28).

(*E*)-α,β-Dideuteriostyrene (6-α,β-(*E*)-d_2). In a 500 mL round-bottomed flask (*E*)-α-deuterio-β-triphenylstannylstyrene (17.0 g, 37.5 mmol) was suspended in freshly distilled ether (150 mL). The procedure used to make **6**-β-(*E*)-*d* was followed to provide 2.89 g (72.6%) of *cis*-α,β-d_2-styrene (**6**-α,β-(*E*)-d_2). A small sample was purified by preparative GC (1.5-m, 10% SE-30, 68 °C): ^{1}H-NMR δ 5.20–5.26 (m, 1.5% of 1 H), 5.72 (t, J = 2.5 Hz, 1 H), 7.20–7.45 (m, 5 H) (compare ref. 15*c* and 30); MS m/z (rel. intensity) 106 (100, M$^+$), 105 (59), 80 (47), 79 (67), 51 (44), 39 (19).

General procedure for (1*R*)-menthyl (1*S*,2*S*)-(+)-2-phenylcyclopropanecarboxylates[10]. To a 100 mL three-necked flask were added $Cu(OTf)_2$ (86.5 mg, 0.24 mmol), (1*S*,2*S*)-(−)-1,2-di(2,4,6-trimethylbenzylamino)-1,2-diphenylethane (**5**, 350.3 mg,

0.72 mmol) and 1,2-dichloroethane (12.5 mL, distilled from CaH_2). The blue solution was stirred for 10 min at rt under argon. After that time phenylhydrazine (2.8 mL, 0.29 mmol) was added and the solution turned orange. After stirring for 10 min, styrene (2.5 g, 24.1 mmol) was added neat or as a pentane solution. (1*R*)-Menthyl α-diazoacetate or (1*R*)-menthyl α-deuteriodiazoacetate (10.8 g, 48.2 mmol) dissolved in 1,2-dichloroethane (18.8 mL) was then added dropwise to the stirred solution using a syringe pump, set at an addition rate of 0.67 mL h^{-1}. Stirring was continued for 30 min after the addition of the diazoacetate was complete. Analysis of the crude reaction mixture by analytical gas chromatography (Ultra 2) showed one dominant (85%) and three other cyclopropane diastereomers (Fig. 1). The mixture was partially concentrated and then purified by column chromatography (12 cm × 5 cm, silica gel, 40 : 1, pentane–ether) to remove the fumarate and maleate esters. The fractions containing the cyclopropane diastereomers were combined and concentrated under reduced pressure. The yellow solid that remained was recrystallized from 12.0 mL of absolute ethanol. After 2 days at room temperature, the crystals were collected by suction filtration and washed with cold absolute ethanol (50 mL). The white solid was analyzed by capillary GC. If required, it was recrystallized a second time from absolute ethanol. The homogeneous product was dried under vacuum and shown to be a single cyclopropane diastereomer 99.9% pure by analytical GC (Ultra 2) (Fig. 2).

General procedure for the formation of methyl esters. To a 5 mL flask were added 25% NaOH (1 mL), methanol (1.5 mL), and (1*R*)-menthyl (1*S*,2*S*)-(+)-2-phenylcyclopropanecarboxylate (300 mg, 1.0 mmol), and the mixture was heated to reflux for 3 h. After that time the solution was cooled to rt, diluted with H_2O (2 mL) and extracted with ether (5 × 5 mL). The aqueous layer was acidified with concentrated HCl (pH 3) and extracted with ether (5 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Treatment of the concentrate with diazomethane[41] gave the desired methyl ester.

(1*R*)-Menthyl (1*S*,2*S*)-(+)-2-phenylcyclopropanecarboxylate and methyl (1*S*,2*S*)-(+)-2-phenylcyclopropanecarboxylate. Two reactions using a total of 5.0 g (48 mmol) of styrene and (1*R*)-menthyl diazoacetate were run, and product mixtures were purified as described above to give 10.7 g (74%) of (1*R*)-menthyl (1*S*,2*S*)-(+)-2-phenylcyclopropanecarboxylate as fluffy white needles, mp 81–83 °C. A portion was hydrolyzed and treated with diazomethane to yield methyl (1*S*,2*S*)-(+)-2-phenylcyclopropanecarboxylate. Analysis by GC using a column with a chiral stationary phase (G-TA γ-cyclodextrin (Astec, octakis(2,6-di-*O*-pentyl-3-trifluoroacetyl)-γ-cyclodextrin), 10 m × 0.25 mm × 0.125 μm film thickness, 70 °C for 27 min, inc. 8 °C min^{-1} to 110 °C, 110 °C for 5 min). No signal for the (1*R*,2*R*) enantiomer was apparent, and the sample was judged to be better than 99% ee (Fig. 5). A small sample of the methyl ester was purified by preparative GC (1 m, 17% Carbowax, 198 °C): ^{1}H NMR δ 1.28–1.38 (m, 1 H), 1.56–1.66 (m, 1 H), 1.87–1.96 (m, 1 H), 2.48–2.59 (m, 1 H), 3.72 (s, 3 H), 7.05–7.35 (m, 5 H) (compare ref. 9 and 42); ^{13}C NMR δ 17.0, 23.9, 26.3, 51.9, 126.2, 126.5, 128.5, 140.0, 173.9 (compare ref. 42); MS *m*/*z* (rel. intensity) 176 (44, M^+), 145 (20), 144 (42), 117 (100), 116 (48), 115 (98), 91 (38), 77 (10), 63 (12), 39 (17) (compare ref. 9 and 42). Another sample purified by preparative GC had $[\alpha]_D$ +390 (*c* 0.26, $CHCl_3$) (compare ref. 13, $[\alpha]_D$ +335 (*c* 3.79, EtOH) for the (1*S*,2*S*) isomer).

(1*R*)-Menthyl (1*S*,2*S*)-(+)-1-*d*-3-^{13}C-2-phenylcyclopropanecarboxylate (1-1-*d*-3-^{13}C) and methyl (1*S*,2*S*)-(+)-1-*d*-3-^{13}C-2-phenylcyclopropanecarboxylate (7-1-*d*-3-^{13}C). Styrene-β-^{13}C (**6**-β-^{13}C, 10.08 g, 96.0 mmol) was reacted (in four installments) with (1*R*)-menthyl α-deuteriodiazoacetate and purified as described above to give 19.30 g (67%) of (1*R*)-menthyl) (1*S*,2*S*)-(+)-1-*d*-3-^{13}C-2-phenylcyclopropanecarboxylate (**1**-1-*d*-3-^{13}C). A portion was hydrolyzed and treated with diazomethane to yield methyl (1*S*,2*S*)-(+)-1-*d*-3-^{13}C-2-phenylcyclopropanecarboxylate (**7**-1-*d*-3-^{13}C). Analysis by GC using the G-TA γ-cyclodextrin column showed it to be better than 99% ee. A small sample was purified by preparative GC: ^{1}H NMR δ 1.04 (dt, J = 163.8, 5.8, Hz, 0.5 H), 1.32 (ddd, J = 166.6, 9.3, 4.7 Hz, 0.5 H), 1.59 (dt, J = 163.8, 5.8 Hz, 0.5 H), 1.87 (ddd, J = 166.6, 9.3, 4.7 Hz, 0.5 H), 2.48–2.59 (m, 1 H), 3.72 (s, 3 H), 7.05–7.35 (m, 5 H).

(1*R*)-Menthyl (1*S*,2*S*)-(+)-1,(3*R*)-d_2-2-phenylcyclopropanecarboxylate (1-1,(3*S*)-d_2) and methyl (1*S*,2*S*)-(+)-1,(3*R*)-d_2-2-phenylcyclopropanecarboxylate (7-1,(3*S*)-d_2). (*E*)-β-Deuteriostyrene (**6**-β-(*E*)-*d*, 10.26 g, 97.7 mmol) was reacted (in four installments) with (1*R*)-menthyl α-deuteriodiazoacetate and purified as described above to give 20.75 g (71%) of (1*R*)-menthyl (1*S*,2*S*)-(+)-1,(3*S*)-d_2-2-phenylcyclopropanecarboxylate (**1**-1,(3*S*)-d_2). A portion of this ester was hydrolyzed and treated with diazomethane to provide methyl (1*S*,2*S*)−(+)-1,(3*R*)-d_2-2-phenylcyclopropanecarboxylate (**7**-1,(3*S*)-d_2). Analysis by GC using a G-TA γ-cyclodextrin column showed the methyl ester was better than 99% ee. A small sample was purified by preparative GC: ^{1}H NMR δ 1.31 (d, J = 6.4 Hz, 1 H), 2.52 (d, J = 6.4 Hz, 1 H), 3.72 (s, 3 H), 7.05–7.35 (m, 5 H).

(1*R*)-Menthyl (1*S*,2*S*)-(+)-1,3,3-d_3-2-phenylcyclopropanecarboxylate (1-1,3,3-d_3) and methyl (1*S*,2*S*)-(+)-1,3,3-d_3-2-phenylcyclopropanecarboxylate (7-1,3,3-d_3). β,β-d_2-Styrene (**6**-β,β-d_2, 11.0 g, 103.8 mmol) was reacted (in four installments) with (1*R*)-menthyl α-deuteriodiazoacetate and purified as described above to give 19.99 g (64%) of (1*R*)-menthyl (1*S*,2*S*)-(+)-1,3,3-d_3-2-phenylcyclopropanecarboxylate (**1**-1,3,3-d_3). A portion of this ester was hydrolyzed and treated with diazomethane to yield methyl (1*S*,2*S*)-(+)-1,3,3-d_3-2-phenylcyclopropanecarboxylate. A small sample of the methyl ester was purified by preparative GC: ^{1}H NMR δ 2.52 (s, 1 H), 3.72 (s, 3 H), 7.05–7.35 (m, 5 H).

(1*R*)-Menthyl (1*S*,2*S*)-(+)-1,2,(3*S*)-d_3-2-phenylcyclopropanecarboxylate (1-1,2,(3*S*)-d_3) and methyl (1*S*,2*S*)-(+)-1,2,(3*S*)-d_3-2-phenylcyclopropanecarboxylate (7-1,2,(3*S*)-d_3). *cis*-α,β-Dideuteriostyrene (**6**-α,β-(*E*)-d_2, 10.27 g, 96.9 mmol) was reacted (in four installments) with (1*R*)-menthyl α-deuteriodiazoacetate and purified as described above to give 17.82 g (61%) of (1*R*)-menthyl (1*S*,2*S*)-(+)-1,2,(3*S*)-d_3-2-phenylcyclopropanecarboxylate (**1**-1,2,(3*S*)-d_3). More than 2.2 g of additional **1**-1,2,(3*S*)-d_3) of 99.9% homogeneity was obtained through collecting and recrystallizing a second crop of crystals. A portion of this ester was hydrolyzed and treated with diazomethane to make a small sample of methyl (1*S*,2*S*)-(+)-1,2,(3*S*)-d_3-2-phenylcyclopropanecarboxylate (**7**-1,2,(3*S*)-d_3), which was purified by preparative GC: ^{1}H NMR δ 1.31 (s, 1 H), 3.72 (s, 3 H), 7.05–7.35 (m, 5 H) (compare ref. 15).

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