Intramolecular Regioselective Insertion into Unactivated Prochiral Carbon−Hydrogen Bonds with Diazoacetates of Primary Alcohols Catalyzed by Chiral Dirhodium(II) Carboxamidates. Highly Enantioselective Total Synthesis of Natural Lignan Lactones

Jeffrey W. Bode, Michael P. Doyle,* Marina N. Protopopova, and Qi-Lin Zhou

Department of Chemistry, Trinity University, San Antonio, Texas 78212

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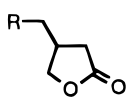
Intramolecular insertion into unactivated prochiral C−H bonds of 3-aryl-1-propyl diazoacetates catalyzed by dirhodium(II) tetrakis[methyl 1-(3-phenyl propanoyl)imidazolidin-2-one-4(*R* or *S*)-carboxylate], Rh_2(4*R*-MPPIM)$_4$ or Rh_2(4*S*-MPPIM)$_4$, occurs in 91−96% ee and with virtually complete regiocontrol for the formation of β-benzyl-γ-butyrolactones. This methodology has been applied to the total synthesis of dibenzylbutyrolactone lignans (−)- and (+)-enterolactone, (−)- and (+)-hinokinin, and (+)-arctigenin from substituted cinnamic acids in 19−27% overall yields. Aryltetralin lignan (+)-isodeoxypodophyllotoxin was prepared from the reactant 3,4-(methylenedioxy)cinnamic acid in 36% yield overall, and the lactone precursor to (+)-isolauricerisinol was formed in 96.5% ee and 23% yield overall. Applications of the chiral Rh_2(MPPIM)$_4$ catalysts to fully aliphatic systems resulting in the formation of β-substituted-γ-butyrolactones with high regiocontrol and with 93−96% ee have demonstrated the generality of this methodology. A model that provides accurate predictions of β-substituted-γ-butyrolactone absolute configurations in these asymmetric metal carbene transformations is described.

The synthesis of enantiomerically pure β-substituted γ-butyrolactones of general structure **1** represents a significant challenge for which there have been few



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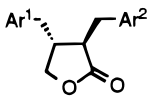

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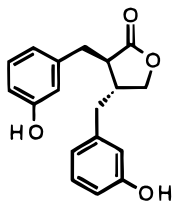
solutions.[1,2] These structures are indigenous to a broad spectrum of natural products of which lignan lactones **2** are prominent.[3] Alkylation or carbonyl addition reactions of **1** afford a convenient stereocontrolled entry into virtually all of the structurally diverse class of lignans,[1,3,4] many of which, including (−)-enterolactone (**3**) and (+)-arctigenin (**4**), have noteworthy biological and medicinal properties.[3,5−7]

Numerous strategies have been developed to achieve stereocontrolled syntheses of naturally occurring lignans,[1,3,4] including diastereoselective conjugate addition to chiral 2(5*H*)-furanones and dihydrofurans,[8] select cycloaddition reactions,[9] and the employment of chiral oxazolines.[10] However, diastereoselective alkylation of **1** remains the most general and versatile of known methodologies. Enantioselective syntheses of **1** have been achieved through resolution of alkylated succinic acid esters,[11] from dichloroketene addition to optically active alkenyl sulfoxides,[12] from *l*-malic acid via chiral *N*-alkyl α,β-unsaturated lactams,[8b] from functionalized ketene thioacetals prepared by chiral oxazolidinone-



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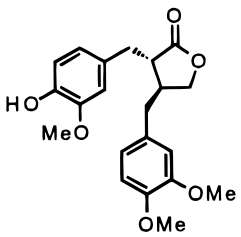

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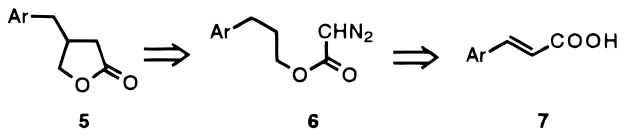
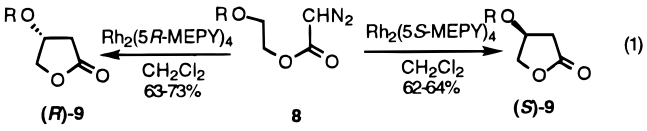
Scheme 1



directed alkylation,[13] by conjugate addition to butenolides that possess directive chiral accessories,[14] from *l*-glutamic acid,[15] and from chiral dihydrofuryl ketones, enantioselective deprotonation, or cycloaddition−lipase-mediated resolution.[16] Of methods that do not require access to chiral auxiliaries, reactants from the chiral pool, or resolution, asymmetric catalytic hydrogenation of itaconic acid esters, followed by selective hydride reduction, has been successfully employed (≥94% ee) in several lignan total syntheses.[17] In addition, we have recently given a preliminary account of an alternative methodology in which a chiral dirhodium(II) carboxamidate catalyst controls highly enantioselective carbene insertion into an unactivated C−H bond of 3-aryl-1-propyl diazoacetates,[18] which themselves are conveniently accessible from cinnamic acids (Scheme 1). We now report that this catalytic methodology, which requires regiocontrol as well as enantiocontrol, is general for the synthesis of **1** in high enantiomeric purity, and we describe its use for the total synthesis of representative natural lignans.

Results and Discussion

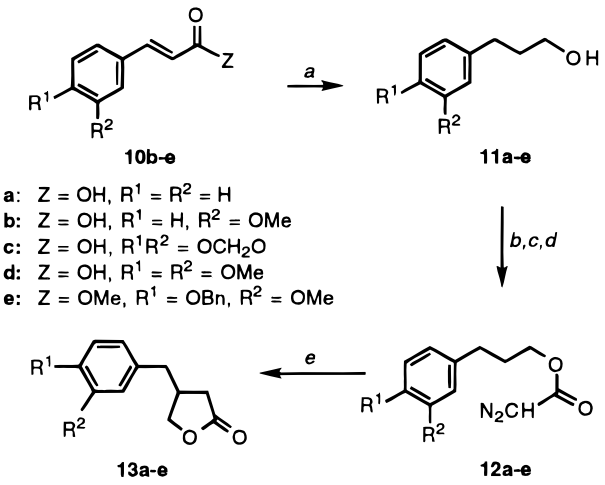
In developing an effective general methodology for the synthesis of **5** in high enantiomeric excess three obstacles must be overcome. The first is enantioselectivity, and here dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*R* or *S*)-carboxylate], Rh_2(5*R*-MEPY)$_4$ or Rh_2(5*S*-MEPY)$_4$, has proven to be moderately successful with enantiomeric excesses up to 91% for C−H insertion reactions of 2-alkoxyethyl diazoacetates (eq 1).[19] Use of Rh_2(5*S*-



(1)

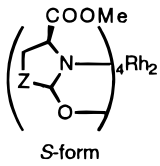
MEPY)$_4$ yielded (*S*)-**9**, and Rh_2(5*R*-MEPY)$_4$ provided (*R*)-**9**. The second challenge to selectivity is regiocontrol and, whereas there is generally a high preference for the formation of five-membered ring products in dirhodium(II)-catalyzed C−H insertion reactions,[20] both the oxygen-activated and benzylic C−H bonds in **6** are potential sites for insertion.[21] The third obstacle is chemoselectivity since the aryl group of **6**, which is activated by alkoxy substituents, is capable of aromatic cycloaddition.[22]

Scheme 2[a]



[a]Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 3 h; (b) diketene, NEt_3, THF, rt; (c) MsN_3, NEt_3, THF, rt; (d) LiOH, THF, H_2O, 5-7 h; (e) Rh_2L_4 (1-2 mol %), CH_2Cl_2, reflux

The synthesis of diazoacetates **12a**−**e** was accomplished from the corresponding cinnamic acids by initial reduction with $LiAlH_4$ followed by a one-pot diketene condensation−diazo transfer−deacylation procedure in 50−60% overall yield, following purification (Scheme 2). Diazo decomposition of 3-phenyl-1-propyl diazoacetate (**12a**) was evaluated first to determine the extent of selectivity for C−H insertion and the stereochemistry for product formation. Chiral dirhodium(II) catalysts representing four carboxamidate ligand classes (**14a**−**d**) were employed, each possessing a dirhodium(II) core



14a: Z = CH_2: Rh_2(5*S*-MEPY)$_4$
14b: Z = O: Rh_2(4*S*-MEOX)$_4$
14c: Z = $NCOCH_3$: Rh_2(4*S*-MACIM)$_4$
14d: Z = $NCOCH_2CH_2Ph$: Rh_2(4*S*-MPPIM)$_4$

encased with four bridging amide ligands in a (2,2-*cis*) geometry,[23−25] and the results obtained with their use are listed in Table 1. Only **13a** and the *β*-lactone product

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Table 1. Diazo Decomposition of 3-Phenylprop-1-yl Diazoacetate Catalyzed by Chiral Dirhodium(II) Carboxamidates[a]

catalyst[b]	yield, % **13a** + **15**[c]	**13a:15**[d]	isolated yield **13a**, %[e]	% ee **13a**[f]
Rh_2(4*S*-MEOX)$_4$	76	93:7	42	51(*S*)
Rh_2(5*R*-MEPY)$_4$	49	94:6	23	72(*R*)
Rh_2(4*S*-MPPIM)$_4$	59	93:7	50	87(*S*)
Rh_2(4*R*-MPPIM)$_4$	76	93:7	56	91(*R*)

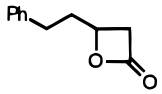
[a] Reactions were performed in refluxing CH_2Cl_2 with 2.0 mol % of catalyst. [b] Rh_2(4*S*-MACIM)$_4$ gave **13a:15** = 90:10 with **13a** in 82% ee. [c] Weight yield after bulb-to-bulb distillation of reaction mixture. [d] Determined by ^{1}H NMR integration of relevant absorptions; **15** undergoes thermal decomposition in GC analyses. [e] Yield following radial chromatography; >99% pure **13a**. [f] GC analysis on a 30-m Chiraldex A-DA column, ±2%. Configurational assignment in parentheses.

Table 2. Diazo Decomposition of 3-(*m*-Methoxyphenyl)prop-1-yl Diazoacetate Catalyzed by Dirhodium(II) Carboxamidates[a]

catalyst	yield %[b]	purity **13b**, %[c]	% ee **13b**[d]
Rh_2(4*S*-MEOX)$_4$	56	93	45(*S*)
Rh_2(5*R*-MEPY)$_4$	66	93	68(*R*)
Rh_2(4*S*-MACIM)$_4$	25[e]	80	84(*S*)
Rh_2(4*S*-MPPIM)$_4$	66	98	91(*S*)
Rh_2(4*R*-MPPIM)$_4$	63	98	93(*R*)

[a] Reactions were performed in refluxing CH_2Cl_2 with 2.0 mol % of catalyst. [b] Weight yield after chromatographic purification of reaction mixture. [c] Determined by GC and/or ^{1}H NMR integration of relevant absorptions. Includes water insertion and C−H insertion byproducts. [d] GC analysis on a 30-m Chiraldex A-DA column. Configurational assignment in parenthesis. [e] Major byproducts were those from carbene dimer formation (14%) and water insertion (20%).

15 from insertion into the oxygen-activated C−H position



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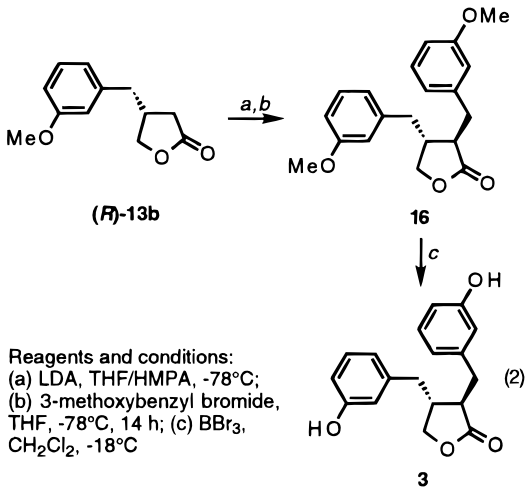
were obtained; insertion into the benzylic position was not observed nor was aromatic cycloaddition. There is a strong preference for the formation of **13a**, and changing the catalyst does not measurably influence regioselectivity. However, enantioselectivity is markedly increased from 51% ee with the use of Rh_2(4*S*-MEOX)$_4$ to 89 ± 2% ee with Rh_2(4*S*-MPPIM)$_4$. Although 2.0 mol % of catalyst was employed for the reactions listed in Table 1, use of only 1.0 mol % Rh_2(4*S*-MPPIM)$_4$ gave nearly identical results (51% versus 59% yield). In these insertion reactions the catalysts with the *S*-configuration formed the γ-lactone product having the *S*-configuration, and Rh_2(4*R*-MPPIM)$_4$ produced (*R*)-**13a**.

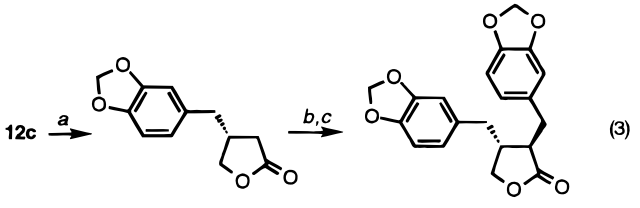
(−)- and (+)-Enterolactone. Diazoacetate **12b** was similarly evaluated for enantioselective/regioselective/chemoselective C−H insertion, and these results are reported in Table 2. Isolated yields and % ee values were variable, dependent on the catalyst, but use of Rh_2(4*S*-MPPIM)$_4$ and Rh_2(4*R*-MPPIM)$_4$ gave **13b** cleanly without noticeable intramolecular insertion or cycloaddition byproducts (<2%) and with minimal competition from carbene dimer formation and water insertion. With the Rh_2(4*S*-MACIM)$_4$ catalyst the product from aromatic cycloaddition to the 1,2-position was detected, but only in minor amounts, and overall yields were low. As is evident from the data in Tables 1 and 2, % ee increases through the catalyst series Rh_2(MEOX)$_4$ < Rh_2(MEPY)$_4$ < Rh_2(MACIM)$_4$ < Rh_2(MPPIM)$_4$, and Rh_2(MPPIM)$_4$ is the catalyst of choice for these insertion reactions. Alkylation of (*R*)-**13b** and removal of the *O*-methyl groups (eq 2) provided the naturally occurring (−)-enterolactone



(**3**) in 70% overall yield. Similar treatment of (*S*)-**13b** gave (+)-enterolactone in 46% yield from diazoacetate **12b**.

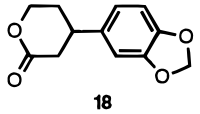
Neither dirhodium(II) caprolactamate, Rh_2(cap)$_4$, nor Rh_2(OAc)$_4$ were effective in converting **12b** to **13b**; under the same conditions as those used with catalysts **14a**−**d**, only products from carbene dimer formation and water insertion were produced. Thus the advantages of chiral dirhodium(II) carboxamidates as catalysts extends beyond stereocontrol by decreasing the relative rate for bimolecular reactions. Indeed, the same restrictions placed by **14a**−**d** on molecular motion in intramolecular cyclization inhibit intermolecular processes that provide unwanted byproducts.

(−)- and (+)-Hinokinin (**17**) were prepared from **12c** in 43−47% overall yield by a two-step procedure involving initial C−H insertion catalyzed by Rh_2(MPPIM)$_4$ followed by alkylation (eq 3). Conversion of **12c** to **13c** occurred



Reagents and conditions: (a) Rh_2(4*R*-MPPIM)$_4$ (2.0 mol %), CH_2Cl_2, reflux; (b) LDA, THF/HMPA, -90°C; (c) (1,3-benzo-dioxol-5-yl)methyl bromide, THF, -90°C → -78°C, 16 h.

with 95 ± 2% ee, and the C−H insertion reactions catalyzed by Rh_2(MPPIM)$_4$ were remarkably free of byproducts. With Rh_2(5*R*-MEPY)$_4$ catalysis, however, a minor product, amounting to 7% of the isolated product yield, was separated and identified as δ-lactone **18**.



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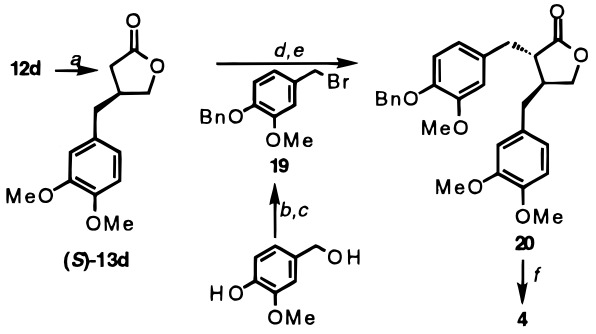
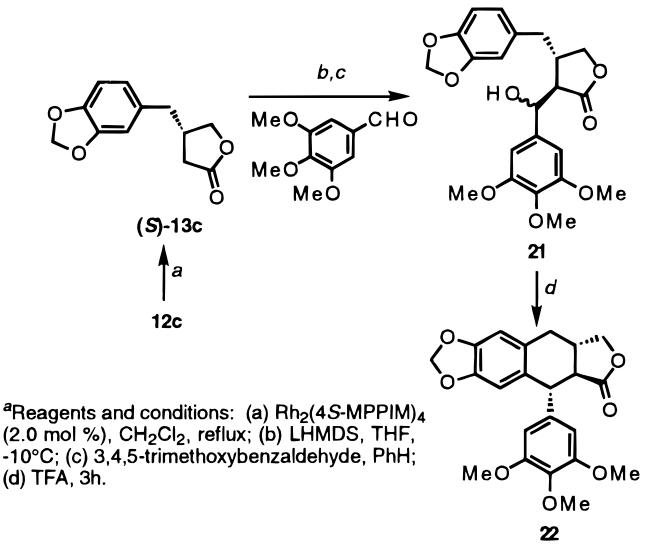
(−)-Arctigenin. Naturally occurring (+)-arctigenin

Scheme 3[a]



[a]Reagents and conditions: (a) $Rh_2(4S\text{-MPPIM})_4$ (1.3 mol %), CH_2Cl_2, reflux; (b) K_2CO_3, 18-crown-6, BnBr, $PhCH_3$; (c) PBr_3, Et_2O, 3 h, rt; (d) LDA, THF/HMPA, -78°C; (e) **19**, THF, -78°C, 12 h; (f) H_2, 5% Pd/C, EtOAc/HOAc.

Scheme 4[a]

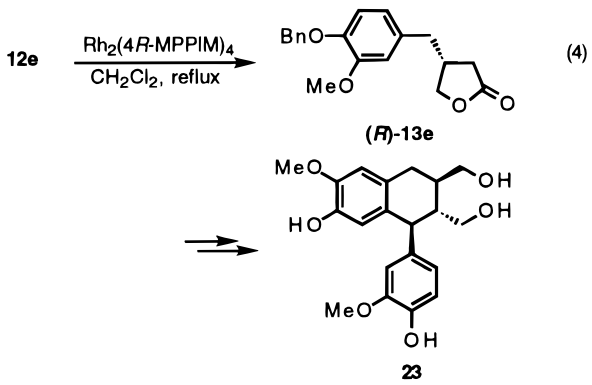


[a]Reagents and conditions: (a) $Rh_2(4S\text{-MPPIM})_4$ (2.0 mol %), CH_2Cl_2, reflux; (b) LHMDS, THF, -10°C; (c) 3,4,5-trimethoxybenzaldehyde, PhH; (d) TFA, 3h.

(**4**)[26] was synthesized from 3,4-dimethoxycinnamic acid in a convergent nine-step, seven-pot sequence (Scheme 3). The key lactone intermediate **13d** was prepared with 94% ee in 62% isolated yield with the use of $Rh_2(4S\text{-MPPIM})_4$. Alkylation of **13d** with 4-(benzyloxy)-3-methoxybenzyl bromide (**19**), prepared in two steps from 4-hydroxy-3-methoxybenzyl alcohol, afforded the *O*-benzyl protected disubstituted γ-lactone **20**. Hydrogenolysis to remove the benzyl group provided (+)-arctigenin (**4**) in 94% optical purity and in 19% overall yield from commercial reactants.

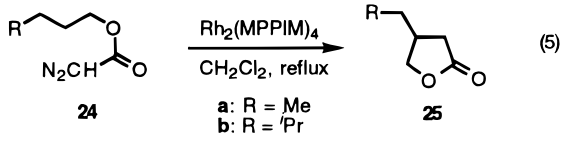
(+)-Isodeoxypodophyllotoxin. The preparation of (+)-isodeoxypodophyllotoxin (**22**)[27] from chiral monosubstituted γ-lactone (*S*)-**13c** illustrates the operational versatility of this methodology for the synthesis of aryltetralin lignan lactones (Scheme 4). Condensation of (*S*)-**13c** with 3,4,5-trimethoxybenzaldehyde in the presence of excess LiHMDS produced a mixture of epimeric alcohols (**21**) in quantitative yield. Upon treatment with trifluoroacetic acid, **21** underwent intramolecular Friedel−Crafts ring closure to form **22** as a single diastereoisomer. A single crystallization afforded (+)-isodeoxypodophyllotoxin with >99% enantiomeric purity in 68% yield. Overall, **22** was prepared in 36% yield from the reactant cinnamic acid, and this synthesis could be performed without chromatographic purification of any synthetic intermediate except **12c**.

(+)-Isolauricerisinol. To further illustrate the versatility and tolerance of this methodology for the synthesis of lignan lactones, the benzyloxy-protected lactone (*R*)-**13e** was prepared from the corresponding diazoacetate **12e** (eq 4) in 59% isolated yield with 96.5% ee. The



diazoacetate **12e** was prepared from 4-hydroxy-3-methoxycinnamic acid by protection of the phenol and acid functional groups and then conversion to **12e** according to Scheme 2. The formation of (*R*)-**13e** in good yield and with exceptional enantiocontrol further demonstrates that the bulky aryl substituent does not interfere with the excellent enantiodirecting selectivities that characterize the $Rh_2(MPPIM)_4$ catalysts. The utility of (*R*)-**13e** for the preparation of lignans is exemplified in its previously reported uses for the syntheses of (+)-isolauricerisinol (**23**)[28] and several other naturally occurring lignans.[29]

General Methodology for Highly Enantioselective Synthesis of β-Substituted γ-Lactones from Primary Alcohols. To determine if use of the $Rh_2(MPPIM)_4$ catalysts could be extended to aliphatic systems without pendant aryl groups, diazoacetates **24a,b** were prepared and subjected to diazo decomposition (eq 5). The diazoacetates were prepared from commercial alcohols according to Scheme 2 in 60 and 54% yields,

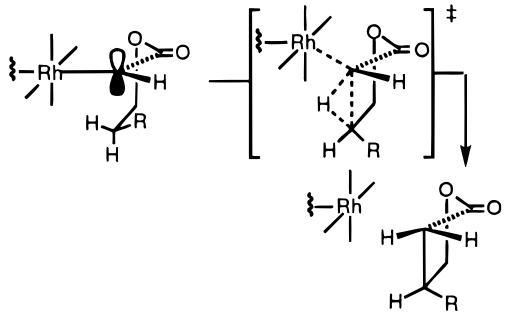


respectively. Treatment of **24a** with 1.0 mol % $Rh_2(4S\text{-MPPIM})_4$ afforded (*S*)-**25a** in 52% isolated yield (96% ee) with only 4% of the β-lactone as byproduct. The β-isobutyl-γ-lactone (*S*)-**25b** was prepared in 60% yield (95% ee) using $Rh_2(4S\text{-MPPIM})_4$ together with 5% of the corresponding β-lactone byproduct. In neither case were δ-lactone byproducts observed. In addition, β-methoxy-γ-butyrolactone (*S*)-**9**[19] was produced from **8** (R = Me) in nearly quantitative yield (93% ee) with catalysis by $Rh_2(4S\text{-MPPIM})_4$.

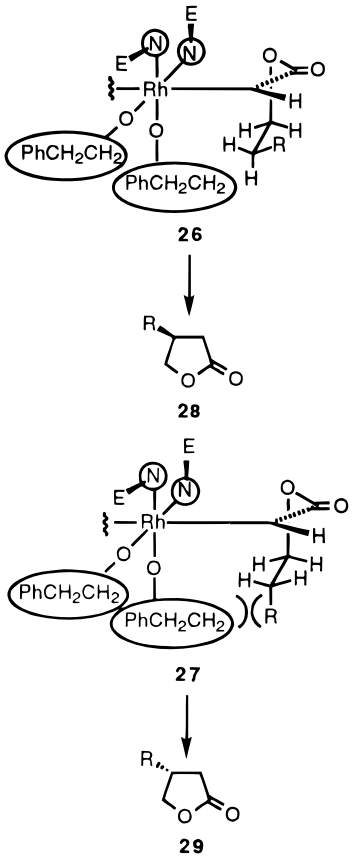
According to our view of the mechanism for C−H insertion (see Scheme 5), reaction is initiated by overlap of the metal carbene's carbon p-orbital with the σ-orbital of the reacting C−H bond. The formation of C−C and C−H bonds is concurrent with dissociation of the dirhod-

(26) Suzuki, H.; Lee, K. H.; Haruna, M.; Iida, T.; Ito, K.; Huang, H.-C. *Phytochemistry* **1982**, *21*, 1824.
(27) (a) Zavala, F.; Guenard, D.; Robin, J.-P.; Brown, E. *J. Med. Chem.* **1980**, *23*, 546. (b) Kuhn, M.; von Wartburg, A. *Helv. Chim. Acta* **1967**, *50*, 1546.
(28) Brown, E.; Daugan, A. *Heterocycles* **1987**, *26*, 1169.
(29) Brown, E.; Daugan, A. *J. Nat. Prod.* **1991**, *54*, 110.

Scheme 5



Scheme 6



ium(II) species (Scheme 5).[30] As hydrogen migrates to the carbene center, the substituents on the carbon where insertion is taking place rotate toward the resting positions that conform to their placement in the product. The absolute configurations of the C−H insertion products formed in the Rh_2(MPPIM)$_4$-catalyzed reactions are predictable from the model in Scheme 6 which depicts the *S*-MPPIM-ligated catalyst with the bound carbene in a resting position that minimizes interactions with the ligand's ester (E) attachments.[31] The two rotomers, **26** and **27**, are positioned to undergo C−H insertion resulting in enantiomeric lactones **28** and **29**. The high preference for **28** with Rh_2(4*S*-MPPIM)$_4$, and this catalyst's enhancement of enantiocontrol over Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$, is consistent with steric repulsion between anti R and the *N*-3-phenylpropanoyl attachment of the imidazolidinone ligands in **27**. Thus the syn conformer **26** provides the lower energy transition state for C−H insertion, even when R is as small as ethyl (**25a**) or methoxy [(*S*)-**9**]. Catalytic diazo decomposition of diazoacetates derived from primary alcohols occurs with highly enantioselective C−H insertion using Rh_2(MPPIM)$_4$ catalysts, and this is indeed a general and effective methodology for the synthesis of β-substituted-γ-butyrolactones in high enantiomeric purity.

Experimental Section

General. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from internal Me_4Si (TMS). Mass spectra were obtained using electron ionization on a quadrapole instrument. Infrared spectra were recorded as a thin film on sodium chloride plates or as solutions as indicated, and absorptions are reported in wavenumbers (cm^{-1}). Melting points are uncorrected. Elemental analyses were performed at Texas Analytical Laboratories, Inc. Anhydrous THF was distilled from Na/benzophenone; CH_2Cl_2 was dried over calcium hydride for 24 h and then distilled prior to use in catalytic reactions. Diketene was distilled under reduced pressure. Methanesulfonyl azide was prepared from methanesulfonyl chloride and sodium azide, but was not distilled.[32] The preparation of the enantiomeric forms of Rh_2(MEPY)$_4$,[23] Rh_2(MEOX)$_4$,[24] and Rh_2(MPPIM)$_4$[25] and the synthesis of Rh_2(4*S*-MACIM)$_4$[25] have been previously reported. 2-Methoxyethyl diazoacetate and its lactone products (**9**) have been described.[24]

3-Phenylprop-1-yl Diazoacetate (12a). To a continuously stirred solution of 3-phenyl-1-propanol (5.02 g, 36.8 mmol), triethylamine (0.018 g, 0.17 mmol), and a catalytic amount (<2 mg) of DMAP in 30 mL of anhydrous THF at room temperature was added diketene (3.11 g, 37.0 mmol) in 25 mL of THF. The resulting solution was stirred overnight at room temperature after which the light yellow reaction solution was combined with 50 mL of ether and 30 mL of brine. The aqueous layer was washed twice with 50 mL portions of ether, and the combined ether solution was washed twice with 50 mL portions of brine and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford 7.61 g of a light yellow oil identified as 3-phenyl-1-propyl acetoacetate (34.5 mmol, 94% yield); ^{1}H NMR δ 7.32−7.24 (comp, 2 H), 7.23−7.16 (comp, 3 H), 4.17 (t, J = 6.5 Hz, 2 H), 3.45 (s, 2 H), 2.69 (t, J = 7.3 Hz, 2 H), 2.28 (s, 3 H), 2.04−1.93 (comp, 2 H), enol form at 5.02 (s, 1 H), 1.96 (s, 3 H).

To a continuously stirred solution of the acetoacetate (7.61 g, 34.6 mmol) and triethylamine (4.35 g, 43.0 mmol) in 35 mL of CH_3CN was added methanesulfonyl azide (5.20 g, 43.0 mol) in 20 mL of the same solvent dropwise over 30 min. The resulting solution was stirred overnight at room temperature whereupon $LiOH\cdot H_2O$ (4.4 g, 100 mol) dissolved in 30 mL of H_2O was added, and stirring was continued for 7 h. The resulting solution was diluted with brine and then washed with two 50 mL portions of 3:1 ether:EtOAc. The combined organic solution was washed with 40 mL of brine and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The resulting orange liquid was purified by column chromatography on silica (10:1 hexanes:EtOAc) to afford 5.32 g of **12a** (26.1 mmol, 79% yield) as a yellow oil; ^{1}H NMR δ 7.31−7.20 (comp, 2 H), 7.19−7.14 (comp, 3 H), 4.73 (br s, 1 H), 4.18 (t, J = 6.5 Hz, 2 H), 2.68 (t, J = 7.6 Hz, 2 H), 2.02−1.92 (comp, 2 H); IR ν 2114 (C=N$_2$), 1705 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.75; H, 5.94; N, 13.70.

4-(Phenylmethyl)-2(3*H*)-dihydrofuranone, (*R*)-13a. A solution of 3-phenylprop-1-yl diazoacetate (0.099 g, 0.48 mmol) in 5 mL of rigorously dried CH_2Cl_2 was added via syringe pump at a rate of 0.40 mL/h to a refluxing solution of 8.8 mg of Rh_2(4*R*-MPPIM)$_4$(CH_3CN)$_2$ (0.009 mol, 2 mol %) dissolved in 7 mL of dry CH_2Cl_2. The initial purple color of the reaction

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(31) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837.

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solution turned to olive green by the end of the substrate addition. Refluxing was continued for an additional 3 h, the reaction solution was cooled to room temperature, and the catalyst was removed by filtration on silica gel (CH_2Cl_2). The resulting light brown oil was distilled, bp 95−100 °C (0.25 torr), to produce 64.8 mg (0.368 mmol, 76% yield) of a mixture of (*R*)-**13a** and **15**. This mixture was further purified by radial chromatography on silica (hexane:EtOAc = 8:1) to afford 49.8 mg (0.282 mmol, 56% yield) of (*R*)-**13a**; $[\alpha]^{29}_D = +6.7°$ (*c* 0.574, EtOH); lit.[13] $[\alpha]^{29}_D = +6.6°$ (*c* 0.92, EtOH) for enantiomerically pure (*R*)-**13a**; ^{1}H NMR δ 7.35−7.21 (m, 3 H), 7.15 (d, J = 8.1 Hz, 2 H), 4.33 (dd, J = 9.0, 6.8 Hz, 1 H), 4.04 (dd, J = 9.0, 5.9 Hz, 1 H), 2.91−2.76 (comp, 3 H), 2.60 (dd, J = 17.4, 7.8 Hz, 1 H), 2.29 (dd, J = 17.4, 6.8 Hz, 1 H). ^{13}H NMR δ 177.1, 138.2, 128.7, 126.4, 70.4, 42.9, 36.4, 31.3, 29.7. Enantiomeric excesses were determined by GC analysis on a 30-m Chiraldex A-DA column operated at 148 °C: 126 min ((*S*)-**13a**) 129 min ((*R*)-**13a**).

A minor product identified as the β-lactone **15** was isolated in <5% chemical yield from the diazo decomposition reactions performed with Rh_2(4*S*-MEOX)$_4$; ^{1}H NMR δ 7.35−7.16 (comp, 5 H), 4.53−4.47 (m, 1 H), 3.48 (dd, 1 H, J = 5.8, 16.4 Hz), 3.03 (dd, 1 H, J = 4.3, 16.4 Hz), 2.89−2.68 (comp, 2 H), 2.17−2.02 (comp, 2 H); ^{13}C NMR δ 176.8, 138.2, 128.8, 128.6, 126.8, 72.6, 38.9, 37.1, 34.2.

3-(3-Methoxyphenyl)prop-1-yl Diazoacetate (12b). A mixture of 3-methoxycinnamic acid (**10b**, 9.65 g, 54.2 mmol) and 5% Pd/C (0.2 g) in methanol/EtOAc (80 mL, 1:1) was shaken in a Parr hydrogenation apparatus under 2 atm of H_2 for 4 h. After filtering through a Celite plug, the solvent was evaporated under reduced pressure to provide 9.6 g of 3-(3-methoxyphenyl)propanoic acid (53 mmol, 98% yield), which was used without further purification.

To a rapidly stirred suspension of $LiAlH_4$ (2.1 g, 55 mmol, 1.5 equiv) in 80 mL of refluxing THF was added over 50 min a solution of 3-(3-methoxyphenyl) propanoic acid (6.7 g, 38 mmol) in 20 mL of THF. After addition was complete, refluxing was continued for an additional 40 min, and then the mixture was cooled to room temperature, poured into ice−water which was then poured into a solution of 5% HCl over ice and extracted once with ethyl ether (100 mL) and twice with 70-mL portions of EtOAc. The combined organic extract was washed with a saturated solution of $NaHCO_3$ (50 mL) and brine (100 mL) and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure to provide 6.3 g of 3-(3-methoxyphenyl)propan-1-ol (**11b**, 38 mmol, 100% yield).

To a solution of **11b** (6.2 g, 37 mmol) in 50 mL of anhydrous THF was added 80 mg of NaOAc and then, dropwise at room temperature, a solution of diketene (4.8 g, 55 mmol, 1.5 equiv) in 10 mL of THF. The reaction solution was continually stirred for 10 h at room temperature and then refluxed for 1.5 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexanes:EtOAc, 3:1 → 2:1) to provide 8.8 g (35 mmol, 95% yield) of a colorless oil identified as 3-(3-methoxyphenyl)prop-1-yl acetoacetate: ^{1}H NMR δ 7.21 (td, J = 7.4, 1.2 Hz, 1 H), 6.77 (d, J = 7.4 Hz, 2 H), 6.74 (s, 1 H), 4.16 (t, J = 6.5 Hz, 2 H), 3.80 (s, 3 H), 3.46 (s, 2 H), 2.67 (t, J = 7.0 Hz, 2 H), 2.28 (s, 3 H), 2.03−1.93 (m, 2 H) with enol form at 5.02 (s, 1 H), 2.17 (s, 3 H); ^{13}C NMR δ 167.1, 159.7, 142.6, 129.5, 120.8, 114.2, 111.3, 64.7, 55.2, 50.1, 32.1, 30.2, 30.0.

A solution of methanesulfonyl azide (6.6 g, 54 mmol, 1.5 equiv) in 70 mL of anhydrous acetonitrile was added dropwise over 20 min to a solution of 3-(3-methoxyphenyl)prop-1-yl acetoacetate (8.8 g, 35 mmol) and triethylamine (5.5 g, 54 mmol, 1.5 equiv) in 60 mL of anhydrous acetonitrile. The resulting yellow solution was stirred for 12 h at room temperature, after which the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes:EtOAc, 2:1 → 1:1) to give 10.3 g of 85% pure diazoacetoacetate (32 mmol, 90% yield): ^{1}H NMR δ 7.18 (t, J = 7.8 Hz, 1 H), 6.76−6.68 (comp, 3 H), 4.24 (t, J = 6.5 Hz, 2 H), 3.77 (s, 3 H), 2.68−2.63 (comp, 2 H), 2.44 (s, 3 H), 2.05−1.95 (comp, 2 H).

The diazoacetoacetate (10.3 g, 32 mmol) was dissolved in 40 mL of acetonitrile and added in one portion to a solution of $LiOH\cdot H_2O$ (4.9 g, 117 mmol, 3.7 equiv) in 100 mL of H_2O. The reaction mixture was stirred for 1.5 h at room temperature whereupon the resulting dark brown solution was extracted with EtOAc (3 × 75 mL), and the organic extract was then washed with brine (75 mL), saturated aqueous citric acid (75 mL), and brine (2 × 75 mL). After drying over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexanes:EtOAc, 3:1) to afford 5.50 g of a yellow oil identified as **12b** (23.5 mmol, 74% yield): ^{1}H NMR δ 7.19 (dd, J = 8.7, 7.6 Hz, 1 H), 6.77−6.70 (m, 3 H), 4.74 (br s, 1 H), 4.16 (t, J = 6.6 Hz, 2 H), 3.77 (s, 3 H), 2.65 (t, J = 7.8 Hz, 2 H), 1.95 (tt, J = 7.8, 6.6 Hz, 2 H); ^{13}C NMR δ 159.5, 142.5, 129.2, 120.6, 114.0, 111.1, 63.9, 54.9, 45.9, 31.9, 30.1; IR ν 2113 (C=N$_2$), 1695 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.46; H, 5.99; N, 12.02.

4-[(3-Methoxyphenyl)methyl]dihydro-2(3*H*)-furanone (13b). A solution of diazoacetate **12b** (0.65 g, 2.8 mmol) in 20 mL of rigorously dried CH_2Cl_2 was added via syringe pump at a rate of 2.0 mL/h to a refluxing solution of Rh_2(MPPIM)$_4$ (78 mg, 56 mmol, 2.0 mol %) in 40 mL of dry CH_2Cl_2 under N_2. The initial blue/purple color of the reaction solution turned to olive green by the end of the substrate addition. After addition was complete, the reaction solution was cooled to room temperature, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes:EtOAc, 4:1), and 0.379 g of pure **13b** (1.84 mmol, 66% yield) was isolated as a colorless oil: ^{1}H NMR δ 7.26 (s, 1 H), 7.24 (t, J = 8.0 Hz, 1 H), 6.82−6.69 (comp, 2 H), 4.36 (dd, J = 9.2, 6.9 Hz, 1 H), 4.06 (dd, J = 9.2, 6.1 Hz, 1 H), 3.80 (s, 3 H), 2.94−2.81 (m, 1 H), 2.80−2.72 (comp, 2 H), 2.65 (dd, J = 17.5, 8.0 Hz, 1 H), 2.33 (dd, J = 17.5, 6.9 Hz, 1 H); ^{13}C NMR δ 176.8, 159.9, 139.8, 129.8, 120.9, 114.6, 111.8, 72.6, 55.2, 38.9, 37.0, 34.2. Spectral data were consistent with that previously reported.[8b] Enantiomeric excesses were determined from GC analysis on a 30-m Chiraldex A-DA column (Table 1) operated at 150 °C for 10 min then programmed at 0.2 °C/min to 180 °C: 181.8 min ((*S*)-**13b**), 184.5 min ((*R*)-**13b**). The major byproducts from these catalytic reactions were carbene dimers and the water insertion product. Carbene dimer formation was controlled by adjusting the rate of addition of the diazo compound but varied with the catalyst employed. Water insertion, especially in small scale reactions, was minimized by using rigorously dried solvents, reagents, and equipment. The solvent CH_2Cl_2 was dried over CaH_2 for 12−20 h prior to use. Diazoacetate **12b** and the septa employed were dried in a desiccator over KOH and Drierite for at least 15 h prior to use. All glassware, stirring bars, and needles were oven dried. The weighing of reagents and preparation of solutions took place in a glove bag under N_2.

(3*S*,4*S*)-3,4-Bis[(3-methoxyphenyl)methyl]dihydro-2(3*H*)-furanone (16). To lactone **13b** (0.300 g, 1.28 mmol, 95% ee) in 10 mL of anhydrous THF at −78 °C was added 1.5 mL of 1.5 M LDA (in cyclohexane, 2.31 mmol, 1.8 equiv) and 0.7 g of HMPA (3.8 mmol, 3 equiv). After 0.5 h a solution of 3-methoxybenzyl bromide (0.48 g, 2.3 mmol, 1.8 equiv) in 1.0 mL of THF was added in one portion to the reaction solution, and the resulting mixture was stirred for an additional 14 h at −78 °C and then warmed to −40 °C (2 h) and to +10 °C (1 h). The excess base was quenched at 0 °C with 20 mL of saturated aqueous NH_4Cl, and the resulting solution was extracted with ethyl ether (1 × 10 mL) and ethyl acetate (2 × 10 mL). The combined organic layer was washed three times with 40-mL portions of water and once with 20 mL of brine and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes:EtOAc, 4:1) to afford 0.36 g of (*S*)-**16** (1.02 mmol, 80% yield) as a light brown viscous oil: ^{1}H NMR δ 7.20 (t, J = 7.9 Hz, 1 H), 7.16 (t, J = 7.9 Hz, 1 H), 6.80−6.71 (comp, 4 H), 6.60−6.50 (comp, 2 H), 4.09 (dd, J = 9.0, 6.9 Hz, 1 H), 3.84 (dd, J = 9.0, 7.3 Hz, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.05 (dd, J = 14.0, 5.0 Hz, 1 H), 2.89 (dd, J = 14.0, 7.0 Hz, 1 H), 2.76−2.53 (comp, 4 H);

^{13}C NMR δ 178.5 (159.8$_3$, 159.7$_9$), 139.5, 139.3, 129.7, 129.6, 121.6, 120.9, 114.8, 114.5, 112.3, 111.8, 71.2, 55.1, 55.1, 46.3, 41.2, 38.5, 35.1. Spectral data were consistent with those previously reported.[33] Enantiomeric excesses were determined by optical rotation relative to that for optically pure (*R*)-**16** prepared from L-malic acid, $[\alpha]^{23}_D = -42.3$ (*c* 0.98, $CHCl_3$);[33] for example, observed $[\alpha]^{23}_D = +40.9$ (*c* 1.20, $CHCl_3$) for product from C−H insertion catalyzed by Rh_2(4*S*-MPPIM)$_4$ (96 + 3% ee). A similar procedure was employed to obtain (*R*)-**16** (64% yield): $[\alpha]^{23}_{D\ =} -39.2$ (*c* 0.78, $CHCl_3$) which specifies 93% ee.

(3*S*,4*S*)-3,4-Bis[(3-hydroxyphenyl)methyl]dihydro-2-(3*H*)-furanone, (*S*)-3. To a rapidly stirred solution of lactone (*S*)-**16** (0.31 g, 0.95 mmol) in 20 mL of anhydrous CH_2Cl_2 at 0 °C was added BBr_3 (3.81 mL of 1.0 M solution in CH_2Cl_2, 4 equiv) dropwise during 15 min. Stirring was continued at 0 °C for 1 h and then at −18 °C for 12 h, after which the reaction solution was quenched with water (10 mL) and then extracted twice with 10-mL portions of CH_2Cl_2. The combined organic solution was washed with brine and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was passed through a plug of silica gel to provide 0.278 g (0.933 mmol, 98% yield) of (+)-enterolactone, (*S*)-**3**, as a slightly brown gum, $[\alpha]^{23}_D = +38.8$ (*c* 0.51, $CHCl_3$). Further purification by flash chromatography yielded 0.25 g (88% yield) of (*S*)-**3**: $[\alpha]^{23}_D = +38.3$ (*c* 0.24, $CHCl_3$); lit. $[\alpha]_D$ for (*R*)-**3** = −43 (*c* 0.29, $CHCl_3$),[14] −40.5 (*c* 0.553, $CHCl_3$),[33] −38.4 (*c* 0.5, $CHCl_3$).[34] Natural (−)-enterolactone, (*R*)-**3**, was prepared by a similar procedure (68% yield): $[\alpha]^{23}_D = -38.4$ (*c* 0.25, $CHCl_3$). Rotational values were highly dependent on concentration and temperatures.[14]

3-(1,3-Benzodioxol-5-yl)prop-1-yl Diazoacetate (12c). To a stirred suspension of $LiAlH_4$ (1.34 g, 35.3 mmol) in 50 mL of anhydrous THF heated at 40−45 °C was added 3,4-(methylenedioxy)cinnamic acid (3.84 g, 20.0 mmol) as a solid in portions during 40 min. The reaction mixture was refluxed for 1.5 h, cooled to room temperature, and then poured into a dilute aqueous solution of HCl saturated with NaCl. The aqueous solution was extracted with EtOAc (200 mL), and the organic solution was washed with saturated $NaHCO_3$ (70 mL) and brine (100 mL). After drying over anhydrous $MgSO_4$, the solvent was evaporated to produce 3.34 g of 3-(1,3-benzodioxol-5-yl)propan-1-ol (18.8 mmol, 94% yield); ^{1}H NMR δ 6.72 (d, *J* = 7.9 Hz, 1 H), 6.69 (d, *J* = 1.2 Hz, 1 H), 6.63 (dd, *J* = 7.9, 1.2 Hz, 1 H), 5.91 (s, 2 H), 3.64 (t, *J* = 6.6 Hz, 2 H), 2.62 (t, *J* = 7.3 Hz, 2 H), 1.90−1.78 (comp, 2 H), 1.95 (br s, 1 H).

The title compound was prepared from 3-(1,3-benzodioxol-5-yl)propan-1-ol in 56% yield by the same set of steps and under the same conditions as those reported for **12b**; ^{1}H NMR δ 6.72 (d, *J* = 7.9 Hz, 1 H), 6.66 (d, *J* = 1.1 Hz, 1 H), 6.61 (dd, *J* = 7.9, 1.1 Hz, 1 H), 5.91 (s, 2 H), 4.75 (br s, 1 H), 4.16 (t, *J* = 6.6 Hz, 2 H), 2.60 (t, *J* = 7.3 Hz, 2 H), 1.96−1.86 (comp, 2 H); ^{13}C NMR δ 160.2, 147.5, 145.7, 134.8, 121.0, 108.7, 108.1, 100.7, 63.9, 46.0, 31.7, 30.5; IR ν 2125 (C=N$_2$), 1701 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_4N_2$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.12; H, 4.91; N, 11.33.

4-(1,3-Benzodioxol-5-ylmethyl)dihydro-2(3*H*)-furanone (13c). A solution of diazoacetate **12c** (0.305 g, 1.23 mmol) in 10 mL of rigorously dried CH_2Cl_2 was added via syringe pump at a rate of 0.8 mL/h to a refluxing solution of Rh_2(4*S*-MPPIM)$_4$ (34 mg, 25 μmol, 2.0 mol %) in 10 mL of dry CH_2Cl_2 under N_2. The initial blue/purple color of the reaction solution turned to olive green by the end of the substrate addition. After cooling to room temperature, the reaction solution was filtered through a plug of silica which was subsequently rinsed with 10 mL of CH_2Cl_2, and the solvent was evaporated under reduced pressure. After spectral and GC analyses, the residue was purified by radial chromatography (hexanes:EtOAc, 4:1) to give 0.181 g of pure lactone (*S*)-**13c** (0.823 mmol, 67% yield); $[\alpha]^{23}_D = -4.62$ (*c* 0.93, $CHCl_3$) for reaction performed with Rh_2(4*S*-MPPIM)$_4$, lit. $[\alpha]^{20}_D$ +4.8 (*c* 1.14, $CHCl_3$),[27b] +5.22 (*c* 1.13, $CHCl_3$)[15a] for (*R*)-**13c**. Enantiomeric excesses were determined from GC analysis on a 30-m Chiraldex A-DA column operated at 90 °C for 30 min and then programmed at 0.5°/min to 195 °C: 122.6 min for (*S*)-**13c**, 125.0 min for (*R*)-**13c**. For reactions performed with Rh_2(4*R*-MPPIM)$_4$ (57% isolated yield); $[\alpha]^{23}_D = +4.42$ (*c* 1.56, $CHCl_3$), and 95 ± 2% ee by GC analysis. ^{1}H NMR δ 6.73 (d, *J* = 7.9 Hz, 1 H), 6.61 (d, *J* = 1.3 Hz, 1 H), 6.57 (dd, *J* = 7.9, 1.3 Hz, 1 H), 5.92 (s, 2 H), 4.31 (dd, *J* = 9.1, 6.7 Hz, 1 H), 4.00 (dd, *J* = 9.1, 6.0 Hz, 1 H), 2.85−2.70 (m, 1 H), 2.70−2.60 (comp, 2 H), 2.58 (dd, *J* = 17.5, 8.0 Hz, 1 H), 2.25 (dd, *J* = 17.5, 6.8 Hz, 1 H); ^{13}C NMR δ 176.8, 148.0, 146.4, 131.9, 121.6, 108.8, 108.4, 101.0, 72.5, 38.7, 37.3, 34.1. Spectral data were consistent with those values reported previously.[17c]

A minor product, amounting to only 7% of the product yield, was isolated as a second chromatography fraction from the reaction catalyzed by Rh_2(5*R*-MEPY)$_4$ and was identified as the δ-lactone **4-(1,3-benzodioxol-5-yl)tetrahydropyran-2-one:** ^{1}H NMR δ 6.76 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.8 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.94 (s, 2 H), 4.48 (ddd, *J* = 11.5, 4.9, 3.9 Hz, 1 H), 4.34 (ddd, *J* = 11.5, 10.4, 3.8 Hz, 1 H), 3.20−3.08 (m, 1 H), 2.86 (ddd, *J* = 17.6, 5.9, 1.6 Hz, 1 H), 2.54 (dd, *J* = 17.6, 10.5 Hz, 1 H), 2.18−2.07 (m, 1 H), 2.04−1.89 (m, 1 H); ^{13}C NMR δ 170.6, 148.1, 146.7, 136.7, 119.4, 108.6, 106.8, 101.2, 68.6, 37.8, 37.3, 30.5.

(3*S*,4*S*)-3,4-Bis(1,3-benzodioxol-5-ylmethyl)dihydro-2-(3*H*)-furanone, (*S*,*S*)-17. To a rapidly stirred solution of lactone (*S*)-**13c** (0.160 g, 0.727 mmol) in 10 mL of anhydrous THF at −90 °C was added HMPA (0.44 g, 2.4 mmol, 3.4 equiv) and 1.1 mL of 1.5 M LDA (in cyclohexane, 1.6 mmol, 2.3 equiv). After 0.5 h at −90 °C, 1,3-benzodioxol-5-ylmethyl bromide (0.352 g, 1.64 mmol, 2.3 equiv) in 5 mL of THF was added, and the reaction mixture was warmed to −78 °C and left stirring at this temperature for 16 h. The reaction mixture was then warmed to −20 °C and held there for 2 h, and then the excess base was quenched. Workup as described for **16** and purification by radial chromatography (silica; hexanes: EtOAc, 4:1) afforded 0.182 g of (+)-hinokinin as a colorless viscous oil (**(*S*,*S*)-17**, 0.514 mmol, 70% yield); $[\alpha]^{23}_D = +29.4°$ (*c* 0.90, $CHCl_3$). (−)-Hinokinin was prepared by an identical procedure in 76% isolated yield; $[\alpha]^{23}_D = -28.8$ (*c* 0.99, $CHCl_3$), lit.[14] $[\alpha]^{23}_D$ −36 (*c* 1.00, $CHCl_3$). Spectral data were identical to those reported in the literature.[16a]

3-(3,4-Dimethoxyphenyl)prop-1-yl Diazoacetate (12d). To a stirred suspension of $LiAlH_4$ (1.09 g, 28.8 mmol) in 60 mL of anhydrous THF was added 3,4-dimethoxycinnamic acid (3.85 g, 18.5 mmol) as a solid in portions over 30 min. The reaction mixture was refluxed for 4 h, cooled to room temperature, and quenched with 2 mL of EtOAc. Upon addition of 2 mL of H_2O, 2 mL of 10% aqueous NaOH, and 5 mL of H_2O, yellow salts formed which were filtered under vacuum and washed with EtOAc (60 mL). The resulting solution was washed with brine (60 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide 3.24 g of a 3-(3,4-dimethoxyphenyl)propan-1-ol (**11d**) (16.5 mmol, 90% yield) as a pale yellow oil. ^{1}H NMR δ 6.82−6.73 (comp, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.69 (t, *J* = 6.4 Hz, 2 H), 2.67 (t, *J* = 7.4 Hz, 2 H), 1.92−1.84 (comp, 2 H), 1.53 (br s, 1 H).

To a solution of **11d** (4.21 g, 21.0 mmol), triethylamine (0.200 g, 2.0 mmol), and a catalytic amount (≥2 mg) of DMAP in 30 mL of anhydrous THF was added, dropwise at room temperature, a solution of diketene (2.00 g, 24.0 mmol) in 20 mL of THF. The resulting solution was stirred at room temperature overnight after which triethylamine (2.32 g, 23.0 mmol) was added, followed by dropwise addition of methanesulfonyl azide (2.80 g, 23.0 mmol) in 20 of mL THF over 30 min, and the composite was stirred overnight at room temperature. To the resulting orange solution was added $LiOH{\cdot}H_2O$ (2.65 g, 63.0 mmol) in 25 mL of H_2O, and stirring was continued for 5.5 h. The reaction mixture was then diluted with brine and washed with two portions of 3:1 ether: ethyl acetate (60 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide an orange liquid. Purification by flash chromatography on silica gel (hexanes:EtOAc = 3:1) afforded 2.98 g of **12d** (11.3 mmol, 65% yield) as a yellow oil. ^{1}H NMR δ 6.80 (d, *J* =

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8.3 Hz, 2 H), 6.73−6.70 (comp, 2 H), 4.76 (br s, 1 H), 4.19 (t, J = 6.6 Hz, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.64 (t, J = 7.6 Hz, 2 H), 1.96 (tt, 2 H, J = 7.6, 6.6 Hz); ^{13}C NMR δ 165.9, 148.8, 147.2, 133.6, 120.1, 111.6, 111.2, 64.1, 55.8, 55.9, 55.7, 31.6, 30.5; IR ν 2109 (C═N_2), 1693 (C═O) cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.93; H, 6.10; N, 10.59.

4-[(3,4-Dimethoxyphenyl)methyl]dihydro-2(3*H*)-furanone (13d). A solution of diazoacetate **12d** (0.159 g, 0.60 mmol) in 4 mL of rigorously dried CH_2Cl_2 was added via syringe pump at a rate of 0.4 mL/h to a refluxing solution of Rh_2(4*S*-MPPIM)$_4$ (10.8 mg, 1.3 mol %) in 7 mL of dry CH_2Cl_2. The initial blue/purple color of the reaction solution turned to olive green by the end of the substrate addition. Refluxing was continued for an additional 3 h, the reaction solution was cooled to room temperature, and the catalyst was removed by filtration on a short plug of silica gel (CH_2Cl_2). Removal of the solvent under reduced pressure provided 0.112 g of (*S*)-**13d** (0.47 mmol, 79% yield) as a light yellow oil. Purification by radial chromatography (4:1 hexanes:EtOAc) afforded 89 mg of the lactone (0.37 mmol, 62% yield) as a clear oil. Enantiomeric excesses were 94% with baseline separation by GC analysis on a 30-m Chiraldex A-DA column operated at 175 °C for 1 h and then programmed at 0.5 °C/min to 200 °C: 153.1 min (**13d,** *S*-enant), 155.2 min (**13d,** *R*-enant); $[\alpha]^{25}_D = -7.30$ (*c* 1.11, $CHCl_3$) (with 1.3 mol % Rh_2(4S-MPPIM)$_4$); $[\alpha]^{24}_D = +7.50$ (*c* 0.971, $CHCl_3$) (with 2.0 mol % Rh_2(4R-MPPIM)$_4$); lit.[11] $[\alpha]_D = -7.52$ (*c* 1.9, $CHCl_3$) of optically pure (*S*)-**13d**; ^{1}H NMR δ 6.81 (d, J = 8.0 Hz, 2 H), 6.69 (dd, J = 8.0, 2.0 Hz, 1H), 6.66 (d, J = 2.0 Hz, 1 H), 4.34 (dd, J = 9.1, 6.8 Hz, 1 H), 4.04 (dd, J = 9.1, 6.0 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.91−2.76 (m, 1 H), 2.74−2.70 (comp, 2 H), 2.61 (dd, J = 17.4, 7.9 Hz, 1 H), 2.29 (dd, J = 17.4, 6.7 Hz, 1 H). Using 2.0 mol % Rh_2(4*R*-MPPIM)$_4$, (*R*)-**13d** was isolated in 61% yield (94% ee) after purification by radial chromatography.

4-(Benzyloxy)-3-methoxybenzyl Bromide (19). To a rapidly stirred slurry of 4-hydroxy-3-methoxybenzyl alcohol (3.00 g, 19.5 mmol), potassium carbonate (6.22 g, 45.0 mmol), and 18-crown-6 (0.040 g, 1 mol %) in 35 mL of toluene was added a solution of benzyl bromide (2.56 g, 15.0 mmol) in 15 mL of toluene over 20 min. The reaction mixture was refluxed overnight after which the mixture was diluted with 40 mL of ether and washed with 5% NaOH (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (60 mL). The ether layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide 3.11 g of a pale yellow solid identified as 4-(benzyloxy)-3-methoxybenzyl alcohol (14.4 mol, 96% yield); mp 63−65 °C; lit.[35] mp 64−65 °C; ^{1}H NMR δ 7.44−7.25 (comp, 5 H), 6.94 (s, 1 H), 6.86−6.82 (comp, 2 H), 5.15 (s, 2 H), 4.60 (s, 2 H), 3.90 (s, 3 H), 1.64 (br s, 1 H).

To a solution of this alcohol (2.00 g, 8.26 mmol) in 30 mL of anhydrous ether under N_2 was added in one portion PBr_3 (0.400 mL, 4.21 mmol) at room temperature, and the resulting solution was stirred for 3 h. After dilution with ether (20 mL), the reaction solution was washed with H_2O (2 × 40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (50 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide 2.12 g of **19** (6.91 mmol, 84% yield) as a white solid: mp 67−70 °C; lit.[36] mp 73 °C; ^{1}H NMR δ 7.44−7.26 (comp, 5 H), 6.94 (d, J = 2.1 Hz, 1 H), 6.88 (dd, J = 8.2, 2.1 Hz, 1 H), 6.81 (d, J = 8.2 Hz, 1 H), 5.16 (s, 2 H), 4.48 (s, 2 H), 3.90 (s, 3 H).

(3*S*,4*S*)-3-[(3-Methoxy-4-hydroxyphenyl)methyl]-4-[3,4-dimethoxyphenyl)methyl]dihydro-2(3*H*)-furanone. (+)-Arctigenin (4). To a rapidly stirred solution of (*S*)-**13d** in 8 mL of anhydrous THF at −78 °C was added 0.35 mL of 1.5 M LDA (in cyclohexane, 0.48 mmol, 1.9 equiv) and 0.15 g of HMPA (0.76 mmol, 1.6 equiv). After 0.5 h a solution of 4-(benzyloxy)-3-methoxybenzyl bromide (**19**) (0.13 g, 0.41 mmol, 1.6 equiv) in 1.0 mL of THF was added in one portion, and the resulting mixture was stirred for 12 h at −78 °C and warmed to −20 °C (2 h) and then to 0 °C (2 h). The excess base was quenched at 0 °C with 10 mL of saturated aqueous NH_4Cl, and the solution was extracted with ether (10 mL) and EtOAc (2 × 10 mL). The combined organic layer was washed with H_2O (2 × 30 mL) and brine (30 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes:EtOAc, 4:1) to afford 0.092 g of (3*S*,4*S*)-3-[(3-methoxy-4-(benzyloxy)phenyl)methyl]-4-[(3,4-dimethoxyphenyl)methyl]dihydro-2(3*H*)-furanone (**20**) (0.20 mmol, 79% yield): ^{1}H NMR δ 7.43−7.26 (comp, 5 H), 6.95−6.47 (comp, 6 H), 5.12 (s, 2 H), 4.14−4.11 (m, 1 H), 3.89−3.86 (m, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.00−2.86 (comp, 2 H), 2.62−2.49 (comp, 4 H).

To a solution of this lactone (0.092 g, 0.20 mmol) in 10 mL of EtOAc and 1 mL of AcOH was added 5% Pd/C (0.05 g, 10 mol %). The resulting mixture was stirred under H_2 (balloon pressure), and the reaction was monitored by TLC (hexanes:EtOAc = 2:1). After 1.5 h, the reaction mixture was combined with 20 mL of EtOAc and 20 mL of H_2O. The organic layer was washed sequentially with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide 0.068 g of (+)-arctigenin (0.18 mmol, 92% yield) as a light brown oil. Further purification by radial chromatography (CH_2Cl_2:MeOH = 99:1) yielded 0.060 g (0.16 mmol, 82% yield) of **4** as an amorphous white solid: $[\alpha]^{25}_D = +27.1$ (*c* 0.56, EtOH, 94% ee); lit.[26] $[\alpha]_D = +28.05$ (*c* 1.23, EtOH) of naturally occurring **4**; ^{1}H NMR δ 6.82 (d, J = 7.9 Hz, 1 H), 6.75 (d, J = 8.2 Hz, 1 H), 6.63 (d, J = 1.9 Hz, 1 H), 6.61 (dd, J = 7.9, 1.9 Hz, 1 H), 6.55 (dd, J = 8.2, 1.9 Hz, 1 H), 6.46 (d, J = 1.9 Hz, 1 H), 5.56 (br s), 4.17−4.12 (m, 1 H), 3.91−3.85 (m, 1 H), 3.85 (s, 3 H), 3.82 (s, 6 H), 2.98−2.48 (comp, 2 H), 2.67−2.43 (comp, 4 H).

(+)-Isodeoxypodophyllotoxin (22). To 1.0 mL of 1.0 M LHMDS (in THF, 1.0 mmol) stirred under N_2 at −10 °C was added in one portion a solution of (*S*)-**13c** (0.065 g, 0.26 mmol) and 3,4,5-trimethoxybenzaldehyde (0.052 g, 0.26 mmol) in 3.5 mL of benzene. A precipitate formed immediately, and the reaction mixture was warmed to 10 °C, stirred for 2 min and then quenched with 2.5 mL of 50% aqueous HCl cooled to −20 °C. The resulting solution was diluted with EtOAc (10 mL), and the organic phase was washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL) and then dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure provided 0.116 g of the epimeric alcohols **21** (0.26 mmol, 100% yield) as an oil: ^{1}H NMR δ 6.64 (s, 2 H), 6.58 (d, J = 7.9 Hz, 1 H), 6.47 (s, 1 H), 6.30 (d, J = 7.9 Hz, 1 H), 5.91 (s, 2 H), 5.25 (br s, 1 H), 4.81 (d, J = 7.9 Hz, 1 H), 4.39 (dd, J = 8.5, 7.9 Hz, 1 H), 4.14 (dd, J = 8.8, 7.9 Hz, 1 H), 4.00−3.92 (m, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 2.87−2.14 (comp, 3 H).

The mixture of epimers (80 mg, 0.18 mmol) was dissolved in 3 mL of rapidly stirred TFA, and the reaction was monitored by ^{1}H NMR. After 3 h, the reaction solution was diluted with EtOAc (15 mL), washed with H_2O (10 mL), 5% $NaHCO_3$ solution (10 mL), and brine (15 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure provided 69 mg of reddish brown solid. A single recrystallization from boiling CH_2Cl_2 triturated with ether afforded 52 mg of (+)-isodeoxypodophyllotoxin (**22**) (0.122 mmol, 68% yield) as white needles: $[\alpha]^{25}_D = +86.7°$ (*c* 0.51, $CHCl_3$, 100% ee), mp 252−253 °C; lit.[28,37] $[\alpha]_D = +84.5$ ($CHCl_3$), mp 252−254 °C; ^{1}H NMR δ 6.60 (s, 1 H), 6.41 (s, 2 H), 6.35 (s, 1 H), 5.96−5.84 (comp, 2 H), 4.53 (dd, J = 8.7, 6.4 Hz, 1 H), 4.08−3.94 (comp, 2 H), 3.85 (s, 3 H), 3.82 (s, 6 H), 3.02-2.88 (comp, 2 H), 2.63−2.48 (comp, 2 H); ^{13}C NMR δ 175.4, 153.1, 146.6, 138.7, 127.8, 110.0, 109.9, 108.5, 108.4, 106.4, 101.1, 70.9, 60.9, 56.2, 48.7, 46.7, 40.1, 32.9.

Methyl 4-(Benzyloxy)-3-methoxycinnamate (10e). A rapidly stirred solution of 4-hydroxy-3-methoxycinnamic acid (10.12 g, 52.0 mmol) in 80 mL of methanol was cooled to 5 °C, $SOCl_2$ (3.88 mL, 52.5 mmol) was added dropwise over 5 min,

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and the resulting solution was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in 1:1 ether:EtOAc (60 mL) and then washed with saturated $NaHCO_3$ solution (40 mL) and brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide 10.8 g of 4-hydroxy-3-methoxycinnamic acid methyl ester (52.0 mmol, 100% yield) as a light brown oil: ^{1}H NMR δ 7.63 (d, J = 15.9 Hz, 1 H), 7.06−7.03 (comp, 2 H), 6.92 (d, J = 8.2 Hz, 1 H), 6.29 (d, J = 15.9 Hz, 1 H), 5.86 (br s, 1H), 4.14 (s, 3 H), 4.11 (s, 3 H).

To a rapidly stirred slurry of this ester (5.00 g, 24.0 mmol), potassium carbonate (7.88 g, 57.0 mmol), and a catalytic amount of 18-crown-6 (0.015 g) in 90 mL of toluene was added a solution of benzyl bromide (3.88 g, 22.8 mmol) in 15 mL of toluene over 30 min. The reaction mixture was refluxed overnight after which the mixture was diluted with 70 mL of ether and 20 mL of EtOAc, washed with 5% aqueous NaOH (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (75 mL). The ether layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide 6.21 g of the title compound (22.1 mmol, 92% yield) as a white solid: mp 98.5−99.5 °C. ^{1}H NMR δ 7.62 (d, J = 15.9 Hz, 1 H), 7.44−7.33 (comp, 5 H), 7.07−7.02 (comp, 2 H), 6.87 (d, J = 8.2 Hz, 1 H), 6.30 (d, J = 15. 9 Hz, 1 H), 5.19 (s, 2 H), 3.92 (s, 3 H), 3.80 (s, 3 H); ^{13}C NMR δ 167.6, 150.2, 149.7, 144.7, 136.5, 128.6, 128.0, 127.7, 127.2, 122.3, 115.6, 113.4, 110.2, 70.8, 56.0, 51.6. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.73; H, 6.08. Found: C, 72.76; H, 6.12.

3-[4-(Benzyloxy)-3-methoxyphenyl]prop-1-yl Diazoacetate (12e). To a stirred suspension of $LiAlH_4$ (0.069 g, 18.2 mmol) in 90 mL of anhydrous THF was added **10e** (2.35 g, 7.83 mmol) as a solid in portions over 10 min. The reaction mixture was refluxed under N_2 for 3 h, cooled to room temperature, and quenched with 1 mL of EtOAc. Upon addition of 1 mL of H_2O, 1.5 mL of 10% aqueous NaOH, and 3 mL of H_2O, grey salts formed which were filtered under vacuum and washed with EtOAc (100 mL). The resulting solution was washed with brine (70 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide 2.05 g of 3-[4-(benzyloxy)-3-methoxyphenyl]propan-1-ol (**11e**) (17.9 mmol, 95% yield) as a colorless oil. If necessary, further purification was performed by flash chromatography on silica gel (1:2 hexanes:EtOAc). ^{1}H NMR δ 7.25−7.29 (comp, 5 H), 6.80 (d, J = 8.2 Hz, 1 H), 6.75 (d, J = 2.0 Hz, 1 H), 6.67 (dd, J = 8.2, 2.0 Hz, 1 H), 5.13 (s, 2 H), 3.88 (s, 3 H), 3.67 (t, J = 6.4 Hz, 2 H), 2.65 (t, J = 7.6 Hz, 2 H), 1.87 (tt, J = 6.4, 7.6 Hz, 2 H).

To a solution of this alcohol (1.85 g, 6.8 mmol) and triethylamine (0.200 g, 2.0 mmol) in 30 mL of anhydrous THF was added, dropwise at room temperature, a solution of diketene (0.631 g, 7.5 mmol) in 20 mL of THF. The resulting solution was stirred at room temperature overnight whereupon triethylamine (1.00 g, 8.2 mmol) was added to the reaction solution, followed by dropwise addition of methanesulfonyl azide (0.836 g, 8.2 mmol) in 20 mL THF over 30 min, and stirring was continued overnight at room temperature. To the resulting orange solution was added $LiOH\cdot H_2O$ (0.867 g, 20.4 mmol) in 30 mL of H_2O, and stirring was continued for 5.5 h. The reaction mixture was diluted with brine and extracted with three portions of 1:1 ether:EtOAc (60 mL). The combined organic layer was washed with brine (70 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to provide an orange liquid. Purification by flash chromatography on silica gel (hexanes:EtOAc = 4:1) provided 1.04 g of **12e** (3.05 mmol, 45% yield) as a yellow glass. ^{1}H NMR δ 7.45−7.26 (comp, 5H), 6.80 (d, J = 8.2 Hz, 1 H), 6.72 (d, J = 1.9 Hz, 1 H), 6.65 (dd, J = 8.2, 1.9 Hz, 1 H), 5.12 (s, 2 H), 4.73 (br s, 1 H), 4.17 (t, J = 6.5 Hz, 2 H), 3.88 (s, 3 H), 2.62 (t, J = 7.6 Hz, 2 H), 1.94 (tt, J = 7.6, 6.5 Hz, 2 H); ^{13}C NMR δ 166.8, 149.6, 146.4, 137.3, 134.3, 128.5, 127.7, 127.2, 120.2, 114.2, 112.2, 71.2, 64.1, 55.9, 46.1, 31.6, 30.4; IR: ν 2108 (C═N_2), 1686 (C═O) cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 67.08; H, 5.96; N, 8.15.

4-[[4-(Benzyloxy)-3-methoxyphenyl]methyl]dihydro-2-(3*H*)-furanone (13e) was formed by the catalytic decomposition of diazoacetate **12e** in the presence of Rh_2(4*R*-MPPIM)$_4$ (1.0 mol%, 59% yield, 96.5% ee). $[\alpha]^{24}_D$ = +3.7 (*c* 1.03, $CHCl_3$); mp 79 °C; lit.[28] $[\alpha]_D$ = +4 ($CHCl_3$) of optically pure (*R*)-**13e**, mp 80−81.5 °C. ^{1}H NMR δ 7.44−7.27 (comp, 5 H), 6.82 (d, J = 8.1 Hz, 1 H), 6.68 (s, 1 H), 6.62 (d, J = 8.1 Hz, 1 H), 5.13 (s, 2 H), 4.33 (d, J = 9.1, 6.7 Hz, 1 H), 4.03 (dd, J = 9.1, 5.8 Hz, 1 H), 3.88 (s, 1 H), 2.88−2.75 (m, 1 H), 2.72−2.68 (comp, 2 H), 2.57 (dd, J = 17.3, 7.9 Hz, 1 H), 2.28 (dd, J = 17.3, 6.7 Hz, 1 H); ^{13}C NMR δ 176.8, 149.8, 147.0, 137.1, 131.3, 128.5, 127.9, 127.2, 120.6, 114.3, 112.4, 72.6, 71.1, 56.0, 38.6, 37.2, 34.2; *m/z* mass spectrum, *m/z* (relative abundance) 313 (M + 1, 1.1), 312 (M, 5.2), 221 (1.1) 137 (1.5), 107 (2.2), 105 (2.0), 92 (8), 91 (100); IR ν 1774 (C═O) cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.05; H, 6.45. Found: C, 73.07; H, 6.42.

For the purpose of chiral GC analysis, (*R*)-**13e** was converted to 4-[(4-hydroxy-3-methoxyphenyl)methyl]dihydro-2(3*H*)-furanone by hydrogenolysis over Pd/C in EtOAc:AcOH (99:1) under balloon pressure of H_2; ^{1}H NMR δ 6.86 (d, J = 8.2 Hz, 1 H), 6.67−6.64 (comp, 2 H), 5.53 (br s, 1 H), 4.33 (dd, J = 6.8, 9.1 Hz, 1 H), 4.04 (dd, J = 5.8, 9.1 Hz, 1 H), 3.89 (s, 3 H), 2.82−2.79 (m, 1 H), 2.72−2.69 (comp, 2 H), 2.62 (dd, J = 8.0, 17.4 Hz, 1 H), 2.29 (dd, J = 6.6, 17.4 Hz, 1 H). Other spectral characteristics were identical to those previously reported.[29] Enantiomeric excesses were determined by GC analysis on a 30-m Chiraldex A-DA column operated at 175 °C for 1 h and then programmed at 0.5 °C/min to 200 °C: 189.8 min (***S***), 192.7 min (***R***).

1-Butyl Diazoacetate (24a). The title compound was prepared from 1-butanol by the same procedure as that described for **24b** in 60% yield as a clear yellow oil; bp 37 °C (0.7 torr); ^{1}H NMR δ 4.74 (br s, 1 H), 4.17 (t, J = 6.7 Hz, 2 H), 1.63 (tt, J = 7.6, 6.7 Hz, 2 H), 1.37 (tq, J = 7.6, 7.1 Hz, 2 H), 0.94 (t, J = 7.1 Hz, 3 H). ^{13}C NMR δ 166.8, 64.6, 45.9, 30.7, 18.9, 13.5; IR ν 2110 (C═N_2), 1697 (C═O) cm^{-1}. Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.7; H, 7.09; N, 19.72. Found: C, 50.58; H, 7.13; N, 19.70.

4-Methyl-1-pentyl Diazoacetate (24b). To a continuously stirred solution of 4-methyl-1−pentanol (2.15 g, 21.1 mmol) and triethylamine (0.40 g, 3.9 mol) in 25 mL of THF was added diketene (1.86 g, 221 mmol) in 15 mL of THF. The resulting yellow solution was stirred overnight at room temperature whereupon triethylamine (2.58 g, 25.3 mmol) and methanesulfonyl azide (3.06, 25.3 mmol) in 15 mL of THF were added to the reaction flask. The resulting dark orange solution was stirred overnight at room temperature at which time was added $LiOH\cdot H_2O$ (2.66 g, 63.6 mmol), and stirring was continued for an additional 4 h. The reaction mixture was diluted with 30 mL of brine and extracted with three 35 mL portions of 2:1 ether:EtOAc. The combined organic solution was washed with 60 mL of brine and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The resulting orange liquid was purified by flash chromatography on silica gel (hexanes:EtOAc = 8:1), and collection of the yellow band provided 1.94 g of **24b** (11.4 mmol, 54% yield) as a clear yellow oil; ^{1}H NMR δ 4.73 (br s, 1 H), 4.14 (t, J = 6.7 Hz, 2 H), 1.69−1.52 (comp, 3 H), 1.26−1.18 (m, 2 H), 0.89 (d, J = 6.7 Hz, 6 H); ^{13}C NMR δ 166.7, 65.0, 45.8, 34.7, 27.5, 26.5, 22.2; IR ν 2111 (C═N_2), 1697 (C═O) cm^{-1}. Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.28; N, 16.46. Found: C, 56.35; H, 8.38; N, 16.54.

4-Ethyldihydro-2(3*H*)-furanone (25a). This lactone was prepared according to the procedure described for **13e** by catalytic decomposition of **24a** (0.100 g, 0.72 mmol) with Rh_2(4*S*-MPPIM)$_4$ (10 mg, 1.0 mol %). Purification by bulb-to-bulb distillation provided 0.042 g of **25a** (0.37 mmol, 52% yield, 95% ee) as a clear oil which contained 4% of the β-lactone. ^{1}H NMR δ 4.42 (dd, J = 7.3, 9.4 Hz, 1 H), 3.94 (dd, J = 7.6, 9.4 Hz, 1 H), 2.63 (d, J = 8.3, 17.0 Hz, 1 H), 2.49 (hept, J = 7.3 Hz 1 H), 2.20 (dd, J = 7.6, 17.0 Hz, 1 H), 1.81−1.38 (comp, 2 H), 0.98 (t, J = 7.3 Hz, 3 H). Other spectral characteristics were identical to those previously reported.[38] Enantiomeric

(38) (a) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *Chem. Pharm. Bull.* **1985**, *33*, 61. (b) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.*, **1982**, *104*, 5564.

excesses were determined by GC analysis on a 30-m Chiraldex A-DA column operated at 80 °C: 57.7 min (***S*-25a**), 59.5 min (***R*-25a**).

4-(2-Methyl-1-propyl)dihydro-2(3*H*)-furanone (25b). This lactone was prepared by catalytic decomposition of **14b** (0.183 g, 1.08 mmol) according to the procedure described for **13e** with Rh_2(4*S*-MPPIM)$_4$ (22 mg, 1.5 mol %). Purification by bulb-to-bulb distillation provided 0.090 g (60% yield) of a clear oil which contained approximately 5% of the β-lactone. This material was further purified by column chromatography on silica gel (hexanes:EtOAc) to afford 0.042 g of **25b** (0.29 mmol, 28% yield) as a clear oil; bp 40−41 °C (0.7 torr); ^{1}H NMR δ 4.42 (dd, J = 8.9, 8.0 Hz, 1 H), 3.89 (dd, J = 8.9, 7.1 Hz, 1 H), 2.69−2.57 (comp, 2 H), 2.22 (m, 1 H), 1.58 (oct, J = 6.7 Hz, 1 H), 1.37 (t, J = 7.1 Hz, 2 H), 0.93 (d, J = 6.7 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 177.2, 73.5, 42.2, 34.7, 33.8, 26.3, 22.6, 22.4; IR ν 1773 (C=O) cm^{-1}. Enantiomeric excesses were determined following $LiAlH_4$ reduction by GC analysis on a 30-m Chiraldex G-DA column operated at 90 °C for 60 min then programmed at 1.0 °C/min to 185 °C: 103.0 min (***R*-25b**), 116.7 min (***S*-25b**). Anal. Calcd for $C_8H_{14}O_2$: C, 67.58; H, 9.92. Found: C, 67.48; H, 9.81.

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Supporting Information Available: Copies of NMR spectra of **15** and **18** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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