Rhodium-Mediated Intramolecular C−H Insertion: Probing the Geometry of the Transition State

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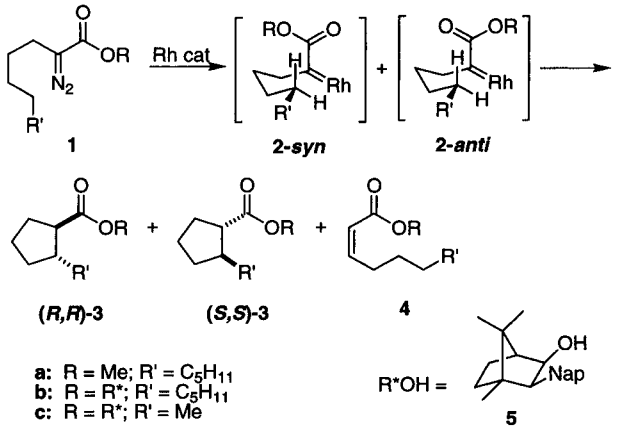
The unsymmetrical α-diazo ester **1b**, derived from the chiral naphthylborneol **5**, was cyclized with a set of rhodium carboxylates (L = CF_3CO_2, CH_3CO_2, $CH_3(CH_2)_6CO_2$, $(CH_3)_3CCO_2$). The ratio of the three major products ((*R*,*R*)-**3b**, (*S*,*S*)-**3b**, **4b**) was determined. It was found that the rhodium catalyst derived from pivalic acid gave the highest ratio of **3b**:**4b**. Lowering the temperature of the reaction (L = $(CH_3)_3CCO_2$) increased both the yield and the diastereoselectivity of the cyclization. From these results and from our computational analysis, it is concluded that the ester carbonyl and the rhodium carbenoid are probably syn in the transition state leading to cyclization.

Introduction

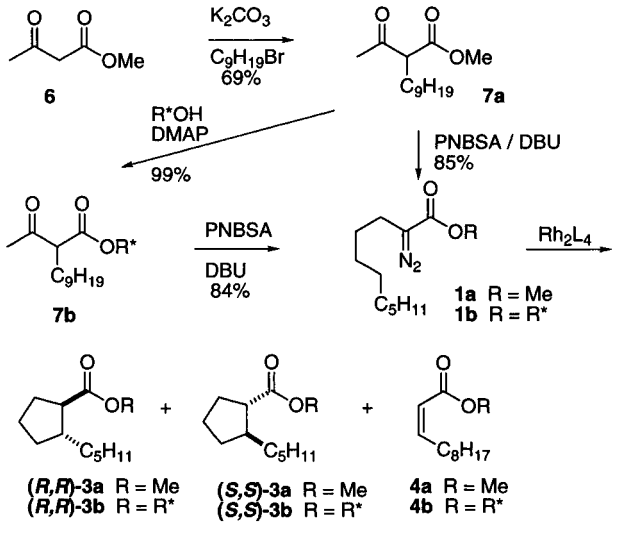
Dirhodium tetracarboxylate catalysts are known[1,2] to convert suitable α-diazo esters to acylcyclopentanes (e.g., **1** → **3**). We have reported[2e] a computational approach that reliably predicts the dominant diastereomer from such a rhodium-mediated cyclization. In attempting to extend this computational approach to the design of an effective enantiomerically pure rhodium catalyst, we found that we were missing a key piece of data, the dihedral angle between the ester carbonyl and the rhodium carbenoid at the point of commitment to cyclization (**2-*syn*** vs **2-*anti***). We and others have, in the past, speculated that the ester carbonyl and the rhodium carbenoid could be syn,[3] anti,[4] or orthogonal,[4a] but no experimental or computational evidence in favor of any of these had been put forward. Since our computational methods did not allow us to answer this question directly, we have devised an indirect approach based on the cyclization of α-diazo ester **1b**, derived from the naphthylborneol **5**.[4c] Our conclusion from this study is that the ester carbonyl and the rhodium carbenoid are *syn* in the transition state leading to the cyclization of esters such as **1**.



Establishment of the Analytical Procedure

Methyl 2-acetylundecanoate (**7a** in Scheme 1), prepared by alkylating methyl acetoacetate (**6**), was con-

Scheme 1



(1) For general reviews of rhodium-mediated C−H insertions, see: (a) Taber D. F. *Comprehensive Organic Synthesis*; Pattenden, G., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 1045−1062. (b) Doyle, M. P. In *Homogeneous Transition Metal Catalysts in Organic Synthesis*; Moser, W. R., Slocum, D. W., Eds.; ACS Advanced Chemistry Series, No. 230; American Chemical Society: Washington, D.C., 1992; Chapter 30. (c) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797−1815. (d) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160.

(2) For more recent work on rhodium-mediated C−H insertions, see: (a) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983−5986. (b) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Cañas, F.; Pierson, D. A.; Bastan, A. van; Müller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507−4508. (c) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8991−9000. (d) Ferris, L.; Haigh, D.; Moody, C. J. *Tetrahedron Lett.* **1996**, *37*, 107−110. (e) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547−556.

(3) (a) For the cyclopropanation of α-diazo esters, see: Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919−939. (b) For the cyclization of α-diazo ketones, see ref 1a.

(4) (a) For the cyclization of α-diazo-*β*-keto esters to form lactones, see: Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958−964. For the cyclization of α-diazo-*β*-keto esters to form cyclopentanones, see: (b) Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935−5937. (c) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28−34. For the cyclopropanation of α-diazo esters see: (d) Doyle, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305−316. (e) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468−9479. For the cyclization of α-diazo esters, see: (f) Taber, D. F.; You, K. K. *J. Am. Chem. Soc.* **1995**, *117*, 5757−5762. (g) Reference 2e. (h) For the cyclization of α-diazo ketones, see ref 1a.

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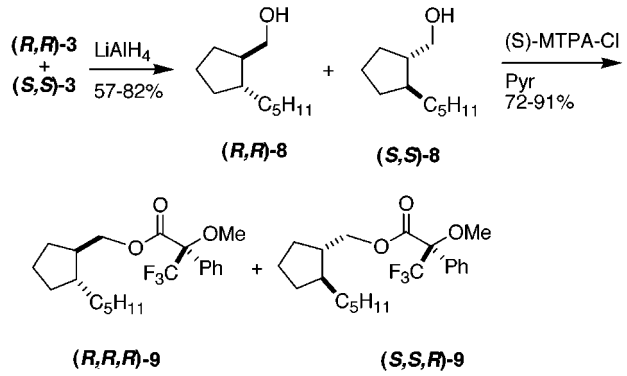
Scheme 2



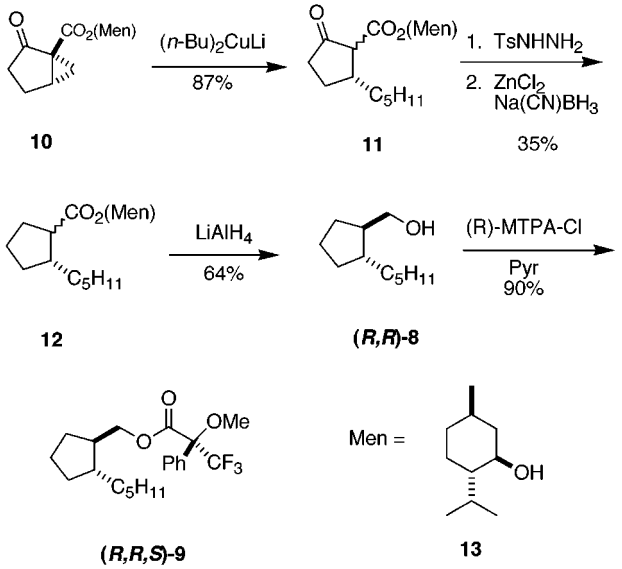
verted to the α-diazo ester **1a** by treatment with DBU and *p*-nitrobenzenesulfonyl azide.[5] Ester **1a** was then subjected to rhodium-catalyzed cyclization at room temperature to yield a 1:1 mixture of trans cyclic esters (*R*,*R*)-**3a** and (*S*,*S*)-**3a** as well as alkene **4a**.

The cyclic esters were separated from the alkene and reduced with $LiAlH_4$ (Scheme 2). The resulting primary alcohols (*R*,*R*)-**8** and (*S*,*S*)-**8** were converted to their corresponding (*R*)-Mosher esters[6] ((*R*,*R*,*R*)-**9** and (*S*,*S*,*R*)-**9**) using (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. Quantitative ^{13}C NMR showed good resolution of several carbon signals, with the best being a pair of signals at δ 44.26 and 44.33 arising from a ring methine. Examination of the ^1H NMR spectrum also showed useful resolution of the ABX patterns of the oxygenated methylenes, with multiplets centered at δ 4.30 and 4.25 for one pair and δ 4.15 and 4.10 for the other. No useful separation was observed in the ^{19}F NMR spectrum.

Determination of the Absolute Configuration of Ester 3

To correlate the NMR signals of ester **3** with an absolute configuration, we prepared an enantiomerically enriched sample of the *R*,*R*-alcohol (*R*,*R*)-**8**. The synthetic pathway that we chose is shown in Scheme 3.[7] The menthyl ester **10** was prepared and separated from its diastereomer following the literature procedure.[8] The activated cyclopropane was opened[9] with lithium di-*n*-butyl cuprate[10] to give **11**. The ketone carbonyl was removed by a modified Wolff−Kishner procedure,[11] and the resulting ester (**12**) was reduced with $LiAlH_4$. The trans alcohol (*R*,*R*)-**8** was separated and esterified to give (*R*,*R*,*S*)-**9**, using the same procedure as before but now

Scheme 3



employing the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The ^1H NMR spectra of (*R*,*R*,*S*)-**9** showed the ABX pattern of the oxygenated methylene as multiplets centered at δ 4.25 and 4.15, and the ^{13}C NMR spectra showed a major signal at δ 44.33.

Cyclization of the Naphthylbornyl Ester (1b)

The naphthylborneol **5** was prepared in five steps from camphor as previously described.[4c] Using this alcohol, methyl ester **7a** (Scheme 1) was converted to **7b** via DMAP-catalyzed transesterification,[12] and this ester was carried on to diazo ester **1b**. On exposure to the rhodium catalysts, **1b** was converted to a mixture of the cyclopentanecarboxylates (*R*,*R*)-**3b** and (*S*,*S*)-**3b** and the alkene **4b**. The ratio of cyclization to elimination was determined by ^1H NMR of the crude product. The mixture was then reduced with $LiAlH_4$ (Scheme 2) and chromatographed to recover the chiral auxiliary **5** in good yield. Also collected were alcohols (*R*,*R*)-**8** and (*S*,*S*)-**8**, which were converted to their (*R*)-Mosher esters ((*R*,*R*,*R*)-**9** and (*S*,*S*,*R*)-**9**). The Mosher esters were analyzed by quantitative ^{13}C NMR to determine the diastereomeric ratio from the cyclization.[13]

The chiral diazo ester **1b** was cyclized with four commonly used rhodium carboxylate catalysts (Table 1). It was found that rhodium pivalate[14] (entry 4) was most efficient for forming the cyclopentanes and that rhodium trifluoroacetate (entry 1) was best for forming the alkenes.[15] For the pivalate, both the yield of the cyclization and the diastereoselectivity improved at lower temperature (entry 5).

(5) Taber, D. F.; You, K.; Song, Y. *J. Org. Chem.* **1995**, *60*, 1093−1094.

(6) For the preparation and use of Mosher esters, see: (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. (b) Balani, S. K.; Boyd, D. R.; Cassidy, E. S.; Greene, R. M. E.; McCombe, K. M.; Sharma, N. D.; Jennings, W. B. *Tetrahedron Lett.* **1981**, *22*, 3277−3280.

(7) For other methods of making enantiomerically enriched alcohol (*R*,*R*)-**8**, see, for example: (a) Suemune, H.; Okano, K.; Akita, H.; Sakai, K. *Chem. Pharm. Bull.* **1987**, *35*, 1741−1747. (b) Chen, M. Y.; Fang, J. M.; Tsai, Y. M.; Yeh, R. L. *J. Chem. Soc., Chem. Commun.* **1991**, 1603−1604. (c) Fang, C. L.; Suemune, H.; Sakai, K. *J. Org. Chem.* **1992**, *57*, 4300−4303.

(8) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699−4702.

(9) Corey, E. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1972**, *94*, 4014−4015.

(10) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615−5616.

(11) Taber, D. F.; Wang, Y.; Stachel, S. J. *Tetrahedron Lett.* **1993**, *34*, 6209−6210.

(12) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618−3619.

(13) It was not possible to separate all of the methyl ester **7a** from **7b**, but the percentage of (*R*,*R*)-**3a** and (*S*,*S*)-**3a** was determined readily by ^1H NMR, and the amount of racemic alcohol ((*R*,*R*)-**8** and (*S*,*S*)-**8**) was calculated and corrected for when determining the diastereomer ratio from the cyclization.

(14) Rhodium pivalate [dirhodium tetrakis[μ-(2,2-dimethylpropanato O:O′)]] was synthesized by refluxing commercially available rhodium trifluoroacetate in 8 equiv of pivalic acid for 24 h followed by removal of excess acid under vacuum. The crude catalyst was purified by flash chromatography using an MTBE petroleum ether gradient: TLC R_f (10% MTBE/petroleum ether) = 0.52. For leading references to the preparation of other rhodium carboxylates, see: (a) Felthouse, T. R.

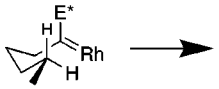
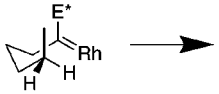
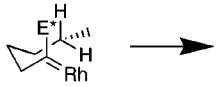
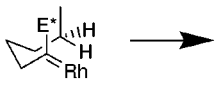
Table 1. Influence of the Ligand Bound to Rhodium on the Diastereoselectivity of the Cyclization of Ester 1b

entry	ligand	reaction temp (°C)	yield (%)	(*R*,*R*)-**3b**:(*S*,*S*)-**3b**:**4b**
1	CF_3CO_2	18	89	1.5:1.0:4.2
2	CH_3CO_2	18	92	2.6:1.0:0.9
3	n-$C_7H_{15}CO_2$	18	82	3.8:1.0:0.7
4	$(CH_3)_3CCO_2$	18	99	8.4:1.0:1.0
5	$(CH_3)_3CCO_2$	−78	99	14:1.0:1.0

Computational Analysis of the Naphthylbornyl-Derived Ester (1b)

A critical consideration in extending our previous computational analysis[2e] to the naphthylbornyl-derived ester **1b** is that, assuming that the rhodium carbenoid and the ester carbonyl should be coplanar, they could be either syn or anti at the point of commitment to product formation. Thus, there are eight competing transition states. The minimizations for each of the eight "points of commitment" were carried out following the approach we have previously described,[2e] and the global minima, determined by a meticulous grid search, for each are summarized in Table 2.

Table 2. Transition States and Products Resulting from Cyclization of Naphthylbornyl 2-Diazoheptanoate (1b)

possible diastereomeric T.S.	possible diastereomer	Relative energy of the transition state in kcal / mol	
		syn	anti
	 (*R*,*R*)-3c	3.37	0.00
	 (*R*,*S*)-3c	10.02	18.64
	 (*S*,*S*)-3c	4.35	14.38
	 (*S*,*R*)-3c	8.30	9.97

E* = CO_2R^*

Analysis

The syn and the anti conformations leading to (*R*,*R*)-**3c**, illustrated in Table 2, are calculated to be the two lowest energy transition states for the cyclization of **1b**. Of the two, the anti conformation (Rh carbene and carbonyl coplanar but pointing in opposite directions) is the more stable, by 3.37 kcal/mol. If steric factors alone governed the outcome of these cyclizations, we would expect that the anti transition state leading to (*R*,*R*)-**3c** would be competing with the syn transition state leading to (*S*,*S*)-**3c**. The former would be favored by 4.35 kcal/mol. We have found, based on many examples,[2e] that if the difference in transition state energies is greater than 2 kcal/mol, then a single product will be formed in high (>95%) diastereomeric excess. We do not observe such high diastereoselectivity in the cyclization of **2b**, so we conclude that steric factors *alone* do not govern the stereochemical outcome of this cyclization.

We propose that there is in fact a substantial electronic preference, not reflected in the Mechanics calculations, for the ester carbonyl and the C═Rh bond to be *syn* at the point of commitment to cyclization. This preference is strong enough to overcome the calculated steric preference (3.37 kcal/mol) for the anti transition state. The competition then is between the syn transition state leading to (*R*,*R*)-**3c** and the syn transition state leading to (*S*,*S*)-**3c**. The relative energies of these two transition states differ by less than 1 kcal/mol, so we predict, and observe, low diastereoselectivity.[16]

We have posed this syn/anti question using a sterically demanding ester for which there is a significant conformational bias in favor of the anti transition state. We therefore believe that the conclusion that there is a substantial preference for the ester carbonyl and the C═Rh bond to be syn at the point of commitment to cyclization is general and not limited to this particular case.

Conclusions

We have observed that changing the ligand on the rhodium carboxylate changes the product distribution from the cyclization of **1b**. This is not surprising considering that, electronically, the ligands exert substantial control over the reactivity of the carbenoid. It is apparent[2] that a strongly electron-withdrawing ligand will result in a more reactive carbenoid and that, with such a ligand, commitment to product formation will occur while the carbenoid carbon and the target C−H are still some distance apart. By changing the ligand from octanoate to pivalate, the reactivity of the carbenoid is apparently attenuated, resulting in a tighter transition state.[2c] The distance between the carbenoid carbon and the target C−H is then smaller at the point of commitment, bringing the chiral ester in closer proximity to the reaction center where it can better influence the product distribution by the handedness of its steric bulk. The improved cyclization procedure described here suggests that naphthylborneol **5** could become of significant practical value as a chiral auxiliary for rhodium-mediated intramolecular C−H insertion reactions.

Prog. Inorg. Chem. **1982**, *29*, 73−166. (b) Jardine, F. H.; Sheridan, P. S. In *Comprehensive Coordination Chemistry, IV*; Wilkinson, G., Ed.; Pergamon Press: New York, 1987; pp 901−1096. (c) Reference 1c and references within.

(15) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908−2910.

(16) In our hands, calculations based on the Doyle model[5] have succeeded in predicting the major product formed in each of the examples given in our recent paper.[2e] We find that the *minimum* difference in the "transition state energies" necessary for high diastereoselectivity (>95%) following the Doyle model is about 1 kcal/mol. In the case of the naphthylbornyl-derived ester **1c**, the Doyle model predicts that the (*R*,*R*)-**3** diastereomer is favored over any other >3 kcal/mol, indicating that (*R*,*R*)-**3** should be formed as a single diastereomer. Experimentally, we find that the ratio of (*R*,*R*)-**3** to (*S*,*S*)-**3** is 8.4:1.0. Therefore, we conclude that the unconstrained Doyle model is not sufficiently predictive in the case of more complex esters such as **1c**.

While we have had some success,[2e] we are aware of the limitations inherent in a transition-state model for rhodium-mediated C−H insertion that attempts to predict product ratios on the basis of MM2 calculations. Arbitrary decisions limiting the several degrees of freedom possible in the transition state could lead one to a model for the "point of commitment" to cyclization that would be far from reality. The work described here is important because it offers *experimental* evidence for a key rotational degree of freedom, the dihedral angle between the ester carbonyl and the rhodium carbenoid.

Experimental Procedures[17]

Computational Analysis. Structure minimization was carried out using Mechanics as provided in the Tektronics CAChe System Version 2.8. CAChe Mechanics uses an augmented version of Allinger's MM2 force field. Details of this computational approach have been published.[2e]

Methyl 2-Acetylundecanoate (7a). To a solution of methyl acetoacetate (**6**) (4.5 mL, 42 mmol) in 20 mL of DME were added potassium carbonate (5.8 g, 42 mmol) and tetrabutylammonium iodide (770 mg, 2.1 mmol). 1-Bromononane (4.0 mL, 21 mmol) was introduced via syringe, and the mixture was warmed to reflux for 24 h. The reaction mixture was then cooled and partitioned between 3 M aqueous HCl and petroleum ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was distilled under reduced pressure (bath = 140 °C/0.5 mmHg), and the distillate was chromatographed to give **7a** as a colorless oil (3.50 g, 69% yield from 1-bromononane). This product gave spectra consistent with those previously reported for **7a**.[15]

3-*exo*-(2-*exo*-(1-Naphthyl))bornyl 2-Acetylundecanoate (7b). A 100 mL sidearm flask was equipped with a Dean−Stark water trap filled with 4 Å molecular sieve and a reflux condenser. The flask was charged with methyl ester **7a** (1.27 g, 5.23 mmol), naphthylborneol **5** (1.47 g, 5.23 mmol), DMAP (13 mg, 0.105 mmol), and 50 mL of dry toluene. The solution was warmed to reflux for 3 days and then cooled. It was then partitioned between saturated aqueous ammonium chloride and ethyl acetate. The combined organic extract was dried (Na_2SO_4) and concentrated. The mixture was separated into two fractions by column chromatography. One fraction contained 0.04 mmol of **7a**, 0.43 mmol of **7b**, and 1.29 mmol of recovered alcohol **5** and was not purified further. The second fraction contained 1.21 mmol of unreacted **7a** and 3.63 mmol of **7b** (quantitative yield based on starting materials recovered). Most of the methyl ester was removed by distillation (bath = 140 °C/0.5 mmHg), yielding 1.62 g of a 94:6 mixture of the expected chiral ester (**7b**) and methyl ester (**7a**). A portion of the mixture was further distilled to give an analytical sample of **7b**: TLC R_f (10% MTBE/petroleum ether) = 0.55; IR (film) 1738, 1716, 787 cm^{-1}; ^1H NMR δ 8.0−7.4 (m, 7H), 5.54 (dd, J = 8.8, 4.9 Hz, 1H), 4.07 (d, J = 7.9 Hz, 1H), 2.68 (t, J = 7.3 Hz, 0.5H), 2.54 (t, J = 7.3 Hz, 0.5H), 2.2−0.6 (m, 36H); ^{13}C NMR δ u 202.0, 168.8, 135.0, 133.5, 133.1, 49.3, 48.2, 42.4, 31.8, 29.3, 29.1, 29.0, 27.2, 27.0, 26.7, 23.7, 22.6; d 128.9, 127.2, 126.6, 126.1, 125.1, 124.5, 123.3, 80.4, 59.6, 55.2, 51.2, 27.6, 23.9, 21.4, 14.6, 14.0; EI MS m/z (rel intensity) 490 (M^+, 9), 380 (8), 262 (30), 207 (13), 170 (100), 141 (34), 121 (10), 95 (8); HRMS (calcd for $C_{33}H_{46}O_3$) 490.3447, found 490.3428. Anal. Calcd for $C_{33}H_{46}O_3$: C, 80.77; H, 9.45. Found C, 80.68; H, 9.30.

Methyl 2-Diazoundecanoate (1a). A dry 5 mL reactivial was charged with **7a** (200 mg, 0.83 mmol), 2.5 mL of dry CH_2Cl_2 (0.25M), and DBU (0.25 mL, 1.65 mmol). The temperature was lowered to 0 °C, and *p*-nitrobenzenesulfonyl azide (PNBSA) (377 mg, 1.65 mmol) was added in the dark. The reaction was stirred for 1 h at 0 °C and 1 h at ambient temperature. The reaction mixture was then partitioned between 3 M aqueous NaOH and CH_2Cl_2. The combined organic extract was then dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield **1a** (159 mg, 85% from **7a**) as a yellow oil. This product gave spectra consistent with those previously reported for **1a**.[15]

3-*exo*-(2-*exo*-(1-Naphthyl))bornyl 2-Diazoundecanoate (1b). A dry 50 mL round-bottom flask was charged with a 94:6 mixture of **7b** and **7a** (1.49 g, 3.14 mmol), 25 mL of dry CH_2Cl_2 (0.25M), and DBU (0.95 mL, 6.27 mmol). The temperature was lowered to 0 °C, and *p*-nitrobenzenesulfonyl azide (PNBSA) (1.43 g, 6.27 mmol) was added in the dark. The reaction was stirred for 1 h, during which time the water bath went from 0 °C to ambient temperature. The reaction mixture was partitioned between 3 M aqueous NaOH and CH_2Cl_2. The combined organic extract was then dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield a 93:7 mixture of **1b** and **1a** (1.2 g, 84% yield for both compounds) as a yellow oil. For **1b**: TLC R_f (10% MTBE/petroleum ether) = 0.50; IR (film) 2081, 1682, 784 cm^{-1}; ^1H NMR δ 8.1−7.3 (m, 7H), 5.52 (d, J = 8.7 Hz, 1H), 4.07 (d, J = 8.7 Hz, 1H), 2.0−0.9 (m, 33H); ^{13}C NMR δ u 175.3, 135.8, 133.5, 133.4, 49.3, 48.2, 42.6, 35.2, 34.8, 31.9, 31.8, 29.1, 28.8, 28.3, 27.5, 24.7, 24.4, 23.9, 22.6; d 149.6, 128.7, 127.0, 126.5, 125.9, 125.5, 125.0, 124.3, 123.6, 119.4, 79.9, 79.3, 55.5, 51.4, 51.2, 50.5, 43.5, 42.9, 24.1, 21.6, 14.9, 14.8, 14.1.

Rhodium-Mediated C−H Insertion Reactions. The CH_2Cl_2 was distilled over calcium hydride and then passed through a pad of anhydrous K_2CO_3 just prior to use. The requisite diazo compound (**1a** or **1b**) was dried before use by dilution of the sample with toluene and subsequent evaporation. It was then diluted in the CH_2Cl_2 to a concentration of approximately 0.25 M, and the temperature was adjusted. The rhodium catalyst (1 mol %) was dissolved in 0.1 mL of CH_2Cl_2, and the temperature of the catalyst solution was adjusted to the experimental conditions desired. The catalyst solution was then added to the substrate dropwise as rapidly as foaming would allow and then stirred until the reaction was complete as determined by TLC (usually within 1/2 h). The resulting light green solution was filtered through silica and evaporated. For the reaction at −78 °C, the solution was allowed to warm to ambient temperature overnight.

In an unoptimized run, this procedure was applied to the methyl diazo ester **1a**. Reaction of **1a** with Rh_2Piv_4 at ambient temperature yielded a 3:1 mixture of cyclic esters (*R*,*R*)-**3a** and (*S*,*S*)-**3a** to alkene **4a**. Chromatography yielded the pure racemic trans ester (40% from **1a**).

(*R,*R**)-(2-Pentyl)cyclopentanemethanol ((*R*,*R*)-8 and (*S*,*S*)-8).** A mixture of esters (**3a** = 0.020 mmol, **4a** = 0.024 mmol, **3b** = 0.185 mmol, **4b** = 0.151 mmol) (total 159 mg, 0.380 mmol) was diluted in 2 mL of THF in a 5 mL reactivial. One equivalent of $LiAlH_4$ (14 mg, 0.38 mmol) was added to the stirring solution, and the reaction was followed by TLC. Over the next 4 h, the temperature was raised to 50 °C, and 2 more equiv of $LiAlH_4$ was added. When the reaction was judged complete by TLC, it was cautiously quenched with 50 μL of H_2O, 50 μL of 3 M aqueous NaOH, and finally 150 μL of H_2O. The resultant slurry was filtered through Celite, and the salts were rinsed with 20 mL of MTBE and 20 mL of acetone. The filtrate was evaporated and chromatographed to yield 90.2 mg (96%) of the recovered chiral alcohol **5** and a clean cut of a mixture of alcohols (*R*,*R*)-**8** and (*S*,*S*)-**8** (20.1 mg, 57%). Yields are based on a complete reaction where one would expect 0.336 mmol (94 mg) of **5** and 0.205 mmol (35 mg) of a mixture of (*R*,*R*)-**8** and (*S*,*S*)-**8**. For the clean (*R*,*R*)-**8** and (*S*,*S*)-**8**: TLC R_f (10% MTBE/petroleum ether) = 0.18; IR (film) 3320, 1464, 1070, 780 cm^{-1}; ^1H NMR δ 3.61 (dd, J = 10.4, 5.2 Hz, 1H), 3.42 (dd, J = 10.4, 7.5 Hz, 1H), 1.8−1.1 (m, 15H), 0.85 (t, J = 6.7, 3H); ^{13}C NMR δ u 66.8, 35.8, 32.7, 32.2, 29.4, 28.1, 24.4, 22.7; d 48.2, 42.1, 14.1; EI MS m/z (rel intensity) 152 (7), 131 (7), 109 (20), 96 (80), 81 (100), 67 (63), 55 (51). Anal. Calcd for $C_{11}H_{20}O$: C, 77.58; H, 13.02. Found: C, 77.19; H, 12.64.

(*R,*R**)-(2-Pentyl)cyclopentanemethyl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate ((*R*,*R*,*R*)-9 and (*S*,*S*,*R*)-9).** The mixture of (*R*,*R*)-**8** and (*S*,*S*)-**8** (10 mg, 0.0587 mmol) was diluted in 0.2 mL of pyridine that had been distilled from

(17) For general experimental procedures, see: Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723−5728. Exceptions are noted.

KOH. The commercially available (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was also first distilled. An excess of the acid chloride (0.036 mL, 0.194 mmol) was added to the solution, resulting in the formation of a precipitate. The slurry was heated to dissolve the precipitate, which reformed on cooling. The heating and cooling cycle was repeated two more times to ensure complete reaction, which was verified by TLC. The reaction mixture was then partitioned between ethyl ether and 3 M aqueous HCl. The combined organic extract was dried (Na_2SO_4) and evaporated to yield 38 mg of a 1.0:2.2 mixture of the Mosher ester and the acid resulting from excess acid chloride as determined by ^{1}H NMR. The acid can be removed by washing the organic layer with 3 M aqueous NaOH, but this is unnecessary since it does not interfere with the % de calculation. A small portion of **9** was further purified to give an analytical sample: TLC R_f (10% MTBE/petroleum ether) = 0.73; IR (film) 1750, 1273, 1168, 1122, 1000, 720 cm^{-1}; ^{1}H NMR δ 7.5−7.4 (m, 5H), 4.3−4.1 (m, 2H), 3.53 (s, 3H), 1.9−1.1 (m, 16H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ u 166.7, 132.4, 121.9, 84.6 (q, J = 27.8 Hz), 69.9, 35.2, 32.4, 32.0, 29.7, 28.0, 24.1, 22.6; d 129.5, 128.4, 127.6, 55.4, 44.3, 42.5, 14.1; EI MS *m*/*z* (rel intensity) 386 (M$^+$, 0.11), 317 (0.76), 235 (0.18), 189 (64), 153 (35), 139 (11), 111 (46), 97 (85), 83 (90), 69 (80), 55 (100); HRMS (calcd for $C_{21}H_{29}O_3F_3$) 386.2069, found 386.2071.

Menthyl 2-Oxo-5-(1-pentyl)cyclopentanecarboxylate (11). CuI (845 mg, 4.44 mmol) was suspended in 10 mL of ether at −20 °C. A solution of *n*-BuLi in hexane (3.7 mL, 2.40 M, 8.88 mmol) was added dropwise to produce a black solution that was stirred at −20 °C for 15 min. A solution of cyclopropane **10** (618 mg, 2.22 mmol) in 10 mL of THF was added dropwise over 10 min, and the mixture was stirred at −20 °C for 2 h. The cooling bath was removed, and the mixture was allowed to warm to room temperature before it was partitioned between saturated aqueous ammonium chloride and MTBE. The organic extract was dried (Na_2SO_4), filtered through a pad of silica gel, and evaporated to a green oil. Column chromatography of the crude oil yielded keto ester **11** (615 mg, 82% from **10**) as a clear oil: TLC R_f (10% MTBE/petroleum ether) = 0.48; IR (film) 1756, 1722, 1258 cm^{-1}; ^{1}H NMR δ 4.8−4.6 (apparent dt, J = 4.4, 10.9 Hz, 1H), 2.76 (d, J = 11.2 Hz, 1H), 2.5 (m, 1H), 2.9−0.8 (m, 30H), 0.74 (d, J = 6.0, 3H); ^{13}C NMR δ u 212.2, 169.3, 40.6, 38.5, 35.2, 34.2, 31.9, 27.5, 27.1, 23.1, 22.5; d 75.2, 46.9, 41.6, 31.4, 27.0, 25.8, 22.0, 20.8, 15.9, 14.0; FAB MS *m*/*z* (rel intensity) 337 (M + 1, 8), 335 (M − 1, 9), 199 (100), 181 (78), 139 (44); HRMS (calcd for $C_{21}H_{36}O_3$) 336.2664, found 336.2665.

Menthyl 2-(1-Pentyl)cyclopentanecarboxylate (12). The keto ester **11** (563 mg, 1.67 mmol), tosylhydrazine (384 mg, 2.06 mmol), and 3 mL of THF were combined in a 5 mL reactivial and warmed to 65 °C for 43 h. The mixture was allowed to cool enough to permit the addition of $Na(CN)BH_3$ (146 mg, 2.32 mmol) and $ZnCl_2$ (320 mg, 2.34 mmol). It was then warmed to 65 °C for an additional 21 h. The mixture was allowed to cool and then was partitioned between MTBE and, sequentially, saturated aqueous sodium bicarbonate and 3 M aqueous HCl. The organic extract was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography to yield ester **12** (188 mg, 35% from **11**) as a clear oil: TLC R_f (10% MTBE/petroleum ether) = 0.74; IR (film) 1727, 1458, 1172 cm^{-1}; ^{1}H NMR δ 4.63 (apparent dt, J = 4.4, 10.9 Hz, 1H), 2.25 (m. 1H), 2.1−0.8 (m, 33H), 0.72 (d, J = 7.0, 3H); ^{13}C NMR δ u 176.4, 40.9, 35.4, 34.3, 32.7, 32.0, 30.5, 27.9, 24.9, 23.2, 22.6; d 73.7, 51.1, 46.8, 44.4, 31.0, 25.3, 21.1, 20.4, 16.2, 15.0; EI MS *m*/*z* (rel intensity) 185 (4), 167 (4), 138 (63), 123 (12), 95 (59), 83 (86), 69 (60), 55 (100); HRMS (calcd for $C_{21}H_{38}O_2$) 322.2872, found 322.2884.

***(R,R)*-(2-Pentyl)cyclopentanemethanol ((*R,R*)-8).** Menthyl ester **12** (180 mg, 0.56 mmol) was dissolved in 1 mL of THF in a sealed reactivial. To this was added $LiAlH_4$ (42 mg, 1.1 mmol), and the mixture was allowed to stir for 1 h at ambient temperature and 1 h at 100 °C. The mixture was then allowed to cool, and 50 μL of H_2O, 50 μL of 3 M aqueous NaOH solution, and 150 μL of H_2O dissolved in 150 μL of THF were added sequentially to the vigorously stirring mixture. The resultant slurry was then filtered through Celite, and the solvent was evaporated under vacuum. The difference in the TLC R_f of (*R*,*R*)-**8** and menthol (**13**) was very small with all solvent systems explored so column chromatography yielded three fractions: (A) pure **13** (26 mg), (B) a 1:2 mixture of **13** and (*R*,*R*)-**8** (68 mg), and (C) pure (*R*,*R*)-**8** (14 mg). The overall yield of **13** is 54%, and the overall yield of (*R*,*R*)-**8** is 64%. Fraction C gave spectra that were identical to those of the racemic (*R*,*R*)-**8**/(*S*,*S*)-**8** mixture.

***(R,R)*-(2-Pentyl)cyclopentanemethyl (*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetate ((*R,R,S*)-9).** Ester (*R*,*R*,*S*)-**9** was prepared by the same procedure as for (*R*,*R*,*R*)-**9** and (*S*,*S*,*R*)-**9** except that the commercially available (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was employed: TLC R_f (10% MTBE/petroleum ether) = 0.73; IR (film) 1832, 1748, 1272, 1170, 1123 cm^{-1}; ^{1}H NMR δ 7.5−7.3 (m, 5H), 4.4−4.1 (m, 2H), 3.54 (s, 3H), 2.0−1.1 (m, 16H), 0.86 (t, J = 7.0, 3H); ^{13}C NMR δ u 166.7, 132.4, 121.9, 85−84 (m), 69.8, 35.2, 32.4, 32.0, 29.6, 28.0, 24.1, 22.6; d 129.5, 128.3, 127.3, 55.4, 44.4, 42.5, 14.0; FAB MS *m*/*z* (rel intensity) 387 (M + 1, 2), 386 (M, 2), 385 (M − 1, 7), 235 (3), 203 (8), 189 (100), 165 (7), 153 (75), 139 (11), 105 (21); HRMS (calcd for $C_{21}H_{29}O_3F_3$) 386.2069, found 387.2145 (M + 1).

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Supporting Information Available: ^{1}H and ^{13}C spectra for all new compounds (16 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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