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Facially Selective and Regioselective Carbometalation of Cyclopropenes by Aryl Grignard Reagents

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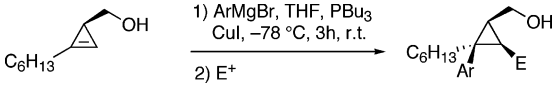

Described is a Cu-catalyzed methodology for adding aryl Grignard reagents to 3-hydroxymethylcyclopropene derivatives with high regio- and diastereoselectivity. The cyclopropylmetals can be trapped with a variety of electrophiles to generate highly substituted cyclopropanes.

Introduction

Cyclopropanes are the centerpieces of many rearrangements and cycloaddition reactions that rapidly build molecular complexity in a stereospecific fashion.[1] Accordingly, considerable effort has been directed toward the efficient production of highly substituted chiral derivatives.[2] Diastereoselective carbometalation and hydrometalation reactions of cyclopropenes have been the subject of recent attention,[3] as such transformations are well suited to the preparation of highly functionalized cyclopropanes.[4] In general, organometallic reagents react with 1-alkylcyclopropenes in a regioselective fashion to form quaternary centers.[4] In 1980, Bension and Richey described a method for delivering allyl Grignard reagents to the syn face of 1-alkyl-3-hydroxymethylcyclopropenes.[5] Araki and co-workers showed that allylindium reagents can also add with excellent diastereoselectivity to cyclopropene derivatives.[3l−o] Our group described a Cu-catalyzed carbomagnesation procedure that expanded the scope to alkyl, alkenyl, and alkynyl nucleophiles.[3p] These reactions are highly regio- and diastereoselective, and recently, an enantioselective variant has been described.[3r]

Despite the relatively broad scope of the hydroxyl-directed carbometalation protocols, the addition reactions of aryl nu-

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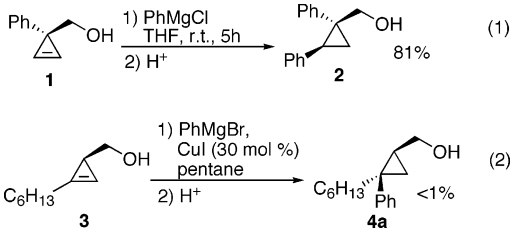
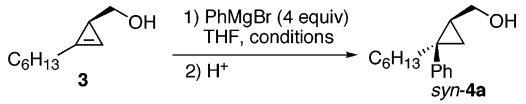
cleophiles were limited.[6] For cyclopropene derivatives such as **1**, which lack substituents on the alkene, our group has shown that the diastereoselective additions of Grignard reagents proceed cleanly without a catalyst.[3r] Thus, phenylmagnesium chloride adds to cyclopropene **1** to produce **2** in 81% yield (eq 1). However, the alkyl-substituted cyclopropene **3** is unreactive in the absence of a catalyst, and the previously reported conditions[3p] for carbometalation (10−30 mol % CuI, pentane, room temperature) gave only small amounts of adduct **4a** (eq 2).



Results and Discussion

To address the poor reactivity of **3**, we surveyed a number of copper catalyst systems for carbometalation (Table 1). While CuBr was an ineffective catalyst for the carbometalation (entry 1), CuI (30 mol %, THF, room temperature) gave *syn*-**4a**, *anti*-**4a**, and an isomeric material in a 7:1:0.6 ratio, respectively (entry 2). The inclusion of PBu_3 (1.2 equiv)/CuI (0.3 equiv) improved the selectivity for *syn*-**4a** to 87% at room temperature (entry 3), although no reaction took place when PBu_3 was included without CuI (entry 4). Tributylphosphine is well established as a ligand for Cu-catalyzed conjugate additions of Grignard reagents,[7] and PBu_3 has been utilized as a ligand in the CuBr/$Fe(acac)_3$ co-catalyzed arylmagnesation of alkynes.[8] Decreasing the reaction temperature also had a beneficial effect on the diastereoselectivity. For reactions conducted at 0 °C, the selectivity for *syn*-**4a** increased to 87% under phosphine-free conditions (entry 5) and to 91% with 30 mol % CuI and 1.2 equiv of PBu_3 (entry 6). The selectivity for *syn*-**4a** was further increased to >96% when the reaction was carried out at −78 °C, but the reaction only proceeded to ∼80% conversion after 3 h (entry 7). To avoid long reaction times at −78 °C, which would necessitate cryogenic cooling, the reaction with 30 mol % CuI and 1.2 equiv of PBu_3 was conducted for 3 h at −78 °C, and then slowly allowed to warm to room temperature over the course of 2 h. The selectivity for *syn*-**4a** was still excellent (96%) (entry 8). The carbometallation reaction did not reach completion with 10 mol % CuI/40 mol % PBu_3 (entry 10). The optimal ratio of PBu_3/CuI was 4:1; an experiment with a 2:1 ratio gave relatively low selectivity for *syn*-**4a** (entry 9). An experiment conducted with 3 equiv of PhMgBr and 30% CuI/1.2 equiv PBu_3 did not proceed to completion, but still gave *syn*-**4a** in 61% yield (entry 12). PhMgI works with an efficiency that is comparable to PhMgBr: *syn*-**4a** was obtained in 83% isolated yield and with >96% *syn*-selectivity (entry 11). Interestingly, the selectivity for *syn*-**4a** was considerably lower when PBu_3 was replaced by PPh_3: 28% of *anti*-**4a** was formed in a reaction carried out at 0 °C with 30 mol % of CuI and 1.2 equiv of PPh_3 (entry 13).

TABLE 1. Optimization of Conditions for Carbometalation



entry	conditions	*syn*-selectivity[a]
1	CuBr (10 mol %), 27 °C, 48 h	no reaction
2	CuI (30 mol %), 27 °C, 1 h	81% *syn*
3	CuI (30 mol %), PBu_3 (1.2 equiv), 27 °C, 1 h	87% *syn*
4	PBu_3 (40 mol %), 27 °C, 48 h	no reaction
5	CuI (30 mol %), 0 °C, 1 h	87% *syn*
6	CuI (30 mol %), PBu_3 (1.2 equiv), 0 °C, 1 h	91% *syn*
7	CuI (30 mol %), PBu_3 (1.2 equiv) −78°C, 3 h, quenched at −78 °C	>96% *syn* 80% conversion[b]
8	CuI (30 mol %), PBu_3 (1.2 equiv) −78 °C, 3 h, then warmed to r.t., 2 h	96% *syn* 83% yield[c]
9	CuI (30 mol %), PBu_3 (60 mol %) −78 °C, 3 h	92% *syn*
10	CuI (10 mol %), PBu_3 (40 mol %) −78 °C, 3 h, then warmed to r.t., 8 h	32% yield[c,e]
11	CuI (30 mol %), PBu_3 (1.2 equiv) with 4 equiv of PhMgI −78 °C, 3 h, then warmed to r.t., 5 h	>96% *syn* 83% yield[c]
12	CuI (30 mol %), PBu_3 (1.2 equiv) with 3 equiv of PhMgBr −78 °C, 3 h, then warmed to r.t., 8 h	96% *syn* 64% yield[c,e]
13	CuI (30 mol %), PPh_3 (1.2 equiv), −78 °C, 1 h	64% *syn*[d]

[a] Syn selectivity refers to the percentage of *syn*-**4a** relative to all isomers of **4a**, as determined by GC and GC/MS analysis of the crude reaction mixture. [b] Conversion (%) of the starting material as determined by GC or GC/MS analysis. Unless indicated, the starting material was completely consumed in other reactions. [c] Isolated yield. [d] The ratio of *syn*-**4a** to its anti diastereomer was 2.3:1. [e] Conversion of starting material was incomplete.

The conditions from entry 8 of Table 1 were then applied to cyclopropene **3** and a range of aryl Grignard reagents (Table 2). Regioselective and diastereoselective delivery of the aryl nucleophiles proceeded to selectively produce trisubstituted cyclopropanes of structure **4** after aqueous quench. While regioselectivity was high for all of the nucleophiles in Table 2, the facial selectivity was sensitive to steric factors. Thus, the reaction of **3** with *o*-tolylmagnesium bromide gave a 3:2 mixture of syn and anti diastereomers, whereas phenylmagnesium bromide and *m*-tolylmagnesium chloride gave the *syn*-diastereomers of **4a** and **4d** with 96% and 93% selectivity, respectively. Steric considerations also influence the additions of naphthyl Grignard reagents: β-naphthylmagnesium bromide gives **4e** with more than 95% selectivity for the syn diastereomer, whereas α-naphthylmagnesium bromide gives **4i** as a 5:1 mixture of syn and anti diastereomers.

Carbometalation reactions of cyclopropenes give rise to configurationally stable cyclopropylmetals that can be captured by a variety of different electrophiles.[4] As shown in Table 3,

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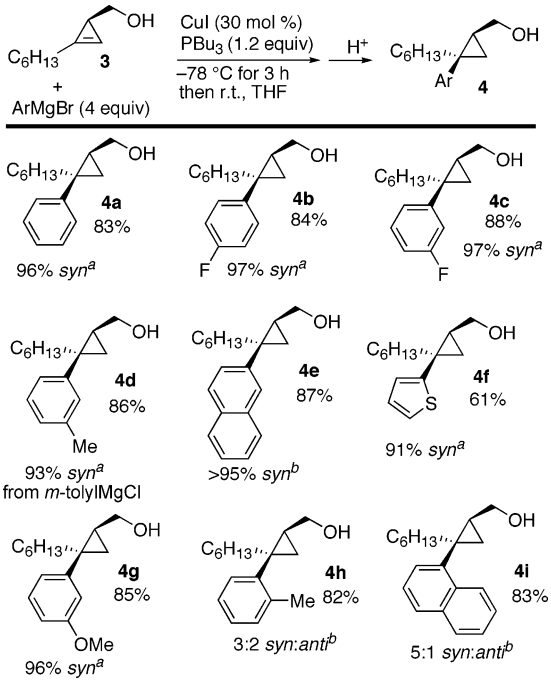
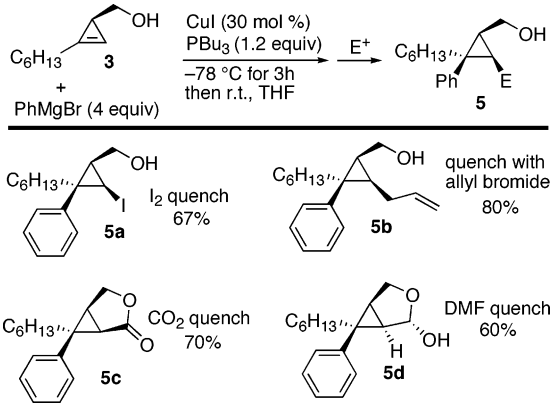
TABLE 2. Carbometalation by Aryl Grignard Reagents



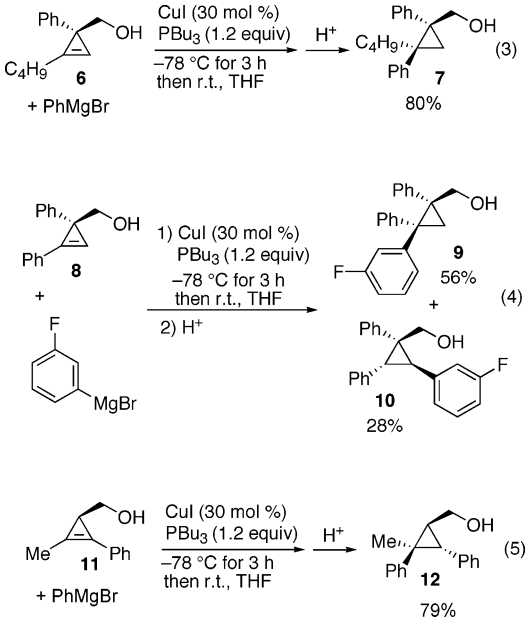
[a] Syn selectivity refers to the percentage of the product relative to all isomers of **4**, as determined by GC and GC/MS analysis of the crude reaction mixture. [b] Syn selectivity was measured by analysis of the crude reaction mixture by ^{1}H NMR.

TABLE 3. Carbometalation with Capture by Electrophiles



tetrasubstituted cyclopropanes of structure **5** are obtained when the product of phenylmagnesium bromide is quenched with I_2, allyl bromide, CO_2, or DMF.

The additions of arylmagnesium bromides to trisubstituted cyclopropenes **6**, **8**, and **11** were also studied (eqs 3−5). The addition of phenylmagnesium bromide to 1-butyl-3-phenyl-3-hydroxymethylcycloprop-1-ene (**6**) proceeded smoothly and with high selectivity to produce **7** after aqueous quench (eq 3). Analogous reaction of 3-fluorophenylmagnesium bromide with 1,3-diphenyl-3-hydroxymethylcycloprop-1-ene (**8**) also proceeded with high facial selectivity but gave a mixture of regioisomers **9** and **10** in a 2:1 ratio (eq 4). There was precedent that aromatic substituents on the cyclopropene double bond can alter the sense of regioselectivity in cyclopropene carbometalation.[3e,p] We hypothesize that the electronic (rather than steric) effect of the 1-phenyl substituent is responsible for the relatively low regioselectivity in the carbometallation of **8**. Based on this hypothesis, it was expected that the carbometallation of 1-phenyl-2-methyl-3-hydroxymethylcycloprop-1-ene (**11**) would take place with high regioselectivity. Indeed, the reaction of **11** with PhMgBr/CuI/PBu_3 produced tetrasubstituted cyclopropane **12** in 79% yield and with high isomeric purity (>95%) after aqueous workup (eq 5).



Assignments of stereochemistry were made by comparing the chemical shifts of carbometallation products to known compounds in the literature. The influence of a *syn*-phenyl group in compound **13** manifests in an upfield chemical shift for the methylene protons of the hydroxymethyl group. Thus, the methylene protons of **13** resonate at 3.20−3.24 ppm, whereas those of **14** resonate at relatively low field (3.71−3.91 ppm).[9] The assignment of stereochemistry for **4a** was based on comparison to **13** (Figure 1). High-field chemical shifts were observed for the methylene resonances of all of the carbometallation products described in Table 2. Analogously, the assignment of stereochemistry of **12** was based on the comparison to the chemical shifts of compounds **15**[10a] and **16**[10b] (Figure 1). The methylene protons of **12** resonate at chemical shifts that are similar to those of **15**, and upfield relative to **16**. Chemical shift anisotropy is also observed in the ^{1}H NMR spectra of **7**. The methylene protons of the hydroxymethyl group of **7** resonate at 3.02 and 3.53 ppm. Analogous protons on compounds **17**[3p] and **18**[3p] resonate at relatively low field (3.71 and 3.92 ppm for **17**; 3.61 and 3.78 ppm for **18**). On the butyl chain of **7**, the methylene protons closest to the cyclopropane are diastereotopic, and one of these protons resonates at high field (0.55−0.61 ppm) because of the influence of the *syn*-phenyl group. High field resonances had also been assigned to the analogous protons on compounds **17** (0.61 ppm) and **18** (0.47 ppm).[3p]

It is plausible that the Grignard reagent plays a non-innocent role in the mechanism of PBu_3/CuI catalyzed arylmagnesation reaction. Prior studies from our laboratories have suggested that

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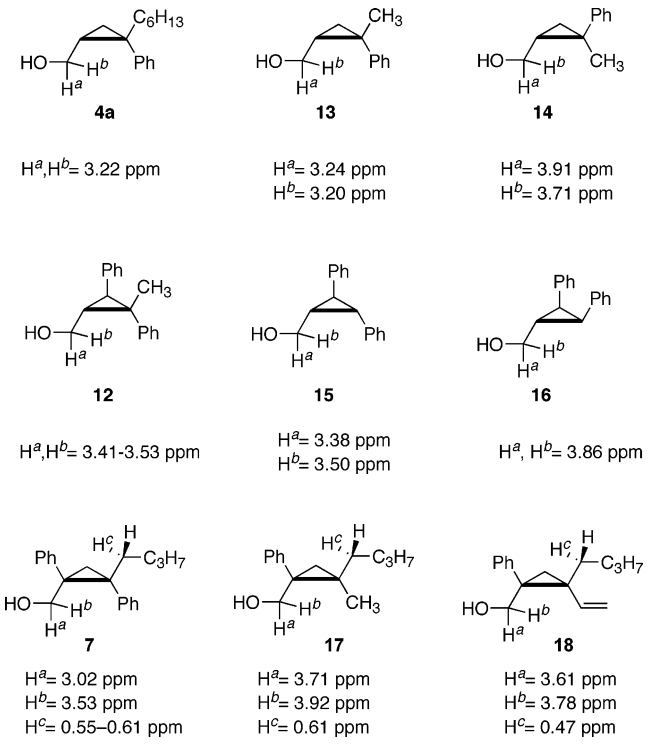

FIGURE 1. Stereochemical assignments for **4a**, **7**, and **12**.

the uncatalyzed reactions of cyclopropene derivatives with Grignard reagents are higher order in the Grignard reagent,[3q,r] and recent studies by Feringa and co-workers have shown that the rates of Cu-catalyzed enantioselective conjugate addition reactions are dependent on catalyst, substrate and Grignard reagent.[11] An excess of the aryl Grignard reagent is required for the reactions described herein, and it is plausible that the mechanism involves the cooperative action of magnesium and copper.

Conclusions

In summary, CuI/PBu_3 catalyzes the addition of aryl Grignard reagents to 3-hydroxymethylcyclopropene derivatives. The carbometalations are highly regio- and diastereoselective, and give rise to stereochemically complex cyclopropane derivatives that are not readily accessed using existing methodology.

Experimental

1α,2β-Diphenyl-1β-hydroxyphenylcyclopropane (2). Phenylmagnesium chloride (5.0 mL of a 1.0 M solution in THF, 5.0 mmol) was added dropwise via syringe to a solution of **1**[3r] (146 mg, 1.00 mmol) in THF (10 mL) that had been cooled by an ice bath. The reaction mixture was allowed to stir for 30 min at 0 °C. The ice bath was then removed, and the mixture was allowed to warm to room temperature and stir for 5 h. The mixture was again cooled by the ice bath, and reaction was quenched with aq HCl (0.5 M) and subsequently extracted with ether (25 mL). The aqueous layer was separated and twice extracted with additional ether (2 × 25 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (gradient of ethyl acetate/hexane) on silica gel to give 181 mg (0.81 mmol, 81%) of compound **2** as a white solid: mp 80.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50−7.52 (m, 2H), 7.33−7.40 (m, 6H), 7.24−7.30 (m, 2H), 3.56 (d, J = 3.2 Hz, 2H), 2.60 (dd, J = 6.4, 6.4 Hz, 1H), 1.46−1.49 (m, 1H), 1.40−1.44 (m, 1H), 1.20−1.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.0 (u). 138.3 (u), 129.41 (dn), 129.36 (dn), 129.0 (dn), 128.9 (dn), 127.2 (dn), 127.0 (dn), 67.3 (u), 35.0 (u), 30.2(dn), 16.0 (u); IR (KBr, cm^{-1}) 3050, 1601, 1495, 1447, 1202, 1044, 766, 697; HRMS (CI) m/z [M + NH_4^+] calcd for $C_{16}H_{20}NO$ 242.1545, found 242.1546.

General Procedures for Cu-Catalyzed Aryl Grignard Additions. To a 100 mL flame-dried round-bottomed flask were added CuI (57 mg, 0.30 mmol), distilled THF (50 mL), and PBu_3 (0.30 mL, 1.2 mmol) under nitrogen atmosphere. The mixture was allowed to stir at room temperature for 10 min, after which point the solution became colorless and homogeneous. The mixture was cooled by a cold bath at −78 °C (acetone/dry ice). Compound **3**[3p] (154 mg, 5.0 mL of a 0.20 M THF solution, 1.00 mmol) was added, followed by the appropriate aryl Grignard reagent (4.0 mmol). The reaction mixture was allowed to stir at −78 °C for 3 h. Without removing the cold bath, the mixture was gradually allowed to warm to room temperature while the dry ice dissipated (about 2 h). The reaction mixture was then quenched with the appropriate electrophile. For reactions that were quenched by water, distilled H_2O was added, and the mixture was rendered acidic by 3 M HCl. The solvent was removed under reduced pressure, and the aqueous layer was extracted with 3 × 30 mL portions of diethyl ether. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (10% diethyl ether in hexane) to provide the title compounds.

1α-Hexyl-2β-hydroxymethyl-1β-phenylcyclopropane (4a). The general procedure was followed using 4.0 mL of a 1.0 M phenylmagnesium bromide solution in THF (4.0 mmol). The yield of **4a** was 83% (193 mg, 0.83 mmol) as clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.30 (m, 4H), 7.19−7.22 (m, 1H), 3.22 (d, J = 6.8 Hz, 2H), 1.94−1.98 (m, 1H), 1.43 (br, 1H), 1.15−1.43 (m, 10H), 0.78−0.86 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.6 (u), 129.9 (dn), 128.2 (dn), 126.3 (dn), 64.2 (u), 41.8 (u), 31.8 (u), 31.6 (u), 29.3 (u), 26.81 (u), 26.79 (dn), 22.6 (u), 15.0 (u), 14.1 (dn); IR (neat, cm^{-1}) 3314 (br), 1448, 1378, 1034, 765, 701, 639; HRMS (CI) m/z [M^+] calcd for $C_{16}H_{24}O$ 232.1827, found 232.1837.

1α-Hexyl-2β-hydroxymethyl-1β-(4-fluorophenyl)cyclopropane (4b). The general procedure was followed using 4.0 mL of a 1.0 M 4-fluorophenylmagnesium bromide solution in THF (4.0 mmol). The yield of **4b**, a clear colorless oil, was 84% (210 mg, 0.84 mmol): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25−7.28 (m, 2H), 6.97−7.00 (m, 2H), 3.24 (d, J = 6.8 Hz, 2H), 1.88−1.92 (m, 1H), 1.53 (br s, 1H), 1.12−1.28 (m, 10H), 0.78−0.86(m, 4H), 0.77(t, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.4 (d, J = 243 Hz, u), 137.3 (d, J = 3 Hz, u), 131.4 (d, J = 7 Hz, dn), 115.0 (d, J = 21 Hz, dn), 64.1 (u), 41.9 (u), 31.8 (u), 31.0 (u), 29.3 (u), 26.8 (u), 26.7 (dn), 22.6 (u), 15.2 (u), 14.1(dn); IR (neat, cm^{-1}) 3354 (br), 2926, 2857, 1511, 1220, 1042, 838, 812, 730; HRMS (CI) m/z [M^+] calcd for $C_{16}H_{23}FO$ 250.1733, found 250.1732.

1α-Hexyl-2β-hydroxymethyl-1β-(3-fluorophenyl)cyclopropane (4c). The general procedure was followed using 4.0 mL of a 1.0 M 3-fluorophenylmagnesium bromide solution in THF (4.0 mmol). The yield of **4c** was 88% (220 mg, 0.88 mmol) as clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21−7.27 (m, 1H), 7.06−7.09 (m, 1H), 6.98−7.01 (m, 1H), 6.88−6.92(m, 1H), 3.22 (d, J = 6.8 Hz, 2H), 1.94−1.97 (m, 1H), 1.42 (br s, 1H), 1.12−1.30 (m, 10H), 0.80−0.85(m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.7 (d, J = 244 Hz, u), 144.4 (d, J = 7 Hz, u), 129.6(d, J = 8 Hz, dn), 125.5(d, J = 2 Hz, dn), 116.8 (d, J = 21 Hz, dn), 113.3 (d, J = 21 Hz, dn), 64.0 (u), 41.6 (u), 31.8 (u), 31.5 (d, J = 2 Hz, u), 29.3 (u), 26.9 (dn), 26.8 (u), 22.6 (u), 15.1 (u), 14.1(dn); IR (neat, cm^{-1}) 3343 (br), 2927, 2856, 1585, 1488, 1439, 1038, 879, 785, 705; HRMS (CI) m/z [M^+] calcd for $C_{16}H_{23}FO$ 250.1733, found 250.1732.

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1α-Hexyl-2β-hydroxymethyl-1β-(3-methylphenyl)cyclopropane (4d). The general procedure was followed using 4.0 mL of a 1.0 M *m*-tolylmagnesium chloride solution in THF (4.0 mmol). The yield of **4d** was 86% (212 mg, 0.86 mmol) as clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00−7.18 (m, 4H), 3.23 (d, J = 6.8 Hz, 2H), 2.33 (s, 3H), 1.90−2.01 (m, 1H), 1.12−1.26 (m, 11H), 0.81−0.85(m, 4H), 0.76−0.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.5 (u), 137.8 (u), 130.5 (dn), 128.1(dn), 127.1 (dn), 126.8 (dn), 64.3 (u), 41.8 (u), 31.8 (u), 31.5 (u), 29.4 (u), 26.9 (u), 26.8 (dn), 22.7 (u), 21.5 (dn), 14.9 (u), 14.1 (dn); IR (neat, cm^{-1}) 3344 (br), 2925, 2856, 1456, 1033, 785, 731, 709; HRMS (CI) *m*/*z* [M^+] calcd for $C_{17}H_{26}O$ 246.1984, found 246.1985.

1α-Hexyl-2β-hydroxymethyl-1β-(2-naphthyl)cyclopropane (4e). The general procedure was followed using 8.0 mL of a 0.5 M 2-naphthylmagnesium bromide solution in THF (4.0 mmol). The yield of **4e** was 87% (245 mg, 0.87 mmol) as a clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76−7.81 (m, 3H), 7.68 (s, 1H), 7.41−7.48 (m, 3H), 3.18−3.27 (m, 2H), 2.06−2.12 (m, 1H), 1.19−1.38 (m, 11H), 0.94−0.97 (m, 1H), 0.86−0.89 (m, 1H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 133.3, 132.2, 128.3, 128.0, 127.8, 127.5 (2C), 125.9, 125.4, 64.1, 41.5, 31.7, 29.7, 29.3, 26.8, 26.7, 22.5, 15.1, 14.0; IR (neat, cm^{-1}) 3295 (br), 2925, 1032, 856, 819, 745; HRMS (CI) *m*/*z* [M^+] calcd for $C_{20}H_{26}O$ 282.1984, found 282.1990.

1α-Hexyl-2β-hydroxymethyl-1β-thiophen-2-ylcyclopropane (4f). The general procedure was followed using 4.0 mL of a 1.0 M thiophen-2-ylmagnesium bromide solution in THF (4.0 mmol). Flash chromatography was performed rapidly to minimize losses of **4f**, which is only moderately stable on silica gel. The yield of **4f** was 61% (145 mg, 0.61 mmol) as clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15−7.16 (m, 1H), 6.91−6.93 (m, 1H), 6.82−6.83 (m, 1H), 3.47−3.50 (m, 1H), 3.18−3.23 (m, 1H), 1.94−2.02 (m, 1H), 1.17−1.39 (m, 11H), 0.83−0.95(m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.3 (u), 126.7 (dn), 126.0 (dn), 124.0 (dn), 63.6 (u), 41.9 (u), 31.8 (u), 29.2 (u), 28.4 (dn), 27.0 (u), 26.5 (u), 22.6 (u), 16.9 (u), 14.1 (dn); IR (neat, cm^{-1}) 3290 (br), 2926, 2856, 1462, 1027, 730, 692; HRMS (CI) *m*/*z* [M + H] calcd for $C_{14}H_{23}OS$ 239.1470, found 239.1458.

1α-Hexyl-2β-hydroxymethyl-1β-(3-methoxyphenyl)cyclopropane (4g). The general procedure was followed using 4.0 mL of a 1.0 M 3-methoxyphenylmagnesium bromide solution in THF (4.0 mmol). The yield of **4g** was 85% (223 mg, 0.85 mmol) as clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19−7.23 (m, 1H), 6.88−6.90 (m, 1H), 6.84−6.85 (m, 1H), 6.73−6,76 (m, 1H), 3.80 (s, 3H), 3.19−3.29 (m, 2H), 1.95−2.00 (m, 1H), 1.09−1.30 (m, 11H), 0.76−0.85 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5 (u), 143.3 (u), 129.2 (dn), 122.2 (dn), 115.9 (dn), 111.3 (dn), 64.2 (u), 55.2 (dn), 41.7 (u), 31.8 (u), 31.6 (u), 29.3 (u), 26.9 (dn), 26.8 (u), 22.6 (u), 15.0 (u), 14.1 (dn); IR (neat, cm^{-1}) 2926, 2855, 1600, 1581, 1453, 1236, 1089, 780, 706; HRMS (CI) *m*/*z* [M^+] calcd for $C_{17}H_{26}O_2$ 262.1933, found 262.1925.

1α-Hexyl-2β-hydroxymethyl-1β-(2-methylphenyl)cyclopropane (*syn*-4h) and 1β-Hexyl-2β-hydroxymethyl-1α-(2-methylphenyl)cyclopropane (*anti*-4h). The general procedure was followed using 4.0 mL of a 1.0 M *o*-tolylmagnesium bromide solution in THF (4.0 mmol). The yield of **4h** (syn/anti = 3/2) was 81% (200 mg, 0.81 mmol) as a clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) (resonances attributable to *syn*-**4h**) δ 7.07−7.16 (4H), 3.62−3.69 (m, 1H), 2.84 (dd, J = 8.4 and 11.2 Hz, 1H), 2.41 (s, 3H), 2.06−2.18 (m, 1H), 1.01−1.43 (m, 11H), 0.80−0.88 (m, 5H), (resonances attributable to *anti*-**4h**) δ 7.07−7.16 (m, 4H), 3.62−3.69 (m, 1H), 3.21−3.26 (m, 1H), 2.41 (s, 3H), 1.68−1.78 (m, 1H), 1.01−1.43 (m, 11H), 0.80−0.88 (m, 4H), 0.59−0.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) (resonances, both diasteromers) δ 139.2 (u), 139.1 (u), 138.3 (u), 137.5 (u), 131.5 (dn), 131.3 (dn), 130.9 (dn), 130.3 (dn), 126.4 (dn), 126.3 (dn), 125.4 (dn), 125.1 (dn), 64.8 (u), 63.6 (u), 41.3 (u), 39.3 (u), 31.8 (u), 31.7 (u), 31.2 (u), 30.2 (u), 29.5 (u), 29.4 (u), 27.4 (dn), 27.0 (u), 26.8 (u), 26.1 (dn), 22.6 (u), 19.7 (dn), 19.3 (dn), 18.6 (u), 15.4 (u), 14.1 (dn); IR (neat, cm^{-1}) 3307 (br), 2926, 2855, 1454, 1032, 762, 731; HRMS (CI) *m*/*z* [M^+] calcd for $C_{17}H_{26}O$ 246.1984, found 246.1992.

1α-Hexyl-2β-hydroxymethyl-1β-(1-naphthyl)cyclopropane (*syn*-4i) and 1β-Hexyl-2β-hydroxymethyl-1α-(1-naphthyl)cyclopropane (*anti*-4i). The general procedure was followed using 16.0 mL of a 0.25 M 1-naphthylmagnesium bromide solution in THF (4.0 mmol). The yield of **4i** (syn/anti = 5/1) was 83% (234 mg, 0.83 mmol) as clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) (resonances attributable to ***syn*-4i**) δ 8.30 (d, J = 8.4 Hz, 1H), 7.85−7.88 (m, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.25−7.57 (m, 4H), 3.25−3.30 (m, 1H), 2.93−3.00 (m, 1H), 2.34−2.41 (m, 1H), 1.62−1.66 (m, 1H), 1.40−1.50 (m, 1H), 0.95−1.33 (m, 11H), 0.85−0.88 (m, 1H), 0.77−0.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.7 (u), 134.0 (u), 132.3 (u), 129.0 (dn), 128.8 (dn), 127.3 (dn), 125.8 (dn), 125.6 (dn), 125.4 (dn), 124.7 (dn), 64.2 (u), 40.2 (u), 31.8 (u), 30.8(u), 29.2 (u), 27.8 (dn), 27.3 (u), 22.6 (u), 15.1 (u), 14.0 (dn), (resonances attributable to ***anti*-4i**) δ 8.42 (d, J = 8 Hz, 1H), 7.85−7.88 (m, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.25−7.57 (m, 4H), 3.64−3.73 (m, 1H), 3.33−3.39 (m, 1H), 1.96−2.13 (m, 2H), 0.95−1.33 (m, 11H), 0.85−0.88 (m, 1H), 0.80−0.83 (m, 3H); IR (neat, cm^{-1}) 3319 (br), 2927, 1088, 1047, 802, 779, 732; HRMS (CI) *m*/*z* [M^+] calcd for $C_{20}H_{26}O$ 282.1984, found 282.1976.

1α-Hexyl-2β-hydroxymethyl-3β-iodo-1β-phenylcyclopropane (5a). The general procedure was followed using 4.0 mL of a 1.0 M phenylmagnesium bromide solution in THF (4.0 mmol). The reaction was quenched by the addition of iodine (1.5 g, 6.0 mmol), and the mixture was then allowed to stir at room temperature for 2 h. Distilled H_2O was added followed by saturated aq $Na_2S_2O_3$ until the organic layer was almost colorless. The aqueous layer was extracted with 3 × 30 mL portions of diethyl ether. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (10% diethyl ether in hexane) to provide **5a** (240 mg, 0.67 mmol, 67%) as a clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.36 (m, 2H), 7.25−7.29 (m, 2H), 7.20−7.22 (m, 1H), 3.87−3.91 (m, 1H), 3.27−3.33 (m, 1H), 2.95 (d, J = 8.0 Hz, 1H), 1.65−1.68 (m, 1H), 1.58−1.62 (m, 1H), 1.44−1.52 (m, 1H), 1.17−1.28 (m, 9H), 0.83 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5 (u), 131.0 (dn), 128.1 (dn), 127.0 (dn), 66.3 (u), 43.6 (u), 35.0 (u), 31.8 (u), 29.2 (u), 28.5 (dn), 26.6 (u), 22.6 (u), 14.1 (dn), 5.3 (dn); IR (neat, cm^{-1}) 3317 (br), 2926, 1021, 764, 703; HRMS (CI) *m*/*z* [M − OH] calcd for $C_{16}H_{22}I$ 341.0766, found 341.0759.

1α-Hexyl-2β-hydroxymethyl-3β-allyl-1β-phenylcyclopropane (5b). The general procedure was followed using 4.0 mL of a 1.0 M phenylmagnesium bromide solution in THF (4.0 mmol). The reaction was quenched by the addition of allyl bromide (0.80 mL, 6.0 mmol), and the reaction mixture was allowed to stir at room temperature for 10 h. Distilled H_2O was added, and the aqueous layer was extracted with 3 × 30 mL portions of diethyl ether. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (10% diethyl ether in hexane) to provide **5b** (218 mg, 0.80mmol, 80%) as a clear colorless oil. A small amount of **4a** (12 mg, 0.05mmol, 5%) was also isolated: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26−7.32 (m, 2H), 7.19−7.24 (m, 1H), 7.15−7.18 (m, 2H), 5.98−6.08 (m, 1H), 5.08−5.17 (m, 2H), 3.80 (dd, J = 5.6, 11.2 Hz, 1H), 3.28 (dd, J = 8.8, 11.6 Hz, 1H), 2.36−2.43 (m, 1H), 1.67−1.74 (m, 1H), 1.38−1.53 (m, 3H), 1.16−1.34 (m, 10H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.4 (dn), 139.3 (u), 131.0 (dn), 128.1(dn), 126.2 (dn), 114.8 (u), 61.2 (u), 44.7(u), 34.4 (u), 31.9 (u), 30.5 (u), 29.3 (u), 28.8 (dn), 26.6 (u), 25.7 (dn), 22.7 (u), 14.1 (dn); IR (neat, cm^{-1}) 3323 (br), 2926, 1016, 909, 732, 705; HRMS (CI) *m*/*z* [M − OMe] calcd for $C_{18}H_{25}$ 241.1956, found 241.1955.

6-*exo*-Hexyl-6-*endo*-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (5c). The general procedure was followed using 4.0 mL of a 1.0 M phenylmagnesium bromide solution in THF (4.0 mmol). The reaction was quenched by the addition of carbon dioxide, which was passed through a drying tube filled with 4 Å molecular sieves

and bubbled into the reaction solution at a rate of ~1 bubble/s. The reaction mixture was allowed to stir at room temperature for 5 h while the CO_2 was introduced. The reaction solution was then rendered acidic by 3 M HCl and was allowed to stir at room temperature for 10 h. The aqueous layer was extracted with 3 × 30 mL portions of ethyl acetate. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (10% diethyl ether in hexane) to provide **5c** (181 mg, 0.70 mmol, 70%) as a clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.38 (m, 2H), 7.26−7.31 (m, 3H), 4.30 (dd, J = 5.2, 10 Hz, 1H), 4.03 (d, J = 9.6 Hz, 1H), 2.36−2.41 (m, 2H), 1.64−1.68 (m, 1H), 1.17−1.38 (m, 9H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9 (u), 135.2 (u), 129.6 (dn), 128.9 (dn), 127.7 (dn), 66.6 (u), 40.8 (u), 37.6 (u), 31.7 (u), 30.8 (dn), 30.0 (dn), 29.1 (u), 26.4 (u), 22.5 (u), 14.0 (dn); IR (neat, cm^{-1}) 2928, 1758, 1178, 1043, 982, 776, 704; HRMS (CI) m/z [M^+] calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1611.

6-*exo*-Hexyl-6-*endo*-phenyl-2-*exo*-hydroxy-3-oxabicyclo[3.1.0]-hexane (5d). The general procedure was followed using 4.0 mL of a 1.0 M phenylmagnesium bromide solution in THF (4.0 mmol). In another 100 mL round-bottomed flask, anhydrous DMF (2.0 mL) and THF (5.0 mL) were allowed to stir under nitrogen atmosphere. The reaction mixture was then transferred dropwise via syringe to the flask containing the DMF solution. The resulting mixture was allowed to stir at room temperature for 2 h. Distilled H_2O was added, and the aqueous layer was extracted with 3 × 30 mL portions of diethyl ether. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (10% diethyl ether in hexane) to provide **5d** (156 mg, 0.60 mmol, 60%) as a clear colorless oil, along with **4a** (58 mg, 0.25 mmol, 25%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.31 (m, 2H), 7.20−7.24 (m, 1H), 7.09−7.11 (m, 2H), 5.09 (app d, J = 4.0 Hz, 1H), 4.00 (dd, J = 3.2, 8.8 Hz, 1H), 3.69 (d, J = 8.8 Hz, 1H), 3.26 (d, J = 4.4 Hz, 1H), 1.93−1.87 (m, 2H), 1.36−1.43 (m, 2H), 1.16−1.21 (m, 8H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.7 (u), 129.2 (dn), 128.1 (dn), 126.4 (dn), 97.4 (dn), 65.9 (u), 41.2 (u), 35.5 (dn), 33.2 (u), 31.8 (u), 29.4 (u), 28.3 (dn), 26.4 (u), 22.7 (u), 14.1 (dn); IR (neat, cm^{-1}) 3375 (br), 2928, 1080, 995, 768, 704; HRMS (CI) m/z [M + H] calcd for $C_{17}H_{25}O_2$ 261.1855, found 261.1847.

1α-Butyl-1β,2α-diphenyl-2β-hydroxymethylcyclopropane (7). The general procedure was followed using compound **6**[3p] (202 mg, 5.0 mL of a 0.2 M THF solution, 1.00 mmol) and 4.0 mL of a 1.0 M phenylmagnesium bromide solution in THF (4.0 mmol). The residue was chromatographed on silica gel (10% diethyl ether in hexane) to provide **7** (225 mg, 0.80 mmol, 80%) as clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22−7.45 (m, 10H), 3.53 (dd, J = 4.8, 11.6 Hz, 1H), 3.02 (dd, J = 7.2, 11.6 Hz, 1H), 1.70−1.76 (m, 1H), 1.46 (dd, J = 1.6, 4.8 Hz, 1H), 1.17 (d, J = 5.2 Hz, 1H), 0.96−1.13 (m, 5H), 0.66 (t, J = 6.8 Hz, 3H), 0.55−0.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.8 (u), 140.3 (u), 130.4 (dn), 129.5 (dn), 128.5 (dn), 128.3 (dn), 126.8 (dn), 126.4 (dn), 69.7 (u), 38.5 (u), 38.4 (u), 36.4 (u), 29.2 (u), 22.6 (u), 20.4 (u), 14.0 (dn); IR (neat, cm^{-1}) 2933, 1032, 1016, 762, 738, 696; HRMS (CI) m/z [M − OH] calcd for $C_{20}H_{23}$ 263.1800, found 263.1795.

1α,2α-Diphenyl-2β-(3-fluorophenyl)-1β-hydroxymethylcyclopropane (9) and 1α,3α-Diphenyl-2β-(3-fluorophenyl)-1β-hydroxymethylcyclopropane (10). The general procedure was followed using compound **8**[12,13] (222 mg, 5.0 mL of a 0.2 M THF solution, 1.00 mmol) and 4.0 mL of a 1.0 M 3-fluorophenylmagnesium bromide in THF (4.0 mmol). The residue was chromatographed on silica gel (7% diethyl ether in hexane) to provide **9** (180 mg, 0.57 mmol, 57%) as a white solid and **10** (85 mg, 0.27 mmol, 27%) as clear colorless oil. The combined isolated yield of two diasteromers was 84%.

9: mp 108−110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15−7.36 (m, 7H), 7.07−7.12 (m, 1H), 6.89−6.98 (m, 6H), 3.98 (dd, J = 4.8, 11.6 Hz, 1H), 3.38 (dd, J = 6.4, 11.6 Hz, 1H), 2.21 (d, J = 5.2 Hz, 1H), 1.74 (d, J = 5.6 Hz, 1H), 1.36 (t, J = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.8 (d, J = 245 Hz), 145.1 (d, J = 7 Hz), 141.6, 138.2, 130.1, 130.0 (d, J = 8 Hz), 129.0, 128.2, 127.6, 126.7, 125.83, 125.79, 117.1 (d, J = 21 Hz), 113.7 (d, J = 21 Hz), 69.2, 42.2, 40.2, 22.0; IR (neat, cm^{-1}) 3210 (br), 1585, 1486, 1048, 795, 754, 705, 691; HRMS (CI) m/z [M − OH] calcd for $C_{22}H_{18}F$ 301.1393, found 301.1388.

10: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.36 (m, 2H), 7.19−7.26 (m, 6H), 7.06−7.14 (m, 3H), 6.96−7.02 (m, 1H), 6.84−6.87 (m, 2H), 3.82 (dd, J = 6.0, 11.6 Hz, 1H), 3.51 (dd, J = 6.8, 11.6 Hz, 1H), 3.21 (d, J = 6.8 Hz, 1H), 2.82 (d, J = 6.4 Hz, 1H), 1.20 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.9 (d, J = 244 Hz, u), 140.3 (d, J = 7 Hz, u), 138.3 (u), 137.5 (u), 131.0 (dn), 130.0 (d, J = 8 Hz, dn), 128.4 (dn), 127.83 (dn), 127.79 (dn), 127.1 (dn), 125.9 (dn), 124.9 (d, J = 3 Hz, dn), 116.2 (d, J = 21 Hz, dn), 113.8 (d, J = 21 Hz, dn), 67.8 (u), 44.1 (u), 34.2 (d, J = 2 Hz, dn), 32.2 (dn); IR (neat, cm^{-1}) 3361 (br), 1612, 1586, 1491, 1262, 1099, 1043, 792, 696, 669; HRMS (CI) m/z [M − OH] calcd for $C_{22}H_{18}F$ 301.1393, found 301.1393.

1β,3α-Diphenyl-2β-hydroxymethyl-1α-methylcyclopropane (12). The general procedure was followed using **11**[14] (160 mg, 5.0 mL of a 0.2 M THF solution, 1.0 mmol) and 4.0 mL of a 1.0 M phenylmagnesium bromide solution in THF (4.0 mmol). The residue was chromatographed on silica gel (7% diethyl ether in hexane) to provide **12** (188 mg, 0.79 mmol, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45−7.28 (m, 2H), 7.32−7.38 (m, 6H), 7.22−7.27 (m, 2H), 3.41−3.53 (m, 2H), 2.49 (d, J = 6 Hz, 1H), 1.77 (dd, J = 6.4, 13.6 Hz, 1H), 1.27 (br s, 1H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.1 (u), 138.3 (u), 129.2 (dn), 129.1 (dn), 128.6 (dn), 128.2 (dn), 126.6 (dn), 126.2 (dn), 64.0(u), 33.5 (u), 32.1 (dn), 31.8 (dn), 23.7 (dn); IR (neat, cm^{-1}) 3296 (br), 1025, 763, 740, 696; HRMS (CI) m/z [M − OH_2] calcd for $C_{17}H_{16}$ 220.1252, found 220.1249.

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Supporting Information Available: General experimental considerations and evidence for stereochemical assignments are provided. ^{1}H NMR and ^{13}C NMR spectra are displayed for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For the preparation of nonracemic **8**: Liao, L.-a.; Zhang, F.; Yan, N.; Golen, J. A.; Fox, J. M. *Tetrahedron* **2004**, *60*, 1803.

(13) Racemic **8** could be prepared by DIBAL reduction[3p] of methyl 1,2-diphenylcycloprop-2-ene carboxylate.[12]

(14) Wu, H.-P.; Weakley, T. J. R.; Haley, M. M. *Chem. Eur. J.* **2005**, *11*, 1191.