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Regio- and Stereocontrol in the Michael-Initiated Ring-Closure Reactions of γ,δ-Epoxy-α,β-unsaturated Esters, Ketones, Sulfones, and Amides

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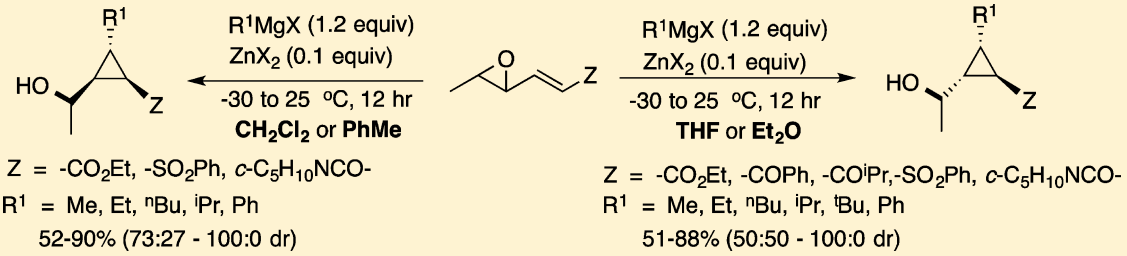
Supporting Information



ABSTRACT: Organozincates or Grignard reagents in the presence of zinc catalysts undergo Michael initiated ring closure (MIRC) reactions with γ,δ-epoxy-α,β-enoates, enones, enesulfones, and enamides to afford 1,2,3-trisubstituted cyclopropanes. The direction of diastereoselectivity is solvent dependent for alkyl Grignard reagents reacting with epoxy enoates, ensulfones, and enamides but solvent independent for the enones. Excellent diastereoselectivity can be achieved for the epoxy enoates, enones, and ensulfones, while the enamides afford modest diastereoselectivity under optimal conditions. The MIRC reaction can be achieved with phenylmagnesium chloride and these substrates under reaction conditions designed to minimize biphenyl formation.

INTRODUCTION

The rich functionality of γ,δ-epoxy-α,β-enoates (e.g., **1**) provides opportunities for nucleophilic attack at the epoxide, alkene, and ester functionalities. We, and others, have examined copper reagents for preferential S_N2'-allylic substitution on these substrates with the aim of controlling the variable regio- and stereoselectivity of the reaction.[1,2] The modest to good regio- and stereoselectivities observed with the epoxyenoate led us to examine the reactions of 5-acetoxy-4-halo-2-enoates with copper reagents where good to excellent regio- and stereoselectivities were observed.[3] However, a variety of heteroatom nucleophiles, particularly metal halides,[4] effect direct S_N2-substitution on the epoxide at the allylic position of epoxyenoates, and in an effort to extend this regiochemistry to carbon nucleophiles we examined the possibility of using zinc reagents that were reported to be S_N2-regioselective on simple allylic epoxides.[5] Recently, an effective iron-catalyzed protocol for S_N2-selectivity on these substrates has been reported.[6] Our studies have uncovered a Michael initiated ring closure[7] (MIRC) reaction involving organozincates and γ,δ-epoxy-α,β-unsaturated substrates.

Little and Dawson coined the term Michael initiated ring closure (MIRC) to describe the addition of lithium thiolate or amide nucleophiles to α,β-unsaturated carbonyl systems containing an appended electrophile, which upon reaction with the resultant carbonyl enolate anion formed a ring.[8] Application of this strategy of nucleophilic conjugate addition−cyclization has been tabulated in a number of reviews[7] with the principal approach relying on conjugate addition of phosphonium,[9] sulfonium,[10] arsonium,[11a,b] or telluronium[11c,d] ylides[12] where the leaving group is attached to the nucleophile effecting conjugate addition.[7a] Conjugate addition of enolates generated from α,α-dichloroimines represent another example of this tactic.[13]

The protocol has been successfully applied for the construction of three-, four-,[14] five-, six-, and seven-membered rings. Michael acceptors containing a leaving group in the γ-position are largely limited to γ-halo-α,β-unsaturated esters,[7b,15,16] ketones,[15,16] sulfones,[15,17] and nitroalkenes[15] since participation of γ,δ-epoxy-α,β-unsaturated substrates in MIRC reactions have been limited to bis-activated alkenes[14b,18] or use of dithianyl[19] anions as other organolithium and Grignard reagents failed. Cyclopropane formation has been achieved by conjugate addition of organolithium reagents to γ-chloro-α,β-unsaturated acylphosphanes,[20] and an efficient MIRC enantioselective synthesis of *trans*-1,2-disubstituted cyclopropyl esters and ketones[16] appears limited to 4-halocrotonates and 4-haloketones given our recent work on γ,δ-epoxy-α,β-enonates, which undergo allylic substitution in the presence of Grignard reagents and Cu(I) salts.[2,3] Zinc glycinate enolates participate[14a,21] in MIRC reactions, and γ-phosphoryl enoates[14a,21] have been employed. MIRC reactions leading to five- and six-membered rings have been observed with cuprate-mediated

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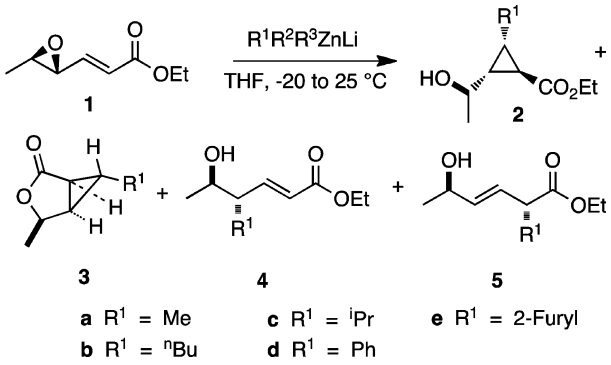
Table 1. Reaction of Triorganozincate Reagents with Ethyl 4,5-Epoxy-2,3-hexenoate (1)



					% yield[b]			
entry	R^1	R^2	R^3	temp (°C) (h)[a]	**2**	**3**	**4**:**5**	dr **2**[c]
1	Me	Me	Me	25 (12)	65			100:0
2	^{n}Bu	^{n}Bu	^{n}Bu	−20 (2)	74	5		96:4
3	^{n}Bu	Me	Me	−20 (3)	71	5		98:2
4	^{n}Bu	Me	^{t}Bu	−20 (3)	83			100:0
5	^{n}Bu	^{t}Bu	^{t}Bu	−20 (4)	70			97:3
6	^{n}Bu	C_6H_9[d]	C_6H_9[d]	−20 to 25			56[e]	
7	^{i}Pr[f]	Me	Me	−20 (6)	61		18[g]	100:0
8	Ph[h]	Me	Me	−20 to 25 (12)	32			100:0
9	2-furyl	Me	Me	−20 to 25 (12)			57[i]	

[a]Reactions were run in THF at the indicated temperature and quenched at that temperature unless otherwise noted. [b]Yields are based upon isolated products purified by column chromatography. [c]Diastereomeric ratios were determined from integration of the ^{1}H NMR carbinol CH-hydrogen absorptions or via peak heights of the ^{13}C NMR carbinol carbon absorptions. The minor diasteromer is either **25** or **26** (Scheme 1, R = ^{n}Bu). [d]C_6H_9 = 1-hexynyl. [e]Isomer ratio of **4**:**5** = 76:24. [f]The magnesium zincate was employed. [g]An inseparable 1:1 mixture of regioisomers **4**:**5** was obtained. [h]Run in Et_2O. Biphenyl was obtained in 37% yield. [i]The ratio of **4**:**5** > 95:5 and **5** was not detected in the NMR spectrum.

conjugate addition reactions and have been the subject of recent investigations.[22]

Although compatible with a wide range of functional groups, monoalkyl and dialkylzinc reagents[23] are generally unreactive toward common electrophiles in the absence of additives[24] or transmetalation to transition metals (e.g., Pd, Cu, Ni, Ti, Zr) that can mediate a variety of transformations.[23,25] Reported 1,4-conjugate additions of RZnX or R_2Zn to enoates appear to involve radical mediated pathways promoted by molecular oxygen.[26] Organozincates[27] (i.e., R_3ZnM, R_4ZnM_2), readily prepared by transmetalation from organolithium and Grignard reagents or by halogen−zinc exchange, effect halogen−metal exchange, open epoxides,[5] and undergo 1,4-conjugate addition reactions[28,29] with sterically unhindered enones. Zincate conjugate additions to enoates are limited to two examples involving a β-unsubstituted enoate[26b] and an intramolecular ring closure involving a tetracoordinate zincate (i.e., $R_3R^1ZnLi_2$).[30] The more reactive silyl- and stannylorganozincates transfer the heteroatom ligand to enals, enones, enoates, and enamides in conjugate addition reactions.[27,31] Zincate structural studies[32,33] and mechanistic studies on conjugate addition reactions have been reported.[34] Difficult conjugate additions of organozincates to vinylpyridines have been effected with Ni catalysis,[35] which have also been utilized to promote asymmetric conjugate additions of dialkylzinc reagents to chalcones[36] and to effect 1,4-additions of trialkylindium reagents to enones, enoates and ennitriles.[37]

We now report a general MIRC methodology for the regio- and stereoselective preparation of 1,2,3-trisubstituted cyclopropanes from γ,δ-epoxy-α,β-unsaturated ketones, esters, sulfones, and amides involving unprecedented zincate mediated conjugate additions.

RESULTS AND DISCUSSION

Treatment of the epoxide of ethyl sorbate (**1**) with either lithium trimethyl- or tri-*n*-butylzincate in THF afforded clean conjugate addition−epoxide opening to give **2a**,**b** with high regioselectivity and diastereoselectivity (Table 1, entries 1 and 2), although lithium trimethylzincate required higher temperatures and longer reaction times (entry 1). The only other product observed was the known lactone **3b**[38] arising from the hydroxy ester via intramolecular trans-esterification either under the reaction conditions or during workup. Similar results were obtained with mixed lithium trialkylzincate reagents where two of the ^{n}Bu-ligands were replaced with methyl or ^{t}Bu ligands (entries 3−5). In all cases, the latter two ligands functioned as nontransferable ligands relative to the ^{n}Bu-ligand when used in various combinations. Transfer of the ^{n}Bu group generally gave two cyclopropane products, as evidenced by DEPT NMR studies, with very high diastereoselectivity (entries 2, 3, and 5). The relative stereochemistry of the major isomer **2** was established by X-ray crystallography of a derivative (vida infra), and the minor isomer is unlikely to be the diastereomer leading to **3** since we could not convert **3** to the hydroxy ester via trans-esterification procedures.

Utilization of 1-hexyne as a potentially residual nontransferable ligand altered the course of the reaction pathway. Here, S_N2-epoxide opening afforded **4b** as the major product along with significant amounts of the S_N2'-allylic substitution product **5b** (entry 6) in a 76:24 ratio. The mixed isopropyldimethylzincate selectively transferred the ^{i}Pr group

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but gave significant amounts of **4c** and **5c** as a 1:1 mixture of regioisomers (entry 7). These products (i.e., **4b-c** and **5b-c**) were identified by comparison of the NMR spectra with the known compounds.[2] The mixed phenyldimethylzincate gave poor yields of conjugate addition−epoxide opening accompanied by substantial amounts of biphenyl (entry 8), while the 2-furyldimethylzincate gave epoxide opening without conjugate addition (entry 9). The formation of biphenyl could not be suppressed by changing the solvent or reaction temperature.

In an effort to isolate the conjugate addition reaction from the ring-closing reaction, the temperature profile of the reactions was examined (Table 2). Although conjugate addition

Table 2. Temperature and Solvent Dependence in the Reaction of $^{n}Bu_3ZnLi$ with Ethyl 4,5-Epoxy-2,3-enoate (1)

entry	temp[a] (°C)	time (h)	1:2b:3b[b]	dr 2b[c]	% yield[d]
1	−78	3	100:0:0		
2	−55	2	60:40:0		
3	−55	4	45:55:0		
4	−35	3	0:94:6		
5	−20	0.5	16:72:12		
6	−20	1	0:95:5		
7	−20	2	0:95:5	96:4	82
8[e]	−20	3	0:98:2	97:3	81
9[f]	−20	3	0:0:100		82

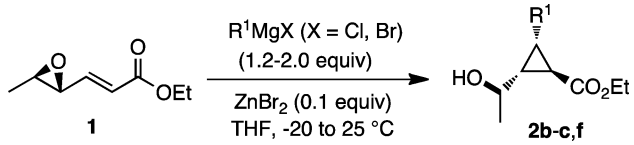
[a]The reaction was carried out at this temperature for the specified time in THF unless otherwise noted. [b]The ratio was determined by integration of ^{1}H NMR absorptions. [c]The dr of **2b** was determined by integration of ^{1}H NMR absorptions of the carbinol methine proton. DEPT NMR experiments established the cyclopropane composition for each diasteromer. [d]Yields are based upon isolated products purified by column chromatography. [e]The reaction was carried out in Et_2O. [f]The reaction was carried out in CH_2Cl_2.

and epoxide opening did not occur at −78 °C (entry 1), both reactions occurred slowly at −55 °C (entries 2 and 3) and rapidly at −20 °C (entries 5−7). In no instance could the conjugate addition reaction be disentangled from the epoxide opening reaction, suggesting that cyclopropane formation is competitive with or faster than the conjugate addition reaction. The reaction was also facile in Et_2O and CH_2Cl_2, although in the latter solvent the diastereoselectivity was reversed leading subsequently to formation of lactone **3b**.

In an effort to minimize the amount of organometallic reagent required, procedures catalytic in zinc(II) salts were employed. Treatment of **1** with ^{n}BuMgCl in the presence of TMSCl and with no added $ZnBr_2$ gave a complex mixture of products along with complete consumption of starting epoxide.[39] However, utilization of 0.1 equiv of $ZnBr_2$ gave the cyclopropane products in yields comparable to those obtained with stoichiometric amounts of zincate reagents (Tables 2 and 3) with the exception of MeMgCl, which gave 65% yield of **2a** under stoichiometric conditions and only recovered starting material under conditions catalytic in $ZnBr_2$ (Table 1, entry 1 vs Table 3, entry 1).

The reactions of *γ,δ*-epoxy-*α,β*-unsaturated ketones, sulfones, and amides with Grignard reagents and catalytic amounts of $ZnBr_2$ were examined to explore the generality and scope of this MIRC methodology (Table 4). Reaction of *γ,δ*-epoxy-*α,β*-unsaturated phenyl ketone **6** with methyl-, ethyl-, *n*-butyl-, and *i*-propylmagnesium halides in the presence of catalytic amounts of zinc bromide (10 mol %) in THF gave good yields of MIRC products **10a−d** with excellent diastereoselectivities (entries 1−

Table 3. Zinc Bromide Catalyzed Reaction of Grignard Reagents with Ethyl 4,5-Epoxy-2,3-hexenoate (1)



1 **2b-c,f**

entry	R^1	R^1 MgX[a] (equiv)	product	% yield[b]
1	Me	2.0	**2a**	*c*
2	Et	2.0	**2f**	73
3	^{n}Bu	2.0[d]	**2b**	85
4	^{n}Bu	2.0	**2b**	85
5	^{n}Bu	1.2	**2b**	85
6	^{i}Pr	2.0	**2c**	80
7	^{i}Pr	1.2	**2c**	82

[a]Reactions were carried out from −20 °C to room temperature unless otherwise noted. [b]Yields are based upon isolated material purified by column chromatography. [c]Only recovered starting material was obtained. [d]TMSCl (2.0 equiv) was added.

7). The direction of diastereoselectivity was unaffected by solvent polarity affording the same major diastereomer in both THF and CH_2Cl_2 (entries 2 vs 4 and 5 vs 6). Although epoxy isopropyl enone **7** gave cyclopropanes in excellent yields and diasteoselectivities upon reaction with ^{n}BuMgCl (entries 9−11), ^{i}PrMgCl (entry 12), or ^{t}BuMgCl (entry 13) in the presence of catalytic amounts of $ZnBr_2$, MeMgCl failed to react with **7** upon stirring at room temperature for 36 h (entry 8), while reaction in toluene gave recovered starting material or, in one instance, S_N2-opening of the epoxide at the allylic position.

The chemical yields and diastereoselectivities in the reactions of *γ,δ*-epoxy-*α,β*-unsaturated phenyl sulfone **8** with Grignard reagents were dependent upon the solvent employed (Table 4, entries 14−21). Enesulfone **8** failed to react with MeMgCl and $ZnBr_2$ (10 mol %) in THF (entry 14) but did afford cyclopropane **16a** diastereoselectively and in good yield (entry 15) when toluene was employed. Reaction of **8** with ^{n}BuMgCl and catalytic amounts of zinc bromide (10 mol %) in THF gave cyclopropane **12c** with poor diastereoselectivity (i.e., 58:42 dr, entry 16), while reaction in dichloromethane or toluene completely reversed the diastereoselectivity affording **16c** as a single diastereomer (entries 17 and 18). Although reaction of **8** with ^{i}PrMgCl in THF gave trace amounts of product **12d** along with recovered starting material (entry 19), use of toluene gave the cyclopropane **16d** in excellent yield and diastereoselectivity (entries 20 and 21). The reactions of epoxy enamide **9** gave modest yields and poor to modest diastereoselectivities of cyclopropanes **13c** and **17c** under all reaction conditions examined (entries 22−25). Reaction of **9** with ^{i}PrMgCl gave a complex mixture of reaction products when run in either THF (entry 26) or CH_2Cl_2.

Although the MIRC reactions of trialkylzincates with epoxyenoate **1** gave good product yields under either stoichiometric or catalytic protocols, the utilization of arylzincates gave low yields of cyclopropane **2d** and considerable quantities of biphenyl (Table 1, entry 8).[40] Initial attempts to suppress biphenyl formation in the reaction of lithium phenyldimethylzincate by using a variety of solvents failed with both coordinating (e.g, THF, Et_2O) and non-coordinating (e.g., CH_2Cl_2, toluene) solvents. However, significant product formation (i.e., **2d**) was obtained by reverse addition of phenylmagnesium bromide to a solution of

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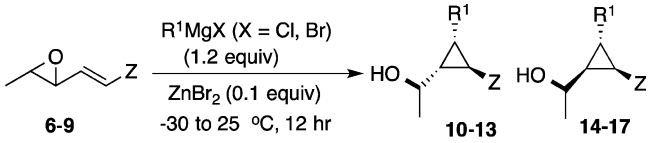
Table 4. Reaction of 4,5-Epoxy-2,3-hexenyl Ketones 6 and 7, Sulfone 8, and Amide 9



6, **10**, **14** Z = PhCO-
7, **11**, **15** Z = ^{i}PrCO-
8, **12**, **16** Z = $PhSO_2$-
9, **13**, **17** Z = c-$C_5H_{10}NCO$-

a R = Me
b R = Et
c R = ^{n}Bu
d R = ^{i}Pr
f R = ^{t}Bu

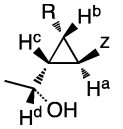
entry	epoxide	R^1	solvent	major ROH	% yield[a]	dr[b]
1	**6**	Me	THF	**10a**	57	100:0
2	**6**	Et	THF	**10b**	63	100:0
3	**6**	Et	Et_2O	**10b**	63	100:0
4	**6**	Et	CH_2Cl_2	**10b**	61	100:0
5	**6**	^{n}Bu	THF	**10c**	67	100:0
6	**6**	^{n}Bu	CH_2Cl_2	**10c**	66	100:0
7	**6**	^{i}Pr	THF	**10d**	63	100:0
8	**7**	Me[c]	THF	**11a**		
9	**7**	^{n}Bu	THF	**11c**	88	100:0
10	**7**	^{n}Bu	THF	**11c**	69[d]	100:0
11	**7**	^{n}Bu	CH_2Cl_2	**11c**	85	100:0
12	**7**	^{i}Pr	THF	**11d**	82	95:5
13	**7**	^{t}Bu	THF	**11f**	82[e]	100:0
14	**8**	Me	THF	**12a**		
15	**8**	Me	PhMe	**16a**	78	7:93
16	**8**	^{n}Bu	THF	**12c**	78	58:42
17	**8**	^{n}Bu	CH_2Cl_2	**16c**	83	0:100
18	**8**	^{n}Bu	PhMe	**16c**	90	0:100
19	**8**	^{i}Pr	THF	**12d**	trace	
20	**8**	^{i}Pr	PhMe	**16d**	83	0:100
21	**8**	^{i}Pr	PhMe	**16d**	82	0:100
22	**9**	^{n}Bu	THF	**13c**	73	50:50
23	**9**	^{n}Bu	Et_2O	**17c**	51	47:53
24	**9**	^{n}Bu	PhMe	**17c**	63	36:64
25	**9**	^{n}Bu	CH_2Cl_2	**17c**	52	27:73
26	**9**	^{i}Pr	THF	**13d**	*f*	

[a]Yields are based upon isolated products purified by column chromatography. [b]Diastereomeric ratios (i.e., **10**–**13**:**14**–**17**) were determined from integration of the ^{1}H NMR of the carbinol proton absorptions or via peak heights in the ^{13}C NMR spectra corresponding to the carbinol carbon peak absorptions. [c]Stirred at room temperature for 30 h with no observation of product formation. [d]The reaction was conducted at 25 °C for 12 h. [e]The reaction was conducted at 0 °C for 12 h. In a separate experiment, the reagent $^{t}Bu_3ZnLi$ gave **11f** in 73% yield (0–25 °C, 12 h). [f]A complex mixture of products was obtained in both THF and CH_2Cl_2.

epoxyenoate **1** and catalytic amounts of ZnX_2 (X = Br, Cl, I, OAc) in less polar solvents (Table 5, entries 2–10), although only trace amounts of **2d** were obtained in THF (entry 1). Addition of $Ni(acac)_2$ had little, if any, effect on product yield (entry 5). The lowest yields of undesired biphenyl were obtained with $Zn(CN)_2$ (entries 11–14), and lower yields of **2d** were obtained as the temperature was lowered (entries 13 and 14) with concomitant increase in the yield of **3d**. Utilization of higher temperatures and inverse addition of the Grignard reagent allows competitive conjugate addition of the in situ generated zincate reagent to the Michael acceptors with the ZnX_2-catalyzed coupling reaction leading to biphenyl. Conducting these reactions at higher temperatures (i.e., 25 °C, entries 11 and 12) to maximize product yield resulted in higher diastereoselectivity in the addition process leading to mixtures of **2d**:**3d** with modest selectivity in comparison to the excellent diastereoselectivity obtained with the alkyl Grignard reagents (Tables 1 and 2). Utilizing $Zn(CN)_2$ and reverse addition, modest to good yields of cyclopropanes could be obtained from enones **6** and **7** at lower reaction temperatures (entries 15–18), enesulfone **8** (entries 19–21), and enamide **9** (entries 22–23). Diastereoselectivity mirrored prior observations with the ketones **6** and **7** giving largely diastereomer **A**, sulfone **8**, and amide **9** giving diastereomer **B** as the major product in noncoordinating solvents (Table 5). Grignard reagents derived from 4-bromo-*N*,*N*-dimethylaniline or 4-iodoanisole gave only biaryl coupling products.

DETERMINATION OF STEREOCHEMISTRY

The inability to convert cyclopropyl ester **2b** into lactone **3b** in the presence of base or acid suggested the trans disposition of the carbinol and carboalkoxy substitutents, and this tentative assignment was reinforced as lactone **3b** was obtained when the reaction was performed in CH_2Cl_2 (Table 2, entry 9). The relative stereochemistry of the 1,2,3-trisubstituted cyclopropyl esters was confirmed by reduction of **2b** to the diol whose bis-3,5-dinitrobenzoyl derivative provided suitable crystals for X-ray crystallography, which could not be obtained for the 3,5-dinitrobenzoyl derivative of the secondary alcohol **2b**. X-ray structural determinations were also obtained on the 3,5-dinitrobenzoyl derivatives derived from the major (**12c**) and minor (**16c**) diastereomers of cyclopropyl sulfone **12c** and for amides **13e** and the 3,5-dinitrobenzoyl derivative of **17e**.



2d Z = CO_2Et, R = Ph
10b Z = COPh, R = Et
11e Z = CO^{i}Pr, R = Ph

In order to determine the relative stereochemistry of the substituents present in the cyclopropyl ketone derivatives, NOESY NMR spectra were obtained for ketones **10b** and **11e** and compared with spectra for ester **2d**. The presence of phenyl substitutents on the ring or attached to the acyl group dispersed the cyclopropyl proton absorptions necessary for performing NOESY experiments. The H^a, H^b, H^c, and H^d proton assignments for **2d**, **10b**, and **11e** were determined from COSY NMR experiments. In the NOESY spectra of these compounds, strong coupling was observed between H^a and H^d and H^b and H^c, while weak coupling was observed between H^a and H^b, H^a and H^c, and H^c and H^d confirming the assigned stereochemistry. Thus, both alkyl and aryl Grignard reagents react with epoxy enones and enoates in THF to give the same relative stereochemistry about the cyclopropane ring.

DIASTEREOSELECTIVITY AND SOLVENT EFFECTS

Intriguingly, ester **1** affords only diastereomer **2b** in THF and only lactone **3b** in CH_2Cl_2 upon reaction with $^{n}Bu_3ZnLi$ (Table 2). A plausible rationalization invokes minimization of $A^{1,3}$-strain[2,41] in the transition state structures arising from conformers **18**–**20** (Scheme 1) where stability of the conformers is expected to be **18** > **20** > **19** and the solvent-dependent nature of the zincate reagent involving solvent

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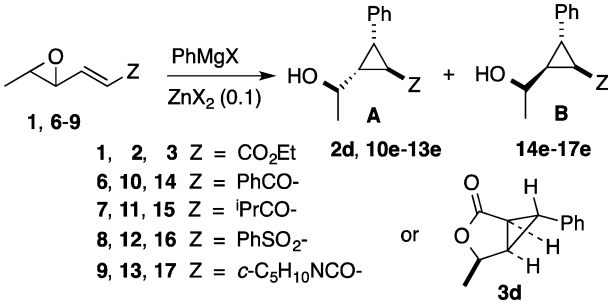
Table 5. Zinc-Catalyzed Reaction of Phenylmagnesium Bromide with 4,5-Epoxy Enoate 1, Enones 6 and 7, Enesulfone 8, and Enamide 9



entry	epoxide	catalyst[a]	solvent	T (°C) (time)[b]	A	A, % yield[c]	B or 3d, % yield[c]	2d:3d or A:B/range[d]	% yield Ph−Ph[c]
1	**1**	$ZnBr_2$	THF	A	**2d**				42
2	**1**	$ZnBr_2$[e]	Et_2O	A	**2d**	48	5	80:20/07	37
3	**1**	$ZnBr_2$[f]	Et_2O	A	**2d**	46	4	83:17/11	22
4	**1**	$ZnBr_2$	Et_2O	B	**2d**	59	5	58:42/16	30
5	**1**	$ZnBr_2$[g]	Et_2O	A	**2d**	63	3	86:14/01	17
6	**1**	$ZnBr_2$	CH_2Cl_2	A	**2d**	32	31	68:39/15	26
7	**1**	$ZnBr_2$	PhMe	A	**2d**	45	17	68:32/09	27
8	**1**	$ZnCl_2$	Et_2O	A	**2d**	57	7	70:30/08	28
9	**1**	ZnI_2	Et_2O	A	**2d**	59	3	82:16/03	31
10	**1**	$Zn(OAc)_2$	Et_2O	A	**2d**	52	5	84:16/03	25
11	**1**	$Zn(CN)_2$	Et_2O	A	**2d**	61	7	86:14/06	6
12	**1**	$Zn(CN)_2$	Et_2O	C	**2d**	61	3	78:22/03	5
13	**1**	$Zn(CN)_2$[h]	Et_2O	D	**2d**	49	17	63:37/05	3
14	**1**	$Zn(CN)_2$[i]	Et_2O	E	**2d**	37	33	44:46/05	11
15	**6**	$Zn(CN)_2$	Et_2O	F	**10e**	63[j]		88:12	11
16	**6**	$Zn(CN)_2$	CH_2Cl_2	F	**10e**	68[j]		90:10	9
17	**6**	$Zn(CN)_2$	PhMe	F	**10e**	64[j]		92:8	8
18	**7**	$Zn(CN)_2$	CH_2Cl_2	E	**11e**	84[j]		100:0	3
19	**8**	$Zn(CN)_2$	Et_2O	G	**12e**	42	30	55:45	13
20	**8**	$Zn(CN)_2$	CH_2Cl_2	G	**16e**	17	64	22:78	8
21	**8**	$Zn(CN)_2$	PhMe	G	**16e**	05	82	7:93	7
22	**9**	$Zn(CN)_2$	CH_2Cl_2	G	**17e**		62[j]	22:78	14
23	**9**	$Zn(CN)_2$	PhMe	G	**17e**		66[j]	19:81	13

[a]The Grignard reagent was added to the mixture of ZnX_2 and epoxide. [b]Temperature (time = h): A = 25 °C (12); B = 0 to 25 °C (12); C = 25 °C (1.5); D = 0 to 25 °C (2); E = −20 to 25 °C (4); F = −30 to 25 °C (3); G = 25 °C (4). [c]Yields are based upon isolated products purified by column chromatography. All reactions involved inverse addition of the Grignard reagent to the substrate and zinc salt. [d]Diastereomeric ratios were determined by averaging values from integration of the ^{1}H NMR absorptions of the methyl attached to the carbinol carbon, the benzyl methine proton, and the ^{13}C NMR peak heights of the carbonyl carbon absorption. The range between the high and low value for the major diastereomer determined from several ^{1}H and ^{13}C absorptions is also given and ranges between 3 and 16 (e.g., 80:20/83:17 to 70:30/86:14) for the sets of measurements. [e]The Grignard reagent was added to the substrate at room temperature over 15 min. [f]The Grignard reagent was diluted with 3.0 mL of Et_2O and added to the substrate over 15 min at room temperature. [g]$Ni(acac)_2$ (0.1 equiv) was added to the zinc salt before adding the Grignard reagent. [h]LiCl (0.2 equiv) was added to the mixture of zinc salt and epoxyenoate **1** before adding the Grignard reagent at 0 °C. [i]The Grignard reagent was diluted with anhydrous Et_2O and added to the zinc salt/epoxide mixture over 30 min at −20 °C. [j]The minor isomer was also present.

separated ion pairs (SSIP) in THF and contact ion pairs in CH_2Cl_2 (CIP). Recent X-ray crystal structures and solution NMR studies have elucidated mixed bimetallic reagents obtained upon mixing Grignard reagents with ZnX_2 (X = Cl, Br) or ZnR_2 compounds in THF[33] and have implicated $[(THF)_6Mg(\eta\text{-}Cl)_3]^+$ $[Zn_2Et_5]^-$ in $ZnCl_2$-mediated addition of EtMgCl to benzophenone.[33b] The structures of these mixed Mg−Zn complexes is dependent upon the alkyl ligand (e.g., ^{t}Bu vs Et)[33] and are in dynamic equilibrium with a variety of zinc species depending upon concentration.[33a] The composition and structures of mixed Mg−Zn complexes in solvents other than THF are unknown but if similar to those shown in Figure 1, it would be reasonable to expect SSIP in THF and tight CIP in PhMe and CH_2Cl_2.

Due to electrostatic dipole−dipole repulsion, the SSIP approaches the alkene π face from the side opposite the polar heteroatom substituent (i.e., the epoxide in **18**) to give conformers **21** and/or **22**, while the CIP approaches the alkene π from the same side as the epoxide oxygen perhaps enhanced by complexation with the magnesium counterion (i.e., from either **18** or **20**) to give conformers **23** and/or **24**. It should be noted that the bimetallic magnesium cations should be more effective Lewis acids than neutral MgX_2 salts that may be present in a dynamic equilibrium.[27b] Conformers **21**−**22** and **23**−**24** can arise directly from the conjugate addition process or by rotation about C−C bond **a** prior to cyclopropane formation. The initial formation of configurational diastereomers arising from zincate attack on the enoate either syn or anti to the epoxide determines the stereochemical outcome

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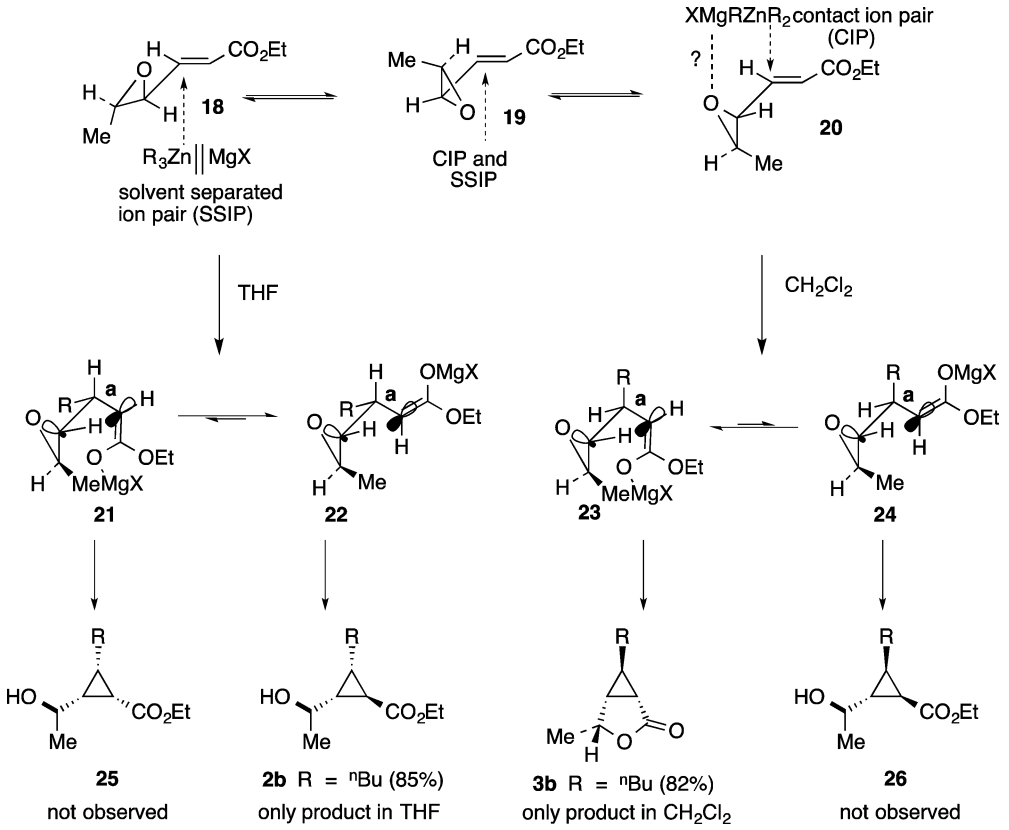
Scheme 1. Stereochemical Models for Cyclopropane Formation from Intermediate Enolates



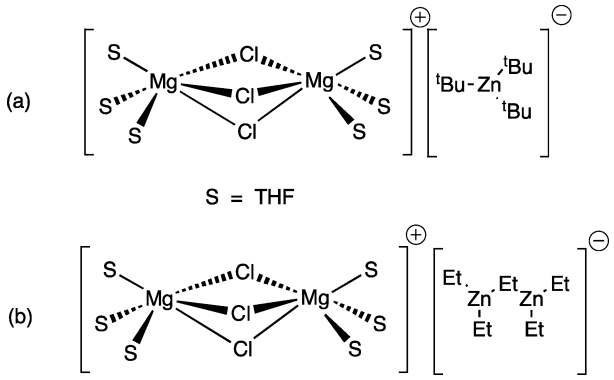


Figure 1. Mixed bimetallic Mg–Zn complexes (a) $[(THF)_6Mg(\eta\text{-}Cl)_3]^+$ $[Zn^tBu_3]^-$ (see ref 33a) and (b) $[(THF)_6Mg(\eta\text{-}Cl)_3]^+$ $[Zn_2Et_5]^-$ (see ref 33b).

during cyclopropane formation. Zincate attack anti to the epoxide leads to conformational diasteromers **21**–**22** with proper orientation to afford cyclopropanes **25** and **2b**, respectively. In conformer **21** the R-group and the enolate are eclipsed about bond **a**, while in conformer **22** they are oriented anti and this anticipated lower energy conformer in the transtition state leads to the observed product **2b**. Similarly, in the transition states corresponding to conformers **23** and **24** arising from zincate syn attack, conformer **24** has the R-enolate eclipsed arrangement about bond **a**, while **23** has the lower energy anti arrangement leading to the observed product **3b**. This analysis implies that the R-group (from the zincate reagent) and the EWG will always be trans to each other. Previous rationalizations invoking a carbanionic lithium enolate[15] seem unlikely given computational studies on enolate anions.[42]

If the solvent affects the syn/anti ratio (i.e., the initial 1,4-addition occurring syn or anti to the epoxide), why is there no solvent effect for the epoxyenones, clean reversal of diastereoselectivity for the epoxyenoates and poor to no diastereoselectivity for the epoxy ensulfones and enamides in THF to excellent (i.e., **8**) to modest (i.e., **9**) reversal of distereoselectivity in CH_2Cl_2? To probe this question, we performed several competition experiments with 1 equiv of Grignard reagent and 0.5 equiv each of two electrophiles. Treatment of 0.5 equiv of enone **7** and enoate **1** with ^{n}BuMgCl [CH_2Cl_2 or THF, $ZnBr_2$ (0.1 equiv), −40 to 25 °C, 12 h)] gave complete conversion of **7** to **11c** with complete recovery of **1**, while reaction of **1** and **8** under the same conditions in CH_2Cl_2 gave a 35:65 ratio of recovered **1**:**8** along with the cyclopropanes **3b** and **12c**. Similarly, reaction of **8** and **9** gave a 73% recovery of **8** and 27% of **9**. These competition experiments establish that the relative rate factors for reaction of **7**: **9**: **1**: **8** are >20:2.7:1.9:1 in CH_2Cl_2.

The relative basicities of the EWGs (i.e., pK_{BH^+}) in **1** and **6**–**9** can be estimated from reported values for similar compounds where $PhSO_2Ph$ (−12.37) < $MeSO_2Me$ (−12.27) < RCOR (−7) < RCO_2R (−6.5) < ROR (−3.5) < THF (−2.05) < $RCONH_2$ [$pK_{BH+}(O)$ = −0.5] in basicity.[43,44] Similarly, the relative electron withdrawing power of the carbonyl and sulfonyl groups can be estimated from Hammett σ_R-substitutent constants decreasing in power with −COMe (0.16) ≈ $-CO_2Me$ (0.16) > $-SO_2Me$ (0.12) > $-CONH_2$ (0.00).[45] The Hammett σ_p-substituent constants give an order of $-SO_2Me$ (0.73) > −COMe (0.47) > $-CO_2Me$ (0.44) > $-CONH_2$ (0.31) correctly predicting a greater reactivity for the

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enone than the enoate but incorrectly predicting the greatest reactivity for the sulfone.[45] Although these parameters specifically measure proton acceptor and donor properties (i.e., the acidity of substituted benzoic acids), respectively, they should qualitatively reflect magnesium complexation and Michael acceptor susceptibility, respectively. From this analysis the sulfone, ketone, and ester are less basic than the epoxide, while the σ_R^+ substitutent constants correlate with the relative rates measured by competition experiments with **7** > **1** > **8** but not with **9**, with **9** > **1** > **8** in reactivity. Thus, the most reactive epoxy ketones **6**-**7** show no solvent dependent diastereoselectivity, while the less reactive ester **1** and sulfone **8** substates do, with the more reactive ester giving excellent but different diastereoselectivity in THF and CH_2Cl_2. The least reactive epoxy sulfone **8** is also the least basic, the second poorest Michael acceptor and shows excellent diastereoselectivity in CH_2Cl_2 and poor diastereoselectivity in THF. Epoxy amide **9** is expected to be the poorest Michael acceptor based upon Hammett σ_R-substitutent constants but is the most basic substrate, and its relative reactivity (i.e., **9** > **1** > **8**) suggests amide−magnesium ion complexation is facilitating the conjugate addition reaction. The correlation of reactivity with diastereoselectivity is clearly seen in the reactions of PhMgCl with epoxy ester **1** (Table 5, entries 11−14) where the less reactive putative phenyl zincate reagent gives poor diastereoselectivity at −20 to 0 °C and better diastereoselectivity at 25 °C that is in turn lower than those obtained with the more reactive alkylzincate reagents (Tables 1−3).

Although the details remain to be elucidated, the observed solvent dependent diastereoselectivity of the epoxy ketones, ester, sulfone, and amide appears to reflect a complex interplay between functional group basicity and electron withdrawing capacity and may also involve structural variation of the mixed Mg−Zn complexes in different solvents. The more reactive epoxy ketones **6** and **7** show no solvent dependent diastereoselectivity, while the most basic epoxy amide **9** never gives a single diastereomer under any reaction conditions. The epoxy ester **1** and sulfone **8** display intermediate behavior.

SUMMARY

In summary, trialkylzincates or Grignard reagents and catalytic amounts of Zn(II) salts react with γ,δ-epoxy-α,β-unsaturated ketones, esters, sulfones, and amides to afford 1,2,3-trisubstituted cyclopropanes via a MIRC process. These unprecedented zincate-mediated conjugate addition reactions display excellent 1,2-trans-2,3-cis cyclopropane diastereoselectivity for the ketone and ester substrates in THF that can be reversed to the 1,2-cis-2,3-trans-isomer for the latter by changing to CH_2Cl_2. The sulfone and amide substrates afford poor cyclopropane diastereoselectivity in THF, while excellent 1,2-cis-2,3-trans distereoselectivity is achieved for the sulfone in CH_2Cl_2 and modest selectivity with the amide. The diastereoselectivity established during the conjugate addition reaction appears to control the subsequent cyclopropane distereoselectivity arising from the epoxide opening-ring closure event. The reaction of triarylzincates or aryl Grignard reagents and Zn(II) salts is complicated by biaryl formation that can be suppressed by inverse addition of the Grignard reagent and use of $Zn(CN)_2$.

The high regio- and diastereoselectivity observed in these reactions provides useful synthetic routes to highly substituted cyclopropane derivatives. The stereo- and regiocontrolled synthesis of cyclopropane derivatives[7a,46−56] is important in both synthesis[48] and medicinal chemistry.[53−56] This is illustrated by recent reviews on enantioenriched,[47] fluorinated-[49] alkylidene-,[50] silylmethyl-substituted-,[51] spiroannulated-,[52] and arylcyclopropanes[53] and the preparation and biological activity of cyclopropyl phosphonates,[54] cyclopropane derived peptidomimetics,[55a] and cyclopropyl-containing α-amino acids.[56]

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded as $CDCl_3$ or C_6D_6 solutions on a 500 MHz NMR instrument. The ^{1}H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS, δ = 0.00)/$CHCl_3$ (δ = 7.28) or C_6H_6 (δ = 7.16) as internal standard. The ^{13}C NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to the $CDCl_3$ signal (triplet, centerline δ = 77.0 ppm) or C_6D_6 signal (multiplet, centerline δ = 128.4 ppm). Infrared (IR) spectra were recorded as neat samples (liquid films on NaCl plates). Gas chromatography−mass spectrometry measurements were performed on a GC coupled to a quadrupole detector at 70 eV. Analytical thin-layer chromatography (TLC) was performed on silica gel plates, 200 mesh with F254 indicator. Visualization was accomplished by UV light (254 nm), and/or a 10% ethanol solution of phosphomolybdic acid. Flash column chromatography was performed with 230−400 silica. The yields are of materials isolated by column chromatography.

Materials. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were distilled from sodium benzophenone ketyl. Toluene was dried over molecular sieves and used for the reactions. ^{n}BuLi (2.5 M in hexane), MeLi (1.6 M in Et_2O), and ^{t}BuLi (1.7 M in pentane) were commercially available and were titrated using *sec*-butyl alcohol and 1,10-phenanthroline monohydrate in THF. ^{n}BuMgCl (2.50 M in THF), EtMgCl (2.0 M in Et_2O), MeMgCl (3.0 M in Et_2O), ^{i}PrMgBr (2.0 M in Et_2O), ^{t}BuMgCl (1.7 M in THF), and PhMgCl (2.80 M in Et_2O) were commercially available and titrated using menthol and 1,10-phenanthroline monohydrate in THF.[57] Zincate reagents were synthesized from the corresponding lithium or magnesium reagents and flame-dried $ZnBr_2$. All glassware was flamed-dried under high vacuum and purged with argon and then cooled under a dry nitrogen atmosphere. Low temperature baths (up to −78 °C) were prepared using thermo flasks using dry ice-2-propanol slush bath mixtures or an ice−NaCl (−23 °C) mixture. All reactions were conducted under a positive, dry argon atmosphere in anhydrous solvents in flasks fitted with a rubber septum.

HRMS data on compounds **2b′**, **2d**, **2f**, **3d**, **10a−e**, **11e**, **12e**, **13c**, **16a,d,e**, and **17c** were analyzed with a Q-TOF detector (hybrid quadrupole time-of-flight MS). Compounds **1**, **3b**, **4b,c,e**, **5b**, **6**, and **9** have been fully characterized and reported.[2,58−60]

General Procedure A: Reaction of Lithium Trialkylzincates (R_3ZnLi) with Ethyl 4,5-Epoxy-2,3-hexenoate (1). To an ice-cold solution of flame-dried $ZnBr_2$ (225 mg, 1.0 mmol) in THF (4.0 mL) under argon was added alkyllithium (3.0 mmol), and the reaction mixture was stirred for 30 min at 0 °C. Ethyl 4,5-epoxy-2,3-hexenoate (156 mg, 1.0 mmol) was added, and the resulting mixture was stirred for 2−12 h at the indicated temperature range. The reaction mixture was quenched with NH_4Cl−NH_4OH aqueous buffer (pH = 7.0, 10.0 mL) and filtered, and the filtrate was extracted with Et_2O (3 × 15.0 mL). The combined organic phase was washed with water (10.0 mL) and brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10−20% EtOAc in petroleum ether, v/v) to give pure compounds.

General Procedure B: Reaction of Mixed Lithium Organozincates ($R^1R^2R^3ZnLi$) with Ethyl γ,δ-Epoxy-α,β-hexenoate. To an ice-cold solution of flame-dried $ZnBr_2$ (225 mg, 1.0 mmol) in THF (4.0 mL) under argon were added R^1Li (1.0 mmol), R^2Li (1.0 mmol), and R^3Li (1.0 mmol), and the mixture was stirred for 30 min at 0 °C. The flask was then transferred to a −20 °C bath, ethyl 4,5-epoxy-2,3-hexenoate

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(156 mg, 1.0 mmol) was added, and the mixture was stirred for the indicated time and temperature range. The reaction mixture was quenched with NH_4Cl−NH_4OH aqueous buffer (pH = 7.0, 10.0 mL) and filtered, and the filtrate was extracted with Et_2O (3 × 15.0 mL). The combined organic phase was washed with water (10.0 mL) and brine (10.0 mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10−20% EtOAc in petroleum ether, v/v) to give pure compounds.

*General Procedure C: Reaction of Alkyl Grignard Reagents with Ethyl 4,5-Epoxy-2,3-unsaturated Ester 1, Ketones **6** and **7**, Sulfone **8**, and Amide **9** in the Presence of Catalytic Amounts of Zinc Bromide.* To an ice-cold solution of flame-dried $ZnBr_2$ (23 mg, 0.1 mmol) in THF or Et_2O or CH_2Cl_2 or toluene (4.0 mL) under argon was added the Grignard reagent (1.2 mmol), and the mixture was stirred for 5 min at 0 °C. The flask was then cooled in a −20 to −30 °C bath, epoxide (1.0 mmol) was added, and the mixture was stirred for 2−12 h with gradual warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl and filtered, and the filtrate was extracted with Et_2O (3 × 15.0 mL). The combined organic phase was washed with water (10.0 mL) and brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography(silica, 10−20% EtOAc in petroleum ether, v/v) to give pure compounds.

*General Procedure D for Reverse Addition: Reaction of Phenylmagnesium Bromide with Ethyl 4,5-Epoxy-2,3-unsaturated Ester **1**, Ketones **6** and **7**, Sulfone **8**, and Amide **9** in the Presence of Catalytic Amounts of Zinc(II) Salt.* To an ice-cold solution of flame-dried Zn(II) salts (0.1 mmol) in Et_2O or CH_2Cl_2 or toluene (4.0 mL) under argon was added epoxide (1.0 mmol), the phenylmagnesium bromide (1.2 mmol) was added dropwise over 15 min, and the mixture was stirred for the indicated time in the given temperature range. The reaction mixture was quenched with saturated aqueous NH_4Cl and filtered, and the filtrate was extracted with Et_2O (3 × 15.0 mL). The combined organic phase was washed with water (10.0 mL) and brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10−20% EtOAc in petroleum ether, v/v) to give pure compounds.

*General Procedure E for Competition Experiments: Reaction of Grignard Reagent (0.5 equiv) with a 1:1 Mixture of Ethyl 4,5-Epoxy-2,3-unsaturated Ester **1** (0.5 equiv) and Other Epoxides (0.5 equiv) Such as 4,5-Epoxy-2,3-unsaturated ketone **7**, 4,5-Epoxy-2,3-unsaturated Sulfone, and a 1:1 Mixture of 4,5-Epoxy-2,3-unsaturated Sulfone (0.5 equiv) with 4,5-Epoxy-2,3-unsaturated Amide (0.5 equiv) in the Presence of Catalytic Amounts of $ZnBr_2$.* To the flame-dried solution of $ZnBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 (4.0 mL) under argon was added ^{n}BuMgCl (0.5 mmol) at −40 °C. To this solution was added a 1:1 mixture of two epoxides under study in CH_2Cl_2 (2.0 mL), and the reaction mixture was allowed to warm to room temperature over 12 h. The reaction was quenched with saturated aqueous NH_4Cl and filtered, and the filtrate was extracted with CH_2Cl_2 (3 × 15.0 mL). The combined organic phase was washed with water (10.0 mL) and brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was subjected to NMR and GC/MS analysis, and the ratio of each component was calculated from the corresponding data.

(1R,2R*,3S*,1′R*)-Ethyl 2-(1-Hydroxyethyl)-3-methylcyclopropane carboxylate (**2a**).* Employing general procedure A and using MeLi (1.88 mL, 1.6 M in Et_2O, 3.0 mmol), flame-dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl 4,5-epoxy-2,3-hexenoate (156 mg, 1.0 mmol) at room temperature gave after purification by flash column chromatography (silica, 20−30% EtOAc/petroleum ether, v/v) **2a** (113 mg, 65%, dr 100:0) as a colorless oil: IR (neat) 3432 (br s), 2967 (s), 2921 (s), 1715 (s), 1434 (s), 1361 (s), 1181 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, J = 6.4 Hz, 3H),1.24−1.14 (m, 1H), 1.25 (t, J = 7.3 Hz, 3H), 1.35 (d, J = 7.8 Hz, 3H), 1.54−1.58 (m, 2H), 1.81 (s, 1H), 3.49−3.61 (m, 1H), 4.11 (q, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1, 14.2, 21.3, 23.3, 26.2, 34.4, 60.5, 66.9, 173.6; mass spectrum m/z (relative intensity) EI 172 (0. 2, M^+), 154 (12), 127 (81), 98 (69), 83 (100), 69 (57), 59 (93), 55 (76). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.56; H, 9.24.

(1R,2R*,3S*,1′R*)-Ethyl 2-(1-Hydroxyethyl)-3-n-butylcyclopropanecarboxylate (**2b**).* Employing general procedure A and using ^{n}BuLi (1.2 mL, 2.5 M in hexane, 3.0 mmol), flame-dried $ZnBr_2$ (225 mg, 1.0 mmol) and ethyl γ,δ-epoxy-α,β-hexanoate (156 mg, 1.0 mmol) gave after purification by flash column chromatography (silica, 10−20% EtOAc/petroleum ether, v/v) **2b** and **2b′** (177 mg, 82%, dr 96:4) as a colorless oil (the application of general procedure C gave 182 mg, 85%, 100:0 dr). **Major (2b)**: IR (neat) 3457 (br s), 2961 (s), 2932 (s), 1724 (s), 1450 (s), 1374 (s), 1176 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 4.6 Hz, 1H), 1.26 (t, J = 6.8 Hz, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.35−1.39 (m, 2H), 1.42−1.48 (m, 4H), 1.59−1.71 (m, 2H), 2.01 (s, 1H), 3.52 (dq, J = 3.2, 9.6 Hz, 1H), 4.13 (q, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.1, 22.4, 23.4, 25.1, 27.0, 27.6, 31.8, 34.4, 60.4, 67.0, 173.7; mass spectrum m/z (relative intensity) EI 214 (0.04, M^+), 196 (2), 169 (100), 157 (43), 141 (12), 128 (52), 123 (15), 99 (59), 81 (66), 55 (59). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.63; H, 10.59. **Minor (2b′)**: IR (neat) 3457 (br s), 2956 (s), 2932 (s), 2850 (s), 1730 (s), 1468 (s), 1374 (s), 1176 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 6.9 Hz, 3H), 1.30−1.38 (m, 4H), 1.34 (d, J = 6.4 Hz, 3H), 1.40−1.67 (m, 6H), 3.15 (dq, J = 3.2, 6.4 Hz, 1H), 4.13 (q, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 22.4, 23.4, 25.7, 27.2, 27.5, 31.8, 35.3, 60.5, 67.4, 173.8; mass spectrum m/z (relative intensity) EI 214 (0. 1, M^+), 197(13), 169 (100), 157 (26), 141 (14), 99 (82), 81 (77), 55 (83); HRMS (ESI) calcd for $[C_{12}H_{22}O_3Na]^+$ 237.1461, found 237.1458.

(1R,2R*,3S*,1′R*)-Ethyl 2-(1-Hydroxyethy)-3-(1-methylethyl)-cyclopropanecarboxylate (**2c**).* Employing general procedure B, at −20 °C, ^{i}PrMgBr (0.50 mL, 2.0 M in Et_2O, 1.0 mmol), MeLi (1.25 mL, 1.6 M in diethyl ether, 2.0 mmol), flame-dried $ZnBr_2$ (225 mg, 1.0 mmol), and ethyl 4,5-epoxy-2,3-hexenoate (156 mg, 1.0 mmol) gave after purification by flash column chromatography (silica, 10−20% EtOAc:petroleum ether, v/v) **2c** (138 mg, 69%, dr 100:0) as a colorless oil (the application of general procedure C gave 160 mg, 80%, 100:0 dr): IR (neat) 3448 (br s), 2941 (br s), 2868 (s), 1727 (s), 1471 (s), 1370 (s), 1179 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, J = 6.4 Hz, 3H), 1.14 (d, J = 6.4 Hz, 3H), 1.19 (t, J = 4.6 Hz, 1H), 1.27 (t, J = 6.8 Hz, 3H), 1.31−1.34 (m, 1H), 1.35 (d, J = 9.6 Hz, 3H), 1.36−1.42 (m, 1H), 1.10 (s, 1H), 1.65 (dt, J = 5.0, 9.6 Hz, 1H), 3.53 (dq, J = 3.2, 6.4 Hz, 1H), 4.12 (q, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.8, 23.0, 23.9, 24.4, 27.4, 35.2, 36.1, 60.5, 67.1, 173.8; mass spectrum m/z (relative intensity) EI 200 (0.3, M^+), 155 (55), 32 (128), 110 (98), 99 (100), 69 (35), 56 (54). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.87; H, 10.2.

(1R,2R*,3S*,1′R*) Ethyl 2-(1-Hydroxyethyl)-3-phenylcyclopropanecarboxylate (**2d**).* Employing general procedure B and using PhMgBr (0.36 mL, 2.8 M in Et_2O, 1.0 mmol), MeLi (1.25 mL, 1.6 M in Et_2O, 2.0 mmol), flame-dried $ZnBr_2$ (225 mg, 1.0 mmol), and ethyl 4,5-epoxy-2,3-hexenoate (156 mg, 1.0 mmol) in Et_2O gave after purification by flash column chromatography (silica, 15−20% EtOAc/petroleum ether, v/v) **2d** (74 mg, 32%, dr 100:0) as a colorless oil. Utilization of general procedure D gave **2d** (157 mg, 61%) as a major product: IR (neat) 3425 (br s), 2976 (s), 2890 (s), 1724 (s), 1447 (s), 1180 (s), 699 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, J = 6.4 Hz, 3H), 1.24 (t, J = 7.3 Hz, 3H), 1.41 (s, 1H), 1.82−1.87 (m, 1H), 1.99 (t, J = 4.3 Hz, 1H), 2.80 (dd, J = 4.1, 9.2 Hz, 1H), 3.14 (dq, J = 6.4, 9.6 Hz, 1H), 4.12 (q, J = 6.9 Hz, 2H), 7.17−7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.5, 23.3, 30.7, 35.9, 60.9, 66.4, 127, 128.5, 128.7, 135.4, 172.9; mass spectrum m/z (relative intensity) EI 234 (0.16, M^+), 216 (0.1), 189 (100), 177 (28), 161 (21), 144 (49), 143 (32), 133 (42), 128 (85), 117 (84), 115 (95), 107 (28), 91 (44), 77 (23), 55 (8); HRMS (ESI) calcd for $[C_{14}H_{18}NaO_3]^+$ 257.1154, found 257.1148.

*6-endo-Phenyl-4-methyl-3-oxabicyclo[3.1.0]hexen-2-one (**3d**).* Employing general procedure D and using PhMgBr (0.43 mL, 2.8 M in Et_2O, 1.0 mmol), flame-dried $Zn(CN)_2$ (12 mg, 0.1 mmol), and ethyl 4,5-epoxy-2,3-hexenoate (156 mg, 1.0 mmol) in Et_2O gave after purification by flash column chromatography (silica, 15−20% EtOAc/petroleum ether, v/v) **3d** (13 mg, 7%) as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (d, J = 5.9 Hz, 3H), 2.26 (dd, J = 2.3, 5.5

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Hz, 1H), 2.30 (t, J = 2.7 Hz, 1H), 2.40−2.43 (m, 1H), 4.80 (dq, J = 1.4, 5.9 Hz, 1H), 6.99−7.24 (m, 5H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 25.7, 28.7, 30.9, 76.6, 125.9, 127.1, 128.7, 137.2, 174.7; mass spectrum *m/z* (relative intensity) EI 188 (40, M^+), 144 (100), 143 (65), 129 (95), 117 (36), 115 (97), 91 (26), 89 (20), 77 (16), 65 (15), 55 (17); HRMS (ESI) calcd for $[C_{12}H_{12}O_2Na]^+$ 211.0730, found 211.0731.

(1R,2R*,3S*,1′R*)-Ethyl 2-(1-Hydroxyethyl)-3-ethylcyclopropane carboxylate (**2f**).* Employing General Procedure C and using EtMgCl (0.6 mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol) and ethyl γ,δ-epoxy-α,β-hexanoate (156 mg, 1.0 mmol) gave after purification by flash column chromatography (silica, 15−25% EtOAc:petroleum ether, v/v) **2f** (136 mg, 73%, dr 100:0) as a colorless oil: IR (neat) 3437 (br s), 2957 (s), 2921(s), 1717 (s), 1427 (s), 1364 (s), 1130 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 4.6 Hz, 1H), 1.26 (t, J = 6.9 Hz, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.38−1.45 (m, 1H), 1.48−1.53 (m, 1H), 1.61 (s, 1H), 1.62−1.69 (m, 2H), 3.15 (dq, J = 5.9, 12.3 Hz, 1H), 4.13 (q, J = 7.3 Hz, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) 14.0, 14.2, 20.7, 23.5, 25.0 29.3, 34.8, 60.5, 67.2, 173.7; mass spectrum *m/z* (relative intensity) EI 186 (0.04, M^+), 170 (0.1), 141 (68), 129 (52), 113 (28), 101 (62), 83 (36), 67 (26), 43 (100); HRMS (ESI) calcd for $[C_{10}H_{18}O_3Na]^+$ 209.1148, found 209.1140.

(E)-(4S,5R*)-Ethyl 4-(2-Furyl)-5-hydroxy-2-hexenoate (**4e**).* In a first flask, furan (0.08 mL, 1.0 mmol) was deprotonated at 0 °C using ^{n}BuLi (0.4 mL, 2.5 M in hexane, 1.0 mmol) in THF (2.0 mL) under argon for 3 h. In the second flask, to a solution of flame-dried $ZnBr_2$ (225 mg, 1.0 mmol) in THF (2.0 mL) under argon were added MeLi (1.25 mL, 1.6 M in Et_2O, 2.0 mmol) and 2-lithiofuran from flask 1, and the resulting mixture was stirred for 30 min at 0 °C. The flask was then transferred to a −20 °C bath, nitromethane (2.0 mL) and ethyl 4,5-epoxy-2,3-hexenoate (156 mg, 1.0 mmol) were added, and the resulting mixture was gradually warmed to room temperature over 12 h. The reaction was quenched with NH_4Cl−NH_4OH aqueous buffer (pH = 7.0, 10.0 mL) and filtered, and the filtrate was extracted with Et_2O (3 x15.0 mL). The combined organic phase was washed with water (10.0 mL) and brine (10.0 mL) and then dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 10−20% EtOAc in petroleum ether, v/v) to give pure compounds **4e** (128 mg, 57%, dr 100:0) as a colorless liquid:[60] IR (neat) 3423 (br, s), 2921 (s), 2852 (s), 1718 (s), 1458 (s), 1262 (s), 1143 (s), 799 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, J = 5.9 Hz, 3H), 1.23 (t, J = 7.3 Hz, 3H), 1.92 (s, 1H), 3.48 (dd, J = 8.7, 5.9 Hz, 1H), 4.06−4.14 (m, 3H), 5.85 (d, J = 15.6 Hz, 1H), 6.25−6.27 (m, 1H), 7.06 (dd, J = 8.7, 15.6 Hz, 1H), 6.08 (d, J = 2.7 Hz, 1H), 7.30 (d, J = 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 20.9, 49.9, 60.6, 69.2, 107.3, 110.5, 124.6, 142.1, 144.5, 152.9, 166.2; mass spectrum *m/z* (relative intensity) EI 224 (0.12, M^+), 206 (57), 178 (100), 139 (39), 133 (73), 128 (56), 111(71), 84 (63), 67 (44), 56 (17).

General Procedure F: Synthesis of Ketodiene. Ketodienes used for the epoxidation reactions were synthesized by using the following procedure. To a solution of LDA (12.0 mL 1.0 M in THF) was added ketone (10.0 mmol in 10.0 mL THF) over 10 min at −78 °C. After 75 min, the mixture of crotonaldehyde (0.70 g, 10.0 mmol) with TMSCl (1.08 g, 10.0 mmol) in THF (5.0 mL) was added dropwise. The solution was removed from the cooling bath and stirred at room temperature for 1 h before refluxing for 4 h. The reaction was quenched with saturated NH_4Cl solution, diluted with water, and extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with water (15.0 mL) and brine (15.0 mL) and then dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The NMR of the product was identical with the one reported in the literature.[59]

(2E,4R,5R*)-4,5-Epoxy-1-phenylhex-2-en-1-one (**6**).*[60] Employing general procedure F and using LDA (18.0 mL 1.0 M in THF), acetophenone (1.8 g, 15.0 mmol), crotonaldehyde (1.05 g, 15.0 mmol), and TMSCl (1.62 g, 15.0 mmol) gave (2*E*,4*E*)-1-phenyl-2,4-hexadien-1-one (1.73 g, 12.5 mmol) as a colorless oil. To the solution of (2*E*,4*E*)-1-phenyl-2,4-hexadien-1-one (10.0 mmol) was added *m*-CPBA (3.0 g, 1.3 equiv, 75% wt in water) at 0 °C in CH_2Cl_2, and the resulting mixture was warmed to room temperature over 12 h. The reaction mixture was quenched with Me_2S (1.0 mL), diluted with water (10.0 mL) and extracted with CH_2Cl_2 (3 × 20.0 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 × 20.0 mL), brine (20.0 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The purification of product using flash column chromatography (silica, 10−15% EtOAc/petroleum ether, v/v) gave pure **6** (1.52 g, 81%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (d, J = 5.0 Hz, 3H), 3.01−3.04 (m, 1H), 3.31 (dd, J = 6.8, 1.9 Hz, 1H), 6.82 (dd, J = 6.9, 15.5 Hz, 1H), 7.20 (d, J = 14.6 Hz, 1H), 7.47−7.96 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 57.7, 57.9, 126.9, 128.6, 128.7, 133.1, 137.3, 144.6, 189.6; mass spectrum *m/z* (relative intensity) EI 188 (M^+, 2), 172 (31), 120 (15), 105 (100), 77 (93), 65 (2), 55 (29).

(2E,4R,5R*)-4,5-Epoxy-1-(1-methylethyl)hex-2-en-1-one (**7**).* Employing general procedure F and using LDA (18.0 mL 1.0 M in THF), 3-methyl-2-butanone (1.29 g, 15.0 mmol), crotonaldehyde (1.05 g, 15.0 mmol), and TMSCl (1.62 g, 15.0 mmol) gave (2*E*,4*E*)-1-methylethyl-2,4-hexadien-1-one (1.73 g, 12.5 mmol) as a colorless oil. To the solution of (2*E*,4*E*)-1-(1-methylethyl)-2,4-hexadien-1-one (1.38 g, 10.0 mmol) in CH_2Cl_2 was added *m*-CPBA (1.3 equiv, 3.0 g, 75% wt. in water) at 0 °C, and the resulting mixture was warmed to room temperature over 4 h. The reaction mixture was quenched with Me_2S (1.0 mL), diluted with water, and extracted with CH_2Cl_2 (3 × 20.0 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 × 20.0 mL) and brine (20.0 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo after purification by flash column chromatography (silica, 10−15% EtOAc/petroleum ether, v/v) gave 7 (1.2 g, 78%) as a colorless oil: IR (neat) 2972 (s), 2933 (s), 2875 (s), 1698 (s), 1674 (s), 1631 (s), 1466 (s), 1383 (s), 1237 (s), 980 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, J = 6.8 Hz, 6H), 1.28 (d, J = 5.0 Hz, 3H), 2.68 (sept, J = 6.8 Hz, 1H), 2. 87 (dq, J = 4.2, 5.0 Hz, 1H), 3.08 (d, J = 6.8 Hz, 3H), 6.35−6.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 18.3, 39.1, 57.6 (2-carbons), 129.6, 142.4, 202.9; mass spectrum *m/z* (relative intensity) EI 154 (0. 18, M^+), 138 (0.97), 110 (26), 95 (100), 83 (67), 67 (18), 55 (36). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.73; H, 9.01.

(2E,4R,5R*)-3,4-Epoxy-1-phenylsulfonyl-2-pentene (**8**).* 1-(Phenylsulfonyl)-(1*E*,3*E*)-pentadiene was prepared by using the procedure reported in the literature.[61] To the ice-cold solution of 1-(phenylsulfonyl)-(1*E*,3*E*)-pentadiene (1.29 g, 6.2 mmol) in CH_2Cl_2 (30.0 mL) was added *m*-CPBA (1.3 equiv, 1.84 g, 75% wt in water), and the mixture was warmed to room temperature over 12 h. The reaction was quenched with Me_2S (1.0 mL), diluted with water (10.0 mL), and extracted with CH_2Cl_2 (3 × 15.0 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 × 15.0 mL), water (15.0 mL), and brine (15.0 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo and gave after purification by flash column chromatography (15−25% EtOAc in petroleum ether, v/v) **8** (1.07 g, 77%) as a colorless solid: mp 83.7−86.1 °C; IR (neat) 3058 (s), 2999 (s), 2930 (s), 1631 (s), 1448 (s), 1308 (s), 1150 (s), 1087 (s), 965 (s), 798 (s), 747 (s), 689 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (dd, J = 2.5, 4.5 Hz, 3H), 2.93 (dq, J = 1.8, 5.0 Hz, 1H), 3.21 (d, J = 5.9 Hz, 1H), 6.62 (d, J = 15.2 Hz, 1H), 6.78−6.82 (dd, J = 6.0, 15.1 Hz, 1H), 7.53−7.88 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 56.0, 58.3, 127.8, 129.5, 132.4, 137.7, 139.9, 142.7. Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39. Found: C, 58.97; H, 5.39.

(2E,4R,5R*)-4,5-Epoxy-1-piperidinohex-2-en-1-amide (**9**).*[62] Using the literature procedure,[63] sorbic acid (1.12 g, 10.0 mmol), triethylamine (2.7 mL, 20.0 mmol), methanesulfonyl chloride (1.07 g, 15.0 mmol), and piperidine (0.88 mL, 15.0 mmol) gave colorless crystals of 2,4-hexadienoylpiperidine (57%). To the solution of (2*E*,4*E*)-2,4-hexadienoylpiperidine (1.79 g, 10.0 mmol) in CH_2Cl_2 was added *m*-CPBA (1.3 equiv, 3 g, 75% wt in water) at 0 °C, and the resulting mixture was warmed to room temperature over 12 h. The reaction mixture was quenched with Me_2S (1.0 mL), diluted with water (10.0 mL), and extracted with CH_2Cl_2 (3 × 20.0 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 × 15.0 mL) and brine (15.0 mL), dried over anhydrous $MgSO_4$, filtered, and

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concentrated in vacuo and gave after purification with flash column chromatography (30−40% EtOAc in petroleum ether, v/v) **9** (1.33 g, 68%) as a colorless liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (dd, J = 1.4, 5.0 Hz, 3H), 1.15−1.62 (m, 6H), 2.87−2.91 (m, 1H), 3.13 (dd, J = 1.8, 3.6 Hz, 1H), 3.43 (s, 2H), 3.54 (s, 2H), 6.53 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 24.6, 25.6, 26.7, 43.2, 47.0, 57.7, 57.9, 128.9, 141.1, 164.4.

(1R,2R*,3S*,1′R*) 2-(1-Hydroxyethyl)-3-methylcyclopropyl-1-phenyl Ketone (**10a**).* Employing general procedure C and using MeMgCl (0.4 mL, 3.0 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 4,5-epoxy-1-phenylhex-2-en-1-one **6** (188 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 20−30% EtOAc/petroleum ether, v/v) **10a** (115 mg, 57%, dr 100:0) as a white amorphous solid: mp 72.3−74.3 °C; IR (neat) 3421 (br s), 2970 (s), 2929 (s), 1660 (s), 1450 (s), 1341 (s), 1223 (s), 701 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36−1.38 (m, 6H), 1.53 (s, 1H), 1.83−1.95 (m, 2H), 2.31 (t, J = 4.6 Hz, 1H), 3.73 (dt, J = 6.4, 13.6 Hz, 1H), 7.48−7.99 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6, 23.4, 25.1, 31.2, 37.9, 67.2, 127.9, 128.5, 132.8, 137.8, 198.8; mass spectrum m/z (relative intensity) EI 204 (0.1, M$^+$), 185 (3), 171 (13), 159 (98), 145 (22), 131 (14), 115 (90), 105 (100), 91 (11), 77 (94), 55 (22); HRMS (ESI) calcd for $[C_{13}H_{16}O_2Na]^+$ 227.1043, found 227.1030.

(1R,2R*,3S*,1′R*) 2-(1-Hydroxyethyl)-3-ethylcyclopropyl-1-phenyl Ketone (**10b**).* Employing general procedure C and using EtMgCl (0.6 mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 4,5-epoxy-1-phenylhex-2-en-1-one **6** (188 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 15−25% EtOAc/petroleum ether, v/v) **10b** (137 mg, 63%, dr 100:0) as a white amorphous solid: mp 71.3−74.1 °C; IR (neat) 3431 (br s), 296 (s), 2918 (s), 1663 (s), 1446 (s), 1347 (s), 1234 (s), 706 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, J = 7.3 Hz, 3H), 1. 37 (d, J = 5.9 Hz, 3H), 1.53−1.57 (m, 1H), 1.61 (s, 1H), 1.76−1.84 (m, 2H), 1.94−1.99 (m, 1H), 2.30 (t, J = 4.6 Hz, 1H), 3.69 (dq, J = 5.9, 9.6 Hz, 1H), 7.48−7.99 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 21.3, 23.7, 30.1, 33.6, 38.3, 67.4, 128.0, 128.7, 132.9, 137.9, 198.9; mass spectrum m/z (relative intensity) EI 218 (0.02, M$^+$), 200 (0.18), 185 (4), 173 (62), 145 (17), 105 (100), 77 (48), 55 (7); HRMS (ESI) calcd for $[C_{14}H_{18}O_2Na]^+$ 241.1199, found 241.1196.

(1R,2R*,3S*,1′R*) 2-(1-Hydroxyethyl)-3-butylcyclopropyl-1-phenyl Ketone (**10c**).* Employing general procedure C and using ^{n}BuMgCl (0.48 mL, 2.5 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 4,5-epoxy-1-phenylhex-2-en-1-one **6** (188 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 15−25% EtOAc/petroleum ether, v/v) **10c** (184 mg, 74%, dr 100:0) as a white amorphous solid: mp 65.9−67.4 °C; IR (neat) 3429 (br s), 2959 (s), 2931 (s), 2860 (s), 1661 (s), 1415 (s), 1354 (s), 1225 (s), 702 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3H), 1.36 (d, J = 5.9 Hz, 3H), 1.38−1.41 (m, 2H), 1.46−1.15 (m, 4H), 1.77−1.82 (m, 2H), 1.95 (dt, J = 4.6, 9.6 Hz, 1H), 2.32 (t, J = 4.1 Hz, 1H), 3.71 (dt, J = 3.6, 6.8 Hz, 1H), 7.49−8.0 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.5, 23.6, 27.5, 30.1, 31.7, 31.9, 38.0, 67.3, 127.9, 128.6, 132.8, 137.7, 198.8; mass spectrum m/z (relative intensity) EI 246 (0.3, M$^+$), 228 (0.4), 201 (99), 185 (8), 159 (14), 145 (23), 133 (15), 117 (8), 105 (100), 91 (11), 77 (58), 55 (15); HRMS (ESI) calcd for $[C_{16}H_{22}NaO_2]^+$ 269.1512, found 269.1503.

(1R,2R*,3S*,1′R*) 2-(1-Hydroxyethyl)-3-(1-methylethyl)-cyclopropyl-1-phenyl Ketone (**10d**).* Employing general procedure C and using ^{i}PrMgBr (0.6 mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 4,5-epoxy-1-phenylhex-2-en-1-one **6** (188 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 20−30% EtOAc/petroleum ether, v/v) **10d** (146 mg, 63%, dr 100:0) as a white amorphous solid: mp 67.3−69.8 °C; IR (neat) 3421 (br s), 2964 (s), 2928 (s), 2871 (s), 1660 (s), 1450 (s), 1364 (s), 1223 (s), 703 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, J = 6.4 Hz, 3H), 1.17 (d, J = 6.4, 3H), 1.25−1.28 (m, 1H), 1.34 (d, J = 5.9 Hz, 3H), 1.42−1.46 (m, 1H), 1.59−1.66 (m, 1H), 1.97 (td, J = 3.6, 8.7 Hz, 1H), 2.30 (t, J = 4.5 Hz, 1H), 3.70 (dq, J = 5.5, 9.6 Hz, 1H), 7.47−7.89 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8, 23.3, 24.0, 27.9, 29.3, 38.8, 40.4, 67.2, 127.9, 128.6, 132.8, 137.8, 198.8; mass spectrum m/z (relative intensity) EI 232 (0.45, M$^+$), 214 (4), 199 (11), 187 (16), 171 (67), 149 (91), 145 (52), 131 (65), 117 (100), 105 (56), 91 (90), 77 (61), 55 (21); HRMS (ESI) calcd for $[C_{15}H_{20}O_2Na]^+$ 255.1356, found 255.1350.

(1R,2R*,3S*,1′R*) 2-(1-Hydroxyethyl)-3-phenylcyclopropyl-1-phenyl Ketone (**10e**).* Employing general procedure D and using PhMgBr (0.43 mL, 2.8 M in hexane, 1.2 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol), and 4,5-epoxy-1-phenylhex-2-en-1-one **6** (188 mg, 1.0 mmol) in toluene gave after flash column chromatography (silica, 15−25% EtOAc/petroleum ether, v/v) **10e** (170 mg, 64%, dr 92:8) as a white solid: mp 69.7−71.3 °C; IR (neat) 3401 (br s), 2962 (s), 2921 (s), 1656 (s), 1449 (s), 1097 (s), 741 (s), 699 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, J = 6.4 Hz, 3H), 1.45 (s, 1H), 2.11−2.14 (m, 1H), 2.03−2.06 (m, 2H), 3.37 (dq J = 6.6, 9.6 Hz, 1H), 7.19−8.00 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 27.7, 33.9, 38.9, 66.6, 127.1, 128.0, 128.5, 128.7, 128.8, 133.1, 135.9, 136.8, 198.0; mass spectrum m/z (relative intensity) EI 248 (0.52, M$^+$-H_2O), 233 (5), 222 (27), 221 (100), 209 (6), 207 (12), 193 (4), 144 (8), 129 (9), 115 (15), 105 (65), 91 (6),77 (31), 65 (52); HRMS (ESI) calcd for $[C_{18}H_{18}NaO_2]^+$ 289.1199, found 289.1195.

(1R,2R*,3S*,1′R*) 2-(1-Hydroxyethyl)-3-butylcyclopropyl-1-(methylethyl) Ketone (**11c**).* Employing general procedure C and using ^{n}BuMgCl (0.48 mL, 2.5 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 4,5-epoxy-1-(1-methylethyl)hex-2-en-1-one **7** (154 mg, 1.0 mmol) in THF gave after flash column chromatography (silica, 15−25% EtOAc/petroleum ether, v/v) **11c** (188 mg, 88%, dr 100:0) as a white solid: mp 52.7−54.5 °C; IR (neat) 3433 (br s), 2966 (s), 2931 (s), 2873 (s), 1687 (s), 1467 (s), 1382 (s), 1143 (s), 1074 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.13 (d, J = 6.8 Hz, 6H), 1.31 (d, J = 6.4 Hz, 3H), 1.33−1.45 (m, 4H), 1.15−1.56 (m, 1H), 1.60 (t, J = 4.5 Hz, 1 H), 1.64−1.72 (m, 3H), 1.75 (s, 1H), 2.71 (sept., J = 6.8 Hz, 1H), 3.56 (dt, J = 5.9, 9.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 18.1 (2 carbons), 22.4, 23.4, 27.2, 30.6, 31.7, 31.9, 37.2, 41.6, 67.1, 212.9; mass spectrum m/z (relative intensity) EI 212 (0.1, M$^+$), 195 (2), 169 (88), 167 (100), 115 (22), 123 (77), 109 (66), 95 (40), 81 (99), 69 (66), 55 (99). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.50; H, 11.56.

(1R,2R*,3S*,1′R*) 2-(1-Hydroxyethyl)-3-(1-methylethyl)-cyclopropyl-1-methylethyl Ketone (**11d**).* Employing general procedure C and using ^{i}PrMgBr (0.6 mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 4,5-epoxy-1-(1-methylethyl)hex-2-en-1-one **7** (154 mg, 1.0 mmol) in THF gave after flash column chromatography (silica, 20−25% EtOAc/petroleum ether, v/v) gave **11d** (164 mg, 82%, dr 95:5) as a white solid: mp 61.8−63.4 °C; IR (neat) 3362 (br s), 2965 (s), 2870 (s), 1686 (s), 1467 (s), 1365 (s), 1143 (s), 1068 (s) cm^{-1}; **major**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, J = 6.4 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.14 (d, J = 3.2 Hz, 3H), 1.15 (d, J = 3.2 Hz, 3H), 1.25−1.28 (m, 1H), 1.31 (d, J = 5.9 Hz, 3H), 1.34−1.47 (m, 2H), 1.59 (t, J = 4.5 Hz, 1H), 1.71 (dt, J = 8.7 Hz, 1H), 2.71 (septet, J = 6.8 Hz, 1H), 3.1 (dq, J = 6.4, 12.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2 (2 carbon), 22.7, 23.1, 23.9, 27.6, 30.8, 38.0, 39.3, 41.6, 67.1, 212.9; mass spectrum m/z (relative intensity) EI 198 (0.06, M$^+$), 180 (1.5), 11 (96), 153 (99), 137 (36), 125 (20), 109 (99), 99 (99), 95 (98), 83 (53), 71 (100), 69 (94), 55 (92). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.83; H, 11.02.

(1R,2R*,3S*,1′R*) 2-(1-Hydroxyethyl)-3-phenylcyclopropyl-1-methylethyl Ketone (**11e**).* Employing general procedure D and using PhMgBr (0.43 mL, 2.8 M in hexane, 1.2 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol), and 4,5-epoxy-1-(1-methylethyl)-hex-2-en-1-one **7** (154 mg, 1.0 mmol) in CH_2Cl_2 gave after flash column chromatography (silica, 15−25% EtOAc/petroleum ether, v/v) **11e** (195 mg, 84%, dr 100:0) as a white solid: mp 61.3−62.4 °C; IR (neat) 3422 (br s), 2971 (s), 2856 (s), 1687 (s), 1459 (s), 1386 (s), 1059 (s), 698 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 6.4 Hz, 3H), 1.41 (s, 1H), 1.84−1.88 (m, 1H), 2.36 (t, J = 5.0 Hz, 1 H), 2.74−2.81 (m, 2H), 3.22 (dq, J = 6.6, 9.6 Hz, 1H), 7.18−7.27 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 18.1, 22.6, 29.1, 33.1, 38.4, 41.9, 66.4, 127, 128.4, 128.7, 135.9, 211.8; mass spectrum m/z (relative intensity) EI 232 (0.23, M$^+$), 218 (0.5), 205 (4), 19 (17), 190 (40), 176 (5), 165 (52), 164 (93), 149 (100), 121

(20), 104 (12), 91 (12), 77 (13), 65 (3); HRMS (ESI) calcd for $[C_{15}H_{20}NaO_2]^+$ 255.1356, found 255.1322.

(1R,2R*,3S*,1′R*) Ethyl 2-(1-Hydroxyethyl)-3-(2,2-dimethylethyl)-1-methylethyl Ketone (**11f**).* Employing general procedure A, ^{t}BuLi (2.0 mL 1.5 M THF/toluene, 3.0 mmol), flame-dried $ZnBr_2$ (225 mg, 1.0 mmol), and 4,5-epoxy-1-(1-methylethyl)hex-2-en-1-one **7** (154 mg, 1.0 mmol) gave after purification by flash column chromatography (silica, 20−30% EtOAc/petroleum ether, v/v) **11f** (155 mg, 73%, dr 100:0) as a white solid. Utilization of general procedure C and using ^{t}BuMgCl (0.71 mL, 1.70 M in THF, 1.2 mmol, $ZnBr_2$ (23 mg, 0.1 mmol) and **7** (154 mg, 1.0 mmol) gave **11f** (174 mg, 82%, 100:0 dr): mp 67.8−69.3 °C; IR (neat) 3441 (br s), 2966 (s), 2851 (s), 1693 (s), 1470 (s), 1053 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (br s, 9H), 1.15 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 1.44−1.48 (m, 1H), 1.67 (dt, J = 9.7, 4.6 Hz, 1H), 1.69 (s, 1H), 1.86 (t, J = 5.1 Hz, 1H), 2.72 (sept, J = 7.4 Hz, 1H), 3.75 (qd, J = 10.1, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 18.3, 24.7, 27.9, 30.2, 31.2, 39.0, 41.6, 42.8, 66.8, 213.5; mass spectrum m/z (relative intensity) EI 212 (0.001, M^+), 194 (M^+-H_2O, 0.18), 167 (23), 143 (8), 125 (17), 109 (24), 99 (26), 83 (17), 71 (46), 57 (23), 55 (26), 43 (100).

(1R,2S*,3S*,1′R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-methylcyclopropane (**16a**).* Employing general procedure C and using MeMgCl (0.53 mL, 2.3 M, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 3,4-epoxy-1-phenylsulfonyl-2-pentene **8** (224 mg, 1.0 mmol) in toluene gave after purification with flash chromatography (silica, 25−35% EtOAc/petroleum ether, v/v) **16a** with minor **12a** (201 mg, 83%, dr 95:5) as colorless solid. **Major (16a):** IR (neat) 3499 (br s), 2972 (s), 2933 (s), 2872 (s), 1447 (s), 1305 (s), 1146 (s), 1091 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 5.9 Hz, 3H), 1.34 (d, J = 6.4 Hz, 3H), 1.39 (q, J = 6.9 Hz, 1H), 1.97−2.06 (m, 1H), 2.24 (dd, J = 5.4, 8.7 Hz, 1H), 2.37 (s, 1H), 4.35 (dq, J = 6.4, 13.3 Hz, 1H), 7.56−7.93 (m, 5H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 17.2, 19.7, 23.9, 38.2, 45.5, 64.7, 127.1, 129.3, 133.4, 141.7; mass spectrum m/z (relative intensity) EI 240 (0. 14, M^+), 223 (2), 183 (100), 161 (7), 143 (24), 125 (49), 99 (87), 83 (55), 77 (67), 55 (37); HRMS (ESI) calculated for $[C_{12}H_{16}O_3SNa]^+$: 263.0712, found 263.0711. **Minor (12a):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, J = 5.9 Hz, 3H), 1.25 (d, J = 6.4 Hz, 3H), 1.25−1.27 (m, 1H), 2.03−2.06 (m, 2H), 3.49−3.53 (m, 2H), 7.56−7.90 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 19.2, 23.0, 31.7, 44.3, 65.9, 127.5, 129.2, 133.5, 140.5; mass spectrum m/z (relative intensity) EI 242 (0.14, M^+), 223 (2), 195 (4), 143 (10), 125 (21), 99 (100), 77 (38), 55 (22).

(1R,2R*,3S*,1′R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-n-butyl cyclopropane (**12c**) and (1R*,2S*,3S*,1′R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-n-butylcyclopropane (**16c**).* Employing general procedure C and using ^{n}BuMgCl (0.48 mL, 2.5 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 3,4-epoxy-1-phenylsulfonyl-2-pentene **8** (224 mg, 1.0 mmol) in THF after purification with flash column chromatography (silica, 25−35% EtOAc/petroleum ether, v/v) gave the mixture of **12c** and **16c** (220 mg, 78%, dr 58:42) as a white solid. The reaction in CH_2Cl_2 gave 234 mg, 83%, dr 0:100 and in toluene gave 215 mg, 89%, dr 0:100. **12c**: mp 80.1−81.6 °C; IR (neat) 3449 (br s), 2960 (s), 2927(s), 2859 (s), 1306 (s), 1147 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, J = 7.0 Hz, 3H), 1.12 (d, J = 6.0 Hz, 3H), 1.25−1.36 (m, 5H), 1.59 (s, 1H), 1.67−1.70 (m, 1H), 1.84−1.89 (m, 2H), 2.05 (t, J = 5.0 Hz, 1H), 3.53 (dq, J = 6.0, 8.5 Hz, 1H), 7.57−7.91 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 22.2, 23.2, 25.3, 26.1, 31.5, 31.9, 43.8, 66.2, 127.6, 129.2, 133.3, 140.6; mass spectrum m/z (relative intensity) EI 282 (3, M^+) 281 (9), 265 (1), 225 (78), 206 (29), 190 (4), 147 (17), 123 (87), 96 (6), 77 (66), 73 (100), 55 (89). Anal. Calcd for $C_{15}H_{22}O_3S$: C, 63.80; H, 7.85. Found: C, 64.07; H, 8.02. **16c**: mp 83.2−84.7 °C; IR (neat) 3448 (br s), 2960 (s), 2929 (s), 2859 (s), 1306 (s), 1147 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, J = 7.3 Hz, 3H), 1.09−1.28 (m, 5H), 1.37 (d, J = 5.9 Hz, 3H), 1.38−1.44 (m, 1H), 1.65 (s, 1H), 1.90−1.95 (dt, J = 6.8, 13.0 Hz, 1H), 2.24 (dd, J = 5.5, 8.7 Hz, 1H), 2.38 (d, J = 1.8 Hz, 1H), 4.36 (dq, J = 6.4, 13.3 Hz, 1H), 7.57−7.93 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 22.1, 23.8, 25.2, 30.9, 32.0, 37.5, 45.0 64.5, 127.3, 129.2, 133.4, 141.4; mass spectrum m/z (relative intensity) EI 282 (0.3, M^+), 265 (1), 237 (27), 225 (80), 195 (13), 143 (39), 123 (96), 97 (40), 77 (66), 57 (63), 55 (100).

(1R,2S*,3S*,1′R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-(1-methylethyl)cyclopropane (**16d**).* Employing general procedure C and using ^{i}PrMgCl (0.6 mL, 2.0 M in Et_2O, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 3,4-epoxy-1-phenylsulfonyl-2-pentene **8** (224 mg, 1.0 mmol) in toluene gave after purification with flash column chromatography (silica, 30−35% EtOAc/petroleum ether, v/v) **16d** (235 mg, 87%, dr 100:0) as a colorless solid: mp 87.4−88.6 °C; IR (neat) 3504 (br s), 2962 (s), 1448 (s), 1303 (s), 1148 (s), 1091(s), 734 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H), 1.25−1.29 (m, 1H), 1.38 (d, J = 6.4 Hz, 3H), 1.40−1.45 (dd, J = 7.3, 14.2 Hz, 1H), 1.73 (q, J = 6.9 Hz, 1H), 1.91 (s, 1H), 2.28 (dd, J = 5.5, 8.7 Hz, 1H), 4.37 (dt, J = 6.4, 12.4 Hz, 1H), 7.57−7.94 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.4, 23.7, 31.5, 32.6, 36.9, 44.5, 64.3, 127.5, 129.2, 133.5, 141.3; mass spectrum m/z (relative intensity) EI 268 (0.12, M^+), 215 (55), 223 (40), 211 (93), 195 (5), 143 (29), 125 (68), 109 (100), 83 (55), 77 (63), 59 (78), 55 (63); HRMS (ESI) calcd for $[C_{14}H_{20}O_3SNa]^+$ 291.1031, found 291.1037.

(1R,2R*,3S*,1′R*) 1-(1-Hydroxyethyl)-2-(phenylsulfonyl)-3-phenylcyclopropane (**12e**) and (1R*,2S*,3S*,1′S*) 1-(1-Hydroxyethyl)-2-(phenyl sulfonyl)-3-phenyl cyclopropane (**16e**).* Employing general procedure D and using PhMgBr (0.43 mL, 2.8 M in Et_2O, 1.2 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol), and 3,4-epoxy-1-phenylsulfonyl-2-pentene **8** (224 mg, 1.0 mmol) in CH_2Cl_2 gave after purification with flash column chromatography (silica, 15−20%, EtOAc/petroleum ether, v/v) the mixture of **12e** and **16e** (263 mg, 87%, dr 4:96) as a white amorphous solid. **12e** (11 mg): mp 89.1−91.2 °C; IR (neat) 3410 (br s), 2926 (s), 2852 (s), 1410 (s), 1311 (s), 1150 (s), 750(s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (d, J = 6.4 Hz, 3H), 1.30 (s, 1), 2.17 (ddd, J = 5.0, 9.2, 14.2 Hz, 1H), 2.81 (t, J = 4.9 Hz, 1H), 2.18−3.24 (m, 1H), 3.30 (dd, J = 5.1, 9.7 Hz, 1H), 7.24−7.35 (m, 5H), 7.63 (t, J = 7.3 Hz, 2H), 7.71 (t, J = 6.9 Hz, 1 H), 8.01 (d, J = 7.8 Hz 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 28.9, 37.9, 46.7, 64.6, 126.8, 127.2, 127.3, 128.6, 129.4, 133.7, 137.2, 141.1 mass spectrum m/z (relative intensity) EI 302 (0.1, M^+), 284 (0.3), 245 (1), 207 (4), 162 (13), 161 (100), 143 (32), 128 (24), 117 (23), 115 (42), 105 (5), 91 (33), 77 (27), 65 (7), 55 (11); HRMS (ESI) calcd for $[C_{17}H_{18}NaO_3S]^+$ 325.0869, found 325.0857. **Major 16e** (252 mg): mp 91.2−93.4 °C; IR (neat) 3370 (br s), 3063 (s), 3030 (s), 2926 (s), 1596 (s), 1495 (s), 1453 (s), 1233 (s), 1017 (s), 766 (s), 700 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, J = 6.4 Hz, 3H), 1.98 (q, J = 7.3, 1H), 2.37 (s, 1H), 2.74 (dd, J = 5.4, 9.1 Hz, 1H), 3.15 (t, J = 5.9 Hz, 1H), 4.54 (dq, J = 6.4, 12.8 Hz, 1H), 6.98−7.98 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 28.9, 37.9, 46.7, 64.6, 126.8, 127.2, 127.3, 128.6, 129.4, 133.7, 137.2, 141.1; mass spectrum m/z (relative intensity) EI 302 (0.1, M^+), 284 (0.2), 245 (1), 207 (7), 162 (12), 161 (100), 143 (33), 129 (23), 117 (24), 115 (42), 91 (33), 77 (27), 65 (7), 55 (12); HRMS (ESI) calcd for $[C_{17}H_{18}NaO_3S]^+$ 325.0869, found 325.0861.

(1R,2R*,3S*,1′R*)2-(1-Hydroxylethyl)-3-butyl-1-N,N-cyclohexylenecyclopropanecarboxamide (**13c**) and (1R*,2S*,3S*,1′R*)-2-(Hydroxylethyl)-3-butyl-1-N,N-cyclohexylenecyclopropanecarboxamide (**17c**).* Employing general procedure C and using ^{n}BuMgCl (0.48 mL, 2.5 M in THF, 1.2 mmol), $ZnBr_2$ (23 mg, 0.1 mmol), and 4,5-epoxy-1-piperidinohex-2-en-1-amide **9** (195 mg, 1.0 mmol) in THF gave after purification with flash column chromatography (silica, 1−3% methanol/CH_2Cl_2, v/v) the mixture of **13c** and **17c** (121 mg, 48%, dr 59:41) as a colorless oil. **Major (13c)**: 71 mg; IR (neat) 3409 (br s), 2931 (s), 2857 (s), 1617 (s), 1456 (s), 1139 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.35 (d, J = 5.9 Hz, 3H), 1.36−1.72 (m, 16H), 3.56 (s, 5H); ^{13}CNMR (125 MHz, $CDCl_3$) 14.0, 22.5, 23.6, 23.8, 24.7, 25.5, 26.4, 26.8, 27.4, 32.2, 33.6, 43.3, 46.7, 67.6, 170.5; ^{1}H NMR (500 MHz, benzene-d_6) δ 0.87−0.89 (m, 6H), 1.10−1.57 (m, 14H), 1.68−1.74 (m, 1H), 1.80−1.85 (m, 1H), 3.09 (s, 2H), 3.30−3.35 (m, 1H), 3.50 (s, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ 14.6, 23.1, 23.3, 24.2, 24.4, 25.3, 26.8, 28.0, 32.8, 34.4, 43.7, 46.8, 67.5, 170.4; mass spectrum m/z (relative intensity) EI 253 (0.4, M^+), 235 (37), 220 (4), 208 (100), 196 (13), 166 (5), 152 (8), 138 (8), 112

(29), 84 (60), 69 (42), 55 (32); HRMS (ESI) calcd for $[C_{15}H_{27}NO_2Na]^+$ 276.1934, found 276.1931. **Minor (17c)**: 50 mg; IR (neat) 3409 (br s), 2931 (s), 2857 (s), 1617 (s), 1456 (s), 1139 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3H), 1.07−1.11 (m, 1H), 1.25 (d, J = 5.9 Hz, 3H), 1.29−1.74 (m, 14H), 3.54−3.64 (m, 4H), 3.71 (s, 1H), 3.91−3.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, 23.0, 23.4, 24.6, 25.6, 26.6, 31.4, 33.1, 57.7, 43.3, 47.1, 64.2, 170.7; ^1H NMR (500 MHz, benzene-d_6) δ 0.88 (t, J = 5.9 Hz, 3H), 1.06−1.35 (m, 14H), 1.38 (d, J = 6.4 Hz, 3H), 2.03 (t, J = 5.9 Hz, 1H), 3.03 (s, 2H), 3.44 (s, 2H), 4.04 (s, 1H), 4.22 (m, 1H), ^{13}C NMR (125 MHz, benzene-d_6) δ 14.6, 23.1, 23.4, 24.5, 25.1, 26.1, 27.1, 32.1, 33.9, 36.7, 43.5, 47.1, 64.7, 171.0; mass spectrum m/z (relative intensity) EI 253 (0.4, M^+), 235 (37), 208 (89), 196 (99), 166 (27), 112 (88), 84 (100), 81 (50), 69 (86), 55 (68); HRMS (ESI) calcd for $[C_{15}H_{28}NO_2]^+$ 254.2115, found 254.2111.

(1R,2R*,3S*,1′R*) 2-(1-Hydroxylethyl)-3-phenyl-1-N,N-cyclohexylenecyclopropanecarboxamide (**13e**) and (1R*,2S*,3S*,1′R*) 2-(1-Hydroxylethyl)-3-phenyl-1-N,N-cyclohexylenecyclopropanecarboxamide (**17e**).* Employing general procedure D and using PhMgBr (0.43 mL, 2.8 M in Et_2O, 1.2 mmol), $Zn(CN)_2$ (12 mg, 0.1 mmol), and 4,5-epoxy-1-piperidinohex-2-en-1-amide **9** (195 mg, 1.0 mmol) in toluene gave after purification with flash column chromatography (silica, 1−3% methanol/CH_2Cl_2, v/v) the mixture of **13e** and **17e** (180 mg, 66%, dr 19:81) as a colorless oil: IR (neat) 3421 (br s), 2911 (s), 2903 (s), 2841 (s), 1621 (s), 1451 (s), 1109 (s), 758 (s) cm^{-1}; **minor (13e):** ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (d, J = 6.0 Hz, 3H), 1.57−1.76 (m, 8H), 2.05 (s, 1H), 2.89 (t, J = 6.0 Hz, 1H), 3.09 (br s, 1H), 3.57 (br s, 3H), 4.15 (dq, J = 10.6, 4.6 Hz, 1H), 7.15−7.35 (m, 5H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 24.6, 25.7, 26.6, 26.7, 28.5, 36.7, 43.5, 47.3, 64.4, 126.2, 128.5, 128.8, 140.9, 169.7; HRMS (ESI) calculated for $[C_{17}H_{23}NNaO_2]^+$ 296.1621, found 296.1607; **major (17e):** ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, J = 10.6 Hz, 3H), 1.57−1.76 (m, 3H), 1.84−1.97 (m, 2H), 2.05−2.08 (m, 2H), 2.23 (t, J = 4.6 Hz, 1H), 2.85 (dd, J = 9.2, 5.5 Hz, 1H), 3.09 (br s, 1H), 3.29−3.34 (m, 1H), 3.64 (br s, 4H), 7.15−7.35 (m, 5H);, ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 22.8, 24.7, 30.0, 35.4, 43.6, 47.2, 66.8, 126.9, 128.5, 128.6, 136.6, 169.6; HRMS (ESI) calcd for $[C_{17}H_{23}NO_2Na]^+$ 296.1621, found 296.1609.

*Reduction of Ethyl 2-(1-Hydroxyethyl)-3-butylcyclopropanecarboxylate (**2b**).* To the solution of ethyl 2-(1-hydroxyethyl)-3-butylcyclopropanecarboxylate **2b** (214 mg, 1.0 mmol) in Et_2O (10.0 mL) at 0 °C was added $LiAlH_4$ (68 mg, 2.0 mmol). The cloudy suspension was stirred at 0 °C for 2 h and then treated with water (2.0 mL), 2 N NaOH (2.0 mL), and water (2.0 mL) at 0 °C. Anhydrous $MgSO_4$ was added, and the resulting mixture was filtered through a plug of Celite eluting with Et_2O (25.0 mL) followed by solvent concentration in vacuo to give title compound **27** (152 mg, 89%) which was used for a further step without purification.

General Procedure G for the Synthesis of 3,5-Dinitrobenzoyl Derivative. The 3,5-dintribenzoyl derivatives were synthesized using a modified literature procedure.[64] To the solution of cyclopropyl alcohol (1.0 equiv) in CH_2Cl_2 under argon were added Et_3N (1.5 equiv per −OH group), 3,5-dinitrobenzoyl chloride (1.5 equiv per −OH group), and a catalytic amount of DMAP (10−20 mg), and the resulting mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (5.0 mL), diluted with water (10.0 mL), and extracted with EtOAc (3 × 10.0 mL). The combined organic layer was washed with brine (10.0 mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 1:9, EtOAc/petroleum ether, v/v) to give pure products which were recrystallized in mixed solvent systems.

(1R,2R*,3R*,1′R*)-1-(1-(3,5-Dinitrobenzoyloxy)ethyl)-2-(1-(3,5-dinitrobenzoyloxy)methyl)-3-n-butylcyclopropane (**28**).* Employing general procedure G and cyclopropanediol **27** (86 mg, 0.5 mmol), Et_3N (153 mg, 1.5 mmol), 3,5-dinitrobenzoyl chloride (523 mg, 1.5 mmol), and catalytic amount of DMAP (20 mg) in CH_2Cl_2 gave after purification by flash column chromatography (silica, 1:9, EtOAc/petroleum ether, v/v) **28** (232 mg, 83%) as colorless solid. The compound on recrystallization in acetone/EtOAc (1:1 mixture) using slow solvent evaporation process afforded a needle-shaped crystal good enough for X-ray crystallography: mp 96.6−98.5 °C; IR (neat) 2927 (m), 2891 (m), 1724 (s), 1633 (b), 1544 (s), 1459 (s), 1345 (s), 1273 (b), 1168 (s), 1075 (s), 721 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 (t, J = 6.4 Hz, 3H), 1.10−1.53 (m, 8H), 1.58 (d, J = 5.9 Hz, 3H), 3.48 (q, J = 6.8 Hz, 1H), 4.36 (dd, J = 7.3, 11.4 Hz, 1H), 4.47 (dd, J = 6.9, 11.5 Hz, 1H), 4.99 (dt, J = 5.9, 12.3 Hz, 1H), 9.19−9.27 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.9, 22.3, 22.6, 23.8, 27.3, 27.8, 32.0, 70.1, 73.9, 122.3, 122.5, 129.3, 129.4, 133.9, 134.3, 148.7, 148.8, 161.7, 162.5.

(1R,2R*,3S*,1′R*)-1-Phenylsulfonyl-2-(1-(3,5-dinitrobenzoyloxy)ethyl)-3-n-butylcyclopropane (**29**).* Employing general procedure G and using **12c** (28 mg, 0.1 mmol), Et_3N (15 mg, 0.15 mmol), 3,5-dinitrobenzoyl chloride (53 mg, 0.15 mmol), and DMAP (2 mg) in CH_2Cl_2 gave after purification by flash column chromatography (silica, 1:9, EtOAc/petroleum ether, v/v) **29** (38 mg, 80%) as yellowish solid. The compounds on recrystallization in acetone/EtOAc (1:1 mixture) using a slow solvent evaporation process afforded a needle-shaped crystal good enough for X-ray crystallography: mp 102.3−105.4 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 0.72 (t, J = 6.5 Hz, 3H), 1.15−1.26 (m, 6), 1.32 (d, J = 6.4 Hz, 3H), 1.91−1.97 (m, 1), 2.18−2.24 (m, 2H), 4.94 (dq, J = 6.4, 9.6 Hz; 1H), 7.60−7.95 (m, 5H), 9.16 (s, 2H), 9.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.4, 22.1, 25.6, 26.3, 29.2, 31.4, 44.2, 71.7, 122.7, 127.8, 129.5 (2,carbon), 133.8, 140.1, 148.8, 161.6.

(1R,2S*,3S*,1′R*)-1-Piperidinylamido-2-(1-(3,5-dinitrobenzoyloxy)ethyl)-3-phenylcyclopropane (**30**).* Employing general procedure G and using **17e** (41 mg, 0.15 mmol), Et_3N (23 mg, 0.23 mmol), 3,5-dinitrobenzoyl chloride (81 mg, 0.23 mmol), and DMAP (3 mg) in CH_2Cl_2 gave after purification by flash column chromatography (silica, 1:9, EtOAc/petroleum ether, v/v) **30** (61 mg, 87%) as yellowish solid. The compounds on recrystallization in CH_2Cl_2/EtOAc (1:1 mixture) using slow solvent evaporation process afforded a needle-shaped crystal good enough for X-ray crystallography: mp 101.2−104.7 °C; IR (neat) 2947 (s), 2911 (s), 2891 (s), 1740 (s), 1665 (br), 1513 (s), 1444 (s), 1367 (s), 1157 (s), 1105 (s), 739 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52 (d, J = 6.5 Hz, 3H), 1.61−1.74 (m, 6H), 1.92−1.99 (m, 1H), 2.28 (dd, J = 9.2, 3.7 Hz, 1H), 3.05 (t, J = 6.0 Hz, 1H), 3.60−3.66 (m, 4H), 5.50 (dt, J = 9.2, 6.4 Hz, 1H), 7.15−7.30 (m, 5H), 9.15−9.21 (m, 3H); ^{13}C NMR (125 MHz, benzene-d_6) δ 21.0, 25.0, 26.1, 27.1, 28.3, 30.0, 34.2, 43.7, 46.9, 74.2, 122.1, 126.9, 127.3, 129.1, 129.3, 134.1, 140.6, 148.5, 162.2, 167.3.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for **2a−d,f**, **3d**, **4e**, **7**, **8**, **10a−e**, **11c−f**, **12c,e**, **13c**, **16a,−e**, **17c,e**, **28**, **29**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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