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VICINAL EPOXYMESYLATES: SUBSTRATES FOR ITERATIVE ORGANOCUPRATE CHEMISTRY

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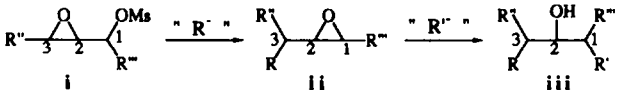
Abstract: *Reacting vicinal epoxymesylates of general structure* **i** *with higher order and mixed higher order organocuprate reagents is shown to be very selective for attack at the least hindered epoxide center. The iterative application of this reaction -- a sequence which consists of cuprate opening of epoxide* **i**, *reformation of an epoxide (***i**→**ii**), *and subsequent cuprate opening of this intermediate epoxide (***ii**→**iii**) -- *provides ready access to acyclic carbon frameworks with up to three contiguous stereogenic centers.*

Vicinal epoxymesylates of general structure **i** contain three electrophilic carbons -- the carbon bearing the mesylate (C_1), the epoxide carbon proximal to the mesylate (C_2), and the epoxide carbon distal to the mesylate (C_3): consequently, nucleophilic addition[2] could result in the formation of any of three mono-addition adducts. Similarly, unsymmetrical epoxides of general structure **ii** could undergo nucleophilic addition at either C_1 or C_2. Consequently, organocuprate methodology which selectively harnesses the reactivities of **i** and **ii** would provide a particularly attractive exploit of these substrates and would be invaluable in carbon framework construction.



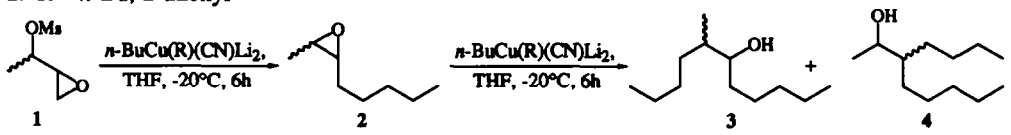
i **ii** **iii**

The higher order organocuprate $[(R)_2Cu(CN)Li_2]$ methodologies pioneered by Lipshutz[3] offered two key insights relevant to the reactivity of **i** and **ii**. First, the higher order organocuprate chemistry of unactivated epoxides is such that attack predictably takes place at the less hindered site.[4] Second, mono-, di-, and trisubstituted epoxides all give ring opening in excellent yield whereas 2° mesylates give no displacement.[5] Together these two observations suggested to us that vicinal epoxymesylate **i**[6] might undergo selective reaction with $(R)_2Cu(CN)Li_2$ at C_3. Subsequent ring closure of the resulting alkoxy intermediate would provide an *in situ* preparation of **ii** which, upon selective reaction at C_1 with a second equivalent of $(R')_2Cu(CN)Li_2$, would deliver bis-adduct **iii**. Clearly an appreciation of the regio- and stereochemical control elements operative in the **i**→**ii**→**iii** sequence is essential in order to exploit the considerable potential of this chemistry. Herein, we report the details of our initial findings in this area,[7] extend this chemistry to mixed higher order cuprates, and report an informative competition study.

The first substrate investigated was vicinal epoxymesylate **1**, readily prepared as a 34:66 *erythro*:*threo* mixture from (±)-3-buten-2-ol by *m*-chloroperoxybenzoic acid epoxidation[8] (CH_2Cl_2, 0°C) and mesylation (MsCl, Et_3N, CH_2Cl_2, -78°→0°C). Not surprisingly,[9] treating this vicinal epoxymesylate with one equivalent of $(n\text{-}Bu)_2Cu(CN)Li_2$ (THF, -20°C) resulted in regiospecific attack at C_4 -- the least hindered position -- as evidenced

by isolation of epoxide **2** on work-up (88% isolated yield). Consistent with the *erythro:threo* ratio of **1**, oxirane **2** was obtained as a 65:35 mixture of *cis* and *trans* isomers, respectively. Subsequent treatment of epoxide **2** with a second equivalent of organocuprate [1.0 eq. $(n\text{-Bu})_2\text{Cu(CN)Li}_2$, THF, -20°C] furnished four isomeric alcohols: an *erythro/threo* mixture of undecanol **3** as a consequence of C2-attack and an *erythro/threo* mixture of octanol **4**

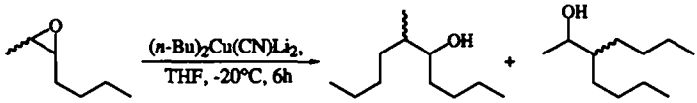
Eq. 1: R = *n*-Bu; 2-thienyl



1 2 3 4

as a consequence of C3-attack. While the combined yield for **2→3+4** was excellent (85%), the C2- versus C3-regioselectivity was only 1.2:1 establishing that a "$\text{-CH}_2\text{R}$ || -CH_3" 1,2-disubstituted epoxide is an ineffective regiocontrol element in this reaction. As a further probe of the factors controlling regioselectivity, pure *cis*-**5a** and pure *trans*-**5b**, prepared by *m*-chloroperoxybenzoic acid oxidation of the corresponding pure 2-heptenes, were treated with $(n\text{-Bu})_2\text{Cu(CN)Li}_2$ resulting in moderate (65/35:*threo*-**6a/7**) and poor (52/48:*erythro*-**6b/7**) regioselective ring opening, respectively.

Eq. 2

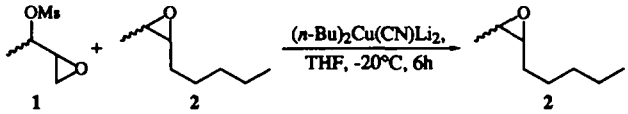


5a; *cis* **5b**; *trans* **6a**; *threo* **6b**; *erythro* **7**

The **1→3+4** transformation can also be performed without isolation of the intermediate epoxide **2** by cannulating the reaction mixture formed from **1** and one equivalent of $(n\text{-Bu})_2\text{Cu(CN)Li}_2$ into another flask containing a second equivalent of $(n\text{-Bu})_2\text{Cu(CN)Li}_2$. Even more simply, the **1→3+4** transformation can be performed as a one-pot operation by treating **1** with excess (3.0 eq.) $(n\text{-Bu})_2\text{Cu(CN)Li}_2$. Operationally, these two procedures are complimentary in that the former allows for the sequential introduction of two different **R** groups (i.e, **1→5→6/7**) while the latter (i.e., **1→3/4**) does not. Taken together these experiments demonstrate the synthetic potential and versatility of vicinal epoxides in carbon framework construction

It was interesting to us that no trace of **3/4** was detected in the crude product obtained from the reaction of **1** and $(n\text{-Bu})_2\text{Cu(CN)Li}_2$. Given the ease with which **2** undergoes ring opening by $(n\text{-Bu})_2\text{Cu(CN)Li}_2$, exclusive formation of **2** in this experiment suggested to us that (i) initial epoxide opening of **1** occurs much faster than subsequent alkoxymesylate → epoxide ring closure (i.e., formation of **2**) or that (ii) formation of **2** is fast but **1** is much more reactive towards $(n\text{-Bu})_2\text{Cu(CN)Li}_2$ than **2**. While it does not completely resolve these possibilities, it is informative to note that treating a THF solution of $(n\text{-Bu})_2\text{Cu(CN)Li}_2$ with an equal molar mixture of **1+2** (i.e., one equivalent of all three reagents; **Equation 3**) gives only **2** (97% yield/recovery) and none of **3/4**.

Eq. 3



1 2 2

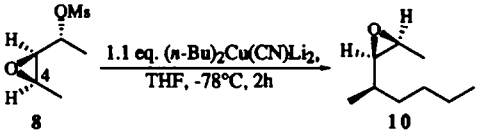
Considering the innate advantages of selective ligand transfer from 'mixed' cuprates[10] and the Lipshutz *et al.*[11] observation that the 2-thienyl moiety is an effective dummy ligand in mixed higher order cyanocuprates [i.e.,

$R_TR_RCu(CN)Li_2]$,[12] we turned to the question of regio- and stereoselectivity in the mixed higher order cyanocuprate chemistry of epoxymesylate **1** and 1,2-disubstituted epoxide **2**. To our delight, substituting *n*-BuCu(2-Th)(CN)Li_2 for (*n*-Bu)$_2$Cu(CN)Li_2 in the reactions depicted in **Equation 1** gives essentially identical results, both in terms of selectivity and reaction conditions. Indeed, the only experimental modifications required were those inherent to introduction of the 2-thienyl ligand.

At this point in the study, it was clear that while vicinal epoxymesylate **i** undergoes regiospecific attack at C3 as long as R" = H, stereoelectronic differences in -CH_2R (i.e., R" = H) and -CH_3 (R"' = CH_3) do not sufficiently differentiate the C1 and C2 electrophilic centers of a 1,2-disubstituted epoxide like **ii**. However, would a C2,C3-disubstituted analog of **i** (i.e., R" & R"' = alkyl) undergo selective organocuprate reaction and would a C3-branched analog of **ii** (i.e., R, R" & R"' = alkyl) be more selective than **2**? If so, organocuprate chemistry of C3-branched 1,2-disubstituted epoxides (cf., **ii**: -R & -R" = alkyl) should be regio- and stereoselective, leading to products with up to three contiguous stereocenters.

To answer these questions, the next substrate investigated was epoxymesylate **8**, readily prepared as a 4:96 *erythro*:*threo* mixture from (±)-(Z)-3-penten-2-ol by *m*-chloroperoxybenzoic acid epoxidation[13] (CH_2Cl_2, 0°C) and mesylation (MsCl, Et_3N, CH_2Cl_2, -78°→0°C). In contrast to **1**, this vicinal epoxymesylate presents the first equivalent of organocuprate with a choice between 2°-mesylate and 2°-epoxide electrophilic centers so, albeit in low yield (37%), we were delighted to find that **8** undergoes exclusive C4-epoxide opening with concomitant ring closure to epoxide **10**. Apparently alkoxymesylate → epoxide ring closure does not occur at -78°C as no traces of the anticipated organocuprate products of **10** (cf., **11**; **Equation 4**) were detected in the crude reaction product. Indeed, the only isolated contaminate was starting material **8**.

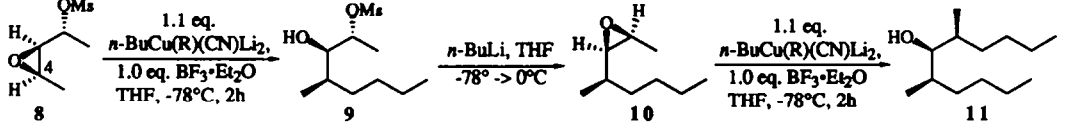
Eq. 4



8 **10**

Confronted with this exciting selectivity but disappointing yield, we turned to Lewis acid activation[14] of **8**: specifically, stoichiometric admixture of $BF_3{\cdot}O(C_2H_5)_2$.[15] As depicted in **Equation 5**, 1.1 eq. (*n*-Bu)$_2$Cu(CN)Li_2 was pretreated with 1.0 eq. of $BF_3{\cdot}O(C_2H_5)_2$ at -78°C in THF. Subsequent addition of vicinal epoxymesylate **8** gave hydroxy mesylate **9** in 70% isolated yield: not surprisingly, the BF_3-complexed alkoxide corresponding to **9** does not undergo ring closure to epoxide **10**. The **9**→**10** transformation is easily effected by *n*-butyllithium in THF. Having established that a higher order organocuprate/$BF_3{\cdot}O(C_2H_5)_2$ mixture selectively engages the less hindered 2°-epoxide electrophilic center in **8**, we turned to **10** and found that it to undergoes selective epoxide opening at the less hindered center giving **11** in 70% yield. Unoptimized, this sequence leads from **8** to **11** in 57% overall yield. The meso nature of **8** was confirmed by ^{13}C NMR and establishes that each transformation in the **8**→**9**→**10**→**11** sequence is stereospecific.

Eq. 5: R = *n*-Bu; 2-thienyl

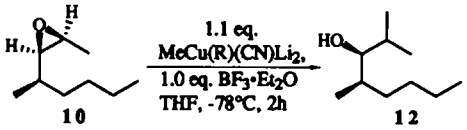


8 **9** **10** **11**

We were pleased to find that the mixed higher order cuprate *n*-BuCu(2-Th)(CN)Li_2, complexed to BF_3•$O(C_2H_5)_2$ (1.0 eq.), also selectively opens **8** at C4, giving **9** (61% isolated yield). In contrast, while **10** readily reacts with (*n*-Bu)$_2$Cu(CN)Li_2/BF_3•$O(C_2H_5)_2$ at -78°C, its reaction with *n*-BuCu(2-Th)(CN)Li_2/BF_3•$O(C_2H_5)_2$ is sluggish at 0°C and room temperature.

The opportunity to sequentially introduce two different alkyl moieties via organocuprates was also investigated. For example, treating **8** with (*n*-Bu)$_2$Cu(CN)Li_2/BF_3•$O(C_2H_5)_2$ gives **10** as described in **Equation 6**. Subsequent reaction of this epoxide with (Me)$_2$Cu(CN)Li_2 complexed to BF_3•$O(C_2H_5)_2$ lead to **12** in 68% overall yield from **8**. However, MeCu(2-Th)(CN)Li_2/BF_3•$O(C_2H_5)_2$ is similarly sluggish in its reaction with **10**.

Eq. 6: R = *n*-Bu; 2-thienyl



10 **12**

The results presented here suggest that vicinal epoxymesylate organocuprate chemistry will afford significant advantage[16] and be of general utility as a strategy for acyclic stereocontrol. Furthermore, starting from readily available, chiral allylic alcohols,[17] the stereocontrol realized will allow translation of one original stereogenic center into three rather quickly. Reactions starting with chiral epoxymesylate and synthetic applications of this chemistry are currently under investigation.

EXPERIMENTAL

Infrared spectra were determined on an IBM FTIR-32 with IBM 9000 data system. NMR Spectra were determined on a QE-300 spectrometer: ^1H at 300 MHz and ^{13}C at 75 MHz. Mass spectra were determined on a Dupont 21-492B analytical instrument. MPLC refers to column chromatography done at 10-50 psi through EM Lobar™ columns packed with LiChroprep Si60 (40-63 μm) with hexane/EtOAc eluent and monitored by refractive index detection. Capillary gas chromatography (GC) was performed on a Hewlett-Packard 5890A gas chromatograph using a DB-1701 column (30 m x .259 mm; film thickness = 0.25 mm) with HP-3390A integrator.

[R*,R*]-(±)- and [R*,S*]-(±)-3,4-Epoxybutane-2-ol.[8] To a solution of *m* -chloroperoxybenzoic acid (6.6g, 38 mmol) in CH_2Cl_2 (38 ml) at 0° C was added (±)-3-buten-2-ol (2.5 g, 34.7 mmol) and the solution stirred overnight at 0° C. After filtration of the crude reaction mixture, the filtrate was washed with satd. solution of 1:1 Na_2SO_4 : Na_2SO_3 and dried over anhyd. Na_2CO_3. Filtration and concentration via rotavap at ambient temperature yielded pure 3,4-epoxybutane-2-ol (2.54 g, 28.8 mmol, 83%). [^1H NMR ($CDCl_3$) ∂ 1.4 (d, J = 6 Hz, 3H), 2.0-2.3 (bs, 1H), 2.7-3.2 (m, 3H), 3.65 (dq, J = 6, 6 Hz, 1H); IR ($CHCl_3$) 3833-3381, 3059-2930, 1373, 974, 831 cm^{-1}. Vpc analysis indicated a ratio of 66 : 34 :: *threo* : *erythro*].

[R*,R*]-(±)- and [R*,S*]-(±)-α-Methyloxiranemethyl Methanesulfonate (1). To a solution of 3,4-epoxybutane-2-ol (2.51 g, 28.5 mmol) in CH_2Cl_2 (57 ml) at -78° C was added triethylamine (3.64 ml, 26.1 mmol) dropwise and the solution stirred for 10 minutes.Then mesylchloride (1.62 ml, 20.8 mmol) was added and the solution allowed to warm to -10°C and stirred at that temperature overnight. After filtration and washing with ice-cold CH_2Cl_2, the filtrate was extracted with one portion of ice-cold satd. $NaHCO_3$, and dried over anhyd. Na_2CO_3. Filtration and concentration via rotavap at ambient temperature yielded pure **1** (3.43 g, 20.6 mmol, 72.4%) which was used without further purification in the next step. [^1H NMR ($CDCl_3$) ∂ 1.45 (d, J = 6 Hz, 3H), 1.5 (d, J = 6 Hz, 3H), 2.6-3.25 (m, 3H), 3.2 (s, 3H), 4.35 (dq, J = 6, 6 Hz, 1H); IR (neat) 3050-2939, 1457, 1419, 1382, 1352, 1174, 963, 914 cm^{-1}].

(±)-*Cis*- and (±)-*Trans*-2-Methyl-3-pentyloxirane (2).[18] To a solution of $(n\text{-}Bu)_2Cu(CN)Li_2$ (1.34 mmol) in 2 ml THF at -78° C was added **1** (153.4 mg, 1.34 mmol) and the solution stirred at -20° C for 6 h. The solution was then recooled to -78° C and quenched with 10% acetic acid in THF solution and then diluted with Et_2O (3 ml). The resulting solution was then filtered thru a short pad of celite and the filtrate transferred to a separatory funnel, the layers were then separated and the aqueous layer extracted with two portions of Et_2O. The combined organics were then dried over anhydrous Na_2CO_3. Filtration, concentration via rotavap and purification via MPLC using H:E::1:1 yielded **2** (270.5 mg, 2.11 mmol, 88%) as a *cis*:*trans*::1.86:1 mixture (determined by capillary GC). [^{1}H NMR ($CDCl_3$) ∂ 0.8-1.0 (m, 6H), 1.0-1.8 (m, 22 H), 2.61 (m, 1H), 2.75 (m,1H), 2.9 (m,1H), 3.1 (m, 1H); IR (neat) 2957, 2928, 2860, 1379, 1261, 858, 804 cm^{-1}].

[5R*,6S*]-(±)- and [5R*,6R*]-(±)-5-Methylundecan-6-ol (3) and [2R*,3R*]-(±)- and [2R*,3S*]-(±)-3-Butyloctan-2-ol (4). To a solution of $n\text{-}Bu_2Cu(CN)Li_2$ (5.08 mmol) in THF (6.8 ml) at -78° C was added **2** (650 mg, 5.08 mmol; 1.86:1::*cis*:*trans*) and the solution stirred at -20° C for 6 h. The solution was then recooled to -78° C and quenched with 10% acetic acid in THF solution, diluted with Et_2O (10 ml), and saturated aqueous NaCl (10 mL) added. The resulting solution was filtered through a short pad of celite and the filtrate transferred to a separatory funnel. The layers were separated and the aqueous layer extracted with two portions of Et_2O. The combined organics were dried over anhydrous Na_2CO_3, filtered, concentrated, and purified by MPLC (hexane:EtOAc::3:1 eluent) giving **3** and **4** in 85% overall yield (804 mg, 4.31 mmol) as a 1.2:1 mixture (determined by capillary GC), respectively. [**3**: ^{1}H NMR ($CDCl_3$) ∂ 0.87 -1.0 (m, 9H), 1.0-1.8 (m, 16H), 3.4-3.6 (m, 1H); IR (neat) 3360-3574, 2957, 2930, 2860 cm^{-1}; exact mass calcd for $C_{12}H_{26}O$ 186.1985, found 186.1992. **4**: ^{1}H NMR ($CDCl_3$) ∂ 0.8-1.0 (m, 6H), 1.2 (d, J = 6 Hz, 3H), 3.7-3.95 (m, 1H); IR (neat) 3365-3584, 2957, 2930, 2859 cm^{-1}; exact mass calcd for $C_{12}H_{26}O$ 186.1985, found 186.2019].

(±)-*Cis*-2-Methyl-3-butyloxirane (5a).[19] To a solution of *m*-chloroperoxybenzoic acid (3.87 g, 22.4 mmol) in CH_2Cl_2 (23 ml) at 0° C was added *cis*-2-heptene (2.0 g, 20.4 mmol) and the resulting solution stirred overnight at 0°C. After filtration of the crude reaction mixture, the filtrate was washed with a saturated aqueous solution of Na_2SO_4:Na_2SO_3 (1:1) and dried over anhydrous. Na_2CO_3. Filtration and removal of solvent at ambient temperature gave pure **5a** (1.94 g, 17.0 mmol, 83.3%) which was used without further purification in the next step [^{1}H NMR ($CDCl_3$) ∂ 0.8-1.0 (m, 3H), 1.2-1.7 (m, 8H), 1.27 (d, J = 5.11 Hz, 3H), 2.8-3.0 (m, 1H), 3.0-3.1 (m, 1H); IR (neat) 2959, 2930, 2874, 1390, 1259, 1217, 1151, 1113, 1032, 752 cm^{-1}].

(±)-*Trans*-2-Methyl-3-butyloxirane (5b).[20] To a solution of *m*-chloroperoxybenzoic acid (3.87 g, 22.4 mmol) in CH_2Cl_2 (23 ml) at 0° C was added *trans*-2-heptene (2.0 g, 20.4 mmol) and the solution stirred overnight at 0°C. After filtration of the crude reaction mixture, the filtrate was washed with a saturated aqueous solution of Na_2SO_4:Na_2SO_3 (1:1) and dried over anhydrous. Na_2CO_3. Filtration and removal of solvent at ambient temperature gave pure **5b** (1.65 g, 14.4 mmol, 71%) which was used without further purification in the next step [^{1}H NMR ($CDCl_3$) ∂ 0.9-1.0 (m, 3H), 1.2-1.7 (m, 8H), 2.55-2.7 (m,1H), 2.7-2.83 (m, 1H); IR (neat) 2961, 2932, 2862, 1381, 1259, 889, 852 cm^{-1}].

[5R*,6S*]-(±)-6-Methyldecan-5-ol and (±)-3-Butylheptan-2-ol (6a and 7). To a solution of $n\text{-}Bu_2Cu(CN)Li_2$ (0.75 mmol) in THF (2.0 ml) at -78° C was added **5a** (86.2 mg, 0.75 mmol) and the solution stirred at -20° C for 6 h. The resulting solution was warmed to 0°C, quenched with saturated aqueous NH_4Cl solution (3 mL), and extracted with Et_2O (3x10 mL). The combined organic layer was dried over anhydrous Na_2CO_3, filtered, concentrated, and purified by MPLC (hexane:EtOAc::3:1 eluent) giving **6a** and **7** in 82% overall yield (107 mg, 0.62 mmol) and in a 1.86:1 ratio (determined by capillary GC), respectively [**6a**: ^{1}H NMR ($CDCl_3$) ∂ 0.9-1.0 (t, J = 6.2 Hz, 3H), 1.0-1.7 (m, 16H), 3.4-3.5 (m, 1H); IR (neat) 3387-3350, 2957, 2932, 2874, 2860, 1466 cm^{-1}; exact mass calcd for $C_{11}H_{22}$ (M-H_2O) 154.1722, found 154.1720. **7**: ^{1}H NMR ($CDCl_3$) ∂ 0.9 (t, J = 6.2, 6H), 1.0-1.62 (m, 14H), 1.14 (d, J = 6.33 Hz, 3H), 3.83 (br, m, 1H); ^{13}C NMR ($CDCl_3$) ∂ 14.39 (C_7 & $C_{7'}$), 20.15 (C_1), 23.46 (C_6 & $C_{6'}$), 29.58 (C_4 & $C_{4'}$), 29.67 (C_5 & $C_{5'}$), 45.15 (C_3), 69.94 (C_2); IR (neat) 3748-3348, 2959, 2928, 2959, 1458, 1037 cm^{-1}; exact mass calcd for $C_{11}H_{22}$ (M-H_2O) 154.1722, found 154.1715]. The structure of **7** was further confirmed by an APT experiment.

[5R*,6R*]-(±)-6-Methyldecan-5-ol and (±)-3-Butylheptan-2-ol (6a and 7). To a solution of n-$Bu_2Cu(CN)Li_2$ (1.04 mmol) in THF (2.0 ml) at -78° C was added **5b** (118.2 mg, 1.04 mmol) and the solution stirred at -20° C for 6 h. The resulting solution was warmed to 0°C, quenched with saturated aqueous NH_4Cl solution (3 mL), and extracted with Et_2O (3x10 mL). The combined organic layer was dried over anhydrous Na_2CO_3, filtered, concentrated, and purified by MPLC (hexane:EtOAc::3:1 eluent) giving **6b** and **7** in 80% overall yield (143 mg, 0.83 mmol) and in a 1.08:1 ratio (determined by capillary GC), respectively [**6b**: ^1H NMR ($CDCl_3$) ∂ 0.79-1.09 (m, 9H),1.09-1.8 (m, 14 H), 3.4-3.6 (br,m, 1H); IR (neat) 3599-3368, 2959, 2930, 2860, 1458, 1022 cm^{-1}. All spectral data for **7** was identical to that obtained from **5a**.].

Competition Experiment: 1 + 2 → 2. To a solution of n-$Bu_2Cu(CN)Li_2$ (3.35 mmol) in THF (4.65 mL) at -78° C was added **1** (556 mg, 3.35 mmol) and **2** (429 mg, 3.35 mmol) as a mixture in THF (1 mL) and the solution stirred at -20° C for 6 h. The solution was then quenched at -20°C with saturated aqueous NH_4Cl (10 mL), diluted with Et_2O (10 ml), filtered thru a short pad of celite, and the filtrate transferred to a separatory funnel. The organic layer was washed with water (10 mL) and the aqueous layer extracted with Et_2O (2x10 mL). The combined organic layer was dried over anhydrous Na_2CO_3, filtered, concentrated, and purified by MPLC (hexane: EtOAc::1:1 eluent) giving **2** (847 mg, 6.61 mmol, 97% yield/recovery). The *cis*:*trans* ratio of **2** was found to be 1.79:1 (determined by capillary GC).

Reaction of 1 with n-(Bu)Cu(2-Th)(CN)Li_2. To a solution of n-(Bu)(2-Th)Cu(CN)Li_2 (3.01 mmol) in of THF (13.8 ml) at -78°C was added **1** (500 mg, 3.01 mmol) in of THF (1 mL) and the solution stirred at -20° C for 6 h. The solution was then recooled to -78°C, quenched with 10% acetic acid in THF, diluted with Et_2O (5 mL), and saturated aqueous NaCl (5 mL) added. The resulting solution was filtered thru a short pad of celite and the filtrate transferred to a separatory funnel and the layers separated. The aqueous layer was extracted with Et_2O (2x10 mL) and the combined organics were dried over anhydrous Na_2CO_3, filtered, concentrated, and purified by MPLC (hexane:EtOAc::1:1 eluent) giving **2** (347.2 mg, 2.708 mmol, 90%). The *cis*:*trans* ratio of **2** was found to be 1.86:1 (determined by capillary GC).

Reaction of 2 with n-(Bu)Cu(2-Th)(CN)Li_2. To a solution of n-(Bu)(2-Th)Cu(CN)Li_2 (2.04 mmol) in THF (8.14 mL) at -78° C was added **2** (261 mg, 2.04 mmol) and the solution stirred at -20° C for 6 h. The solution was then recooled to -78°C, quenched with 10% acetic acid in THF, diluted with Et_2O (5 mL), and saturated aqueous NaCl (5 mL) added. The resulting solution was filtered thru a short pad of celite and the filtrate transferred to a separatory funnel and the layers separated. The aqueous layer was extracted with Et_2O (2x10 mL) and the combined organics were dried over anhydrous Na_2CO_3, filtered, concentrated, and purified by MPLC (hexane:EtOAc::3:1 eluent) giving **3** and **4** (345 mg, 1.85 mmol, 91%). The **3**:**4** ratio was found to be 1.51:1 (determined by capillary GC).

[2α(S*),3α]-(±)-α,3-dimethyloxiranemethanol.[8] To a solution of *m*-chloroperoxybenzoic acid (4.96 g, 28.71 mmol) in CH_2Cl_2 (28 mL) at 0° C was added (±)-*Z*-3-penten-2-ol (2.25 g, 26.1 mmol) and the solution stirred overnight at 0°C. After filtration of the crude reaction mixture, the filtrate was washed with a saturated solution Na_2SO_4:Na_2SO_3 (1:1), dried over anhydrous Na_2CO_3, filtered, and concentrated to give [2α(S*),3α]-(±)-α,3-dimethyloxiranemethanol[8] (1.78 g, 17.4 mmol, 67%; 16:1::*threo*:*erythro* mixture as determined by capillary GC) which was used without further purification in the next step [^1H NMR ($CDCl_3$) ∂ 1.3 (d, J = 6 Hz, 3H), 1.35 (d, J = 6 Hz, 3H), 2.85 (bs, 1H), 2.94 (dd, J = 6.2, 6 Hz, 1H), 3.0 (dq, J = 6, 6 Hz, 1H), 3.72 (dq, J = 6, 6 Hz, 1H); IR (neat) 3408-3200, 2974, 2932, 1653, 1425, 1373, 1265, 1113, 914 cm^{-1}].

[2R*,3R*,4R*]-(±)-4-Methyl-2-[(methylsulfonyl)oxy]octan-3-ol (9). To a solution of [2α(S*),3α]-(±)-α,3-dimethyloxiranemethanol (1.78 g, 17.4 mmol) in CH_2Cl_2 (35 mL) at -78° C was added triethylamine (3.64 ml, 26.1 mmol) dropwise. The solution was stirred for 10 minutes then methanesufonyl chloride (1.62 ml, 20.8 mmol) was added and the solution allowed to warm to -10°C with stirring overnight. After filtration and washing with ice-cold CH_2Cl_2, the filtrate was washed with one portion of ice-cold saturated $NaHCO_3$, dried over anhydrous Na_2CO_3, filtered, and concentrated to give [2α(R*),3α]-(±)-α,3-dimethyloxiranemethyl methanesulfonate (**8**) (2.8 g, 15.5 mmol, 89.3%) which was used without further purification in the next step [^1H NMR ($CDCl_3$) ∂ 1.36 (d, J = 6 Hz, 3H), 1.5 (d, J = 6 Hz, 3H), 2.95-3.27 (m,

2H), 3.15 (s, 3H), 4.54 (dq, J = 6, 6 Hz, 1H); IR (neat) 2988 , 1452 , 1430 , 1382 , 1355 , 1174 , 1116 , 969 , 913 , 807 cm^{-1}].

BF_3•Et_2O (0.46 ml, 3.76 mmol) was added dropwise to a solution of n-$Bu_2Cu(CN)Li_2$ (4.13 mmol) in THF (5 ml) at -78°C. The resulting solution was stirred for 5 minutes at which time a solution of **8** (677 mg, 3.76 mmol) in THF (2 ml) was added slowly dropwise. The reaction was allowed to stir for 2 h at -78°C and quenched at -78°C with excess of 10% acetic acid/THF solution (10 ml). After warming to room temperature, water (10 ml) was added, the mixture was filtered through celite, and the layers separated. The aqueous layer was extracted with Et_2O (2x10 mL), dried over anhydrous Na_2CO_3, filtered, and concentrated. Purification by MPLC (hexane:EtOAc::3:1 eluent) gave pure **9** (627 mg, 2.63 mmol, 70%) [^1H NMR ($CDCl_3$) ∂ 0.90 (t, J = 6.4 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 1.1-1.87 (m, 8H), 1.45 (d, J = 6.38 Hz, 3H), 3.06 (s, 3H), 3.34 (br m, 1H), 4.85 (dq, J = 6.08 Hz, 1H); IR (neat) 3549, 2949-2868, 1458, 1354, 1176, 1118 cm^{-1}].

[2α(R*),3α]-(±)-3-Methyl-2-(1-methylpentyl)oxirane (10). n-BuLi (5.74 mmol, 3.59 ml, 1.6M) was added slowly dropwise to a solution of **9** (5.22 mmol, 124 mg) in THF (0.5 ml) at -78°C. After addition, the reaction mixture was allowed to warm to 0°C where it was stirred until TLC (hexane:EtOAc::3:1) indicated that the reaction was complete (2 h). The mixture was cooled to -20°C and quenched with of saturated aqueous NH_4Cl solution (3 mL). After separating, the aqueous layer was extracted with Et_2O (1x10 mL) and the combined organics were dried over anhydrous Na_2CO_3, filtered, concentrated, and purified by MPLC (hexane:EtOAc::3:1) to yield pure **10** (180 mg, 1.26 mmol, 80.7%) [^1H NMR ($CDCl_3$) ∂ 0.82-1.0 (m, 6H), 1.1-1.6 (m, 7H), 2.61 (m,1H), 3.02 (m, 1H); IR (neat) 2955-2883, 1261, 1070. cm^{-1}; exact mass calcd for $C_8H_{15}O$ ($M-CH_3$) 127.1123, found 127.1120].

Meso-anti,anti-5,7-dimethylundecan-6-ol (11). BF_3•Et_2O (90 μL, 7.03 mmol) was added dropwise to a solution of n-$Bu_2Cu(CN)Li_2$ (7.73 mmol) in THF (1.2 mL) at -78°C. The resulting solution was stirred for 5 minutes at which time a solution of **10** (100.0 mg, 7.03 mmol) in THF (1.2 ml) was added slowly dropwise. After stirring for 2 h at -78°C, the reaction was quenched at -78°C with excess of 10% acetic acid/THF solution (10 ml), warmed to room temperature, and treated with water (10 ml). The mixture was then diluted with Et_2O (10 ml), filtered through celite, the layers separated, and the aqueous layer extracted with Et_2O (1x10 mL). The combined organics were dried over anhydrous Na_2CO_3, filtered, concentrated, and purified by MPLC (hexane:EtOAc::1:1) to yield pure **11** (98.0 mg, 4.89 mmol, 69.6%) [^1H NMR ($CDCl_3$) ∂ 0.82 (m, 12H), 0.95-1.6 (m, 8H), 3.09 (t, J = 5.61 Hz, 1H), 3.5 (s, 1H); ^{13}C NMR ($CDCl_3$) ∂ 13.1 (C_1 & C_{11}), 15.4 (C_5-Me & C_7-Me), 22.1 (C_3 & C_9), 28.5 (C_4 & C_8), 29.5 (C_2 & C_{10}), 34.4 (C_5 & C_7), 80.1 (C_6); IR (neat) 3858-3387, 2945, 2801 cm^{-1}; exact mass calcd for $C_{13}H_{26}$ ($M-H_2O$) 182.2036, found 182.2033].

[3R*,4S*]-(±)-2,4-Dimethyloctan-3-ol (12). BF_3•Et_2O (90 μL, 7.03 mmol) was added dropwise to a solution of $Me_2Cu(CN)Li_2$ (7.73 mmol) in THF (1.2 mL) at -78°C. The resulting solution was stirred for 5 minutes at which time a solution of **10** (100.0 mg, 7.03 mmol) in THF (1.2 ml) was added slowly dropwise. After stirring for 2 h at -78°C, the reaction was quenched at -78°C with excess of 10% acetic acid/THF solution (10 ml), warmed to room temperature, and treated with water (10 ml). The mixture was then diluted with Et_2O (10 ml), the layers separated, and the aqueous layer extracted with Et_2O (1x10 mL). The combined organics were dried over anhydrous Na_2CO_3, filtered, concentrated, and purified by MPLC (hexane:EtOAc::1:1) to yield pure **12** (108.8 mg, 6.87 mmol, 97%) [^1H NMR ($CDCl_3$) ∂ 0.82-1.0 (m, 12H), 1.00-1.9 (m, 8H), 3.1 (dd, J = 11.24, 5.58 Hz, 1H); IR (neat) 3437-3026, 2947-2866, 1383, 1333 cm^{-1}; exact mass calcd for $C_{10}H_{22}O$ 158.1671, found 158.1667].

Reaction of 8 with n-(Bu)Cu(2-Th)(CN)Li_2. BF_3•Et_2O (0.34 mL, 3.05 mmol) was added slowly dropwise to a solution of n-(Bu)(Thienyl)Cu(CN)Li_2 (3.05 mmol) in THF (12 mL) at -78°C and the resulting solution was stirred for 5 minutes. A solution of **8** (500 mg, 2.775 mmol) in THF (0.6 mL) was then added and the reaction was allowed to stir for 2 h at -78°C. After quenching at -78°C with excess of 10% acetic acid/THF solution (10 ml), the mixture was warmed to room temperature, diluted with water (10 mL), filtered through celite, and the layers separated. The aqueous layer was extracted with Et_2O (1x20 mL), dried over anhydrous

Na_2CO_3, filtered, and concentrated. Purification by MPLC (hexane:EtOAc::3:1 eluent) gave pure **9** (402 mg, 1.69 mmol, 61%).

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