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Development of a Robust Procedure for the Copper-catalyzed Ring-Opening of Epoxides with Grignard Reagents

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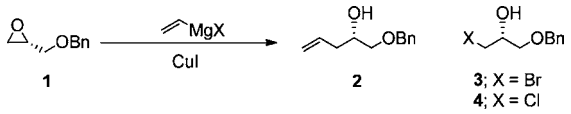
Supporting Information

ABSTRACT: A general procedure for the copper-catalyzed regioselective ring-opening of epoxides with Grignard reagents is described. The procedure developed provides robust reaction conditions which limit the formation of impurities and has been applied successfully using a series of epoxides and Grignard reagents to provide the desired products in >90% yield with excellent regioselectivity and purity.

INTRODUCTION

The ring-opening of chiral epoxides provides an often employed and synthetically valuable entry to enantiomerically pure alcohols.[1] This methodology has been applied successfully in both industrial and academic research.[2] With appropriate selection of epoxide and Grignard reagent, a variety of functionalised alcohols can be prepared.[3] During the course of a recent program, we required multikilogram quantities of enantiopure alcohol **2** as a key intermediate, which we envisaged to be available from the copper-catalyzed addition of vinyl Grignard to benzyl-(*S*)-glycidyl ether **1** (Scheme 1).

Scheme 1. Proposed synthetic route to alcohol 2



1 **2** **3**; X = Br **4**; X = Cl

Examination of the considerable literature for this transformation revealed a number of conflicting protocols, most of which were not immediately attractive for scale-up.[3,4] The reactions were often quoted as being performed under cryogenic conditions (−78 °C to −30 °C), and many highlighted the requirement for a rapid addition of the Grignard reagent.[4,5] Due to the generation of impurities in typical protocols, the product alcohols have been routinely purified by column chromatography. The halohydrin impurity (**3** or **4**) was often the major impurity, and overall the procedures have been found to be difficult to reproduce.[3,4] With this background in mind, we decided to evaluate this reaction with the intention of developing a robust, general protocol that could be applied to the ring-opening of epoxides and would ultimately address all the noted issues. In addition, the protocol was required to be amenable to scale, allowing for multikilogram synthesis of the key synthetic intermediate **2**. An initial study of the conversion of **1** to **2** revealed several issues that would need to be addressed in the development of this reaction for scale-up. In particular, the formation of variable levels of halohydrin impurity (**3** or **4**), the reaction temperature, and reagent addition protocol as well as catalyst loading, all significantly affected the purity profile of the reaction. The quench and workup protocol would also require attention prior to scale-up. Herein is described our investigation towards, and the development of, a robust procedure for the ring-opening of **1** to **2** and its subsequent demonstration as a general protocol for the ring-opening of epoxides using Grignard reagents. The demonstration on scale of the ring-opening of benzyl-(*S*)-glycidyl ether **1**, including safety considerations, is also discussed.

RESULTS AND DISCUSSION

Epoxide **1** in THF was initially treated with a solution of vinylmagnesium bromide in THF under standard literature conditions (≤20 °C). This showed, that, in the absence of a copper halide catalyst in the reaction, bromohydrin **3** was formed as the major product. Despite literature procedures generally employing vinylmagnesium bromide,[1−4] vinylmagnesium chloride was the only vinyl Grignard reagent commercially available on scale, and thus, all further development was conducted with vinylmagnesium chloride.

Preliminary studies using only 10 mol % copper iodide gave satisfactory reactions with the addition of vinylmagnesium chloride over 2−5 min at 0−10 °C to a mixture of epoxide **1** in THF with copper iodide. However, it was noted on larger scale that with an extended addition time of the Grignard reagent, elevated levels of chlorohydrin **4** were formed. For example, addition of the vinylmagnesium chloride over >1 h resulted in formation of up to 20 area % by HPLC (A%) of **4**, with only 62 A % of desired product **2**. Based on a realistic addition time of the Grignard reagent on scale, a series of experiments were conducted to develop optimal conditions for the reaction (Table 1).

These experiments clearly showed that shorter addition times of the Grignard reagent were beneficial for the reaction, (Table 1, entries 1−4) with higher copper loadings (up to 40 mol %, Table 1, entry 6) required if addition times for the Grignard reagent were greater than 1 h. In the course of these experiments, copper chloride (I) was also found as a superior copper source over the iodide equivalent, resulting in cleaner reactions with the formation of only one impurity, chlorohydrin **4** (entry 11).

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Table 1. HPLC data of vinylmagnesium chloride addition to epoxide 1: area % by HPLC @ 210 nm

entry	Grignard (equiv)	CuI loading (mol %)	temp (°C)	addition time (min)	chlorohydrin impurity, **4** (area %)	product, **2** (area %)	SM (area %)
1	1.5	10	0−10	2	0	89.0	0
2	1.5	10	0−10	15	7.2	82.5	0
3	1.5	10	0−10	55	12.7	62.0	0
4	1.5	10	0−10	70	16.7	61.8	0
5	1.5	20	0−10	55	9.4	67.6	0
6	1.5	40	0−10	55	6.7	81.2	0
7[a]	1.5	10	0−10	55	15.1	60.0	0
8[a]	1.5	25	0−10	55	0	73.4	0
9[a]	1.5	25	0−10	10	1.9	61.4	2.8
10[a]	1.5	0	0−10	10	26.6	50.2	16.4
11	1.5	10[b]	0−10	10	5.9	90.1	0.2

[a]Inverse addition protocol. [b]Copper chloride was used.

Table 2. HPLC data for the DoE of vinylmagnesium chloride addition to epoxide 1: area % by HPLC @ 210 nm

entry	Grignard (equiv)	CuCl loading (mol %)	temp (°C)	addition time (min)	chlorohydrin impurity, **4** (area %)	product **2** (area %)	SM (area %)	assay yield[b] (%)
1	1.5	20	−20	105	1.0	98.9	0	96
2	1.5	20	−20	15	1.7	98.1	0	100
3	1.5	20	20	15	40.2	59.8	0	58
4	2.5	20	0	60	5.4	94.5	0	92
5	1.5	20	20	15	12.9	67.1	0	69
6	1.5	20	−20	105	0.4	99.6	0	100
7	1.5	20	−20	15	0.2	99.8	0	96
8	1.5	20	20	105	17.6	62.4	0	59
9	2.5	20	0	60	2.1	97.7	0	91
10	1.5	20	20	105	19.2	60.6	0	58
11	2.5	20	−10	60	0.4	99.6	0	100
12	2.5	20	5	60	5.0	95.0	0	91
13	2.5	20	10	60	10.4	89.6	0	86
14	2.5	20	−5	60	1.0	99.0	0	98
15	2.5	0	−5	60	18.8	61.2	0	60
16	2.5	5	−5	60	1.8	97.6	0.6	95
17	2.5	15	−5	60	1.4	98.6	0	97
18	2.5	5	−5	15	9.5	90.5	0	86
19[a]	2.5	20	−5	60	0.1	69.7	0	62
20	1.5	5	−5	60	0.6	99.4	0	96
21	1.5	5	−5	60	2.1	97.7	0	96

[a]Copper iodide was used. Two other unidentified impurities were observed at 17 and 11 A %. [b]Assay yields were obtained by HPLC using analytical standard prepared by chromatography.

Crucially, these experiments showed that an inverse addition of the epoxide to the Grignard reagent/copper catalyst had the benefit of limiting the formation of the chlorohydrin impurity **4** (Table 1, entry 8). Such an inverse protocol was demonstrated and vinylmagnesium chloride (2.5 equiv) and 20 mol % CuCl (I) premixed to ensure cuprate reagent was available in solution in the presence of epoxide **1** to suppress the formation of **4**. With the addition of epoxide **1** over 1−2 h at 0−5 °C, desired product **2** was obtained with <1% of chlorohydrin **4**.

DoE/Robustness. With a suitable reaction and purity profile in hand, a second round of screening focussed on further development and adding robustness to the existing procedure. A design of experiment (DoE) study was performed to examine the effect of temperature (−20 to +20 °C), stoichiometry of vinylmagnesium chloride (1.5−2.5 equiv), and addition time of the epoxide reagent (15−105 min.). With these three factors, a half-factorial design was set up, and 10 experiments were conducted, including two midpoints (Table 2, entries 1−10). All experiments in this study used the inverse addition protocol.

The key factor being monitored was the level of impurity **4**, and after analysis using the Design Expert (DX6) software package, the clear outcome from these experiments was that temperature was the overwhelming factor in controlling the level of **4** (see Figure 1)

Reactions at +20 °C gave up to 40% of chlorohydrin **4** with assay yields below 60% (Table 2, entries 3, 5, 8, and 10). All other experiments where the temperature was ≤0 °C gave excellent assay yields of product **2**, with the levels of **4** at a maximum of 2−5%, (Table 2, entries 1, 2 and 6). The stoichiometry of Grignard reagent or the rates of epoxide addition were not found to be influential to any significant extent within the ranges studied. In practice, this meant that the epoxide could be added over an extended period (>2 h if necessary to control the exotherm) without detriment to the reaction profile.

To probe the temperature profile of the reaction further, experiments at −10, +5, and +10 °C were conducted to determine the point at which levels of **4** became unacceptable (Table 2, entries 11−14). Reactions at +5 and +10 °C resulted

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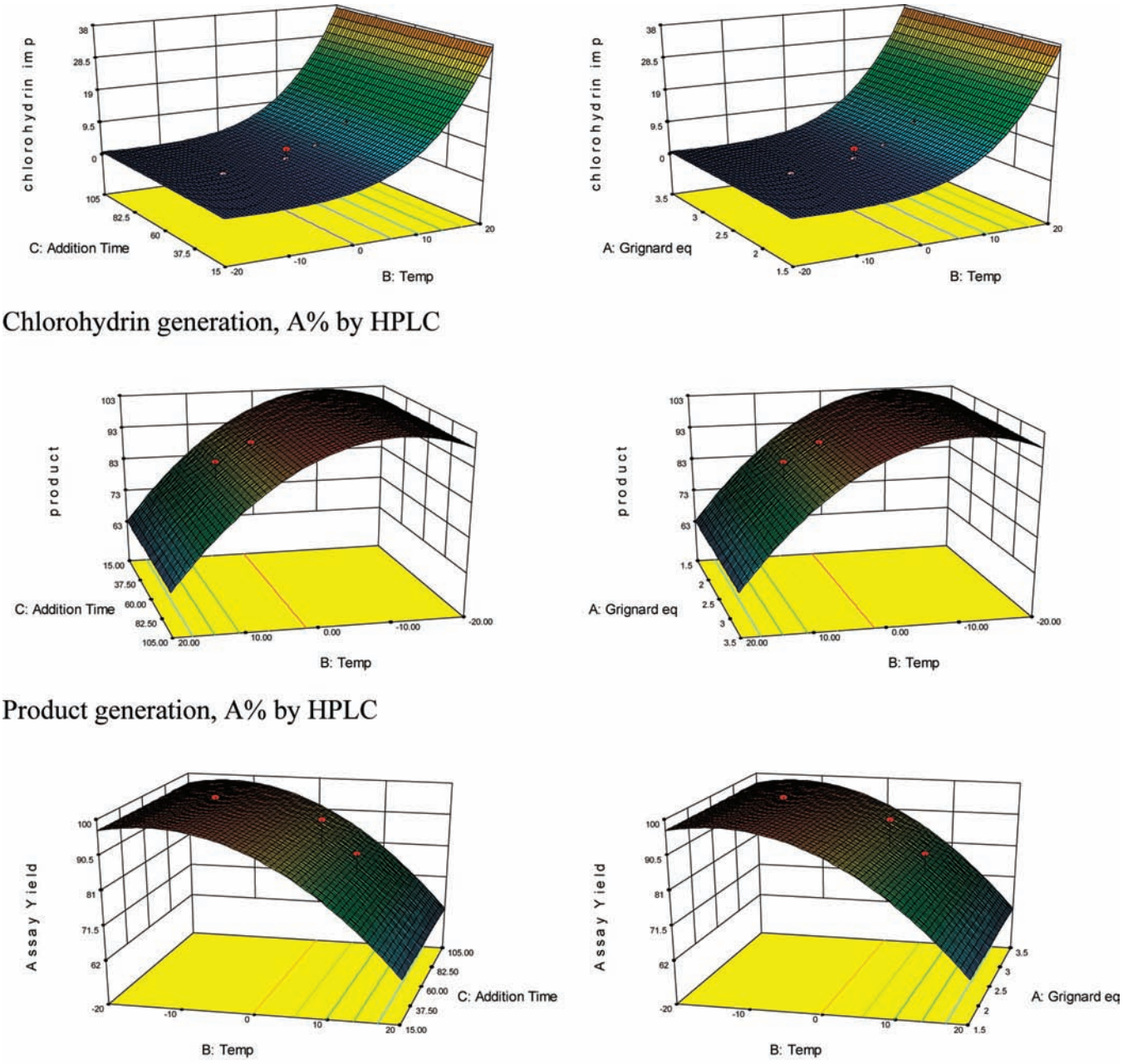
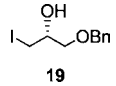


Figure 1. Three dimensional (3D) contour plots showing chlorohydrin **4** level, product generation, and assay yield.

in 5 and 10% of chlorohydrin **4**, respectively. Thus, a temperature window of −5 to 0 °C was deemed most suitable to limit the formation of **4**, with careful temperature control required, as above 0 °C, levels of **4** became significant. For scale-up, it was felt that the ceiling temperature of −5 °C should be used, and the stream of epoxide in THF was precooled to minimise hotspots in the reaction mixture.

The beneficial effect of the copper catalyst was confirmed in this inverse addition protocol in a reaction without copper chloride (entry 15) which gave almost 40% chlorohydrin with a correspondingly low assay yield of product (60%). The previously used copper source (CuI) was also used in this protocol (entry 19) and resulted in two major impurities at 12 and 17%, one of these being the iodohydrin **19** (Figure 2).

Previously, 20 mol % of copper chloride was shown to be enough to limit the level of impurity **4**. Further copper-loading studies between 5 and 15 mol % were carried out and showed that within these limits, the conversion to and assay yield of **2** were consistently high and levels of **4** were similarly low at 1−2% (entries 16 and 17). With a faster addition time (15 min), at low copper loading (5 mol %), elevated levels of chlorohydrin **4** were formed, suggesting that catalyst turnover was not sufficient at this loading (entry 18).



19

Figure 2.

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Finally, experiments to compare the normal addition and inverse addition protocols showed the benefit of the inverse addition. With normal addition of vinylmagnesium chloride to a mixture of **1**/CuCl in THF at −5 °C, up to 6% of **4** was observed and up to 20% at 20 °C (results not in the table). The best conditions resulting from this study were thus deemed to be 1.5 equiv of vinylmagnesium chloride with 5% copper chloride and >60 min addition time of the epoxide starting material at ≤−5 °C.

Workup, Safety Considerations, and Scale-Up. The development of an efficient workup was also key for an improved procedure that was amenable to scale up. Due to the 2.5 equiv of Grignard reagent being used in the initial procedures and the presence of copper residues, the workup was challenging with emulsions formed and many insolubles also present. Direct quenches with acetic acid and ammonium chloride (aq) followed by further acidification with 2 M HCl could be used on laboratory scale, but were not workable on increased scale. Replacing the acid quench with methanol gave much cleaner oil-free mixtures. In conjunction with an age of at least 1 h in 2 M HCl, the workup was improved drastically, removing the need for a tedious filtration to remove insolubles.

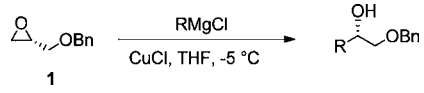
Characterization of the reaction exothermicity was also important to ensure suitable addition times of the epoxide to the Grignard/CuCl mixture would be achievable on scale. A calorimetry experiment (RC-1) showed that the addition of glycidyl ether **1** to a mixture of CuCl (I) and vinylmagnesium chloride in THF gave a heat of reaction of 279 kJ mol^{-1}, coupled with an adiabatic temperature rise of 94 °C over the course of the addition-controlled reaction; thus, an addition time of 1 h with cooling would be sufficient to control any exotherm. The methanol quench resulted in a heat of reaction of 294 kJ $mol,^{-1}$ with an adiabatic temperature rise of 57 °C over the course of the addition-controlled quench (see Supporting Information for graphs). This data was used to show that the exothermic activity resulting from the reaction and quench would be controllable over a realistic addition time of epoxide **1** for a multikilogram reaction in a standard, glass-lined vessel.

These conditions were then successfully demonstrated on 20-kg scale. After HPLC monitoring indicated a complete reaction with the expected reaction profile, the reaction was quenched with MeOH. The ethene byproduct emissions were required to be below 70 mg/m^3 (volatile organic compound emission limit), and thus, the quench was performed over 1 h to ensure adherence to this limit. Finally, treatment with 2 M HCl (aq) and vigorous stirring over at least 1 h were used to break down the colloidal copper and magnesium residues formed during the reaction. The wash sequence incorporated a sodium thiosulphate aqueous wash which assisted in removing copper residues. This protocol afforded 22.2 kg of **2** in 94% assay yield.

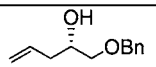
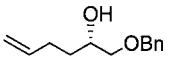
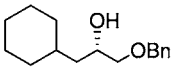
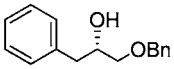
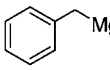
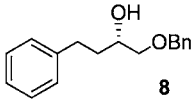
Substrate Scope. The optimised procedure described above was applied to the addition of several other Grignard reagents to a variety of epoxides to evaluate the scope of this protocol.

First, several commercially available Grignard reagents were used in the ring-opening of benzyl-(*S*)-glyicdyl ether **1** (Table 3). Full conversion of the starting epoxide was seen in all cases with no chlorohydrin impurity observed by HPLC and >90% isolated yield in all but one case. In this instance, using allylmagnesium chloride, another product at 15% was observed which is believed to be the corresponding chlorohydrin impurity **4**. The quality of allylmagnesium chloride was difficult to determine by titration, and the precipitation of magnesium chloride salts in the solution is believed to be the cause of this erroneous result.

Table 3. Scope of Grignard reagent addition to benzyl (*S*)-glycidyl ether 1

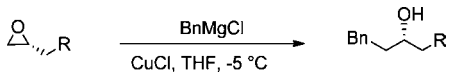


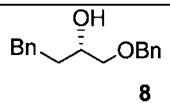
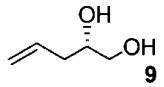
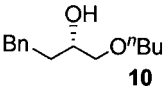
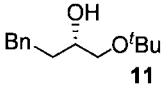
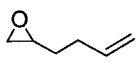
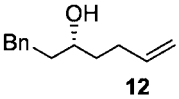
1

Entry	Grignard	Product	Yield (%)
1		 **2**	94
2		 **5**	82
3		 **6**	96
4		 **7**	97
5		 **8**	97

A range of commercially available epoxides was also successfully subjected to ring-opening under the developed conditions. Several aromatic and aliphatic ethers were used, and all showed complete conversion of starting material after addition to the cuprate mixture with excellent isolated yields (Table 4).

Table 4. Addition of benzylmagnesium chloride to a selection of glycidyl ethers



Entry	Epoxide	Product	Yield (%)
1		 **8**	97
2		 **9**	-
3		 **10**	98
4		 **11**	96
5		 **12**	80

An interesting observation was with glycidyl tosylate (Table 4, entry 2) where, during the workup, the tosylate group was hydrolysed, leading to the formation of the diol product **9**.[6] The

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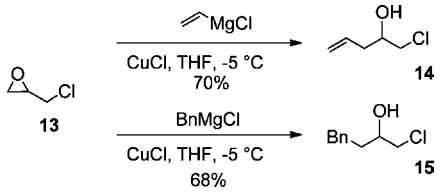
addition of benzylmagnesium chloride to 1,2-epoxy-5-hexene (Table 4, entry 5) also proceeded in good yield, indicating that an ethereal substituent on the epoxide was not required for a clean and selective reaction.

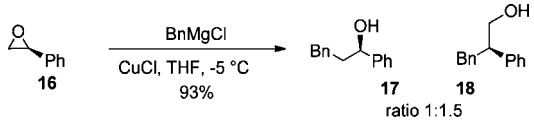
The ring-opening of (±)-epichlorohydrin, **13**, also performed well using the optimised procedure and addition of benzyl- and vinylmagnesium chloride, although lower isolated yields (68−70%) were obtained (Scheme 2), likely due to handling issues with (±)-epichlorohydrin.

Scheme 2. Grignard additions to (±)-epichlorohydrin



R-Phenyloxirane, **16**, was also treated with benzylmagnesium chloride with excellent conversion of starting material and isolated yield (Scheme 3). However, the selectivity of the addition was much lower due to ring-opening at the benzylic position.

Scheme 3. Grignard addition to *R*-phenyloxirane



CONCLUSION

In summary, a highly regioselective and robust procedure for the copper-catalysed addition of Grignard reagents to epoxides has been developed and demonstrated on >20-kg scale. The protocol has also been demonstrated with a range of commercially available epoxides and Grignard reagents to provide the products typically in >90% yield. This robust, noncryogenic procedure limits the formation of impurities, giving clean products ready for further manipulation of these important building blocks.

EXPERIMENTAL SECTION

1-(Benzyloxy)pent-4-en-2-ol (2).[7] To a solution of vinylmagnesium chloride (117 kg, ∼1.6 M, 1.5 equiv) in THF was added copper(I) chloride (0.63 kg, 0.0063 mol) and the mixture cooled to −10 °C. A solution of benzyl-(*S*)-glycidyl ether (20.7 kg, 126.1 mol) in THF (105 L) was added dropwise over 1 h, maintaining temperature between $-10 < T < -5$ °C. The reaction mixture was allowed to warm to 0 °C and diluted with methanol (10.2 kg, 319.7 mol) and then quenched by addition of 2 M HCl (186 L), maintaining temperature between $0 < T < 10$ °C. The reaction mixture was aged for 1 h before being diluted with M*t*BE (105 L) and the aqueous layer separated. The organic layers were washed with 2 M HCl (80 L), water (40 L), 10 w/w% sodium thiosulfate solution (80 L), and again with water (40 L). The resulting solution of product **2** was found to be sufficiently pure to be used directly in the next step (22.2 kg, 94% assay yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.19−7.28 (m, 5H), 5.88−5.78 (m, 1H, J = 17.2, 10.2, 7.1 Hz), 5.15−5.08 (m, 2H), 4.56 (s, 2H), 1.92−1.86 (m, 1H), 1.54−1.51 (dd, 1H, J = 9.5, 1.4 Hz), 1.40−1.16 (dd, 1H, J = 9.5, 7.5 Hz), 2.14−2.11 (d, 1H, J = 1.1 Hz), 2.28−2.25 (t, 2H, J = 6.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 118.0, 114.1, 128.5, 127.8, 127.7, 117.6, 71.9, 71.4, 69.7, 18.0. The ee was determined to be >99% by chiral HPLC in a downstream product.

General. All reagents and solvents were purchased from commercial suppliers and used without further purification. Unless indicated, reactions were carried out under an atmosphere of nitrogen. Reactions were monitored for completion by removing a small sample from the reaction mixture and analysing the sample by HPLC.

Proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded at ambient temperature on a Bruker Avance DPX or DRX (400 MHz) spectrometer. Chemical shifts are reported relative to the residual protons in $CDCl_3$ (δ_H 7.26 ppm) and coupling constants (J) are given in hertz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance DPX or DRX (100 MHz) spectrometer. Chemical shift was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in $CDCl_3$ (δ_C 77.2). Data are reported as follows: Chemical shift (multiplicity, number of protons, coupling constants). Chemical shift was measured in ppm and quoted to the nearest 0.01 ppm. Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported.

HPLC Method. Ascentis Express C18, 100 mm × 4.6 mm, 2.7 μm, and a mobile phase consisting of acetonitrile and 0.1% phosphoric acid (aq)

High resolution mass spectra were recorded by LC/MS using a Waters QToF Premier system, eluting with an acetonitrile and 0.1% formic acid (aq) gradient in combination with positive electrospray mass spectrometry.

Column chromatography was carried out using a CombiFlash Companion system using prepacked packed RediSep silica cartridges.

General Procedure. To a solution of the Grignard reagent (1.5 equiv) in THF was added copper(I) chloride (5 mol. %) and the mixture cooled to −10 °C. A solution of the epoxide (1.0 equiv) in THF (4 mL/g) was added dropwise over 1 h, maintaining temperature between $-10 < T < -5$ °C. The reaction mixture was allowed to warm to 0 °C, diluted with methanol (2.5 equiv), and then quenched by addition of 2 M HCl (2.0 equiv), maintaining temperature between $0 < T < 10$ °C. The reaction mixture was aged for 1 h before being diluted with MTBE (5 mL/g) and the aqueous layer separated. The organic layers were washed with 2 M HCl (2 mL/g), water (2 mL/g), 10% sodium thiosulfate solution (2 mL/g), and again with water (2 mL/g). The combined organic layers were concentrated in vacuo, and an analytical sample was purified by flash column chromatography (gradient elution, 100% hexane to 100% MTBE) to provide the final product.

1-(Benzyloxy)hex-5-en-2-ol (5).[8] The general procedure was followed using 1.5 M solution of allylmagnesium chloride (9.1 mL, 18 mmol) and benzyl-(*S*)-glycidyl ether (2.0 g, 12 mmol) to afford the product as a clear oil (2.1 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18−7.28 (m, 5H), 5.87−5.77 (m, 1H, J = 17.1, 10.2, 6.7 Hz), 5.06−5.01 (dd, 1H, J = 17.1, 1.6 Hz), 4.98−4.95 (dd, 1H, J = 10.2, 1.2 Hz), 4.56

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(s, 2H), 1.87−1.81 (m, 1H), 1.51−1.50 (dd, 1H, J = 9.4, 1.0 Hz), 1.16−1.12 (dd, 1H, J = 9.4, 7.8 Hz), 2.14−2.11 (d, 1H, J = 1.1), 2.27−2.08 (m, 2H,), 1.62−1.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 118.1, 118.0, 128.5, 127.8, 127.8, 114.9, 74.6, 71.4, 69.9, 12.1, 29.8.

1-(Benzyloxy)-1-cyclohexylpropan-2-ol (6).[9] The general procedure was followed using a 1.5 M solution of cyclohexylmagnesium chloride (9.1 mL, 18 mmol) and benzyl-(*S*)-glycidyl ether (2.0 g, 12 mmol) to afford the product as a clear oil (2.9 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.19−7.28 (m, 5H), 4.56 (s, 2H), 1.97−1.90 (m, 1H), 1.50−1.47 (dd, 1H, J = 9.4, 2.9 Hz), 1.12−1.27 (dd, 1H, J = 8.0, 9.4 Hz), 2.11 (s, 1H), 1.81−1.76 (m, 1H), 1.72−1.60 (m, 4H), 1.52−1.15 (m, 2H), 1.10−1.08 (m, 4H), 0.99−0.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 118.1, 128.5, 127.8, 127.8, 75.2, 71.4, 67.9, 40.8, 14.2, 11.9, 12.9, 26.6, 26.4, 26.2.

1-(Benzyloxy)-1-phenylpropan-2-ol (7).[10] The general procedure was followed using a 1.5 M solution of phenylmagnesium chloride (9.1 mL, 18 mmol) and benzyl-(*S*)-glycidyl ether (2.0 g, 12 mmol) to afford the product as a clear oil (2.9 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.19−7.20 (m, 10H), 4.56 (s, 2H), 4.10−4.01 (m, 1H, J = 6.9, 1.4 Hz), 1.54−1.51 (dd, 1H, J = 9.4, 1.4 Hz), 1.41−1.19 (dd, 1H, J = 9.4, 6.9 Hz), 2.81−2.81 (m, 2H), 2.15−2.14 (d, 1H, J = 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 118.1, 118.0, 129.4, 128.5, 127.8, 126.4, 71.6, 71.4, 71.4, 19.9.

1-(Benzyloxy)-4-phenylbutan-2-ol (8).[11] The general procedure was followed using a 1.5 M solution of benzylmagnesium chloride (9.1 mL, 18 mmol) and benzyl-(*S*)-glycidyl ether (2.0 g, 12 mmol) to afford the product as a clear oil (1.0 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18−7.16 (m, 10H), 4.55 (s, 2H), 1.87−1.80 (m, 1H, J = 7.8, 1.5 Hz), 1.52−1.49 (dd, 1H, J = 9.4, 1.5 Hz), 1.18−1.14 (dd, 1H, 9.4, 7.8 Hz), 2.85−2.61 (m, 2H), 2.19−2.18 (d, 1H, J = 1.5 Hz), 1.85−1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.0, 118.0, 128.5, 128.4, 127.8, 127.8, 125.9, 74.6, 71.4, 69.7, 14.8, 11.8;

1-Butoxy-4-phenylbutan-2-ol (10). The general procedure was followed using a 1.5 M solution of benzylmagnesium chloride (11.0 mL, 22 mmol) and *n*-butyl glycidyl ether (2.0 g, 14 mmol) to afford the product as a clear oil (1.2 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18−7.24 (m, 5H), 1.90−1.84 (m, 1H J = 7.9 Hz), 1.58−1.48 (m, 1H), 1.17−1.11 (dd, 1H, J = 9.4, 7.9 Hz), 2.94−2.87 (m, 1H, J = Hz), 2.81−2.71 (m, 1H, J = Hz), 2.46 (s, br, 1H), 1.91−1.74 (m, 2H), 1.67−1.60 (m, 2H, J = 6.6 Hz), 1.49−1.40 (m, 2H, J = 7.4 Hz), 1.00 (t, 1H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.1, 128.5, 128.4, 125.7, 75.1, 71.1, 69.6, 14.9, 11.9, 11.8, 19.4, 14.0. HRMS (ES^+) Calcd for $C_{14}H_{23}O_2$ [M + H] 223.1698, found 223.1709

1-(*tert*-Butoxy)-4-phenylbutan-2-ol (11). The general procedure was followed using a 1.5 M solution of benzylmagnesium chloride (11.2 mL, 22 mmol) and *tert*-butyl glycidyl ether (2.0 g, 14 mmol) to afford the product as a clear oil (1.2 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18−7.24 (m, 5H), 1.82−1.76 (m, 1H, J = 7.8, 1.1 Hz), 1.47−1.44 (dd, 1H, J = 8.8, 1.1 Hz), 1.29−1.25 (dd, 1H, J = 8.8, 7.8 Hz), 2.95−2.88 (m, 1H, J = 9.4 Hz), 2.81−2.74 (m, 1H, J = 9.4 Hz), 2.58−2.57 (d, 1H, J = 2.9 Hz), 1.92−1.74 (m, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.2, 128.6, 128.4, 125.8, 71.2, 70.0, 66.0, 15.0, 11.9, 27.6; HRMS (ES^+) Calcd for $C_{14}H_{23}O_2$ [M + H] 223.1698, found 223.1702

1-Phenylhept-6-en-1-ol (12).[12] The general procedure was followed using a 1.5 M solution of benzylmagnesium chloride (15.3 mL, 10.6 mmol) and 1,5-epoxy-5-hexene (2.0 g, 20.2 mmol) to afford the product as a clear oil (1.1 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18−7.17 (m, 5H), 5.89−5.79 (m, 1H, J = 17.1, 10.2, 6.7 Hz), 5.07−5.02 (dd, 1H, J = 17.2, 1.6 Hz), 4.99−4.96 (dd, 1H, J = 10.2, 1.6 Hz), 1.70−1.61 (m, 1H), 2.28−2.76 (m, 1H), 2.71−2.64 (m, 1H), 2.26−2.09 (m, 2H, J = 6.7 Hz), 1.85−1.70 (m, 2H), 1.65−1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.2, 118.6, 128.5, 125.9, 114.9, 70.9, 19.2, 16.6, 12.1, 10.1.

1-Chloropent-4-en-2-ol (14).[13] The general procedure was followed using a 1.5 M solution of vinylmagnesium chloride (20.3 mL, 12.4 mmol) and epichlorohydrin (1.7 mL, 21.6 mmol) to afford the product as a clear oil (1.8 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.87−5.76 (m, 1H), 5.20−5.15 (m, 2H), 1.92−1.85 (m, 1H, J = 6.7, 1.7 Hz), 1.65−1.61 (dd, 1H, J = 11.1, 1.7 Hz), 1.54−1.49 (dd, 1H, J = 11.1, 6.7 Hz), 2.41−2.10 (m, 2H), 2.24−2.21 (d, 1H, J = 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 111.4, 118.7, 70.7, 49.4, 18.8.

1-Chloro-4-phenylbutan-2-ol (15).[14] The general procedure was followed using a 1.5 M solution of benzylmagnesium chloride (16.2 mL, 12.4 mmol) and (±)-epichlorohydrin (1.7 mL, 21.6 mmol) to afford the product as a clear oil (2.8 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.12−7.19 (m, 5H), 1.85−1.78 (m, 1H, J = 7.1, 1.1 Hz), 1.65−1.62 (dd, 1H, J = 11.1, 1.1 Hz), 1.52−1.48 (dd, 1H, J = 11.1 7.1 Hz), 2.88−2.80 (m, 1H), 2.76−2.69 (m, 1H), 2.21−2.21 (d, 1H, J = 5.0 Hz), 1.91−1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 141.4, 128.6, 128.5, 126.2, 70.7, 50.6, 15.9, 11.8.

1,1-Diphenylpropan-1-ol (17/18).[15,16] The general procedure was followed using a 1.5 M solution of benzylmagnesium chloride (9.2 mL, 18.71 mmol) and *R*-phenyloxirane (1.5 g, 12.5 mmol) to afford the product as a white, crystalline solid (2.3 g, 11.6 mmol, 91% yield) in a 1:1.4 mixture of regioisomers.

17:[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.17−7.17 (m, 10H), 4.72−4.68 (m, 1H), 2.80−2.62 (m, 2H), 2.19−1.99 (m, 2H), 1.91−1.90 (d, 1H, J = 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.5, 141.9, 127.9, 127.8, 126.5, 126.4, 125.2, 125.1, 73.7, 40.2, 32.0

18:[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18−7.09 (m, 10H), 1.82−1.71 (m, 2H), 1.14−1.01 (m, 2H), 2.94−2.89 (m, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.1, 140.1, 129.8, 129.2, 128.8, 128.6, 127.6, 126.8, 66.8, 50.4, 39.0

■ ASSOCIATED CONTENT

Supporting Information

RC-1 calorimetry graphs. This material is available free of charge via the Internet at http://pubs.acs.org/.

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