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Highly Regioselective Copper-Catalyzed *cis*- and *trans*-1-Propenyl Grignard Cleavage of Hindered Epoxides. Application in Propionate Synthesis

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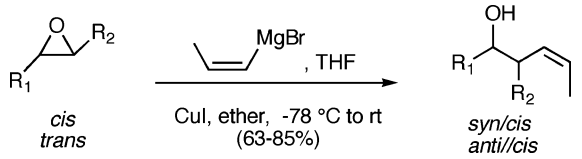

Hindered protected and unprotected epoxy alcohols were regioselectively cleaved using copper-catalyzed *cis*- and *trans*-1-propenylmagnesium bromide. The reaction exhibited good yield and excellent regioselectivity in systems where organocuprates and organoalanes failed. The *cis* Grignard reagent displayed no double-bond isomerization, whereas the *trans* isomer showed partial *trans*-to-*cis* equilibration, which was minimized by controlling the reagent formation conditions. The reaction was shown to be highly useful for the elaboration of the C10−C15 Streptovaricin D *ansa* chain fragment.

Grignard reagents are among the most classical organometallic reagents which continue to see extensive use in C−C bond formation reactions.[1] In addition to their typical use in carbonyl and related nucleophilic addition reactions, they have found widespread applications in transition-metal-catalyzed cross-coupling reactions.[2,3] Grignard reagents have also been used as nucleophiles to perform the cleavage of oxiranes.[4] In this regard, copper(I) salts have been shown to catalyze the addition of Grignard reagents to epoxides to introduce alkyl, allyl, and, less frequently, vinyl groups. Nonetheless, the regioselective ring opening of epoxides by Grignard reagents has been restricted mostly to unhindered epoxides and those activated by an adjacent vinyl or aryl group.[4,5] Disubstituted epoxides present inherent regioselectivity problems, which are also found with other organometallic reagents, such as organocuprates[6] and organoalanes.[7] Moreover, given the presence of Lewis acids (magnesium halide salts) associated with the Schlenk equilibrium,[8] the formation of side products (halohydrin, rearrangement, elimination, etc.) may also be observed when an epoxide is treated with a Grignard reagent.[9]

The cleavage of disubstituted epoxides represents a valuable transformation for the stereoselective generation of two contiguous stereogenic centers. In this regard, we recently reported a study on the cleavage of hindered 3,4-epoxy alcohols by an alkynyl aluminum reagent, as part of our quest for developing a general epoxide-based methodology for the preparation of polypropionates.[7e] In our three-step approach, an epoxide is submitted to a sequence of diethylpropynylalane-mediated oxirane cleavage, alkyne reduction, and stereoselective epoxidation to yield a 3,4-epoxy alcohol (Scheme 1). This methodology may be repeated to produce a new 3,4-epoxy alcohol, which allows for chain elongation in a reiterative fashion.

This successful approach resulted in a series of diastereomeric stereotetrads; nonetheless, some limitations were encountered in the regioselectivity of the cleavage of some epoxy alcohol precursors. For example, the *trans*-epoxy alcohol **1** was effectively cleaved under the alane reaction conditions to produce stereotetrad **2** with high regioselectivity (89:11) and a reasonable 68% yield after separation; however, the closely related epoxy alcohol **5** afforded a 56:44 mixture of the expected 1,3-diol **6** and the 1,4-diol **7** in a very low yield (ca. 28%, Scheme 2). Moreover, when the epoxy alcohol **1** was protected as the methyl ether **3** and subjected to the alkynyl alane conditions, no reaction was observed. Epoxy alcohol **3** represents a potentially useful precursor for the introduction of the C(27) methoxy group present in the rifamycin S *ansa* chain.

These findings prompted us to explore other organometallic pathways to overcome these limitations and to expand the generality of our epoxide-based approach to polypropionates.

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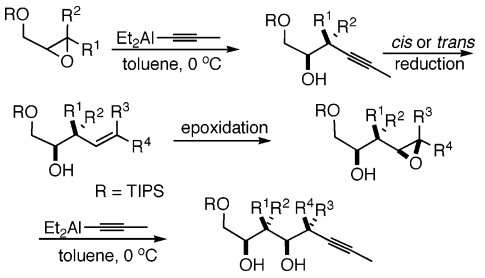
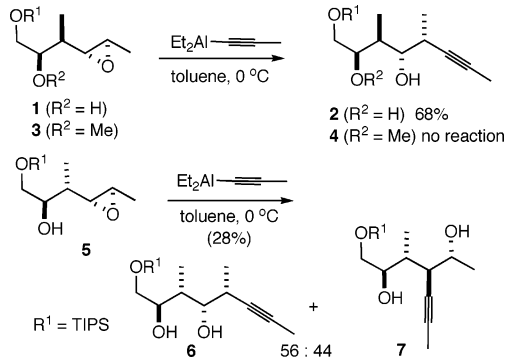
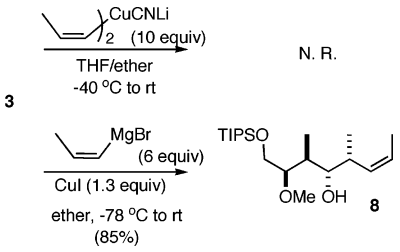
SCHEME 1. General Reiterative Epoxide-Based Approach to Polypropionates



SCHEME 2. Alkynyl Alane Approach to the Cleavage of Disubstituted Epoxide



SCHEME 3. Cleavage of Epoxide 3 by *cis*-1-Propenyl Organometallic Reagents



Herein we describe a general procedure for the reaction of disubstituted epoxides with readily available propenyl Grignard reagents under Cu catalysis to form directly stereodefined alkenyl propionates.

After the unsuccessful attempts to cleave epoxide **3** by means of a propynylalane, we decided to explore the cleavage with a propenyl organometallic reagent (Scheme 3). A potential advantage of this concept would be direct formation of a homoallylic alkenol (**8**) in one step, without the need for the subsequent alkyne to alkene reduction required in the alkynyl alane method.[7e] We first explored higher-order propenyl organocuprates, which have been used in related but less hindered systems, although with moderate regioselectivity.[6a,c] Thus, when epoxide **3** was subjected to a higher-order *cis*-1-propenyl organocuprate reagent, only the starting epoxide was recovered, even after an extensive variation of the reaction conditions, the preparation of the organometallic reagent,[6] and the order of addition.[10]

We then proceeded to test the cleavage of epoxide **3** with an alkenyl Grignard reagent. To our delight, when epoxide **3** was exposed to *cis*-1-propenylmagnesium bromide (6 equiv) in the presence of CuI (1.3 equiv), the desired homoallylic alcohol **8** was obtained in 85% yield and excellent regioselectivity. Moreover, the reaction produced exclusively the *cis* alkenol without detectable double-bond isomerization. The retention of the propenyl geometry was established by its ^{13}C NMR spectrum, which exposed the diagnostic signal for the allylic methyl carbon at 13.0 ppm.[11] Similarly, the out-of-plane infrared absorption band at 680 cm^{-1} corroborates this result. The *cis*-propenyl-substituted alcohol **8** corresponds to the C(24)−C(27) stereotetrad fragment of rifamycin S.

This success taken together with the evident lack of reactivity of epoxide **3** toward the organoalane and organocuprate reagents encouraged us to investigate in more detail the copper-mediated cleavage of other epoxides of synthetic interest for our polypropionate studies[12] by *cis*-1-propenylmagnesium bromide (Table 1). In the case of the primary epoxide **9** (used as a control substrate), the reaction occurred as expected in good yield (ca. >70%) and without detectable double-bond isomerization (entry 1). Next, we focused our attention on the *cis*- and *trans*-disubstituted epoxides **13** and **15**, which correspond to the starting substrates used in our epoxide-based polypropionate synthesis. Again, the epoxides were cleaved in comparable yields and excellent regioselectivity (entries 4 and 5). The less hindered benzyl- and SEM-protected epoxides **17** and **19** showed somewhat diminished regioselectivity (entries 6 and 7). These results demonstrate that useful regioselectivities are attainable even in systems with less significant steric bias. Fortunately, the monoprotected epoxy diol **21** exhibited excellent regioselectivity, which produced only the alkene diol **22** in 85% yield (entry 9). Diol **22** represents a potentially useful precursor for the synthesis of the streptovaricin D polypropionate chain, which possesses an unusual carbomethoxy group at the C(10) position.

To evaluate the extent of the catalytic nature of the reaction, a series of catalyst loading versus concentration of the Grignard reagent was studied. The cleavage was first performed with the unhindered epoxide **9** as a model. The copper catalyst was varied in the range from 5 to 130 mol %. The reaction proceeded smoothly to afford the homoallylic alcohol in comparable yields for all attempts, even at a catalyst loading of 5 mol %. To discard the possibility that the Grignard reagent alone might promote the epoxide cleavage, as has been observed in some allylic cases,[4a] the reaction was performed without the catalyst. After several attempts, the Grignard addition was not observed and only the bromohydrin product was formed, which confirms copper catalysis. To further examine this aspect, the catalyst loading was lowered to 10 mol % for compounds **11**, **19**, and **3** (Table 1, entries 3, 8, and 11). Under these conditions, similar yields (and regioselectivity in the case of **19**) were obtained. Since the free hydroxy group is required for the cleavage of 3,4-epoxy alcohols by propynyl alane reagents (Scheme 2), we decided to apply the copper-catalyzed Grignard conditions (10 mol % of CuI) to the epoxy alcohol **1**. In this case, the expected 1,3-diol product **23** was obtained as the only regioisomer in good yield (entry 12). This result shows an improved regioselectivity for epoxy alcohol **1** compared to the one obtained using the propynylalane conditions (89:11).[7e] The examples in entries 9 and 12 manifest that the copper-catalyzed propenyl Grignard

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(11) All compounds were fully characterized by 1D and 2D NMR (COSY and HMQC) methods. For known compound, the spectral data were compared with the literature values reported in refs 7e and 12.

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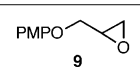
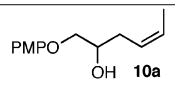
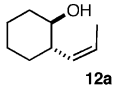
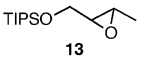
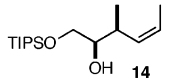
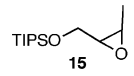
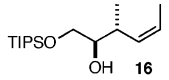
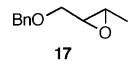
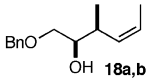
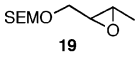
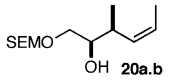
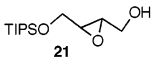
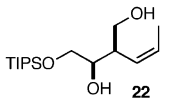
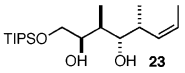
TABLE 1. Yields and Regioselectivities of the Cu-Catalyzed Cleavage of Epoxides with *cis*-1-Propenylmagnesium Bromide

entry	epoxide[a]	condition[b]	product[c]	% yield[d] (ratio)[e]
1	 **9**	A	 **10a**	72
2	**9**	B	**10a**	75
3	 **11**	B	 **12a**	70
4	 **13**	A	 **14**	70[f]
5	 **15**	A	 **16**	63
6	 **17**	A	 **18a,b**	62 (75:25)
7	 **19**	A	 **20a.b**	60 (86:14)
8	**19**	B	**20a,b**	65 (86:14)
9	 **21**	A	 **22**	85
10	**3**	A	**8**	85
11	**3**	B	**8**	75
12	**1**	B	 **23**	74[g]

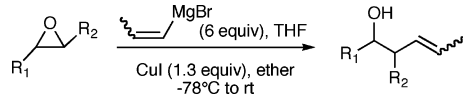
[a] Prepared by the procedures in ref 12. [b] Condition A: 6 equiv of Grignard reagent, 1.3 equiv of CuI, −78 °C. Condition B: 6 equiv of Grignard reagent, 0.1 equiv of CuI, −78 °C. [c] Characterized by NMR spectroscopy. [d] Isolated product yield after distillation or chromatography. [e] Ratio of external epoxide carbon attack versus internal attack, when observed. [f] A 2:1 mixture of cleavage product/starting material eluted from the chromatography column. [g] Yield of crude product; the diol partially decomposed on a silica gel column. The alcohol was transformed to the bistriethylsilyl ether for purification and characterization.

cleavage of hindered epoxides does tolerate a free hydroxy group, diminishing the need for a protection−deprotection sequence.

The Grignard reagent derived from *trans*-1-bromopropene was studied next under the same conditions as employed for the *cis*-propenyl Grignard reagent, to produce the complementary *trans* homoallylic alcohols. Although no major complications were expected, when the *trans*-1-propenylmagnesium bromide was added to epoxide **9**, a 1:1 *cis/trans* mixture was produced. Consequently, to elucidate this unexpected isomerization process, we examined the model epoxides **9** and **11** (Table 2). The propenyl *cis/trans* geometry of the products was again established by ^{13}C NMR spectroscopy, which exposed the diagnostic allylic methyl signals at 12.8−13.5 ppm, compared to 17.9−18.1 ppm for the *trans* isomers.

When epoxide **11** was treated with the *trans* Grignard reagent under the standard copper-mediated conditions (1.3 equiv), also

TABLE 2. *cis/trans* Product Isomerization Studies for Epoxides 9 and 11



entry	propenyl geometry[a]	epoxide	T (°C)	time (min)[b]	product	*trans/cis* ratio[c]
1	*trans*	**9**	25	60	**10a,b**	50:50
2	*trans*	**11**	25	60	**12a,b**	50:50
3	*trans*	**9**	25	<1[d]	**10a,b**	63:37
4	*trans*	**9**	0 to 25	40[e]	**10a,b**	77:23
5	*trans*	**9**	−25 to 25	40[e]	**10a,b**	86:14
6	*trans*	**11**	−25 to 25	40[e]	**12a,b**	71:29
7	*cis*	**9**	25	360	**10a**	<5:95[f]
8	*trans/cis*[g]	**11**	25	180	**12a,b**	6:94

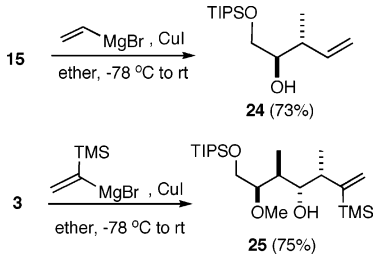
[a] The *cis*/*trans* geometry of the 1-bromopropene staring material was determined by NMR spectroscopy. [b] The Grignard reagent was prepared in THF at room temperature and was allowed to stir for the specified time and temperature after its initial reflux before being transferred to the CuI/ether slurry at −78 °C. [c] The *trans/cis* ratio was determined by NMR spectroscopy. [d] With initial reflux and immediate transfer of the reaction mixture to the CuI/ether slurry. [e] No initial reflux; after the formation of the Grignard reagent had been initiated, the reaction mixture was cooled. [f] No other isomer was detected. [g] 40:60 *trans/cis*.

a 1:1 *cis/trans* mixture of ring-opened products was obtained (entry 2). These unexpected results urged us to explore a systematic temperature and time variation for the formation of the propenyl Grignard reagent. When the organometallic reagent was quickly transferred to the copper iodide slurry (immediately after the initial reflux) and treated with the epoxide **9**, a mixture of *cis* and *trans* alkenols was again formed in a moderate 63:37 *trans/cis* selectivity. The Grignard reagent was then prepared without initial reflux (cooling to 0 or −25 °C after initial reagent formation). The cleavage occurred with improved stereoselectivity (entries 4−6); for example, a 86:14 *trans/cis* ratio was obtained for epoxide **9**. An attempt to prepare the Grignard reagent at an initial temperature below room temperature did not produce the organometallic reagent (data not shown in Table 2). These results reveal that the double-bond isomerization occurs during the formation of the *trans*-propenyl Grignard reagent. It depends on the initial temperature at which the reagent is prepared (reflux versus temperature control), as well as on the time it is allowed to stir before transfer to the copper slurry. Moreover, the isomerization process also takes place, but slowly, during the epoxide cleavage step, as suggested by the differing *trans/cis* product ratio for epoxides **9** and **11**. Since the secondary epoxide **11** reacts slower than **9**, a lower *trans/cis* ratio is expected because there is more time for the isomerization.

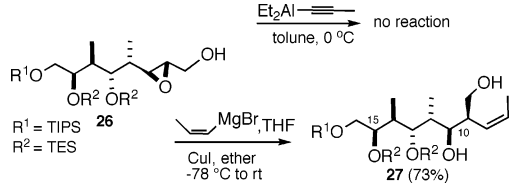
To test the possibility of double-bond isomerization by starting from the *cis*-propenyl Grignard reagent, a solution was prepared as usual and was allowed to stir for up to 6 h at room temperature before treatment with epoxide **9**. Again, only the *cis*-alkenol product was observed (entry 7). Even more significant, when a commercially available 40:60 *trans/cis* mixture of 1-bromopropenes was used to prepare the Grignard reagent and treated with epoxide **10** for 3 h, a 6:94 *trans/cis* mixture was obtained (entry 8).

A similar contra-thermodynamic double-bond isomerization of *trans*-1-propenylmagnesium bromide to its *cis* isomer, but not the reverse, was reported by Beak[13] in a detailed mechanistic study on the addition of *trans*- and *cis*-propenyl organometallic reagents to carbonyl and thiocarbonyl compounds. In this

SCHEME 4. Reaction of Other Alkenyl Grignard Derivatives with Disubstituted Epoxides



SCHEME 5. Application of the Copper-Catalyzed Grignard Approach for the Cleavage of Epoxide 26



investigation, only about 15% *trans*-to-*cis* propenyl isomerization was obtained (in our examples, the *trans*-to-*cis* isomerization is as much as 50%!) for the *trans*-configured Grignard reagent, whereas complete retention was found for the *cis* reagent. Although no detailed explanation for this unusual behavior was offered, the authors ascribed this trend to the difference in reactivity between the propenyl Grignard diastereomers (the *cis* isomer reacts 1.7 times faster than the *trans*). The greater extent of double-bond isomerization observed by us for the epoxide cleavage reaction compared to Beak's nucleophilic addition to thioketones relates again to the lower reactivity of the epoxides since for the latter several hours are required for completion at low temperature (−78 °C to room temperature).

To further assess the scope of the copper-catalyzed epoxide cleavage reaction, we studied two other potentially useful vinyl Grignard derivatives. These included vinylmagnesium bromide and α-(trimethylsilyl)vinylmagnesium bromide (Scheme 4).[5a] In both cases, the disubstituted epoxides were cleaved in good yields (73−75%) and excellent regioselectivities. The vinyl TMS group provides a potentially useful access to other vinyl derivatives, such as α-substituted vinyl bromides.[5a] These examples reveal that this copper-catalyzed alkenyl Grignard cleavage of hindered epoxides is not limited to 1-propenyl Grignard reagents, showing the potential for expansion to other alkenyl Grignard derivatives.

As a final point, we decided to test this copper-catalyzed *cis*-propenyl Grignard approach on the hindered epoxide **26**, related to the currently ongoing synthesis of the Streptovaricin D *ansa* chain.[14] The challenge here is that several previous attempts to cleave the epoxide ring in **26** were unsuccessful with the alkynyl alane protocol (Scheme 5). Indeed, the epoxide **26** was efficiently cleaved to form the tripropionate fragment **27** in good yield (74%), without any detectable regioisomer or double-bond isomerization.[11] Product **27**, which has six contiguous chirality centers, corresponds to the C15−C10 fragment of the streptovaricin D *ansa* chain and contains the C(10) methyl group in an alcohol oxidation state. This fortunate result demonstrates the scope and efficacy of the copper-catalyzed Grignard methodology as a convenient means and as a feasible tool of regioselectively cleaving hindered epoxides for the elaboration of stereodefined polypropionate chains.

The work presented herein, especially the good yields and high regioselectivities, offers a convenient and promising synthetic methodology of applying the copper-catalyzed Grignard reaction to the cleavage of hindered disubstituted epoxides. We emphasize the fact that this useful regio- and stereocontrolled protocol for the synthesis of polypropionate is shorter than the alkynyl alane method and solves the regioselectivity problems encountered with the latter.

Experimental Section

Representative Procedure for the Copper-Catalyzed Cleavage of Epoxides Using Alkenylmagnesium Bromides. Preparations of (2*R,3*S**,4*S**,5*R**,6*Z*)-2-Methoxy-3,5-dimethyl-1-[(triisopropylsilyl)oxy]-6-octen-4-ol (8).** Mg powder (0.22 g atom, 5.4 g, 14 equiv) was added to a round-bottom flask assembled with a dry ice condenser. Freshly distilled THF (100 mL, 2.3 M with respect to Mg) was added to the flask and spiked with I_2. After several minutes, the reaction mixture turned from yellow to turbid gray. Then, the dry ice condenser was cooled to −78 °C and *cis*-1-bromopropene (11.38 g, 94 mmol, 6 equiv) was added. After several minutes, the reaction warmed and refluxed vigorously. The reaction was stirred for 1 h. The solution was transferred via a double-ended needle to a three-neck round-bottom flask containing CuI (0.30 g, 1.6 mmol, 0.10 equiv) in ether (40 mL) at −78 °C. The CuI was previously heated overnight under reduced pressure to remove moisture. After 30 min, the epoxide (5.00 g, 15.8 mmol) was added at −78 °C. The reaction mixture was allowed to reach room temperature and was stirred overnight. At this point, the reaction mixture was quenched with a saturated solution of NH_4Cl (40 mL) and diluted in ether (50 mL). The layers were separated, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to yield the crude alkenol. The crude product was purified by silica gel flash chromatography (12:1 hexane/EtOAc) providing 4.25 g (75%) of pure product. ^{1}H NMR ($CDCl_3$): δ 5.40 (dq, J = 11.0, 6.7 Hz, 1H), 5.23 (ddq, J = 11.0, 8.1, 1.6 Hz, 1H), 3.85 (dd, J = 12.2, 7.9 Hz, 1H), 3.63 (dd, J = 12.2, 5.3 Hz, 1H), 3.60 (ddd, J = 7.9, 5.3, 2.6 Hz, 1H), 3.50 (s, 3H), 3.27 (dd, J = 7.7, 4.4 Hz, 1H), 2.60 (m, 1H), 1.92 (m, 1H), 1.65 (dd, J = 6.7, 1.6 Hz, 3H), 1.05 (d, J = 6.4 Hz, 3H), 1.05 (21H), 0.99 (d, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 133.7 (CH), 122.9 (CH), 83.3 (CH), 80.0 (CH), 64.1(CH_2), 58.4 (CH_3), 36.1 (CH), 35.7 (CH), 17.9 (CH_3), 16.6 (CH_3), 13.0 (CH_3), 12.0 (CH_3), 11.8 (CH). IR (neat, cm^{-1}): ν 3500 (OH), 2940−2865 (CH), 1109, 1066 (C−O), 881 (Si−O), 680 (HC═CH). HRMS−FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{43}O_3Si$, 359.2981; found, 359.2978. Anal. Calcd for $C_{20}H_{42}O_3Si$: C, 66.98; H, 11.80. Found: C, 67.33; H, 11.60.

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Supporting Information Available: Experimental details, spectroscopic data, and copies of ^{1}H and ^{13}C NMR for all epoxide cleavage products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Beak, P.; Yamamoto, J.; Upton, C. J. *J. Org. Chem.* **1975**, *40*, 3052−3062.

(14) Epoxide **26** was prepared from epoxide **1** by the corresponding alkynyl alane methodology (refs 12a,b).