Synthetic Methods

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Diastereoselective Synthesis of Methylenecyclopropanes from Chiral Cyclopropene Derivatives**

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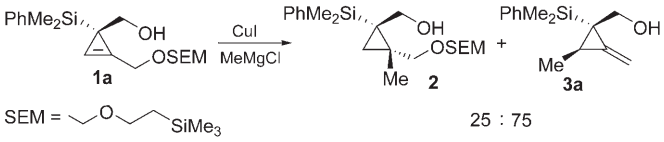
Described herein is a new method for the preparation of chiral methylenecyclopropanes from cyclopropene derivatives and Grignard reagents. Methylenecyclopropanes[1] have broad utility for the rapid generation of molecular complexity through a number of reactions that are enabled by their considerable strain energy (ca. 40 kcal mol^{-1}).[2] Of particular utility is the growing body of stereospecific transformations of methylenecyclopropanes.[1,3] A limitation for the chemistry of methylenecyclopropanes is that there are few preparations of enantiomerically enriched derivatives.[4] The utility of methylenecyclopropanes would be greatly enhanced by a common intermediate approach that provides access to a range of enantiomerically enriched derivatives. Herein, conditions for the selective synthesis of methylenepropanes from chiral cyclopropene precursors[5] are reported, thus providing access to diverse types of highly functionalized methylenecyclopropanes that possess chiral quaternary centers. The cyclopropene precursors are readily available in enantiomerically enriched form.[5b–d]

The discovery that Grignard reagents can convert cyclopropenes into methylenecyclopropanes was serendipitous and resulted from an attempt to use the directed cyclopropene carbometallation reaction to prepare **2** (Scheme 1).[6] Organ-



Scheme 1. Precedent for synthesis of methylenecyclopropanes.

ometallic and metal-hydride reagents normally add to 1-alkylcyclopropenes by introducing the nucleophile to the more substituted side of the multiple bond.[6] The unusual reversal of regioselectivity to produce **3a** suggested a pathway

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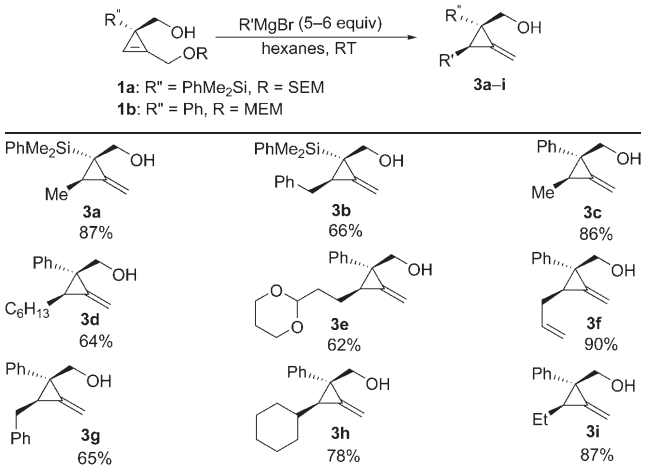
for the diastereoselective synthesis of functionalized methylenecyclopropanes.[7,8]

By following the result in Scheme 1, it was found that changing the Grignard counterion from chloride to bromide can alter the regioselectivity to favor exclusive formation of the methylenecyclopropane. Under the optimized conditions (Table 1), the directed reaction proceeded with excellent

Table 1: Synthesis of methylenecyclopropanes from chiral cyclopropenes.[a]

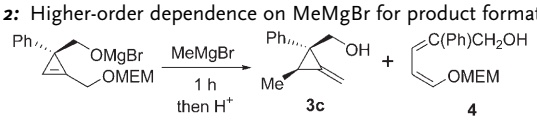


[a] All reactions gave a single isomer (d.r. > 95%) as determined by ^{1}H NMR spectroscopic analysis. Percentages represent yields of isolated product as the average of two runs.

regio- and diastereoselectivity. Methyl-, alkyl- (1° or 2°), allyl-, and benzylmagnesium halides were suitable nucleophiles, and the MEM and SEM ethers (MEM = methoxyethoxymethyl; SEM = 2-(trimethylsilyl)ethoxymethyl) proved to be superior to methyl ethers in terms of both regio- and diastereoselectivity.[9] In contrast to our previous system for cyclopropene carbometallation,[6a] CuI was not needed for the reactions to form methylenecyclopropanes. The precursors for this chemistry are readily available in enantiomerically enriched form. Thus, 3-hydroxymethylcyclopropenes **1a** and **1b** were prepared by a straightforward sequence of $[Rh_2(dosp)_4]$-catalyzed enantioselective cyclopropenation[5b] (70 and 82% *ee*, respectively) and reduction with DIBAL (dosp = (*N*-dodecylbenzenesulfonyl)prolinate; DIBAL = diisobutylaluminum hydride). Furthermore, it was demonstrated that **1b** could easily be resolved to enantiomeric purity by a method that we have described previously.[5d]

The dependence of selectivity on the counterion suggested that the reaction rates might have a higher-order dependence on the concentration of the Grignard reagent. Therefore, reactions of metalated **1b** with varying amounts of MeMgBr were studied (Table 2). Reactions were quenched after one hour (prior to completion). While detailed kinetic analysis was complicated by the heterogeneous nature of the reaction, it was clear that the reaction had a higher-order dependence on the concentration of the Grignard reagent. Only an isomeric diene side product **4** was observed in the reaction of metalated **1b** with a single equivalent of MeMgBr.

Table 2: Higher-order dependence on MeMgBr for product formation.[a]

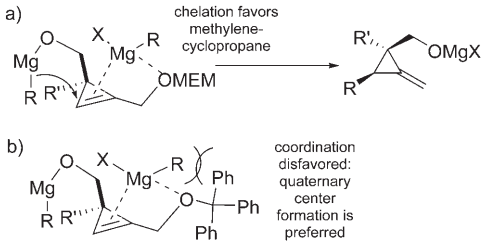


MeMgBr	Conversion [%]	Yield of **3c** [%]	Yield of **4** [%]
1 equiv	40	ca. 0	27
2 equiv	40	20	9
4 equiv	60	43	4

[a] Yields and conversions were measured by ^{1}H NMR spectroscopy; reactions were conducted at 23 °C and quenched after one hour (prior to completion).

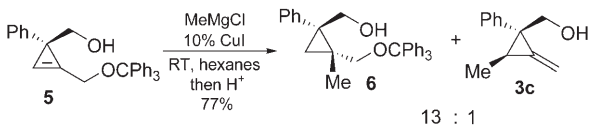
Allowing this reaction to continue overnight did not result in the formation of methylenecyclopropane **3c**. Although the mechanism of the isomerization is unclear at this point, the formation of the diene was suppressed and the yield of **3c** increased when the amount of MeMgBr was increased to two equivalents. The ratio of **3c**:**4** was further increased to 10:1 when the amount of MeMgBr was increased to four equivalents.

The results in Table 2 suggest that the magnesium center may serve a second role as a Lewis acid in the reactions of cyclopropenes with Grignard reagents. The addition of $MgBr_2$ did not have an effect on the rate of the reaction,[10] thus suggesting that an alkyl magnesium species serves as the Lewis acid. We hypothesized that coordination of the magnesium center by the MEM ether group influences the regioselectivity. For substrates that lack a coordinating oxygen atom (that is, 1-(*n*-alkyl)cyclopropenes), it is established that delivery of the nucleophile occurs at the more substituted carbon atom.[6b] Accordingly, it was speculated that a sterically demanding trityl ether group would disfavor metal coordination and restore the "normal" regioselectivity. A working hypothesis of the interactions leading to this difference is shown in Scheme 2. Although only two metal



Scheme 2. a) Plausible model for chelation-controlled nucleophilic delivery. b) Replacement of the MEM group by a trityl group is expected to prevent coordination and reverse regioselectivity.

centers are shown in Scheme 2, a mechanism that is higher-order with respect to concentration of magnesium cannot be ruled out. Regardless, the major roles for magnesium (nucleophilic delivery and Lewis acid activation) are conveyed by Scheme 2, which proves to be a useful and predictive model for chelation control of regioselectivity. Thus, efficient reversal of regioselectivity was observed when trityl ether **5** (Scheme 3) was used instead of the corresponding MEM ether **1b**. The best results were obtained when catalytic CuI



Scheme 3. Reversal of regioselectivity starting from trityl ether **5**.

was included, but the formation of **6** still predominated (4.5:1 ratio of **6**:**3c**) under conditions that were identical to those used to form **3c** from **1b** as described in Table 1.

In summary, general conditions were described for the regio- and diastereoselective synthesis of methylenecyclopropanes from common intermediate precursors. The reaction is counterion-dependent and requires more than one equivalent of Grignard reagent. These observations suggested a Lewis acidic role for the magnesium reagent. This hypothesis was subsequently used to design experiments that reverse the regioselectivity of the nucleophilic delivery. Efforts are currently being made to apply these reactions in target-directed synthesis.

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[8] There was a single example of palladium-catalyzed nucleophilic substitution on a cyclopropenyl methyl ester to give a methylenecyclopropane in 27% yield (as the minor regioisomer of the reaction); see: a) H. Nüske, S. Bräse, A. de Meijere, *Synlett* **2000**, 1467. Recently, a report appeared that describes the addition of soft nucleophiles to a chiral cyclopropene with a bromine atom at the allylic position. Complementary to the work reported here, the facial control in that work is determined by steric considerations; see: b) R. A. Weatherhead-Kloster, E. J. Corey, *Org. Lett.* **2006**, *8*, 171.

[9] The reaction of **1** (where R = Me, R′ = Ph; see Table 1) with MeMgBr still gave **3c** as the major product (ca. 55%), but with significant contamination by the diasteromeric product (ca. 15%) and two regioisomeric products (ca. 30%).

[10] A reaction was conducted that was similar to the second entry in Table 2, with the modification that four equivalents of $MgBr_2$ were added. After one hour, the reaction was quenched, and the yield of the corresponding methylenecyclopropane was measured to be 16% by analysis of the crude product by ^1H NMR spectroscopy.

