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Enantioselective, Facially Selective Carbomagnesation of Cyclopropenes

Xiaozhong Liu and Joseph M. Fox*

Brown Laboratories, Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

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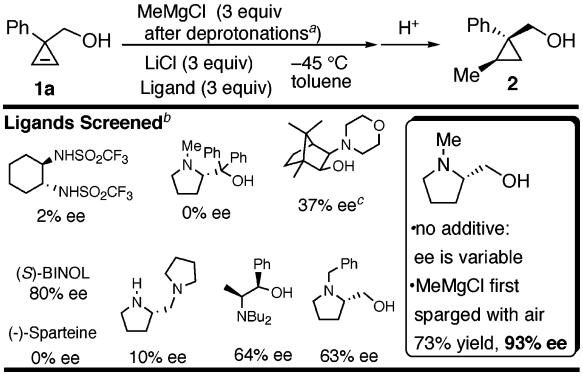
The ability to rapidly transform simple materials into complex molecules is at the core of medicinal research in academia and industry. Multicomponent transformations[1]—those that couple three or more reagents in a single reaction vessel—are especially important, and those that can produce single enantiomer compounds in a regio- and stereoselective manner have broad influence on combinatorial, high throughput, and traditional syntheses. In the context of our program to use the unusual reactivity of high-strain molecules to quickly generate stereochemical complexity and structural diversity,[2] we became attracted to the development of enantioselective carbometalation/electrophilic capture cascades of prochiral cyclopropenes **1**—compounds that can be prepared easily from diazocompounds and TMS acetylene.[3]

The carbometalation of cyclopropenes was first discovered in 1967,[4,5] and occurs more readily and with greater generality than the analogous reactions of unstrained alkenes.[6] An impressive body of work that deals with enantio- and diastereoselective addition reactions of cyclopropenone ketals has been developed in Nakamura's group.[7] We recently demonstrated that a wide range of Grignard reagents add to chiral 3-hydroxymethylcyclopropenes under Cu-catalyzed conditions.[2a] The significance of this work is strengthened by the emergence of general strategies for obtaining enantiomerically enriched cyclopropene carboxylic acids.[2b,c,8] Concurrent with our carbometalation work, Gevorgyan's group reported stereoselective hydro, sila-, and stannastannations of cyclopropenes,[9a] followed by more recent and very elegant catalytic enantioselective hydroborations[9b] and hydrostannations[9c] of cyclopropenes. Cyclopropanes are important synthetic intermediates,[10] and diastereoselective addition reactions of cyclopropenes constitute an attractive alternative to more mainstream routes to nonracemic cyclopropanes,[11] especially when highly functionalized molecules are required or if convergency of synthesis is a premium consideration.

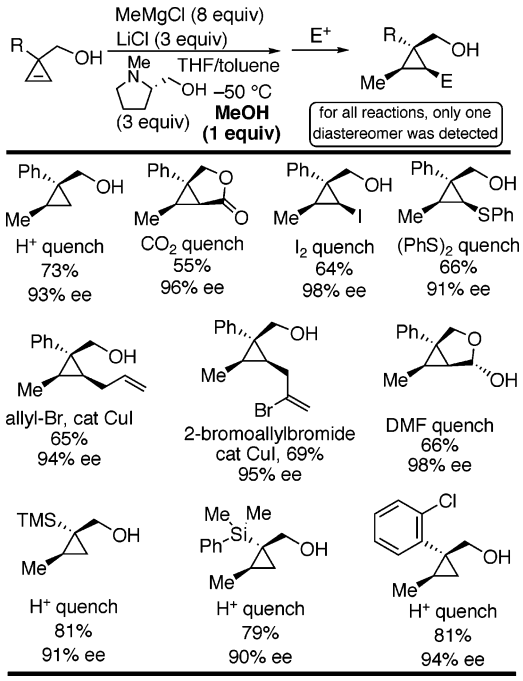
We began our study by showing that a variety of Grignard reagents can simply be combined with **1a** at room temperature to give racemic carbometalation products in high yield and excellent diastereoselectivity. Cyclopropene **1a** is sufficiently reactive so that CuI is not needed to catalyze the addition.[12] We then identified through screening efforts that inexpensive *N*-methylprolinol can induce high enantioselectivity for the addition of MeMgCl. Preequilibration of MeMgCl (7 equiv) with the chiral ligand (3 equiv) in toluene gives a complex that deprotonates and adds to **1a** to give **2** in good yield after aqueous quench (Scheme 1). However, different enantioselectivities were observed with different bottles of MeMgCl—"old" bottles gave the best results. Further studies showed that adventitious air has a beneficial effect. Thus, a solution of MeMgCl from a freshly opened container gave **2** in only 67−75% ee. However, if that same solution of MeMgCl was first sparged with air, the product **2** could reproducibly be obtained in 73% yield and 93% ee.

Scheme 1. Effect of Air on the Enantioselective Carbometalation



[a] Additional MeMgCl was added to deprotonate **1a** and the ligand. [b]For reactions with ligands other than *N*-methylprolinol, MeOH was included. [c]6 equiv of MeMgCl were used.

Table 1. Enantio- and Diastereoselective Cyclopropene Carbometalations



It is well-known that Grignard reagents rapidly reduce oxygen as shown in eq 1.[13a]

$$\mathrm{MeMgCl} \xrightarrow{O_2} \mathrm{MeOOMgCl} \xrightarrow{\mathrm{MeMgCl}} 2\ \mathrm{MeOMgCl} \qquad (1)$$

We therefore rationalized that the role of the oxygen is to produce methoxide, and subsequent experiments showed that an equivalent result could be obtained by replacing air with methanol.[13b,c] The optimized protocol is shown in Table 1. Significantly, the introduc-

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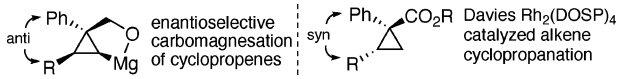


Figure 1. Complementary enantioselective syntheses of cyclopropanes.

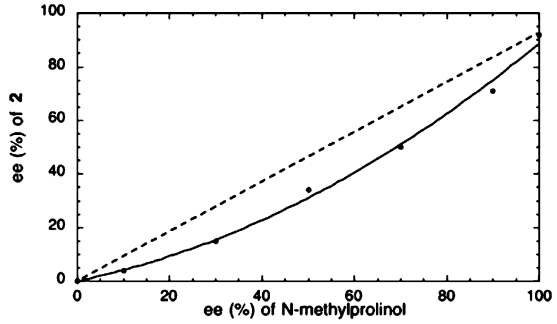
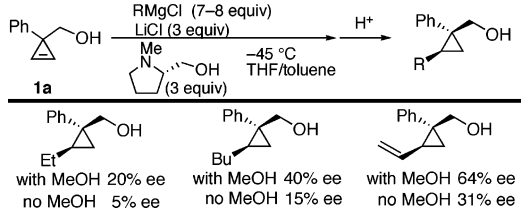


Figure 2. Nonlinear dependence of product ee on ligand ee.

Scheme 2. Enhancement of Enantioselectivity by MeOH Is General



tion of electrophiles creates all three stereocenters in high enantioselectivity for diverse types of tetrasubstituted cyclopropenes as shown in Table 1. Interestingly, we observed that the enantioselectivities differed slightly (and usually advantageously) when electrophiles other than proton are used to quench the reaction. We attribute this to slight kinetic differences in reactivity between the electrophiles toward the diasteromeric cyclopropylmetal/ligand adducts.[14] Also significant is that the reactions in Table 1 proceed with excellent diastereoselectivity that is complementary to the Davies enantioselective cyclopropanation[15] (Figure 1). The practical nature of the method is underscored by the straightforward synthesis of the cyclopropene starting materials and the use of an inexpensive chiral ligand [(*S*)-*N*-methylprolinol]. (*R*)-*N*-Methylprolinol is readily prepared in one step. Furthermore, the *N*-methylprolinol can be recovered in high yield (91%) at the completion of the reaction.

High enantioselectivities for the carbometalation reaction are obtained when the deprotonated ligand and MeMgCl are used in a 1:1 ratio (as measured after deprotonations) and in 3-fold excess. Reactions with smaller excess of the ligand/Grignard complex give products of lower ee. Thus, the reaction proceeds in only 79% ee when the ligand and Grignard reagent are in 2-fold excess, and further decreases to 45% ee when the ratio of deprotonated ligand/MeMgCl/substrate is 1.2:1.2:1. Furthermore, there is a negative nonlinear dependence[16] of ligand ee on the ee of **2**, as shown in Figure 2. Taken together, these observations imply the involvement of at least two chiral ligands in the enantioselectivity-determining step. It is plausible that separate ligand−metal complexes serve both as the nucleophilic delivery agent and as a Lewis acid activator for the cyclopropene.

While the studies reported here focus on the additions of MeMgCl to cyclopropenes, other Grignard reagents also add with high diastereoselectivity. Although the enantioselectivities of those reactions are moderate at this point (Scheme 2), the ability of methoxide to improve enantioselectivity is general. Future studies will further our mechanistic understanding so that we can improve the enantioselectivity under catalytic conditions and increase the range of nucleophiles that add to prochiral cyclopropenes with excellent enantioselectivity.

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Supporting Information Available: Full experimental and characterization details and ^{1}H and ^{13}C NMR spectra; X-ray data for stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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