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Directed Carbozincation Reactions of Cyclopropene Derivatives

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Directed carbometalation reactions of cyclopropenes are powerful reactions for the construction of functionalized cyclopropanes,[1] which are structures that have manifold applications in synthesis.[2] A number of effective carbomagnesiation procedures have been described in recent years,[3] but a limitation has been the reactivity of Grignard reagents toward many functional groups. Most conspicuous has been the intolerance toward the ester functions of cyclopropenes **1** that are available from transition-metal-catalyzed reactions of alkynes with α-diazo esters (Scheme 1).[4] Described herein are carbozincation reactions of cyclopropenes that are directed by ester or oxazolidinone substituents. This straightforward approach to cyclopropane synthesis proceeds with a stereochemical outcome that is complementary to that generally observed in catalytic cyclopropanation reactions of diazo compounds with alkenes.[5]

It is well-established that Cu complexes can catalyze the conjugate addition reactions of organozinc reagents, and mechanistic proposals have invoked the cooperative action of Cu and Zn (Scheme 2a).[6] As cycloprop-2-ene carboxylates are homologues of α,β-unsaturated carbonyl compounds, it was hypothesized that esters would direct the carbozincation of cyclopropenes by analogy (Scheme 2b).

Work by Gevorgyan, Rubin, and Orchin has established that esters can be used as syn-directing groups[7] in catalytic hydroboration reactions[7a] and hydroformylation reactions[7b–d] of cyclopropenes. Pioneering work by Negishi[8] and Nakamura[9] has established that allylzinc reagents add to cyclopropene derivatives. Nakamura has described an enantioselective Fe-catalyzed system for the addition of diorganozinc reagents to cyclopropenone ketals,[3c] and Richey has described additions of Et_2Zn to spiro[2.5]oct-1-enes.[10] However, facially selective carbozincations of cyclopropenes have been unknown to date.

From an optimization study directed toward the preparations of **3a**−**c**, it was determined that additions of diorganozinc reagents could be effectively catalyzed by a variety of Cu(I) salts (see the Supporting Information). CuI and CuCN were the most effective catalysts, leading to carbometalation products with excellent selectivity. Low conversions were observed and large excesses of organozinc reagents required for additions carried out in the absence of a catalyst. An exception was **4b**, which was formed in high yield with or without a catalyst. Solvent choice was an essential parameter: toluene was most effective, whereas the use of THF or diethyl ether led to carbometalation products with low diastereoselectivity. The reactions with Ph_2Zn were most effective in terms of reagent economy: **3c** was obtained in yields of 83 and 70% with 1.0 and 0.6 equiv of Ph_2Zn, respectively (Table 1). Larger amounts of Me_2Zn (4.0 equiv) and Et_2Zn (2.5 equiv) were required for optimal reactivity, as decreasing the amount of these organozinc reagents led to lower yields and increased formation of side products.

The carbozincation protocols were successfully applied to cyclopropenes **2a**−**d** to give cyclopropane products **3**−**6** in good yields with excellent

Scheme 1. Directed Carbozincation of Readily Available Cyclopropenes

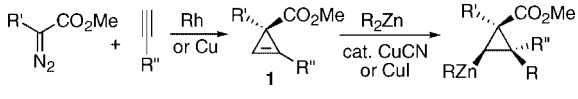
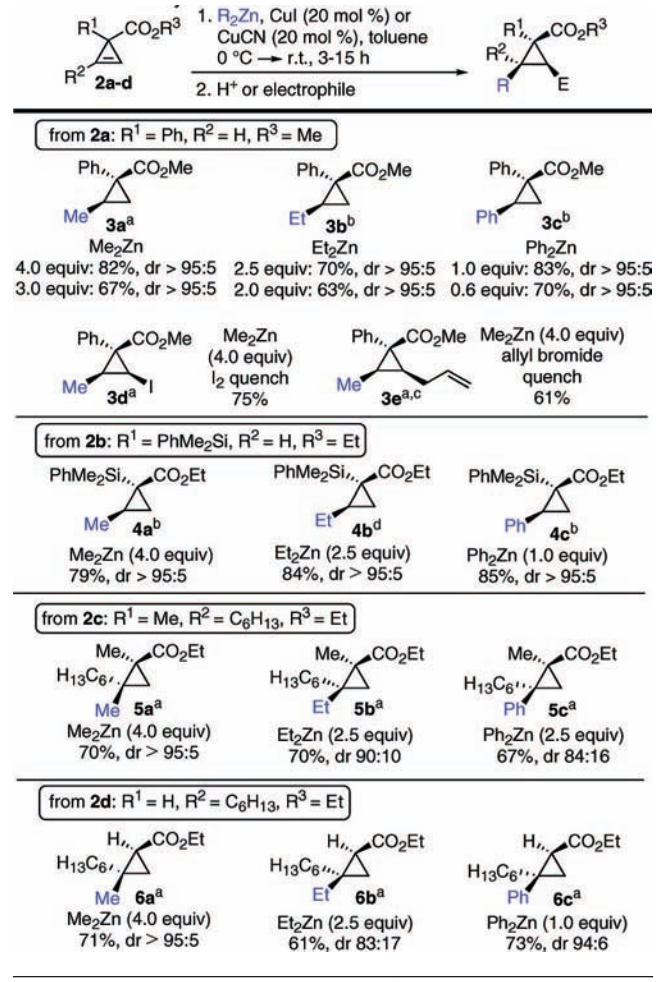
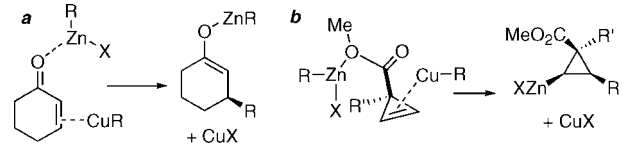


Table 1. Cu-Catalyzed Directed Carbozincation



[a] CuI (20 mol %) was used as the catalyst. [b] CuCN (20 mol %) was used as the catalyst. [c] LiCl (40 mol %) was added. [d] No catalyst was added.

Scheme 2. Scheme for Cu-Catalyzed (a) Conjugate Addition and (b) Directed Carbozincation Reactions of Cyclopropenes



diastereoselectivities (Table 1). Additions to 2-alkyl-substituted cyclopropene carboxylates **2c**−**d** also proceeded with excellent regioselectivity[11] to produce cyclopropanes **5a**−**c** and **6a**−**c** containing quaternary centers. Stereospecific reactions of cyclopropylzinc adducts from **2a** were successful[12] with I_2 and allyl bromide to give adducts **3d** and **3e**, respectively.

As only a limited number of dialkylzinc reagents are commercially available, in situ protocols for generating diorganozinc species[13] were

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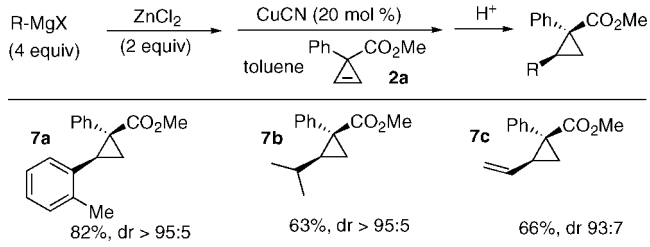
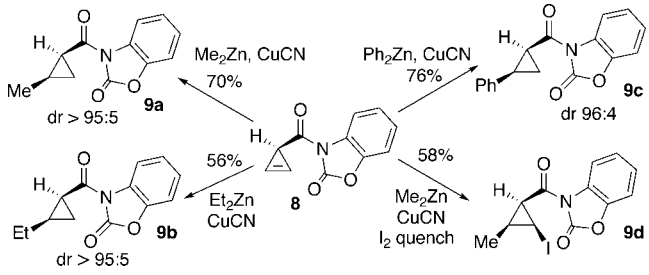
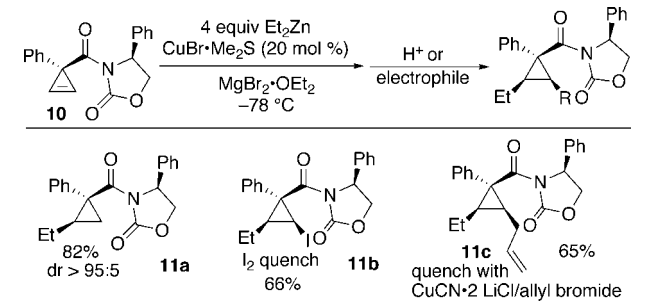
Table 2. Carbometallation with Diorganozinc Reagents Formed in Situ



Scheme 3. Oxazolidinone-Directed Carbozincation Reactions



Scheme 4. Chiral Auxiliary Control of Carbometallation by Et_2Zn



investigated. As shown in Table 2, $(o\text{-tolyl})_2Zn$, $i\text{-Pr}_2Zn$, and $(vinyl)_2Zn$ were prepared from the corresponding Grignard reagents and $ZnCl_2$. Carbozincation adducts were quenched with water to give products **7a**−**c** with >93:7 diastereoselectivity.

It was also demonstrated that acyloxazolidinone auxilaries can direct carbozincation reactions of cyclopropenes. This was particularly important for derivatives of the parent cycloprop-2-ene carboxylic acid, as ester derivatives of this acid are unstable.[14] However, oxazolidinone derivatives such as **8** are readily available and stable under long-term storage.[14] Carbometalation reactions of **8** proceeded with high diastereoselectivity to give adducts **9a**−**d** (Scheme 3).

Also investigated were additions of diorganozinc reagents to a chiral oxazolidinone derivative of 3-phenylcycloprop-2-ene carboxylic acid (Scheme 4). After optimization, it was found that the combination of $CuBr\cdot Me_2S$ and $MgBr_2\cdot OEt_2$ was selective for the addition of Et_2Zn to cyclopropene **10**. After an aqueous quench, **11a** was formed with >95% diastereoselectivity (4 diastereomers are possible). Capture by I_2 and allyl bromide provided **11b** and **11c**, respectively. Compound **11a** could be converted to the corresponding methyl ester in 60% yield by $Sm(OTf)_3$-mediated methanolysis (see the Supporting Information).

In summary, a diastereoselective procedure for the Cu-catalyzed addition of diorganozinc reagents to cyclopropene substrates has been developed. Ester and oxazolidinone functions direct the addition of a variety of nucleophiles with excellent facial selectivity. The regioselectivity is also high for carbozincation reactions of 2-alkyl-substituted cycloprop-2-ene carboxylate esters. The resulting cyclopropylzinc reagents can be captured via stereospecific reactions with electrophiles. The scope of the method is broadened by the ability to utilize organozinc reagents that have been generated in situ from Grignard reagents. Chiral oxazolidinone auxilaries are effective in controlling the diastereoselectivity of the carbometalation reactions.

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Supporting Information Available: Full experimental details, ^1H and ^{13}C NMR spectra, stereochemical assignments, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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