Published in final edited form as:

J Am Chem Soc. 2009 April 22; 131(15): 5382–5383. doi:10.1021/ja900949n.

Directed Carbozincation Reactions of Cyclopropene Derivatives

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Directed carbometallation reactions of cyclopropenes are powerful reactions for the construction of functionalized cyclopropanes¹—structures that have manifold applications in synthesis.² A number of effective carbomagnesation 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 homologs 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 groups⁷ in catalytic hydroboration reactions^{7a} and in hydroformylation^{7b-d} reactions of cyclopropenes. Pioneering work by Negishi⁸ and Nakamura⁹ 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 Et₂Zn to spiro[2.5]oct-1-enes.¹⁰ However, facially selective carbozincations of cyclopropenes were unknown.

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 Supporting Information). CuI and CuCN were the most effective catalysts, and led to carbometallation products with excellent selectivity. Low conversions were observed and large excesses of organozinc reagents were 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 lead to carbometallation products with low diastereoselectivity. The reactions with Ph₂Zn were most effective in terms of reagent economy: **3c** was obtained in 83% and 70% yields with 1.0 equiv and 0.6 equiv of Ph₂Zn, respectively (Table 1). Larger amounts of Me₂Zn (4.0 equiv) and Et₂Zn (2.5 equiv) were required for optimal reactivity, as decreasing the amount of these organozinc reagents led to lower yields and increased side product formation.

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Supporting Information Available: Full experimental details and ¹H, ¹³C NMR spectra are provided, and Stereochemical assignments are described. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The carbozincation protocols were successfully applied to cyclopropenes **2a-d** to give cyclopropane products **3-6** in good yields and excellent diastereoselectivities (Table 1). Additions to 2-alkylsubstituted cyclopropene carboxylates **2c-d** also proceeded with excellent regioselectivity¹¹ to produce quaternary-center-containing cyclopropanes **5a-c** and **6a-c**. Stereospecific reactions of cyclopropylzinc adducts from **2a** were successful¹² with I₂ or allyl bromide to give adducts **3d-e**.

As only a limited number of dialkylzinc reagents are commercially available, *in situ* protocols for generating diorganozinc species¹³ were investigated. As shown in Table 2, (*o*-tolyl)₂Zn, *i*-Pr₂Zn, and vinyl₂Zn were prepared from the corresponding Grignard reagents and ZnCl₂. Carbozincation adducts were quenched with water to give products **7a-7c** with >93:7 diastereoselectivity.

It was also demonstrated that acyloxazolidinone auxiliaries 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 to longterm storage.¹⁴ Carbometallation reactions of **8** proceed 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•Me₂S and MgBr₂•OEt₂ was selective for the addition of Et₂Zn to cyclopropene **10**. After aqueous quench, **11a** is formed with >95% diastereoselectivity (4 diastereomers are possible). Capture by I₂ 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 Supporting Information).

In summary, a diastereoselective procedure has been developed for the Cu-catalyzed addition of diorganozinc reagents to cyclopropene substrates. 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 auxiliaries are effective in controlling the diastereoselectivity of carbometallation reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIH grant GM068640. We thank Glenn P. A. Yap for crystallography.

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Scheme 1.

Directed carbozincation of readily available cyclopropenes

Scheme 3.
Oxazolidinone directed carbozincation reactions

Scheme 4.
Chiral auxiliary control of carbometallation by Et_2Zn

Table 1
Cu-catalyzed directed carbocyclization

$\begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{R}^2 \end{array} \begin{array}{c} \text{CO}_2\text{R}^3 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{R}^3 \end{array} \quad \xrightarrow[2. \text{H}^+ \text{ or electrophile}]{1. \text{R}_2\text{Zn, CuI (20 mol \%)} \text{ or } \text{CuCN (20 mol \%)}, \text{toluene}, 0^\circ\text{C} \rightarrow \text{r.t.}, 3\text{--}15 \text{ h}} \quad \begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{R}^2 \end{array} \begin{array}{c} \text{CO}_2\text{R}^3 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{E} \end{array}$		
from 2a : R ¹ = Ph, R ² = H, R ³ = Me
Me ₂ Zn	Et ₂ Zn	Ph ₂ Zn
4.0 equiv: 82%, dr > 95:5 3.0 equiv: 67%, dr > 95:5	2.5 equiv: 70%, dr > 95:5 2.0 equiv: 63%, dr > 95:5	1.0 equiv: 83%, dr > 95:5 0.6 equiv: 70%, dr > 95:5
Me ₂ Zn (4.0 equiv) I ₂ quench 75%	Me ₂ Zn (4.0 equiv) allyl bromide quench 61%	
from 2b : R ¹ = PhMe ₂ Si, R ² = H, R ³ = Et
Me ₂ Zn (4.0 equiv) 79%, dr > 95:5	Et ₂ Zn (2.5 equiv) 84%, dr > 95:5	Ph ₂ Zn (1.0 equiv) 85%, dr > 95:5
from 2c : R ¹ = Me, R ² = C ₆ H ₁₃ , R ³ = Et
Me ₂ Zn (4.0 equiv) 70%, dr > 95:5	Et ₂ Zn (2.5 equiv) 70%, dr 90:10	Ph ₂ Zn (2.5 equiv) 67%, dr 84:16
from 2d : R ¹ = H, R ² = C ₆ H ₁₃ , R ³ = Et
Me ₂ Zn (4.0 equiv) 71%, dr > 95:5	Et ₂ Zn (2.5 equiv) 61%, dr 83:17	Ph ₂ Zn (1.0 equiv) 73%, dr 94:6
^a CuI (20 mol %) was the catalyst. ^b CuCN (20 mol %) was the catalyst. ^c LiCl (40 mol %) was added. ^d No catalyst was added.		

Table 2
Carbometallation with diorganozinc reagents formed *in situ*