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A Copper-Catalyzed Method for the Facially Selective Addition of Grignard Reagents to Cyclopropenes

Lian-an Liao and Joseph M. Fox*

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

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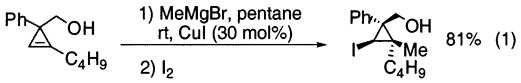
We describe here a general Cu-catalyzed procedure for adding alkyl, alkenyl, and alkynyl Grignard reagents to 3-hydroxymethyl cyclopropenes to directly form stereodefined quaternary centers. We further show that the cyclopropylmetals can be captured with a variety of electrophiles to yield usefully functionalized cyclopropanes (e.g., eq 1).



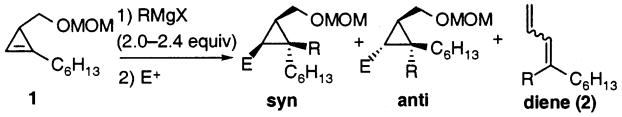
81% (1)

Reactions that produce functionalized cyclopropanes are important tools for the synthetic organic chemist. While cyclopropanes are attractive targets in their own right because they are structural components of many biologically relevant materials,[1] the cyclopropyl group also finds considerable application in the synthesis of complex carbon frameworks.[2] Of particular interest are constructions of five-,[3] six-,[4] and seven[5,6]-membered ring systems by rearrangements of alkenylcyclopropanes—reactions that are noteworthy for their ability to efficiently transfer the relative and absolute stereochemistry of the starting material to the product. The state of the art in cyclopropane synthesis includes a spectrum of highly effective enantioselective protocols;[7] however, intense research efforts are still focused on fundamental issues such as syn/anti selectivity,[7] alkylidenation,[8] and formation of 1,2,3-trisubstituted cyclopropanes.[7] In short, selective and complementary methods for the synthesis of cyclopropanes are still needed so that a greater degree of steric hindrance can be tolerated and a broader range of functional groups introduced. It was in this context that we became interested in the additions of carbanions to cyclopropenes.[9] Addition reactions of Grignard, zinc, and cuprate reagents proceed by a mode of cis-addition, and the resulting cyclopropyl carbanions are configurationally stable.[9] When the double bond of the cyclopropene is substituted with an alkyl group, the reactions are regioselective and produce a quaternary stereocenter.[9] Of particular note is an elegant series of papers by Nakamura on the enantio- and diastereoselective addition reactions of cyclopropenone ketals.[10]

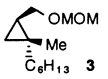
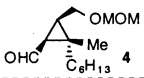
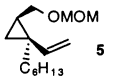
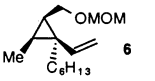
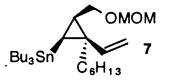
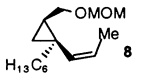
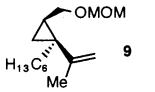
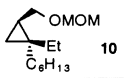
In stark contrast to the relatively large body of literature that concerns nucleophilic addition reactions of symmetrical cyclopropenes,[9,10] there are only four reports that describe facially selective additions to cyclopropenes.[11] The seminal work by Richey and Bension showed that a hydroxymethyl group at the 3-position of the cyclopropene can direct the addition of allyl Grignard reagents to the syn-face in moderate yield.[11a] However, the authors found that the additions of benzyl, cyclopropyl, *tert*-butyl, and methylmagnesium halides failed. Although more recent work by Araki expands the scope of cyclopropene allylations,[11c,d] precedent for facially selective additions of other types of carbanions is limited to a single, low yielding example.[11b]

* To whom correspondence should be addressed. E-mail: jmfox@udel.edu.

Table 1. Addition of Grignard Reagents to MOM-Protected Cyclopropene **1**



1 syn anti diene (2)

Entry	X	R	conditions	syn/anti[a]	diene[b]	yield[c]	major product
uncatalyzed							
1	Cl	Me	pentane, –20 °C 2 h; then H+	95/5	1	75%	 **3**
2	Cl	Me	pentane, –20 °C 2 h; then DMF	95/5	1	63%[e]	 **4**
Reactions with added Cu(I) in pentane at –20 °C							
3	Cl Br	Me	CuCl (10 mol%) 1 h; then H+	96/4	–	85% (from Cl) 86% (from Br)	**3**
4	Br	Me	CuCl (10 mol%) 1 h; then DMF	95/5	–	67%[e]	**4**
5	Br		CuI (30 mol%) 1 h; then H+	96/4	–	81%	 **5**
6	Br		CuI (30 mol%) 1 h; then MeI	97/3	–	83%	 **6**
7	Br		CuI (30 mol%) 1 h; then ClSnBu3	nd[f]	–	77%	 **7**
8	Br	 Me	CuI (30 mol%) 1.5 h (–40 °C); then H+	>96/4	–	81%[e]	 **8**
9	Br	Me	CuI (30 mol%) 1 h (rt); then H+	75/25	–	67%	 **9**
10	Cl	Et	CuCl (30 mol%)	47/52	–	nd[f]	 **10**
			CuI (30 mol%)	41/59	–	nd[f]	

[a] Syn/anti ratios determined by GC. [b] Yield of diene as judged by GC. [c] Isolated yield of the syn/anti mixture unless stated otherwise. Yields are the average of two runs. [d] Conversion of starting material as judged by GC. [e] Isolated as a single isomer. [f] Not determined.

We began our studies by protecting a 3-hydroxymethyl cyclopropene as a MOM ether, hypothesizing that this known directing group could deliver the Grignard reagent to the syn-face of the cyclopropene.[12] However, our initial attempts to develop standard conditions for adding Grignard reagents to cyclopropene **1** were complicated by low conversion, poor selectivity, and rearrangement to diene **2**. After further work, we found that diene formation could be suppressed for the addition of MeMgCl at −20 °C; the reaction is fastest and syn-selectivity is highest (95:5) when pentane is used instead of ethereal solvent. Aqueous quench gave **3** and reaction

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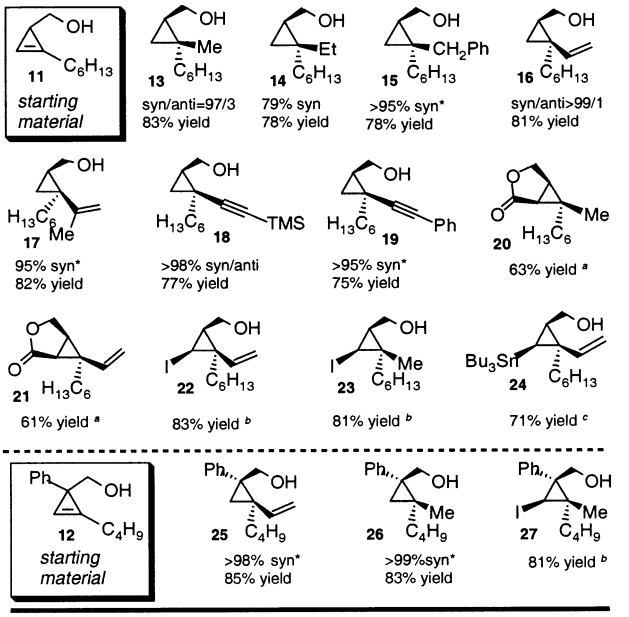
Table 2. Cu-Catalyzed Additions to 3-Hydroxymethylcyclopropenes[a]



[a] General protocol: RMgX (3−4 equiv; 7 equiv for **15**) was added to a suspension of CuI (10−30 mol %) in hydroxymethylcyclopropene/pentane (0.05 M). The mixture was stirred at room temperature for 1 h and quenched with water or (a) CO_2, then H^+, (b) I_2, (c) Bu_3SnCl. Yields are the average of two runs. Syn/anti ratios were assigned when the dr was established by independent synthesis. Otherwise (examples marked by *), %syn represents the lower limit based on analysis of the crude material and the purity (by ^1H NMR, GC) of the isolated material.

with DMF gave **4** in 75 and 63% yields, respectively. While the addition of vinylmagnesium chloride to **1** proceeds in poor yield without a catalyst, the vinyl adducts **5**−**7** can be obtained with excellent control of diastereoselectivity by inclusion of Cu(I). Although cuprates were known to add to cyclopropenes,[9] these examples are the first that employ a Cu-catalyst. While MeMgBr does not add cleanly to **1** without Cu, it adds with an efficiency that is comparable to MeMgCl with 10 mol % CuCl. *cis*-Propen-1-ylmagnesium bromide adds to **1** with high selectivity and in good yield (>96% syn, 82% yield). However, the effect of a geminal methyl group is deleterious (Table 1, entry 9), and the addition of EtMgCl is unselective (Table 1, entry 10).

To simplify and expand the scope of the above methodology, we examined other directing groups. While we did not meet success by replacing MOM with MEM or 2-pyridyl, deleting the MOM group altogether was remarkably effective. As shown in Table 2, very high diastereoselectivity (syn/anti ≥ 95/5) was observed for a variety of alkyl, alkenyl, and alkynyl Grignard reagents. The following details of the results in Table 2 are also noteworthy: (1) The starting materials **11** and **12** are readily prepared in quantity using a Rh-catalyzed reaction of the appropriate diazoester and alkyne.[13] (2) The reactions that yield compounds **18** and **19** are the first examples of acetylide addition to cyclopropenes. (3) Substrate **12** was transformed into products with two chiral quaternary carbons. Although we have not yet fully examined the scope of the reaction with respect to the C-1 substituents of cyclopropenes, we have found that Cu-catalyzed additions to 1,3-diphenyl-3-hydroxymethylcyclopropene proceed with high syn-selectivity but poor regioselectivity. Efforts to improve the regioselectivity of additions to 1-arylcyclopropenes are in place.

The simplicity and versatility of the methods presented here make 3-hydroxymethylcyclopropenes extremely powerful chirons for the assembly of highly functionalized cyclopropanes with chiral quaternary centers, and our results highlight the significance of Doyle and Muller's protocol for catalytic asymmetric cyclopropenation.[14] Goals of future studies will be to improve catalyst turnover numbers, to expand enantioselective preparations and reactions of cyclopropenes, and to broaden the scope and applications for their diastereoselective addition reactions.

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Supporting Information Available: Full experimental and characterization details, ^1H, ^{13}C NMR spectra, and gas chromatograms (if applicable). Assignments of relative stereochemistry are detailed (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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