Letter

Copper(I)-Catalyzed Carbometalation of Nonfunctionalized Cyclopropenes Using Organozinc and Grignard Reagents

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Abstract A highly efficient method was developed for the copper(I)catalyzed carbometalation of various nonfunctionalized and functionalized cyclopropenes. Electrophilic trapping of the cyclopropylmetal intermediates gave multifunctionalized cyclopropanes.

Key words alkenes, catalysis, copper, magnesium, metalation, nucleophilic additions, organometallic reagents, zinc

The development of synthetic approaches to multifunctionalized cyclopropanes is a challenging task in organic chemistry. Nevertheless, because the multifunctional cyclopropane framework is found in various medicines and natural products,¹ many examples of syntheses of cyclopropanes have been reported in the literature. These involve Simmons-Smith cyclopropanation,² cyclopropanation of diazo compounds with a rhodium,³ ruthenium,⁴ cobalt,⁵ silver,⁶ or iron catalysts,⁷ or addition of ylides to carbonyl compounds.⁸ The carbometalation reaction of cyclopropenes is an efficient approach⁹ that has been extensively developed by Fox¹⁰ and Marek¹¹ and their respective coworkers. In these reports, coordination to a copper center of a hydroxy or ester group attached to a cyclopropene skeleton was shown to be essential for high reactivity and stereoselectivity. In contrast, a few methods have been reported for carbometalation of 3,3-dialkylcyclopropenes with no additional functional groups. In 2011, Lautens and coworkers reported an enantioselective palladium-catalyzed carbozincation of cyclopropenes;^{12–14} however, the use of a fluorene derivative as a nonfunctionalized cyclopropene was required to obtain a high yield of the desired product. Therefore, the limited structural versatility available demands the development of new and efficient catalysts for the carbometalation of cyclopropenes.

We previously reported a tandem reaction using cyclopropene, organozinc reagents, and a hydrazone or carbonyl compound.¹⁵ The reaction may take place through carbozincation of the cyclopropene to generate a cyclopropylzinc intermediate, ring opening of which gives an allylzinc intermediate in situ.¹⁶ However, cyclopropanes, other than cyclopropenone acetal showed low reactivities [Scheme 1 (a)]. We therefore examined the generation of cyclopropylzinc intermediates through carbozincation of various cyclopropenes for subsequent ring opening to give allylzinc intermediates. Here, we describe the efficient copper-catalyzed carbometalation of nonfunctionalized cyclopropenes by using organozinc or Grignard reagents [Scheme 1 (b)].



Scheme 1 Reaction of cyclopropenes with organometallic reagents

The reaction conditions were optimized by using 3,3-diphenylcyclopropene (**1a**) as a substrate (Table 1). We found that the reaction of **1a** with diethylzinc (3 equiv) in the presence of copper(I) iodide (20 mol%) and ligand **L1** (25 mol%; Figure 1) promoted carbozincation to give the de-



Figure 1 List of ligands

sired product **2a-Et** in high yield (Table 1, entry 1). In the absence of the copper catalyst or ligand, **2a-Et** was obtained in a low yield (entries 2 and 3). With other ligands, such as **L2**, **L3**, or *N*,*N*',*N*'-tetramethylethylenediamine, product **2a-Et** was obtained in good yield (entries 4–6). Further optimization of the reaction conditions (entries 7–10) showed that the use of copper(I) iodide (5 mol%), diethylzinc (2 equiv), and ligand **L1** (7.5 mol%) gave the desired product **2a-Et** in 86% yield (entry 9). When the Grignard reagent ethylmagnesium bromide was used instead of diethylzinc in the presence of copper(I) iodide and ligand **L1**, product **2a-Et** was obtained in high yield (entries 11 and 12). Therefore, the catalyst system is suitable for use with both organozinc and Grignard reagents.

Table 1 Optimization of the Reaction Conditions

	Ph、 ,Ph	Cul Et ₂ Zn or EtMgi ligand	Br Ph Ph	
	1a	toluene, r.t. 16 h	→ △ 2a-Et	t
Entry	Cul (mol%)	Et ₂ Zn (equiv)	Ligand (mol%)	Yield (%)
1	20	3.0	L1 (25)	91
2	-	1.5	L1 (25)	ND^{a}
3	20	3.0	-	<30
4	20	3.0	L2 (25)	87
5	20	3.0	L3 (25)	73
6	20	3.0	TMEDA (25)	77
7	10	3.0	L1 (15)	85
8	5	3.0	L1 (7.5)	89
9	5	2.0	L1 (7.5)	86
10	1	2.0	L1 (3)	<40
11	5	2.0 ^b	-	56
17	5	2 0b	11 (7 5)	81

^a ND = not detected.

^b EtMgBr was used instead of Et₂Zn.

Using the optimized reaction conditions, we performed carbometalation of 3,3-diphenylcyclopropene (**1a**) with various organometallic reagents (Table 2). Whereas diethylzinc gave the desired product in high yield (entry 1), diisopropylzinc gave a poor yield of the corresponding product 2a-i-Pr; isopropylmagnesium chloride, however, gave a high yield of **2a-i-Pr** (entry 2). On the other hand, cyclopropylzinc bromide gave the corresponding product **2a-c-Pr** in high yield (entry 3). When butyl- or allylmagnesium bromide was used, the corresponding products 2a-n-Bu and 2a-Allyl were obtained in high yields (entries 4 and 6). On the other hand, bulky tert-butyl and isopropenyl magnesium bromides did not give any of the corresponding products (entries 5 and 7). Benzyl- and phenylmagnesium bromide can also be used in this reaction (entries 8 and 9). Next, we examined the reactions of several 3,3-dialkylcyclopropenes. When 3.3-diarylcyclopropenes **1b-d** (Figure 2) bearing an electron-donating or electron-withdrawing group on the benzene ring were used, the corresponding products **2b**-**d** were obtained in high vields (entries 10-12). The spirocyclopropene 1e also gave the desired product 2e in high yield (entry 13). Furthermore, the cyclopropenedicarboxylate 1f gave the desired product 2f in good yield (entry 14).

Table 2 Scope of Substrates

	R ¹ <u>4</u> 1a	$\underline{\underline{X}}^{R^1}$	Cul (5 mol%) R ² M (2.0 equiv) L1 (7.5 mol%) toluene, r.t. 16 h	$\rightarrow \begin{array}{c} R^{1} \\ R^{2} \\ R^{2} \end{array}$	2
Entry	1	Reagent		Product	Yield (%)
1	1a	Et ₂ Zn		2a-Et	86
2	1a	<i>i</i> -PrMgBr		2a- <i>i-</i> Pr	81
3	1a	c-PrZnBr		2a-c-Pr	88
4	1a	BuMgBr		2a-Bu	84
5	1a	t-BuMgBr		-	ND^{a}
6	1a	AllylMgBr		2a-Allyl	85
7	1a	CH ₂ =C(Me)MgBr		-	ND
8	1a	BnMgBr		2a-Bn	77
9	1a	PhMgBr		2a-Ph	93
10	1b	Et ₂ Zn		2b	73
11	1c	Et ₂ Zn		2c	82
12	1d	Et ₂ 2	Zn	2d	98
13	1e	PhMgBr		2e	91
14	1f	Et ₂ Zn		2f	68

^a ND = not detected; unidentified products were obtained.

We also examined the electrophilic trapping of the cyclopropylzinc intermediate **A** (Scheme 2).¹⁷ The reaction using diiodine or allyl bromide after carbozincation of **1a** gave the corresponding multifunctionalized cyclopropanes **3a-Et-I** and **3a-Et-Allyl** in moderate to high yields. When ethylmagnesium bromide was used instead of diethylzinc, the electrophilic trapping reaction proceeded more smoothly T. Nakano et al.



to give **3a-Et-I** and **3a-Et-Allyl**, respectively, in high yields. Furthermore, **3a-Et-Bz** was obtained in high yield by using benzoyl chloride.



We previously reported the allylation of benzaldehyde with an allylzinc intermediate derived from dialkylzinc reagents and a cyclopropene (Scheme 3).^{15a} The carbozinca-

tion and subsequent C-C bond cleavage seem to be essential for allylzincation.¹⁶ We hypothesized that cyclopropylzinc intermediates generated by copper-catalyzed carbozincation participate in the allylzincation of aldehydes in the presence of an appropriate catalyst. However, the desired allylation of benzaldehyde did not proceed, and only the ethyl adduct 2g was observed on TLC analysis, even in the presence of a stoichiometric amount of L1 (Scheme 4).^{18,19} The electrophilic trapping of cyclopropylmetal intermediates by using a Grignard reagent and benzoyl chloride gave the desired product **5a** and **5b**, whereas reactions using other electrophiles with diethylzinc gave complicated mixtures (Table 3).²⁰ These results suggest that the ring opening of cyclopropene might not proceed through carbozincation of the cyclopropenes to generate allylmetal intermediates. Further studies will be required to elucidate the mechanism of the generation of allylmetal intermediates derived from cyclopropenes.



	R Ph - 1g (R = Me) 1h (R = <i>i</i> -Pr)	Cul (5 mol%) Et–M (2.0 equiv) L1 (7.5 mol%) toluene, r.t. 6 h Cul (2 equiv) E–X (3 equiv)						
				R	Ph			
		rt 15 h						
		1, 10 11		E	Et			
				5a (R = Me) 5b (R = <i>i</i> -Pr)				
				(,			
Entry	Substrate	Μ	EX	Product	Yield (%)			
1	1g	ZnEt	I ₂	-	ND ^a			
2	1g	ZnEt	AllylBr	-	ND			
3	1g	ZnEt	BzCl	-	ND			
4	1g	MgBr	I_2	-	ND			
5	1g	MgBr	AllylBr	-	ND			
6	1g	MgBr	BzCl	5a	60 (dr 6:1)			
7	1h	MgBr	BzCl	5b	39 (dr 3:1)			

^a ND = not detected; unidentified products were obtained.

In summary, we have developed a copper(I) iodide and hydrazone amide catalyzed carbometalation of cyclopropenes. The present carbometalation does not require functionalized substrates or expensive transition-metal catalysts. Various organometallic reagents and cyclopropenes can be used in this reaction for the synthesis of multifunctional cyclopropanes. The reaction with additional electrophiles after the carbometalation reaction of cyclopropenes gave the corresponding multifunctional cyclopropanes

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without the generation of a ring-opening product that we reported previously.¹⁴ Further studies with cyclopropenes and organometallic reagents are in progress.



Scheme 4 Reaction of cyclopropylzinc intermediate with benzaldehyde

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379959.

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- (17) Carbozincation and Subsequent Trapping; Typical Procedures

1,1'-(2-Ethylcyclopropane-1,1-diyl)dibenzene (2a-Et); Typical Procedure

A 1.0 M solution of Et_2Zn in toluene (0.6 mL) was added to a solution of Cul (2.9 mg, 0.015 mmol) in toluene (1.5 mL) at r.t., and the mixture was stirred for 30 min. L1 (5.4 mg, 0.023 mmol) and 3,3-diphenylcyclopropene (1a; 57.7 mg, 0.3 mmol) were added at r.t., and the mixture was stirred for 16 h. The reaction was quenched with sat. aq NH₄Cl (2 mL), and the aqueous layer was separated and extracted with EtOAc (3 × 3 mL).

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The organic layers were combined, dried (Na_2SO_4) , concentrated, and purified by column chromatography (silica gel, hexane) to give a colorless oil; yield: 57.2 mg (86%).

1,1'-(2-Ethyl-3-iodocyclopropane-1,1-diyl)dibenzene (3a-Etl); Typical Procedure

A 1.0 M soln of Et_2Zn in toluene (0.6 mL) was added to a solution of Cul (2.9 mg, 0.015 mmol) in toluene (1.5 mL) at r.t. and the mixture was stirred for 30 min. L1 (5.4 mg, 0.023 mmol) and 3,3-diphenylcyclopropene (1a; 57.7 mg, 0.3 mmol) were added at r.t. and the mixture was stirred for 6 h. Cul (116 mg, 0.6 mmol) and a solution of I_2 (228 mg, 0.9 mmol) in CH₂Cl₂ (1.5 mL) were then added, and the mixture was stirred for addi-

tional 15 h at 60 °C. The reaction was quenched with sat. aq NH₄Cl (3 mL), and the aqueous layer was separated and extracted with EtOAc (5×3 mL). The organic layers were combined, dried (Na₂SO₄), concentrated, and purified by column chromatography (silica gel, hexane) to give a colorless oil; yield 95.6 mg (86%).

- (18) Spontaneous decomposition of product **2g** occurred under neutral, acidic, or basic conditions; the reason is unclear.
- (19) When cyclopropene **1f** was used as a substrate, ring opening of the cyclopropylzinc intermediate also did not occur.
- (20) The relative configuration of products **5a** and **5b** could not be determined; see the Supporting Information.

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