

Enantioselective Palladium-Catalyzed
Carbozincation of Cyclopropenes

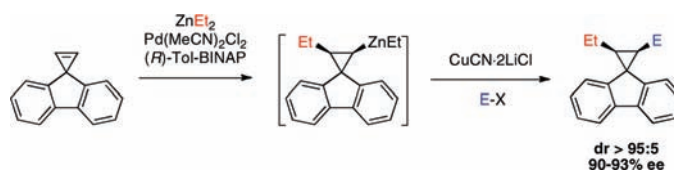
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ABSTRACT



A highly enantioselective palladium-catalyzed carbozincation of cyclopropenes has been developed. The intermediate cyclopropylzinc species, after transmetalation with copper, were trapped with various electrophiles. This one-pot procedure furnished functionalized cyclopropenes with excellent diastereo- and enantioselectivity.

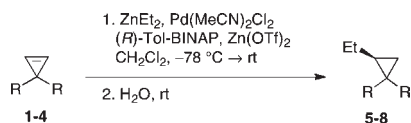
Functionalized cyclopropanes are highly attractive targets in organic synthesis because they are structural components of many biologically relevant materials.^{1,2} Asymmetric transition-metal catalyzed additions to the double bond of cyclopropenes are powerful reactions for the construction of such cyclopropanes since desymmetrization leads to multiple stereocenters in one step. In the past few years, several new catalytic asymmetric addition reactions to cyclopropenes have been developed.³

In the early 2000s, Gevorgyan reported on highly stereo- and regioselective transition-metal catalyzed hydrometala-

tion reactions such as hydroboration,⁴ -stannation,^{5,6} -silylation, and -germylation.⁶ More recently rhodium-catalyzed hydroformylation⁷ and hydroacylation⁸ reactions of cyclopropenes were described. Palladium-catalyzed additions to cyclopropenes such as hydrophosphorination, hydrophosphinylation⁹ and the addition of alkynes have appeared.¹⁰ Carbometalation, on the other hand, offers the possibility to directly functionalize two carbon atoms in a single pot. In 2000 Nakamura has shown an enantioselective iron-catalyzed system for the addition of diorganozinc reagents to cyclopropenone ketals.¹¹ Later Fox reported a directed carbomagnesation of hydroxymethylcyclopropenes in the presence of copper catalysts.¹² Marek

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Table 1. Enantioselective Pd-Catalyzed Carbozincation

entry	cyclopropene	R	product	yield, % ^a	ee, %
1	1		5a	99	91
2	2a	CH ₂ OBn	6a	48	41
3	2b	CH ₂ OBz	6b	59	74
4	2c	CH ₂ OTBS	6c	98	68
5	2d	CH ₂ OTBDPS	6d	86	59
6	3	Ph	7	20	nd ^b
7	4	COOEt	8	0	--

^a Isolated yields. ^b Not determined.

demonstrated a copper-catalyzed carbomagnesation reaction of chiral cyclopropenylcarbinol derivatives.¹³ Recently a copper-catalyzed facially selective carbozincation of cyclopropenes was reported.¹⁴ Noteworthy in this connection are as well the dimetalation reactions of cyclopropenes described by Gevorgyan.^{5b,6} However, there are few asymmetric carbozincation reactions.^{11,14} Herein, we report an efficient approach to highly functionalized cyclopropanes by enantio- and diastereoselective palladium-catalyzed carbozincation of cyclopropenes and stereospecific transformation of the cyclopropylzinc intermediates.

Stimulated by our longstanding interest in the addition of organometallic reagents to strained alkenes,^{15,16} we initiated our studies with 3,3-disubstituted cyclopropene **1** and ZnEt₂ in CH₂Cl₂ in the presence of Pd(dppb)Cl₂.¹⁷ Under these reaction conditions, the carbometalation was found to proceed at low temperature. The choice of solvent proved to be crucial. While the reaction occurred in CH₂Cl₂ with cosolvents such as diethyl ether or pentane, the use of more coordinating solvents such as THF or NMP inhibited catalysis.¹⁸ We noticed variability in our reactions, but the addition of Zn(OTf)₂ solved this problem. The zinc salt seems to increase the reaction rate of the carbometalation step. This finding suggests the formation of a more reactive cationic palladium(II) species.^{15a,c} Exploring an asymmetric variant, ligand-screening¹⁸ under palladium-catalyzed reaction conditions, and subsequent

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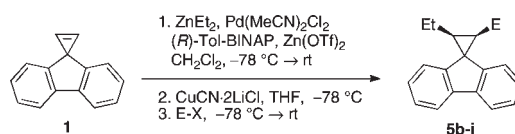
(16) For cyclopropenes, see: Hierbert, S. PhD Thesis, Toronto 2003, 184.

(17) The use of Pd(PPh₃)₄ afforded only starting material.

(18) Leong, P. PhD Thesis, Toronto 2007, 196 and Supporting Information.

trapping of the cyclopropylzinc intermediate with acid gave promising results, and with Tol-BINAP, cyclopropane **5a** could be obtained with 91% ee (Table 1).

The use of unsymmetrical substituted cyclopropenes in the palladium-catalyzed carbozincation yielded the products with moderate enantioselectivity.^{16,18} Therefore we focused our investigations toward broadening the substrate scope on further symmetrical substituted cyclopropenes (Table 1). The carbozincation protocol was applied to cyclopropenes **2a–d** bearing different protecting groups providing the cyclopropanes **6a–d** with low to moderate enantioselectivities. The comparison showed that with the Bz group the product with the highest enantioselectivity was obtained, albeit in a moderate yield. Next, we subjected cyclopropene **3** to a carbozincation. Cyclopropane **7**

Table 2. Investigation of Trapping Reactions

entry	E-X	product	yield, % ^a	dr ^b	ee, %
1	I ₂ ^{c,d}		89	>95:5	90
2	PhCOCl		75	>95:5	93
3	CH ₃ CH ₂ COCl		66	>95:5	93
4			81	>95:5	91
5			93	>95:5	90
6			quant.	>95:5	90
7			93	>95:5	91
8			95 ^e	>95:5 ^f	91

^a Isolated yields. ^b *Cis/trans*. ^c No transmetalation to copper. ^d Pd((S)-Tol-BINAP)Cl₂ was used. ^e Ratio of branched:linear product = 86:14. ^f Mixture of diastereomers at the exo position, dr (3,1') = 85:15, relative configuration not assigned.

was obtained only with 20% yield due to rearrangement of **3**. The reaction with cyclopropene **4** did not provide the desired product. However, the best results were observed with cyclopropene **1**.

Encouraged by the results with cyclopropene **1**, we investigated other trapping reactions of the cyclopropylzinc intermediates (Table 2). Reaction with iodine yielded the desired product **5b** as a single diastereomer with an enantioselectivity of 90%. An excess of nucleophile was used to quench unreacted diethylzinc. For the capture with carbon electrophiles, transmetalation with $\text{CuCN}\cdot 2\text{LiCl}$ was necessary and a range of electrophiles could be successfully¹⁹ reacted with the corresponding copper derivative, providing the products in high yields and with excellent diastereo- and enantioselectivities ranging from 90 to 93%.

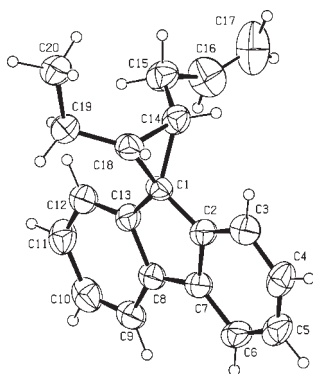


Figure 1. X-ray structure of **5g**.

Reaction with benzoyl chloride and propionyl chloride in a one-pot procedure provided **5c** and **5d**, respectively. Treatment with 2-bromo-1-phenylacetylene furnished the alkynylated product **5e** in 81% yield. Capture with 1-bromo-2-pentyne led to allene **5f** from an $\text{S}_{\text{N}}2'$ pathway, which is known for organocopper reagents prepared from organozinc species. Finally, the copper intermediate could be smoothly allylated with allyl bromide, ethyl 2-(bromomethyl)acrylate, and cinnamyl bromide. In the latter case we observed an 86:14 mixture of branched and linear products. Single crystal

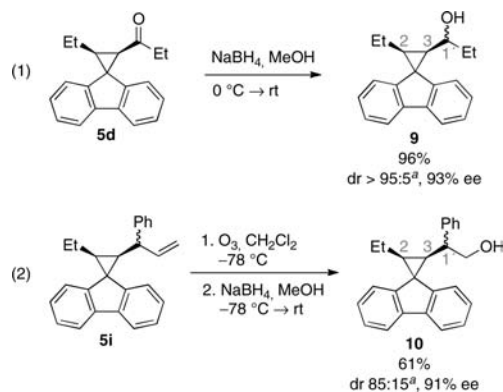
(19) Attempts to react the cyclopropylzinc intermediate, after transmetalation using copper salts, with aldehydes (benzaldehyde, butyraldehyde) were unsuccessful. Neither activation by Lewis acids [$\text{BF}_3\cdot\text{OEt}_2$, $\text{Ti}(\text{O}i\text{Pr})_4$] nor transmetalation to a more reactive titanium species with $\text{ClTi}(\text{O}i\text{Pr})_3$ afforded the desired product. Likewise it was not possible to capture the cyclopropyl copper compound with Michael acceptors like cyclohexenone, ethyl acrylate, or nitroalkenes in the presence of TMSCl or $\text{BF}_3\cdot\text{OEt}_2$. Moreover, the copper species failed to undergo addition to alkynes. Only **5a** was obtained in these reactions.

(20) For analytical reasons we synthesized racemic materials as an HPLC reference by using *rac*-BINAP as a ligand.

X-ray analysis of compound **5g** confirmed the stereochemistry of the substituents (Figure 1).²⁰

After exploring the scope of the electrophilic capture, we investigated the ability to modify the products selectively. Reduction of ketone **5d** with sodium borohydride afforded alcohol **9**, which is the formal adduct of the addition of the cyclopropyl metal intermediate to propionaldehyde, as a single diastereomer (Scheme 1, eq 1). Ozonolysis of compound **5i** and reductive workup afforded **10** in 61% yield (eq 2).

Scheme 1. Derivatization of **5d** and **5i**



^aDr (3,1'), mixture of diastereomers at the exo position, relative configuration not assigned; dr (2,3-*cis,trans*) > 95:5

In summary, a novel enantio- and diastereoselective palladium-catalyzed protocol for the carbocyclization of cyclopropenes has been developed, and the intermediate cyclopropylzinc species were successfully trapped with a range of electrophiles. For the capture with carbon electrophiles, a transmetalation to copper was found to be necessary. Further investigations to expand the scope of the reaction are currently underway.

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Supporting Information Available. Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.