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Palladium-Catalyzed Addition of Alkynes to Cyclopropenes: An Entry to Stereodefined Alkynylcyclopropanes

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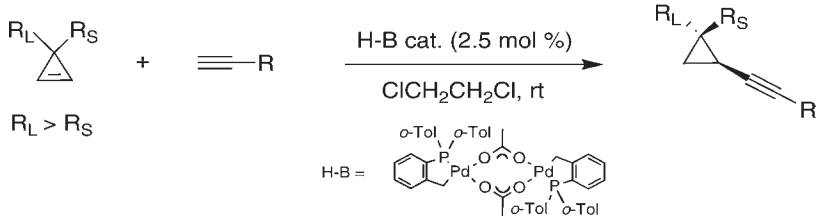
ABSTRACT



The Herrmann−Beller (H−B) phosphapalladacycle catalyzed the addition of terminal alkynes to unsymmetrical gem-disubstituted cyclopropenes to give alkynylcyclopropanes as single diastereomers in good to excellent yields. The stereofacial discrimination at the approach of the bulky alkynylpalladium species is believed responsible for the diastereoselectivity control of the addition reaction.

Transition-metal catalyzed addition of pronucleophiles across carbon−carbon multiple bonds has been regarded as one of the most important and straigthforward methods for carbon−heteroatom bond formation and still remains an intensive area of investigations.[1] Moreover, the products resulting from the simple sum of the reactants make these processes extremely attractive in terms of both efficiency and minimal waste.[2] In these reactions, heteronucleophiles such as amines or alcohols are by far the most employed. The additions of soft carbon pronucleophiles (hydrocarbonation), with pKas typically ranging from 9 to 15, have also been successfully achieved for carbon−carbon bond-forming reactions.[3] Terminal alkynes with raised pK_a values (p$K_a \approx 25$) are also able to participate in additions to alkynes,[4] allenes,[5] 1,3-dienes,[6] styrenes,[7] and electron-deficient alkenes,[8] allowing the incorporation of the alkyne linkage into molecular structures. In contrast, additions to

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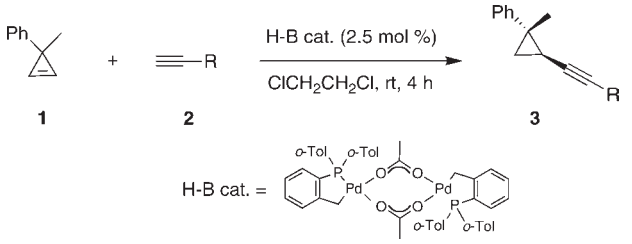
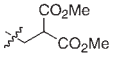
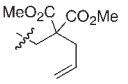
isolated double bonds have met little success since these processes required harsh conditions[9] or air-sensitive catalysts[10] and remained limited in scope with respect to the alkyne partner.

In 2006, Yin and Chisholm reported the palladium-catalyzed addition of alkynes to cyclopropenes utilizing palladium acetate and trimethylphosphonium tetrafluoroborate as a catalyst and triethylamine to promote both the release of free electron-rich phosphine and formation of alkynylpalladium species.[11,12] However, the low diastereoselectivity observed with unsymmetrical gem disubstituted cyclopropenes, affording a 2.5−3.5/1 mixture of *trans*/*cis* adducts, constitutes a major drawback of this coupling. Substituted cyclopropanes are important structural units in a number of natural compounds[13] as well as in relevant bioactive molecules.[14] We were interested in the development of readily accessible and stereodefined alkynylcyclopropane[15] building blocks as precursors, among others, of vinyl- or allenylcyclopropanes. Recently, we disclosed the addition of terminal alkynes across the norbornadiene double bond in the presence of the Herrmann−Beller (H−B) phosphapalladacycle as a catalyst under mild conditions and without an additional promoter or cocatalyst to form 5-*exo*-alkynylnorborn-2-enes.[16] In this note, we report that this bulky and electron-rich phosphapalladacycle is able to catalyze the diastereoselective addition of terminal alkynes to unsymmetrical cyclopropenes affording *exclusively trans* 2,2-disubstituted alkynylcyclopropanes.

Initial studies showed that the addition of phenylethyne (**2a**) to 3-methyl-3-phenylcyclopropene (**1**) occurred smoothly in the presence of 2.5 mol % of the Herrmann−Beller phosphapalladacycle affording adduct **3a** in a quantitative yield (Table 1, entry 1). Interestingly, *this addition was performed at room temperature and in the absence of base*. ^{1}H

Table 1. Herrmann−Beller Phosphapalladacycle Catalyzed Diastereoselective Addition of Alkynes **2** to Cyclopropene **1**[a]



entry	alkyne	R	adduct	yield (%)[b]
1	**2a**	Ph	**3a**	>98
2	**2b**		**3b**	88
3	**2c**	*n*-Bu	**3c**	90
4	**2d**	$SiMe_3$	**3d**	>98
5	**2e**		**3e**	82
6	**2f**		**3f**	90
7	**2g**		**3g**	81
8	**3h**		**3h**	87
9	**2i**		**3i**	70
10	**2j**		**3j**	>98
11	**2k**		**3k**	89
12	**2l**		**3l**	92
13	**2m**		**3m**	84
14	**2n**		**3n**	77
15	**2o**		**3o**	71
16	**2p**		**3p**	93
17	**2q**		**3q**	78
18	**2r**		**3r**	85
19	**2s**		**3s**	86
20	**2t**		**3t**	>98
21	**2u**		**3u**	84
22	**2v**		**3v**	>98
23	**2w**		**3w**	89

[a] Conditions: **1**/**2**/ H−B cat.: 1/1/0.025, 0.25 M in $ClCH_2CH_2Cl$. [b] Yield refers to isolated material.

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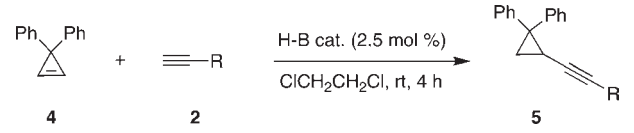
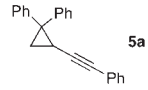
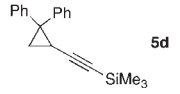
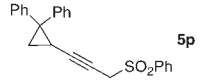
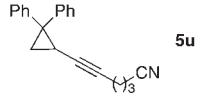
Table 2. Herrmann−Beller Phosphapalladacycle Catalyzed Addition of Alkynes **2** to 3,3-Diphenylcyclopropene **4**[a]



4 2 5

entry	alkyne	adduct	yield (%)[b]
1	**2a**	 **5a**	38 (56)[c]
2	**2d**	 **5d**	50
3	**2p**	 **5p**	65
4	**2u**	 **5u**	42

[a] Conditions: **4**/**2**/ H−B cat.: 1/1/0.025, 0.25 M in $ClCH_2CH_2Cl$. [b] Yield refer to isolated material. [c] Yield refer to addition of **4** and **2a** with syringe pump in 4 h, then stirring for 2 h.

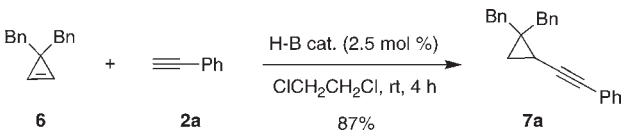
NMR data from the crude reaction mixture revealed **3a** as a single diastereomer and without any formation of a ring-opening adduct.[17] The *trans* stereochemistry of **3a** was assigned on the basis of its ^{1}H NMR and NOESY experiments in full agreement with those of closely related compounds.[11] This stereochemical outcome was observed with a number of functionalized alkynes (Table 1). Electrophilic or nucleophilic functional groups attached to the alkyne were well tolerated within the mild reaction conditions, expanding the scope of this hydroalkynylation. Alternatively, trimethylsilylethyne (**2d**) and 3-hydroxy-3-methylbut-1-yn (**2j**) can be used as a convenient ethyne substitute. In all cases, adducts were obtained as single diastereomers in good to quantitative yields. We assume that this excellent diastereoselectivity derives from the diastereofacial discrimination of the double bond at the approach of the bulky metal species. The sensitivity of the reaction toward the bulkiness of the alkene gem-disubstitution was examined with the symmetrical 3,3-diphenylcyclopropene **4**. Additions of terminal alkynes to cyclopropene **4** under the same reaction conditions afforded alkynylcyclopropanes **5** with significantly decreased yields (Table 2) after complete conversion of the reactants. In these reactions, the formation of polymers accounts for the mass balance.[18]

On the contrary, the addition of **3a** to the less sterically demanding 3,3-dibenzylcyclopropene **6** gave adduct **7a** in a satisfactory 87% yield (Scheme 1).

To span the cyclopropene scope, functionalized unsymmetrical 3,3-disubstituted cyclopropene **8** was examined.

(17) Nakamura, I.; Bajracharya, G. B.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 2297–2299.

Scheme 1. Addition of Phenylethyne **2a** to 3,3-Dibenzylcyclopropene **6**



6 2a 7a

Additionally, it was anticipated that the coupling would be achieved with a high level of diastereoselectivity. The coupling of cyclopropene **8** bearing a masked acetyl substituent with alkynes **2a**, **2d**, or **2j** afforded the expected adducts (Scheme 2). The ^{1}H NMR of the crude reaction mixture revealed the adducts as single diastereomers with the incoming alkynyl group *trans* to the ketal. Interestingly, the mild and practically neutral conditions are appropriate for the survival of the sensitive ketal. However, on purification over silica gel, deprotection of the ketal to ketone occurred to afford methyl alkynylcyclopropyl ketones **9a**, **9d**, and **9j** in 60−90% yield (Scheme 2).

Scheme 2. Diastereoselective Synthesis of Cyclopropyl Ketones **9**

8 2 9

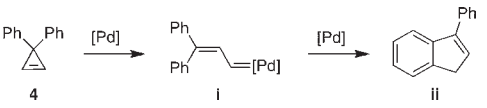
2a
2d
2j

9a R = Ph 90%
9d R = $SiMe_3$ 78%
9j R = $C(Me)_2OH$ 60%

In an ancillary study, the cyclopropenyl ketone **10** appeared to be an excellent partner for the coupling. The addition of **2a** to enone **10** afforded the cyclopropylogous ynone **9a** in a quantitative yield. Once again, **9a** was obtained exclusively with the *trans* stereochemistry (Scheme 3). Gratifyingly, the mildness of the reaction conditions precluded the isomerization of cyclopropenyl ketone to furan.[19]

A plausible mechanism for the coupling of cyclopropenes with terminal alkynes as depicted in Scheme 4 starts with the mononuclear palladacycle **A** provided by the dissociation of the Herrmann−Beller phosphapalladacycle. The alkynylpalladium species **B** could be formed in

(18) We presume the concomitant formation of the vinyl-palladacarbene (**i**) from cyclopropene **4** responsible for the polymerization. In addition, the detection in the crude mixture of 3-phenyl-1*H*-indene (**ii**) formed through intramolecular insertion of palladacarbene (**i**) into an aromatic C−H bond may support our assumption.



4 i ii

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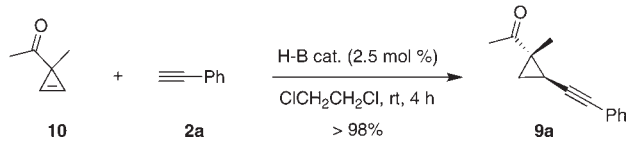
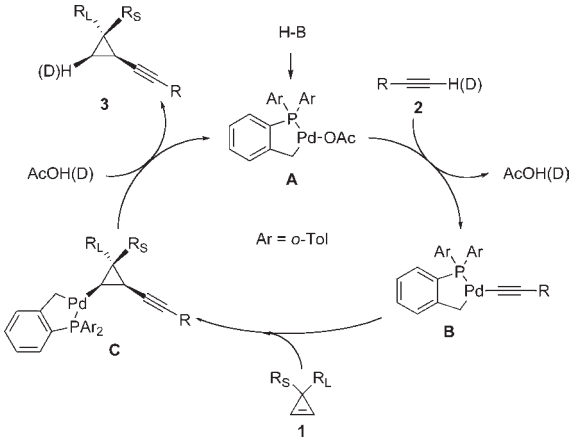
Scheme 3. Diastereoselective Addition of Phenylethyne **2a** to Cyclopropenyl Ketone **10**



Scheme 4. Mechanistic Rationale for the Diastereoselective Addition of Alkynes to Cyclopropenes



the presence of alkyne **2** with the loss of acetic acid. Coordination of the cyclopropene double bond followed by the *syn* carbopalladation afforded the cyclopropylpalladium **C**, which upon demetalation with acetic acid releases the alkynylcyclopropane **3** and regenerates the catalytic species **A**. The **B** → **C** determining step allowing the diastereoselectivity rests on the coordination of palladium through the less hindered face of the cyclopropene. This proposal also accommodates the *syn*-carbopalladation step since the addition of deuterated phenylethyne **D-2a** to 3-methyl-3-phenylcyclopropene (**1**) gave the labeled adduct **D-3a** (82%) incorporating the ^{2}H atom and the alkynyl substituent in a *cis* fashion, along with the non-labeled adduct **3a** (14%) (see Supporting Information).

To illustrate the synthetic utility of alkynylcyclopropanes, compound **3h** was treated with LAH to give the

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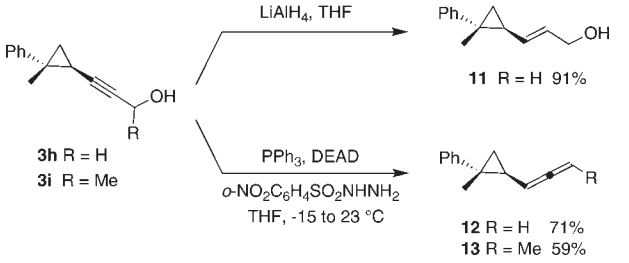
Scheme 5. Useful Transformations of Cyclopropyl-Substituted Propargylic Alcohols



(*E*)-allylic alcohol **11** in 91% yield (Scheme 5). On the other hand, propargyl alcohols **3h** and **3i** were transformed to α-cyclopropyl allenes **12** and **13**, as a 1:1 mixture of diastereomers, through a reductive Mitsunobu reaction in 71% and 59% yields, respectively.[20]

In summary, we have developed an easy access to diastereomerically pure alkynylcyclopropanes through addition of terminal alkynes across the double bond of cyclopropenes. This reaction occurred under neutral and mild conditions and tolerates various electrophilic or nucleophilic functional groups with an air-stable electron-rich phosphapalladacycle as the catalyst. The usefulness of alkynylcyclopropanes was briefly investigated to provide vinylcyclopropanes[21] or allenylcyclopropanes[22] for further synthetic applications.

Acknowledgment. The authors thank the CNRS for supporting this research and MENRT for the doctoral fellowship (K.L.).

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

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(22) For transition-metal catalyzed reactions of allenylcyclopropenes, see: (a) Owada, Y.; Matsuda, T.; Iwasawa, N. *Tetrahedron* **1997**, *53*, 11069–11086. (b) Hayashi, M.; Ohmatsu, T.; Meng, Y.-P.; Saigo, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 837–839. (c) Murakami, M.; Itami, K.; Ubukata, M.; Tsuji, I.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 4–5. (d) Schmittel, M.; Mahajan, A. A.; Bucher, G.; Bats, J. W. *J. Org. Chem.* **2007**, *72*, 2166–2173. (e) Hiroi, K.; Kato, F.; Oguchi, T.; Saito, S.; Sone, T. *Tetrahedron Lett.* **2008**, *49*, 3567–3569. (f) Inagaki, F.; Sugikubo, K.; Miyashita, Y.; Mukai, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2206–2210.