Palladium-catalyzed addition of alkynes to cyclopropenes†

Jiandong Yin and John D. Chisholm*

Received (in Bloomington, IN, USA) 14th November 2005, Accepted 4th January 2006
First published as an Advance Article on the web 19th January 2006
DOI: 10.1039/b516021a

The palladium catalyzed coupling of alkynes and cyclopropenes provides a powerful method for the synthesis of alkynylcyclopropanes, proceeding under mild conditions in the presence of many functional groups (such as esters, carboxylic acids, aldehydes, and alcohols).

Alkyne C–H bonds are particularly susceptible to activation by transition metals, providing an opportunity for the development of new carbon–carbon bond forming reactions. Late transition metals such as palladium are known to activate the C–H bond of alkynes under mild conditions, but the reaction is limited because of the propensity of the alkyne to rapidly form dimers.[1] This dimerization reaction has been exploited by Trost in the selective coupling of electron rich and electron poor alkynes.[2] Catalytically generated palladium acetylides also react as nucleophiles in the 1,4-addition of alkynes to methyl vinyl ketone.[3] Recently our group has undertaken related studies in the coupling of alkynes and cyclopropenes using palladium catalysts.

The cyclopropene olefin was chosen as a coupling partner due to its unusually reactive nature. This feature has been exploited in the addition of silanes, stannanes and boranes to the cyclopropene olefin.[4] Palladium-catalyzed arylation of the cyclopropene alkene is also a facile transformation.[5] Addition of carbon anions to cyclopropenes has also proven to be a useful method for the synthesis of substituted cyclopropanes.[6] Relevant to this work, alkynyl Grignard reagents have been added to cyclopropenes in good yield with excellent diastereoselectivity using copper catalysis.[6e] Typical conditions for the addition of alkynes and other carbon nucleophiles across the cyclopropene olefin requires a stoichiometric amount of at least one metal. Formation of these organometallic reagents usually precludes the presence of other electrophilic functionality, such as aldehydes, ketones, and carboxylic acids. Late transition metal catalysis typically is not limited by the presence of these functional groups, allowing the synthesis of substituted cyclopropanes without the requirement of protecting groups.

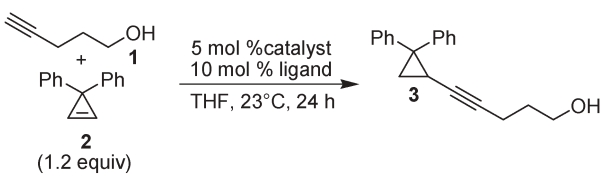
Substituted cyclopropanes are appealing targets due to their presence in many natural products and other biologically relevant molecules.[7] Substituted cyclopropanes also represent important building blocks for organic synthesis, with alkynyl cyclopropanes providing ready access to vinyl cyclopropanes.[8a] Vinyl cyclopropanes are especially prized for their utility in the synthesis of five membered rings,[8] seven membered rings,[9] eight membered rings,[10] heterocycles[11] and polycyclic structures.[12]

Department of Chemistry, 1-014 Center for Science and Technology, Syracuse University, Syracuse, NY 13244, USA.
E-mail: jdchisho@syr.edu; Fax: +1 315 443 4070; Tel: +1 315 443 6894
† Electronic supplementary information (ESI) available: experimental section, references and spectral data. See DOI: 10.1039/b516021a

Initial experiments showed that palladium acetate in the presence of trimethylphosphonium tetrafluoroborate[13] and triethylamine was an effective catalyst system for the addition of 4-pentyn-1-ol (**1**) to 3,3-diphenylcyclopropene (**2**) (Table 1). In contrast to the palladium-catalyzed addition of other proto-nucleophiles to cyclopropenes,[14] the cyclopropane ring remained intact to provide alkynylcyclopropane **3**. Triarylphosphines generate a less effective catalyst system (Table 1, entry 1). Other trialkylphosphines were also effective ligands in the transformation (entries 3 and 4). The triethylamine was assumed to deprotonate the phosphine salt, generating free phosphine, but experiments with (±)-BINAP showed an increase in yield when triethylamine is added to the reaction mixture (entries 5 and 6). This effect may be due to the ability of the amine to act as a proton transfer agent in the catalytic cycle. Other Pd(II) salts were less effective as precatalysts (entries 10 and 11). Control experiments showed that both the palladium catalyst and the phosphine ligands were required (entries 8 and 9).

Alkynes containing various functional groups were then tested in the addition reaction. While 4-pentyn-1-ol provided moderate yield of the addition product, most other alkynes gave good to excellent yield of the corresponding alkynylcyclopropane. Alkynes containing unprotected alcohols, nitriles, esters, carboxylic acids, and aldehydes were used successfully as coupling partners, defining a wide scope of functional groups that are tolerated under the mild reaction conditions.

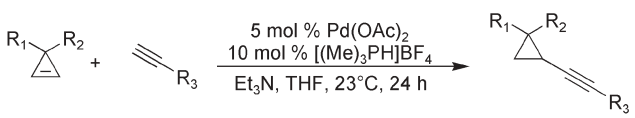
Table 1 Effect of phosphine ligands on the addition of 4-pentyn-1-ol (**1**) to 3,3-diphenylcyclopropene (**2**)

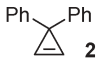
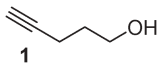
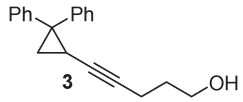
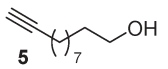
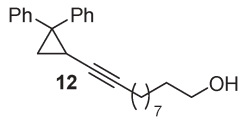
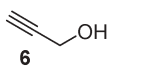
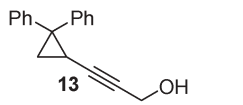
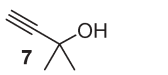
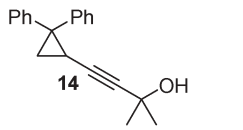
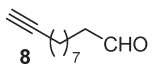
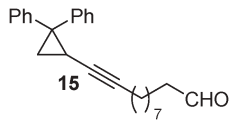
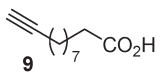
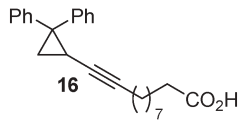
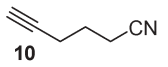
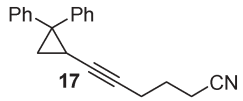
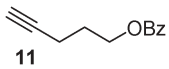
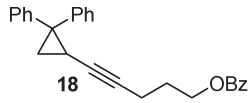
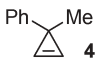
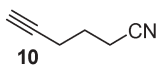
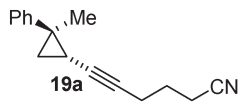
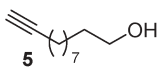
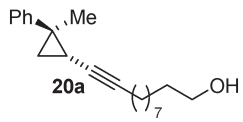
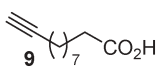
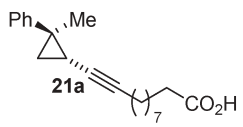


Entry	Catalyst	Ligand	Et_3N	Yield
1	$Pd(OAc)_2$	PPh_3	None	Trace
2	$Pd(OAc)_2$	$[(Me)_3PH]BF_4$	1 equiv.[a]	66
3	$Pd(OAc)_2$	$[(Et)_3PH]BF_4$	1 equiv.	61
4	$Pd(OAc)_2$	$[(Cy)_3PH]BF_4$	1 equiv.	40
5	$Pd(OAc)_2$	(±)-BINAP[b]	None	9
6	$Pd(OAc)_2$	(±)-BINAP[b]	1 equiv.	24
7	$Pd(OAc)_2$	$[(Me)_3PH]BF_4$	None	0
8	$Pd(OAc)_2$	None	1 equiv.	Trace
9	none	$[(Me)_3PH]BF_4$	1 equiv.	0
10	$Pd(OCOCF_3)_2$	$[(Me)_3PH]BF_4$	1 equiv.	Trace
11	$PdCl_2$	$[(Me)_3PH]BF_4$	1 equiv.	Trace

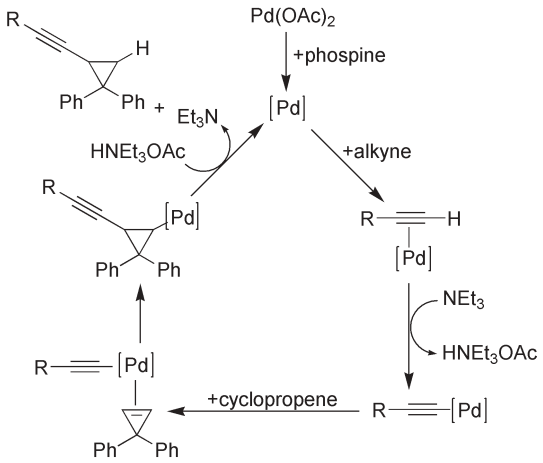
[a] One equivalent with respect to the alkyne starting material. [b] Only 5 mol% of (±)-BINAP was used.

Table 2 Pd-Catalyzed addition of alkynes to cyclopropenes



Entry	Cyclopropene	Alkyne	Product	Yield
1	 **2**	 **1**	 **3**	66%
2	**2**	 **5**	 **12**	99%
3	**2**	 **6**	 **13**	86%
4	**2**	 **7**	 **14**	98%
5	**2**	 **8**	 **15**	63%
6	**2**	 **9**	 **16**	75%
7	**2**	 **10**	 **17**	93%
8	**2**	 **11**	 **18**	65%
9	 **4**	 **10**	 **19a**	80%[a]
10	**4**	 **5**	 **20a**	82%[b]
11	**4**	 **9**	 **21a**	77%[c]

[a] Isolated as a 2.5 : 1 mixture (major isomer shown). [b] Isolated as a 3.5 : 1 mixture (major isomer shown). [c] Isolated as a 3.4 : 1 mixture (major isomer shown).



Scheme 1 Proposed mechanism of the alkyne addition.

Unsymmetrical cyclopropenes were also explored, with 3-methyl-3-phenylcyclopropene (**4**) also proving to be a useful coupling partner. The addition of alkynes to this unsymmetrical cyclopropene led to a mixture of stereoisomers (as determined by ^{1}H NMR) from the alkyne preferring to add from one face of the cyclopropene.

In order to determine the stereochemistry of the major and minor product in the case of **19**, all of the ^{1}H NMR signals were assigned by COSY experiment on the mixture of isomers. A NOESY experiment was then performed on the mixture of diastereomers, which allowed for assignment of the relative configuration of both isomers. Alkyne addition was shown to occur preferentially from the same face as the methyl group for **4**, likely for steric reasons. All of the alkynes used gave similar ratios of *cis* and *trans* isomers, the favored stereoisomer being shown in Table 2. The stereochemistry of the other two examples was assigned by analogy to cyclopropane **19**.

A proposed mechanism for the palladium-catalyzed addition reaction is presented in Scheme 1. First, the active palladium–phosphine complex is generated *in situ*. The palladium complex next coordinates to the alkyne. Deprotonation of the alkyne–palladium complex with triethylamine provides the alkynylpalladium intermediate. Coordination of the cyclopropene is followed by carbometallation of the strained olefin, leading to a cyclopropylpalladium intermediate. This carbometallation is in contrast to the mechanistic studies of the cyclopropene Heck reaction, where addition is thought to take place through a carbocation intermediate.[5] While β-elimination could occur at this stage, this termination event is unfavorable due to the strain of the olefin that would be generated. Protonation of the palladium–carbon bond by triethylammonium acetate occurs instead to provide the alkynyl cyclopropane and regenerate the active catalyst.

In summary, the addition of monosubstituted alkynes to cyclopropenes proceeds well using a palladium catalyst. The reaction conditions are mild, tolerating numerous functional groups (aldehydes, carboxylic acids, *etc.*) whose use is precluded with more reactive organometallic reagents. Further studies on the mechanism and scope of this transformation are currently underway.‡

Notes and references

‡ Representative experimental procedure: A dry 13 × 100 mm test tube was charged with $Pd(OAc)_2$ (4.6 mg, 0.02 mmol) and $HPMe_3BF_4$ (6.6 mg, 0.04 mmol). The mixture was stirred and purged with N_2 and placed in a rt water bath for 3 min. Dry THF (0.4 mL) and Et_3N (56.2 μL, 0.4 mmol) were added, and the mixture was stirred for another 3 min. To this mixture a solution of alkyne **7** (0.4 mmol, 34 mg) and 3,3-diphenylcyclopropene (**2**) (0.48 mmol, 93 mg) in THF (0.4 mL) was added dropwise *via* syringe (the reaction was kept in the room temperature water bath during this addition). Stirring was continued for 24 hours at room temperature. After this time the reaction mixture was concentrated and purified by column chromatography, providing **14** (108 mg, 98% yield) as a yellow oil. TLC R_f = 0.51 (30% EtOAc/70% hexanes); IR (neat) 3384, 3025, 2979, 2927, 2234, 1600, 1496, 1447, 1165, 1138, 951, 895, 752, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10–7.45 (m, 10H), 2.15 (dd, J = 9.0, 6.0 Hz, 1H), 1.68 (dd, J = 5.7, 4.8 Hz, 1H), 1.59 (dd, J = 9.0, 4.8 Hz, 1H), 1.55 (s, broad, 1H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 141.3, 130.5, 128.6, 128.2, 128.1, 126.8, 126.6, 86.4, 82.9, 65.3, 37.9, 31.4, 31.3, 23.4, 15.8. Anal Calc'd for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 86.76; H, 7.33%.

1 (*a*) B. M. Trost, C. Chan and G. Ruhter, *J. Am. Chem. Soc.*, 1987, **109**, 3486; (*b*) B. M. Trost and M. C. McIntosh, *Tetrahedron Lett.*, 1997, **38**, 3207; (*c*) U. Lucking and A. Pfaltz, *Synlett*, 2000, 1261; (*d*) M. Rubina and V. Gevorgyan, *J. Am. Chem. Soc.*, 2001, **123**, 11107; (*e*) C. Yang and S. P. Nolan, *J. Org. Chem.*, 2002, **67**, 591.

2 (*a*) B. M. Trost, M. T. Sorum, C. Chan and G. Rühter, *J. Am. Chem. Soc.*, 1997, **119**, 698; (*b*) L. Chen and C.-J. Li, *Tetrahedron Lett.*, 2004, **45**, 2771.

3 L. Chen and C.-J. Li, *Chem. Commun.*, 2004, 2362.

4 (*a*) M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2002, **124**, 11566; (*b*) M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2003, **125**, 7198; (*c*) M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2004, **126**, 3688.

5 S. Chuprakov, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2005, **127**, 3714.

6 (*a*) H. G. Jr. Richey and R. M. Bension, *J. Org. Chem.*, 1980, **45**, 5036; (*b*) E. Nakamura, M. Isaka and S. Matsuzawa, *J. Am. Chem. Soc.*, 1988, **110**, 1297; (*c*) M. Nakamura, M. Arai and E. Nakamura, *J. Am. Chem. Soc.*, 1995, **117**, 1179; (*d*) M. Nakamura, H. Isobe and E. Nakamura, *Chem. Rev.*, 2003, **103**, 1295; (*e*) L.-A. Liao and J. M. Fox, *J. Am. Chem. Soc.*, 2002, **124**, 14322; (*f*) J. M. Fox and N. Yan, *Curr. Org. Chem.*, 2005, **9**, 719.

7 (*a*) J. Pietruszka, *Chem. Rev.*, 2003, **103**, 1051; (*b*) L. A. Wessjohann, W. Brandt and T. Thiemann, *Chem. Rev.*, 2003, **103**, 1625; (*c*) W. A. Donaldson, *Tetrahedron*, 2001, **57**, 8589; (*d*) D. L. Boger and D. S. Johnson, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1438; (*e*) D. Lamarre, P. C. Anderson, M. Bailey, P. Beaulieu, G. Bolger, P. Bonneau, M. Boes, D. R. Cameron, M. Cartier, M. G. Cordingley, A.-M. Faucher, N. Goudreau, S. H. Kawai, G. Kukolj, L. Lagace, S. R. LaPlante, H. Narjes, M.-A. Poupart, J. Rancourt, R. E. Sentjens, St. George R., B. Simoneau, G. Steinmann, D. Thibeault, Y. S. Tsantrizos, S. M. Weldon, C.-L. Yong and M. Llinas-Brunet, *Nature*, 2003, **426**, 186.

8 (*a*) G. Zuo and J. Louie, *Angew. Chem., Int. Ed.*, 2004, **43**, 2277 (For reduction of a cyclopropyl alkyne to a vinylcyclopropane, see the supplementary material of ref. 8*a*); (*b*) J. E. Baldwin, *Chem. Rev.*, 2003, **103**, 1197; (*c*) T. Hudlicky and J. W. Reed, in *Comprehensive Organic Synthesis*, Vol. 5, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, 899.

9 (*a*) P. A. Wender, H. Takahashi and B. Witulski, *J. Am. Chem. Soc.*, 1995, **117**, 4320; (*b*) P. A. Wender, C. O. Husfeld, E. Langkopf, J. A. Love and N. Pleuss, *Tetrahedron*, 1998, **54**, 7203; (*c*) P. A. Wender, C. O. Husfeld, E. Langkopf and J. A. Love, *J. Am. Chem. Soc.*, 1998, **120**, 1940; (*d*) P. A. Wender, A. J. Dyckman, C. O. Husfeld, D. Kadereit, J. A. Love and H. Rieck, *J. Am. Chem. Soc.*, 1999, **121**, 10442; (*e*) P. A. Wender, C. M. Barzilay and A. J. Dyckman, *J. Am. Chem. Soc.*, 2001, **123**, 179; (*f*) P. A. Wender, J. A. Love and T. J. Williams, *Synlett*, 2003, 11295; (*g*) B. M. Trost, F. D. Toste and H. Shen, *J. Am. Chem. Soc.*, 2000, **122**, 2379; (*h*) B. M. Trost and H. C. Shen, *Org. Lett.*, 2000, **2**, 2523; (*i*) B. M. Trost, H. C. Shen, T. Schulz, C. Koradin and H. Schirok, *Org. Lett.*, 2003, **5**, 4149.

10 (*a*) P. A. Wender, G. G. Gamber, R. D. Hubbard and L. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 2876; (*b*) H. A. Wegner, A. de Meijere and P. A. Wender, *J. Am. Chem. Soc.*, 2005, **127**, 6530.

11 P. A. Wender, T. M. Pedersen and M. J. C. Scanio, *J. Am. Chem. Soc.*, 2002, **124**, 15154.

12 (*a*) P. A. Wender, G. G. Gamber and M. J. C. Scanio, *Angew. Chem., Int. Ed.*, 2001, **40**, 3895; (*b*) B. M. Trost and H. C. Shen, *Angew. Chem., Int. Ed.*, 2001, **40**, 2313; (*c*) B. M. Trost, H. C. Shen, D. B. Horne, F. D. Toste, B. G. Steinmetz and C. Koradin, *Chem.–Eur. J.*, 2005, **11**, 2577.

13 For the use of trialkylphosphonium salts see: M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295.

14 I. Nakamura, G. B. Bajracharya and Y. Yamamoto, *J. Org. Chem.*, 2003, **68**, 2297.