Cascade Reactions

DOI: 10.1002/anie.200905478

Palladium-Catalyzed Intramolecular Carboesterification of Olefins**

Yang Li, Katherine J. Jardine, Runyu Tan, Datong Song, and Vy M. Dong**

Palladium-catalyzed olefin difunctionalization is an attractive strategy for converting simple alkenes into diverse and valuable synthetic products.[1] For example, palladium-catalyzed diamination,[2] aminooxygenation,[3] aminohalogenation,[4] carboamination,[5] carboetherification,[5] and diacetoxylation[6] of unactivated alkenes have been achieved. Polycyclic motifs are commonly found in natural products and medicinal targets.[7] Therefore, developing new methods for constructing rings from simple alkenes represents an important goal. Most palladium-catalyzed cycloadditions involve strained rings (e.g., trimethylenecyclopropanes) or require highly activated olefins (e.g., Michael acceptors).[8] Herein, we report a novel palladium-catalyzed formal [3+2] cycloaddition between propiolic acids[9] and unactivated alkenes. This intramolecular carboesterification results in difunctionalization of an alkene to form C–C and C–O bonds, thereby generating a fused ring system.

Our proposed [3+2] cycloaddition is based on the unique combination of three steps: 1) *trans* chloropalladation, 2) *syn* oxypalladation, and 3) reductive elimination (Figure 1). Both *cis* and *trans* chloropalladation of alkynes are well precedented.[10] Halopalladation of propiolic acids, however, has not been investigated. We envisioned that chloropalladation of a propiolic acid, accompanied by ligand substitution, could generate the novel palladium–carboxylate intermediate **II**.[11] On the basis of mechanistic studies on carboetherification reported by Wolfe,[12] we proposed that **II** would undergo *syn* oxypalladation to form the palladacycle **III**. A C–C bond-forming reductive elimination would produce the lactone **IV**. Finally, oxidation of the Pd^0 species with $CuCl_2$ as the terminal oxidant would regenerate the active Pd^{II} catalyst.[13]

Initial studies began with cyclization of propiolic acid **1a** to afford a 6,7,5-tricyclic product **2a**. As shown in Table 1, in the absence of a catalyst, no reaction was observed. To achieve the desired *trans* chloropalladation of **1a**, we investigated reaction conditions reported by Lu and co-workers in the *trans* chloropalladation of propargylic esters;[14] they demonstrated that cascade reactions initiated by chloropalladation of an alkyne benefit from the use of polar solvents such as MeCN and AcOH.[15] In accordance with these results, using 1 mol% of $[PdCl_2(MeCN)_2]$ and three equivalents of $CuCl_2$ in MeCN, we observed a 48% conversion of **1a** into **2a** (Table 1, entry 2). The reaction efficiency depends on the chloride source and concentration. When nBu_4NCl was added in addition to $CuCl_2$, the product yield increased to 76% (Table 1, entry 3). Changing the chloride source to LiCl additionally improved the yield to 83% (Table 1, entry 4). The reaction was also found to proceed in AcOH, although higher loadings of LiCl were required (Table 1, entries 5 and 6). Increasing the amount of LiCl to more than three equivalents in MeCN did not improve the conversion because of the limited solubility of LiCl in MeCN (Table 1, entry 7).

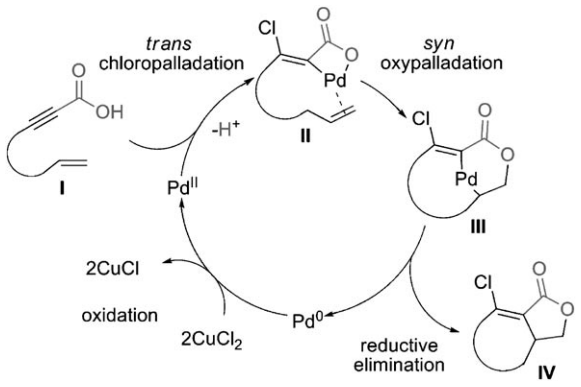
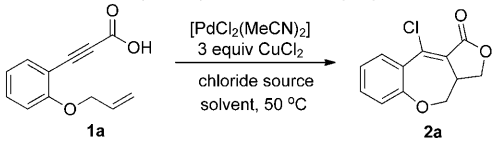


Figure 1. Proposed [3+2] cycloaddition of propiolic acids.

Table 1: Palladium-catalyzed cycloaddition of propiolic acid to olefin.[a]



Entry	[Pd] [mol%]	Solvent	[Cl^-] source (equiv)	Yield [%][b]
1	0	MeCN	–	0
2	1	MeCN	–	48
3	1	MeCN	nBu_4NCl (1)	76
4	1	MeCN	LiCl (3)	83
5	1	HOAc	LiCl (6)	50
6	1	HOAc	LiCl (12)	78
7	1	MeCN	LiCl (12)	81

[a] 0.05 M on 0.1 mmol scale, 15 h. [b] NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard.

[*] K. J. Jardine, R. Tan,[+] Prof. D. Song, Prof. V. M. Dong
Department of Chemistry, University of Toronto
80 St. George Street, Toronto, ON, M5S 3H6 (Canada)
E-mail: dsong@chem.utoronto.ca
vdong@chem.utoronto.ca
Dr. Y. Li
Department of Chemistry, Massachusetts Institute of Technology
77 Massachusetts Avenue, Cambridge, MA 02139-4307 (USA)
[+] To whom correspondence about crystallographic data should be addressed.

[**] We thank the University of Toronto, Canadian Foundation for Innovation, Ontario Ministry of Research and Innovation, and Natural Sciences and Engineering Research Council (NSERC) of Canada for funding. K.J.J. and R.T are grateful for NSERC and Ontario Graduate fellowships, respectively. Dr. Xiaodan Zhao and Prof. Shannon Stahl are thanked for helpful discussions.

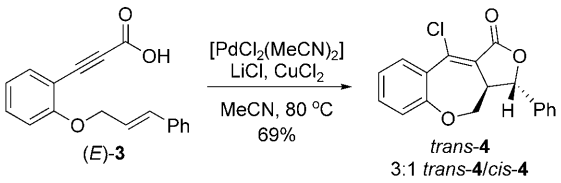
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200905478.

The structure of **2a** was confirmed by X-ray crystallographic analysis (see the Supporting Information for details). Notably, this polycyclic framework makes up the core of a family of natural products having anti-HIV activity.[16] In addition, the vinylchloride functionality provides a handle for additional synthetic manipulations on a tetra-substituted alkene.

Electronic and steric effects of the aromatic ring were examined (Table 2, entries 2–8). Both electron-withdrawing groups (Table 2, entry 4) and weakly electron-donating groups (Table 2, entry 2) *para* to the propiolic acid group were well-tolerated, resulting in 88% and 86% yields, respectively. However, a strongly electron-donating methoxy group at this position resulted in formation of the corresponding product **2c** in 61% yield (Table 2, entry 3). Increasing steric demand *ortho* to the allyl ether group (by substitution with a methyl or a methoxy group) gave high yields of **2e** and **2f** (Table 2, entries 5 and 6). In contrast, increasing the steric demand *ortho* to the propiolic acid group (Table 2, entries 7 and 8) disfavored the desired cyclization and resulted in moderate yields of both **2g** and **2h**, at elevated temperature (80°C). These results suggest chloropalladation is sensitive to steric bulk at the β-position of the propiolic acid derivative.

Replacing the ether oxygen atom with a methylene group resulted in a 71% yield of **2i** (Table 2, entry 9). The introduction of a phenyl substituent on this carbon atom gave a 2.5:1 ratio of diastereoisomers in 52% overall yield, with the major product having 1,3-*cis* stereochemistry (Table 2, entry 10). In contrast, a soft thioether group inhibits the desired reaction completely (Table 2, entry 11), presumably because of coordination to the palladium catalyst.

This methodology can be extended to include 1,2-disubstituted olefins as coupling partners. Cyclization of the substrate (*E*)-**3** under standard reaction conditions resulted in the formation of a 3:1 mixture of *trans*-**4** to *cis*-**4** in 69% overall yield [Eq. (1)]. The products do not epimerize under

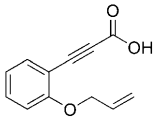
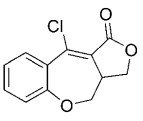
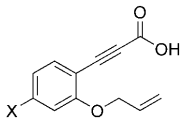
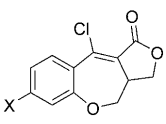
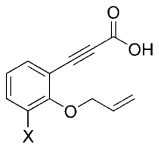
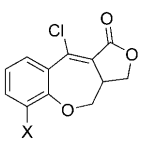
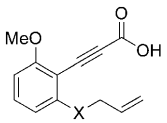
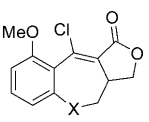
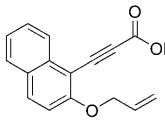
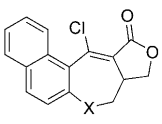
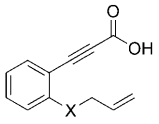
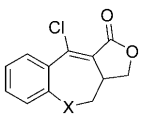


(1)

the reaction conditions, therfore, we believe that olefin isomerization prior to cyclization is responsible for the formation of the minor diastereomer.[12] X-ray crystallographic analysis of both diastereoisomers unambiguously confirmed that *trans*-**4** is the major product (see the Supporting Information).

In summary, a palladium-catalyzed intramolecular formal [3+2] cycloaddition has been achieved using unactivated alkenes. The reaction proceeds efficiently in the presence of air and moisture at low catalyst loadings. Moderate diastereoselectivity can be achieved with 1,2-disubstituted olefins. Future work will focus on expanding the scope and elucidating the mechanism of this unique carboesterification.[17]

Table 2: Palladium-catalyzed cycloaddition of propiolic acid to olefin.[a]

Entry	Substrate	Product	X	Yield[b] [%]
1	 **1a**	 **2a**		82[c]
2	 **1b**	 **2b**	Me	86
3	**1c**	**2c**	MeO	61[d]
4	**1d**	**2d**	F	88
5	 **1e**	 **2e**	Me	85
6	**1f**	**2f**	MeO	90
7	 **1g**	 **2g**	CH_2	71[e]
8	 **1h**	 **2h**		54[e]
9	 **1i**	 **2i**	CH_2	71
10	**1j**	**2j**	CHPh	52[f]
11	**1k**	**2k**	S	0

[a] Reaction conditions: 0.2 mmol scale, $[PdCl_2(MeCN)_2]$ (1 mol%) , LiCl (3 equiv), $CuCl_2$ (3 equiv), 0.05 M in MeCN, 50°C. [b] Yield of isolated product. [c] 1.0 mmol scale. [d] Used 2.0 mol% of [Pd], RT. [e] Run at 80°C. [f] The d.r. = 2.5:1 as determined by NMR spectroscopy.

Experimental Section

A solution of $[PdCl_2(MeCN)_2]$ (0.52 mg in 0.4 mL MeCN, 0.002 mmol) was added to a solution of the propiolic acid derivative (0.2 mmol), LiCl (26 mg, 0.6 mmol, 3 equiv), and $CuCl_2$ (80 mg, 0.6 mmol, 3equiv) in acetonitrile (3.6 mL). The mixture was heated at 50°C for 14 to 20 h. The resulting solution was concentrated in vacuo and the lactone product was isolated after flash column chromatography on silica gel using diethyl ether/hexanes (1:1) as the eluent.

Received: September 30, 2009
Published online: November 24, 2009

Keywords: cascade reaction · cycloaddition · lactones · palladium

[1] For a recent review on palladium-catalyzed alkene difunctionalization reactions, see: K. H. Jensen, M. S. Sigman, *Org. Biomol. Chem.* **2008**, *6*, 4083.
[2] For examples of diamination of olefins, see: a) G. L. J. Bar, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2005**, *127*, 7308; b) J. Streuff, C. H. Hövelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586; c) H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 11688, and references therein; d) P. A. Sibbald, F. E. Michael, *Org. Lett.* **2009**, *11*, 1147.
[3] For examples of aminooxygenation, see: a) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.* **2005**, *127*, 7690; b) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 7179; c) L. V. Desai, M. S. Sanford, *Angew. Chem.* **2007**, *119*, 5839; *Angew. Chem. Int. Ed.* **2007**, *46*, 5737.
[4] M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics* **2004**, *23*, 5618.
[5] For a review on carboetherification and carboamination, see: J. P. Wolfe, *Eur. J. Org. Chem.* **2007**, 571. For a recent carboamination, see: C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 9488.
[6] For examples of diacetoxylation, see: a) Y. Li, D. Song, V. M. Dong, *J. Am. Chem. Soc.* **2008**, *130*, 2962; b) A. Wang, H. Jiang, H. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 3846.
[7] M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 17272.
[8] a) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; b) M. E. Welker, *Chem. Rev.* **1992**, *92*, 97.
[9] For a review on propargyl alcohols and amines in cycloadditions, see: S. Yamazaki, *Chem. Eur. J.* **2008**, *14*, 6026.
[10] For a review on chloropalladation, see: X. Lu, *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 2* (Ed.: E. J. Negishi), Wiley-VCH, Weinheim, **2002**, p. 2267.
[11] *Trans* chloropalladation could also lead to the Pd–Cl intermediate **II** without the Pd–carboxylate bond.
[12] J. P. Wolfe, *Synlett* **2008**, 2913.
[13] S. Ma, X. Lu, *J. Org. Chem.* **1993**, *58*, 1245.
[14] G. Zhu, S. Ma, X. Lu, Q. Huang, *J. Chem. Soc. Chem. Commun.* **1995**, 271.
[15] X. Lu, G. Zhu, Z. Wang, *Synlett* **1998**, 115.
[16] W.-L. Xiao, L.-M. Yang, N.-B. Gong, L. Wu, R.-R. Wang, J.-X. Pu, X.-L. Li, S.-X. Huang, Y.-T. Zheng, R.-T. Li, Y. Lu, Q.-T. Zheng, H.-D. Sun, *Org. Lett.* **2006**, *8*, 991.
[17] One reviewer proposed an interesting alternative pathway that involves carbopalladation to form a seven membered ring bearing a primary alkylpalladium chloride; this intermediate could then undergo ($CuCl_2$ induced) C–O bond-forming reductive elimination.

