

Palladium-Catalyzed Intramolecular Carboesterification of Olefins**

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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 preceded.^[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 Pd⁰ species with CuCl₂ 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

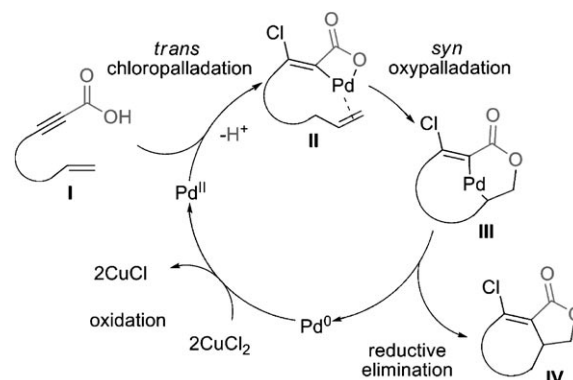


Figure 1. Proposed [3+2] cycloaddition of propiolic acids.

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	<i>n</i> Bu ₄ NCl (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.

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 [PdCl₂(MeCN)₂] and three equivalents of CuCl₂ 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 *n*Bu₄NCl was added in addition to CuCl₂, 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).

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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.

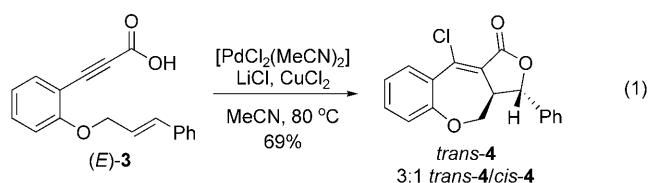
Replacing the ether oxygen atom with a methylene group resulted in a 71% yield of **2i** (Table 2, entry 9). The introduction of a phenyl substituent on this carbon atom gave a 2.5:1 ratio of diastereoisomers in 52% overall yield, with the major product having 1,3-*cis* stereochemistry (Table 2, entry 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

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

Entry	Substrate	Product	X	Yield ^[b] [%]
1				82 ^[c]
2			Me	86
3			MeO	61 ^[d]
4			F	88
5			Me	85
6			MeO	90
7			CH ₂	71 ^[e]
8				54 ^[e]
9			CH ₂	71
10			CHPh	52 ^[f]
11			S	0

[a] Reaction conditions: 0.2 mmol scale, [PdCl₂(MeCN)₂] (1 mol%), LiCl (3 equiv), CuCl₂ (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.



the reaction conditions, therefore, 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]

Experimental Section

A solution of [PdCl₂(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 CuCl₂ (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.

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