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Palladium-Catalyzed Annulation Reactions for Diastereoselective Cyclopentene Synthesis

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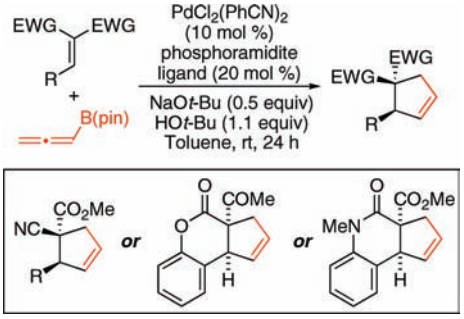
ABSTRACT



Palladium-catalyzed annulation reactions of conjugate acceptors and allenyl boronic ester provide substituted cyclopentenes in high yields and, where applicable, diastereoselectivities. This method provides rapid assembly of building blocks for natural product synthesis, including polycyclic lactone and lactam products. Reactions are hypothesized to initiate by conjugate addition of a nucleophilic propargylpalladium complex.

Cascade reactions are efficient methods for the construction of multiple bonds in a single reaction flask and provide rapid entry to molecular complexity.[1] The versatility of palladium catalysts for a variety of transformations suggests that they may be ideally suited for multistep processes, provided that the catalyst favors one pathway over divergent routes.[2−4] We report a palladium-catalyzed annulation of allenylboronic acid pinacol ester with alkylidene cyanoacetic esters and malononitriles to provide substituted cyclopentenes (eq 1).[5−7]

Nucleophilic organopalladium complexes have gained attention as useful reaction intermediates.[8] Our laboratory

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(2) (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley & Sons: New York, 2004. (b) Muller, T. J. J. *Top. Organomet. Chem.* **2006**, *19*, 149.

(3) For select examples of palladium-catalyzed multistep reactions, see: (a) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. (b) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836. (c) Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2010**, *2*, 192. (d) Coscia, R. W.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 2496. (e) Arai, S.; Koike, Y.; Hada, H.; Nishida, A. *J. Am. Chem. Soc.* **2010**, *132*, 4522. (f) Franzén, J.; Löfstedt, J.; Dorange, I.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2002**, *124*, 11246.

(4) Williams, F. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 4459.

(5) During our studies, a related palladium-catalyzed annulation reaction of alkylidene malononitriles was reported: Lu, S.; Jin, T.; Bao, M.; Yamamoto, Y. *Org. Lett.* **2010**, *12*, 864. Alternative electrophiles including cyanoester **1a** provided low yields (< 30%).

(6) For formal palladium catalyzed [3 + 2] annulation for synthesis of methylenecyclopentanes, see: (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429. (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1986**, *25*, 1. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(7) Examples of cyclopentene synthesis from allenes and enones using phosphine catalysts: (a) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (b) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. From alkynes and enals using amine catalysts:(c) Zhao, G.-L.; Ullah, F.; Deiana, L.; Lin, S.; Zhang, Q.; Sun, J.; Ibrahem, I.; Dziedzic, P.; Córdova, A. *Chem.—Eur. J.* **2010**, *16*, 1585. (d) Jensen, K. L.; Franke, P. T.; Arróniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 1750.

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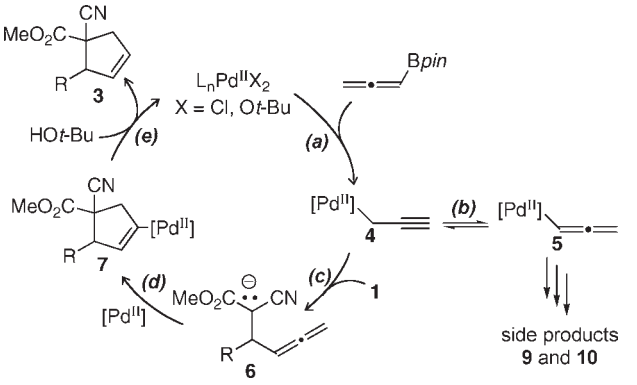
has previously studied these complexes in the conjugate allylation reactions of *N*-acylpyrroles and alkylidene malononitriles.[9] We envision that by utilizing this umpolung reactivity of a propargylpalladium complex we could build molecular complexity through a cascade process. Reactions would initate through nucleophilic attack of the propargylpalladium complex on a conjugate acceptor and subsequently utilize the resultant carbon nucleophile and allene functionalities.[10] However, the reaction selectivity would be complicated by equilibration of propargyl- and allenylpalladium complexes that may occur under these reaction conditions (Scheme 1).[11] Therefore, successful development of the reaction would require identification of catalysts that would be able to control the relative reactivity of these intermediates.

A working model of a catalytic cycle for cyclopentene synthesis from allenylboronic ester and alkylidene cyano esters is outlined in Scheme 1. In analogy to our earlier work, we proposed that allenylboronic ester **2** would be a suitable precursor for formation of the requisite organopalladium complexes in situ.[12] Transmetalation of allenylboronic acid pinacol ester with a Pd(II) catalyst would proceed through an S_E2' mechanism to provide propargylpalladium complex **4** (step a). While equilibration of **4** to provide allenylpalladium complex **5** could occur (step b),[13] we hypothesized that the relative reactivities of complexes **4** and **5** could be modulated by ligand tuning which would allow for the acceleration of one pathway over the alternatives. Conjugate attack of **4** on the electrophile would produce allene **6** (step c).[14] Alternatively, intermediate **6** could arise from migratory insertion of allenylpalladium complex **5** with the electrophile.[15] Finally, endo carbopalladation of the pendant allene and protodepalladation would generate cyclopentene product **3** (steps d and e).[3e,16−20]

Scheme 1. Proposed Annulation Reaction[a]



[a] (a) Transmetalation; (b) isomerization; (c) allenylation of electrophile; (d) carbopalladation; (e) protodepalladation.

During our initial evaluation of reaction conditions we identified several ligands that promoted formation of cyclopentene **3** (Table 1). Mono- and bidentate phosphines provided low conversion (entries 1 and 2). A phosphite ligand provided a mixture of cyclized products presumably resulting from reaction of both allenyl- and propargylpalladium complexes **4** and **5,** as well as linear products arising from the interruption of the catalytic cycle (entry 3). We found that ligation of the palladium catalyst by a monodentate phosphoramidite promoted the selective formation of cyclopentene **3a** in the highest yields (entries 4−5).[21,22] These data support our initial hypothesis that ligand tuning can be used to influence the relative reactivity of complexes **4** and **5**.[23] Notably, with phosphoramidite ligands, acyclic products (**8a** and **9a**) were not formed and

(8) Zanoni, G.; Pontiroli, A.; Marchetti, A.; Vidari, G. *Eur. J. Org. Chem.* **2007**, 3599.

(9) (a) Shaghafi, M. B.; Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2008**, *10*, 4743. (b) Waetzig, J. D.; Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2009**, *65*, 3197. (c) Barczak, N. T.; Grote, R. E.; Jarvo, E. R. *Organometallics* **2007**, *27*, 4863.

(10) A related transformation, enantioselective silver-catalyzed propargylation reaction of imines, has been developed in our laboratories: Wisniewska, H. M.; Jarvo, E. R. *Chem. Sci.* **2011**, *2*, 807.

(11) Examples of reactions involving allenyl- and propargylpalladium complexes: (a) Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. *Organometallics* **1986**, *5*, 716. (b) Ogoshi, S.; Fukunishi, Y.; Tsutsumi, K.; Kurosawa, H. *J. Chem. Soc., Chem. Commun.* **1995**, 2485. (c) Ogoshi, S.; Nishida, T.; Fukunishi, Y.; Tustusmi, K.; Kurosawa, H. *J. Organomet. Chem.* **2001**, *620*, 190. (d) Ma, S.; Zhang, A. *J. Org. Chem.* **2002**, *67*, 2287. (e) Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149. (f) Miyabe, H.; Yousuke, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 1415. (g) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2008**, *130*, 5048. (h) Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196.

(12) Boronic ester **2** is commercially available or may be prepared according to: Tonogaki, K.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 1464.

(13) Allenylpalladium complex **4** would likely be the more stable isomer, see refs 11a−11c.

(14) Examples of S_E2' attack of allenylmetal complexes on aldehydes: (a) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667. (b) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878. (c) Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550.

(15) For a review of the Heck reaction, see ref 2a, Chapter 3.2.

(16) Related cyclization reactions to form heterocycles: (a) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (b) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4257.

(17) Cyclization of allenyl malonates in the presence of vinylbromides proceeds through an alternative mechanism: Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1985**, *26*, 3795.

(18) For endo carbocyclizations of β-dicarbonyls with pendant alkynes, see: (a) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366. (b) McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691.

(19) To confirm that *t*-butanol is indeed the source of the proton in the product, the annulation reaction was performed using deutero-*tert*-butanol. Deuterium was incorporated into the cyclopentene ring solely at the C4 position and in 75% incorporation. See Supporting Information for details.

(20) A similar mechanism could be proposed for the cycloaddition reported by Yamamoto and co-workers, see ref 5.

(21) Synthesis of ligand L1: Bartels, B.; Garcia-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, *10*, 2569.

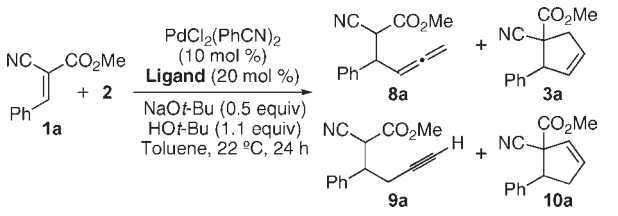
(22) The following control experiments were performed: in the absence of base, $PdCl_2(PhCN)_2$, ligand, or $PdCl_2(PhCN)_2$ and ligand the reaction does not give product. Replacing $PdCl_2(PhCN)_2$, with $Pd_2(dba)_3$ provided only 8% yield, consistent with a mechanism that avoids Pd(0) intermediates.

(23) An alternative mechanism involving scrambling of allenylboronic acid pinacol ester to propargylboronic acid pinacol ester followed by Lewis acid catalysis is possible, however, unlikely. Scrambling of the allenylboronic ester is not observed by ^{1}H NMR under the reaction conditions. Rather, allenylboronic acid pinacol ester decomposes to provide allene (C_3H_4). See Supporting Information1 for details.

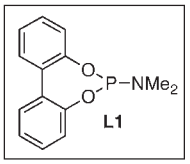
(24) Alternative bases (K_3PO_4, K_2CO_3, Cs_2CO_3, LiO*t*-Bu, KO*t*-Bu) were also examined. Only alkoxide bases gave desired product while all other bases gave product in < 10% yield.

products of reaction of allenylpalladium complex **5** (**9a** and **10a**) were formed only in trace amounts.[24]

Table 1. Palladium-Catalyzed Annulation Reaction



Entry	Ligand	Yield (%)[a] 8a	3a	9a	10a
1	PPh_3	--	33	--	--
2[b]	dppe	--	36	--	5
3	$(PhO)_3P$	--	5	11	6
4[c]	MonoPhos	--	74	--	trace
5[c]	**L1**	--	81	--	trace



[a] Yield determined by ^{1}H NMR spectroscopy by comparison to 2,4-dimethoxybenzene as internal standard. [b] Twelve mol % ligand used. [c] Isolated yield after silica gel chromatography.

With a suitable ligand to promote the annulation reaction, we examined the scope of the formal cycloaddition. A variety of alkylidene cyano esters underwent smooth conversion to cyclopentenes **3** (Table 2). The reaction was tolerant of various substituents, including aryl bromides, as well as chlorides and fluorides. Competitive oxidative addition was not a problem, consistent with our hypothesis that the catalyst remains in the Pd(II) oxidation state throughout the proposed catalytic cycle (Scheme 1).

Excellent control of the relative stereochemistry of the adjacent tertiary and quaternary stereogenic centers was achieved as all products were formed exclusively as a single diastereomer.[25] To determine the relative stereochemistry of the product cyclopentenes, product **3a** was derivatized to produce crystalline material suitable for X-ray diffraction. Selective reduction of the ester using $LiAlH_4$ followed by protection of the alcohol as the *p*-NO_2-benzoyl ester led to crystalline product **12** (Scheme 2). The X-ray structure of ester **12** conclusively shows the aromatic ring is trans to the protected alcohol.

(25) For comparison to the ^{1}H NMR spectra of our catalytic reactions, a mixture of both possible diastereomers of **3b** was prepared using the literature route for synthesis of substituted cyclopentenes. Comparison of the ^{1}H NMR spectra confirmed that in the unpurified reaction mixture from the palladium-catalyzed annulation reaction the minor diastereomer (**3b′**) was not present. See Supporting Information for details.

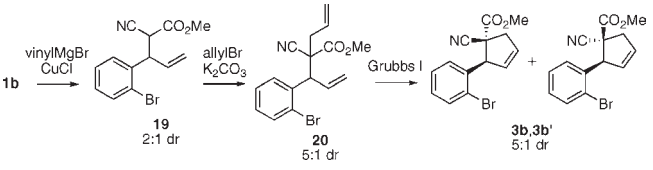
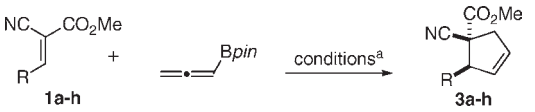


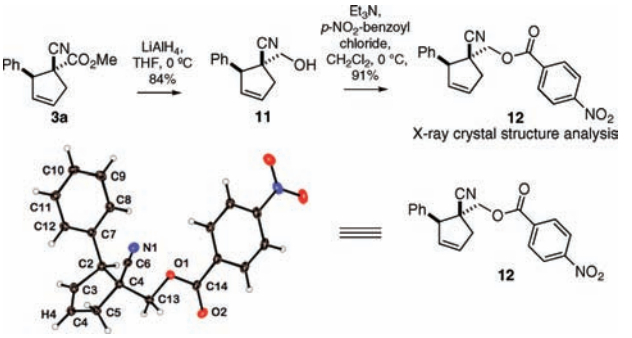
Table 2. Annulation of Benzylidene Cyanoacetic Esters



Entry	R	Substrate	Product	Yield (%)[b]
1		**1a**, R^1 = H	**3a**	81
2		**1b**, R^1 = 2-Br	**3b**	94
3	R^1	**1c**, R^1 = 4-Cl	**3c**	80
4		**1d**, R^1 = 3-CF_3	**3d**	91
5[c]		**1e**, R^1 = 4-Br	**3e**	65
6	Cl, F	**1f**	**3f**	98
7[c,d]	Br, R^2	**1g**, R^2 = OMe	**3g**	60
8[c]	Br, R^2	**1h**, R^2 = F	**3h**	74

[a] Conditions: Substrate (0.20 mmol), allenylboron (3.5 equiv), $PdCl_2(PhCN)_2$ (10 mol %), **L1** (20 mol %), NaO*t*-Bu (50 mol %), HO*t*-Bu (1.1 equiv) in toluene (0.25 M) at 22 °C for 24 h. [b] Isolated yield after silica gel chromatography. [c] One equivalent of NaO*t*-Bu was used. [d] Reaction performed with 20 mol % MonoPhos as ligand.

Scheme 2. Proof of Relative Stereochemistry



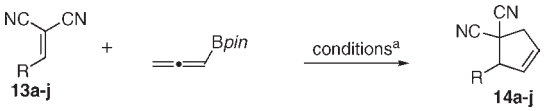
Alternative conjugate acceptors also participated in the annulation reaction (Table 3). A broad range of alkylidene malononitriles (**13**) reacted smoothly under our optimized reaction conditions. The reaction was tolerant of electron-rich and electron-deficient aryl substituents, as well as heterocycles (entry 10).

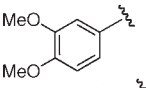
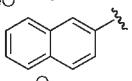
We envisioned that annulation to provide cyclopentenes could be useful in the synthesis of the polycyclic scaffolds of bioactive compounds (Scheme 3). Tricyclic lactam **16** comprises the A, B, and C rings of several melodinus

(26) (a) Cannon, J. R.; Croft, K. D.; Matsuki, Y.; Patrick, V. A.; Toia, R. F.; White, A. H. *Aust. J. Chem.* **1982**, *35*, 1655. (b) Guo, L.-W.; Zhou, Y.-L. *Phytochemistry* **1993**, *34*, 563. (c) Denmark, S. E.; Cottell, J. J. *Adv. Synth. Cat.* **2006**, *348*, 2397.

(27) Jaroch, S.; Hölscher, P.; Rehwinkel, H.; Sülzle, D.; Burton, G.; Hillmann, M.; McDonald, F. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1981.

Table 3. Annulation of Alkylidine and Benzylidene Malononitriles



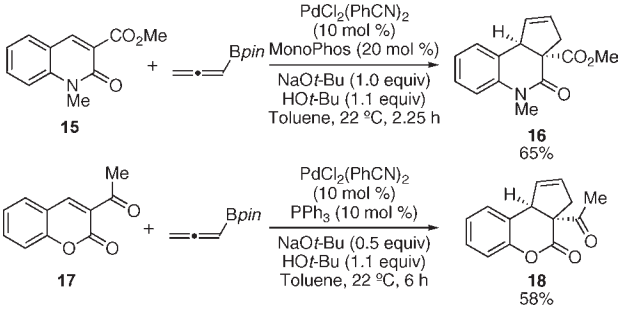
Entry	R	Substrate	Product	Yield (%)[b]
1		**13a**, R^1 = H	**14a**	77
2		**13b**, R^1 = 4-MeO	**14b**	60
3		**13c**, R^1 = 4-Me	**14c**	73
4		**13d**, R^1 = 4-CF_3	**14d**	80
5		**13e**, R^1 = 2-Br	**14e**	63
6		**13f**, R^1 = 3-F	**14f**	77
7		**13g**, R_1 = 4-Cl	**14g**	75
8		**13h**	**14h**	78
9		**13i**	**14i**	92
10[c]		**13j**	**14j**	63

[a] Conditions: Substrate (0.20 mmol), allenylboron (3.5 equiv), $PdCl_2(PhCN)_2$ (10 mol %), **L1** (20 mol %), NaO*t*-Bu (50 mol %), HO*t*-Bu (1.1 equiv) in toluene (0.25 M) at 22 °C for 24 h. [b] Isolated yield after silica gel chromatography. [c] One equivalent of NaO*t*-Bu was used.

alkaloids including scandine[26] and is structurally related to dihydroquinolines that have potent n-NOS inhibitory activity.[27] Tricyclic lactam **16** could be prepared by formal cycloaddition of quinolone **15**. Similarly, subjection of acetyl coumarin to the reaction conditions provided tricyclic lactone **18**.

In conclusion, we have developed a palladium-catalyzed ligand-controlled reaction to access substituted cyclopentenes. Annulation with a variety of benzylidene cyano esters and malononitriles was shown to be general in reactivity. A single diastereomer is obtained when benzylidene cyanoacetic esters are utilized. This method is successful for synthesis of fused heterocyclic ring systems that are the core of natural product scaffolds. The mechanism most likely proceeds by nucleophilic conjugate attack of a propargylpalladium intermediate. Further investigation into the scope and mechanism of the reaction as well as development of complementary reaction pathways is underway.

Scheme 3. Synthesis of Polycyclic Frameworks



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Supporting Information Available. Experimental details, spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.