ORGANIC LETTERS

2002
Vol. 4, No. 21
3679−3681

Synthesis of 2*H*-1-Benzopyrans via Palladacycles with a Metal-Bonded Stereogenic Carbon

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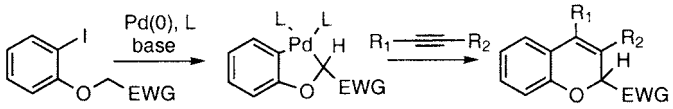
Received July 29, 2002

ABSTRACT

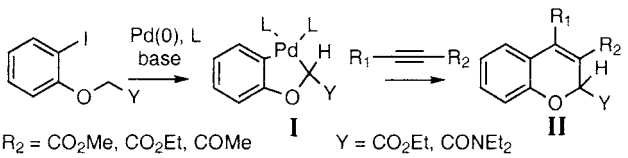


Stable oxapalladacycles have been prepared and converted into a series of highly functionalized 2*H*-1-benzopyrans via regioselective insertion of activated alkynes.

Palladium-catalyzed cascade reactions belong among the most powerful tools for the construction of carbon−carbon bonds.[1] Recently, new pathways for these transformations have been observed and rationalized by proposing palladacycles as intermediates.[2] In this context, systematic exploration of the chemistry of stable palladacycles[3] holds great synthetic promise. We envisioned that palladacycles could be prepared from achiral substrates with concomitant generation of a metal-bonded stereogenic carbon[4] and subsequently serve as templates for the introduction of the stereogenic center into valuable organic targets.

Herein, we describe a convergent synthesis of highly substituted 2*H*-1-benzopyrans based on the above outlined strategy (Scheme 1). Stable oxapalladacycles **I** have been prepared and converted into a series of 2*H*-1-benzopyrans **II** via regiocontrolled insertion of activated unsymmetrical alkynes. In this manner, diverse substituents can be attached to carbons C-2, C-3, and C-4 of the benzopyran skeleton, a feat that is difficult to accomplish by traditional methods.[5] The two-step protocol offers a new solution to the synthetic challenge posed by numerous biologically active compounds[6] featuring a benzopyran core with a stereogenic C-2 carbon. In contrast to previous reports that pointed to a rather limited reactivity of palladium-based complexes,[3a,7] novel palladacycles **I** reacted smoothly with activated alkynes bearing a variety of substituents R_1, including alkyl, aryl, and alkenyl groups (Scheme 1). Results reported herein constitute a foundation for the future development of catalytic and asymmetric variants of this protocol.

Scheme 1. Synthetic Strategy



I **II**

R_2 = CO_2Me, CO_2Et, COMe Y = CO_2Et, $CONEt_2$

R_1 = CO_2Me, Me, *n*-Bu, Ph, 1-cyclohexyl, TMS

(1) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag GmbH: Weinheim, 1998; Chapter 3.

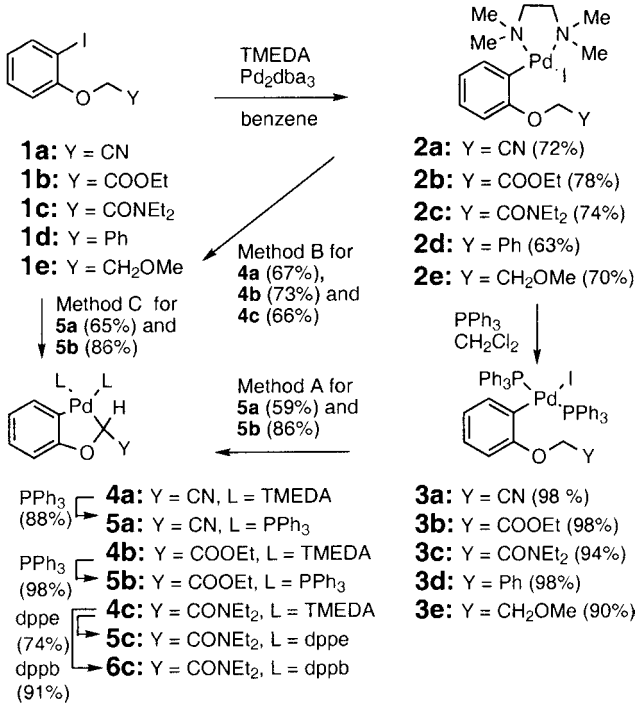
(2) (a) Lautens, M.; Paquin, J.-F.; Piguel, S. *J. Org. Chem.* **2002**, *67*, 3972−3974. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **2001**, *66*, 7372−7379. (c) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725−727. (d) Catellani, M.; Motti, E.; Baratta, S. *Org. Lett.* **2001**, *3*, 3611−3614. (e) Dyker, G. *Chem. Ber.* **1997**, *130*, 1567−1578. (f) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119−122. (g) Echavarren, A. M.; Gonzalez, J. J.; Garcia, N.; Gomez-Lor, B. *J. Org. Chem.* **1997**, *62*, 1286−1291.

(3) For examples of the preparation of stable palladacycles, see: (a) Campora, J.; Lopez, J. A.; Palma, P.; del Rio, D.; Carmona, E.; Valerga, P.; Graiff, C.; Tiripicchio, A. *Inorg. Chem.* **2001**, *40*, 4116−4126. (b) Martin-Matute, B.; Mateo, C.; Cardenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2001**, *7*, 2341−2348. (c) Mateo, C.; Fernandez-Rivas, C.; Cardenas, D. J.; Echavarren, A. M. *Organometallics* **1998**, *17*, 3661−3669. (d) van Belzen, R.; Hoffmann, H.; Elsevier: C. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1743−1745. (e) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1988**, *346*, C27−C30. (f) Diversi, P. Ingrosso, G.; Lucherini, A.; Murtas, S. *J. Chem. Soc., Dalton Trans.* **1980**, *9*, 1633−1637.

10.1021/ol0201456 CCC: $22.00
Published on Web 09/18/2002

Palladacycles **4**−**6** were prepared via several alternative pathways as shown in Scheme 2. Initially, stepwise protocols

Scheme 2. Synthesis of Palladacycles[a]



[a] Method A: *t*-BuOK, THF, rt, 10 min. Method B: *t*-BuOK, $AgNO_3$, THF, rt, 10 min. Method C: (i) Pd_2dba_3, Ph_3P, 55 °C, 30 min, (ii) *t*-BuOK, THF, rt, 10 min, benzene.

were explored. Iodoethers **1a**−**e**, accessible via O-alkylation of *o*-iodophenol,[8] were treated with Pd_2dba_3 and tetramethylethylenediamine (TMEDA) in benzene[9] to yield stable palladium(II) complexes **2a**−**e** that were converted into complexes **3a**−**e** via ligand exchange with Ph_3P.[10] Complexes **3a** and **3b** provided palladacycles **5a** and **5b** in good to excellent yields (59−86%) upon reaction with appropriate bases (LDA or *t*-BuOK). Treatment with *t*-BuOK (1 M in THF) proved to be the method of choice (Method A, Scheme 2). Palladacycles **4a**−**c** bearing the TMEDA ligand have been obtained in 66−73% yields upon treatment of complexes **2a**−**c** with *t*-BuOK and $AgNO_3$ (Method B, Scheme 2). The silver salt is not essential for ring closure, and the additive only facilitates chromatographic purification of highly polar complexes **4a**−**c**. Conversion of complex **2b** into palladacycle **4b** was also induced by PhOK. However, the palladacycle bearing the *N*,*N*-diethylamide group and the Ph_3P ligand could not be obtained from complex **3c** by Method A. Furthermore, while exchange of the TMEDA ligands with Ph_3P proceeded uneventfully with complexes **4a** and **4b** giving palladacycles **5a** and **5b** (Scheme 2), the analogous transformation did not occur with palladacycle **4c** featuring the amide group.[11] When Ph_3P was replaced with the less sterically demanding 1,2-bis(diphenylphosphino)ethane (dppe) and 1,4-bis(diphenylphosphino)butane (dppb) ligands, the exchange reaction afforded the expected palladacycles **5c** and **6c** in good yields (Scheme 2). Thus, it appears that the combined steric bulk of the amide group and of the two Ph_3P ligands may also be responsible for the failure of the ring-closure reaction of complex **3c**. None of the methods described above allowed closure to the palladacyclic ring when complexes **2d,e** and **3d,e** (Y = Ph, CH_2OMe) lacking the electron-withdrawing substituents were employed. Attempts to cyclize complexes **2b** and **3b** by treatment with less basic reagents (DBN, TEA, K_2CO_3) were unsuccessful. Apparently, formation of the Csp^3−Pd bond proceeds via an intramolecular ligand substitution process that requires the presence of low equilibrium concentrations of enolate anions.[12] Finally, a practical high-yielding one-pot preparation of palladacycles **5a,b** from the aryl iodides **1a,b** has been developed (Method C, Scheme 2), which allowed us to routinely prepare the palladacycles on a 1 g scale. Palladacycles **4**−**6** were obtained as air-stable white solids. Structure assignments based on spectroscopic data were

(4) Palladacycles with a metal-bonded stereogenic carbon, other than those containing the norbornane skeleton, are rare. See: (a) Hashmi, A. S. K.; Naumann, F.; Bolte, M. *Organometallics* **1998**, *17*, 2385−2387. (b) Munz, D.; Stephan. C.; Dieck, H. T. *J. Organomet. Chem.* **1991**, *407*, 413−420. However, *cyclopalladated* and *cycloplatinated* complexes with a metal-bonded stereogenic carbon are known and have been prepared in a nonracemic form. See: (c) Ryabov, A. D.; Panyashkina, I. M.; Polyakov, V. A.; Fischer, A. *Organometallics* **2002**, *21*, 1633−1636. (d) Garcia-Ruano, J. L.; Gonzalez, A. M.; Barcena, A. I.; Camazon, M. J.; Navarro-Ranninger, C. *Tetrahedron*: *Asymmetry* **1996**, *7*, 139−148. (e) Spencer, J.; Pfeffer, M. *Tetrahedron*: *Asymmetry* **1995**, *6*, 419−426. (f) Yoneda, A.; Hakushi, T. *Organometallics* **1994**, *13*, 4912−4918. (g) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 567−576.

(5) For the preparation of 2*H*-1-benzopyrans, see: (a) Goujon, J. Y.; Zammattio, F.; Pagnoncelli, S.; Boursereau, Y.; Kirschleger, B. *Synlett* **2002**, 322−324. (b) Parker, K. A.; Mindt, T. L. *Org. Lett.* **2001**, *3*, 3875−3878. (c) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063−4065. (d) Wipf, P.; Weiner, W. S. *J. Org. Chem.* **1999**, *64*, 5321−5324. (e) Grubbs, R. H.; Chang, S. *J. Org. Chem.* **1998**, *63*, 864−866. (f) Hoveyda, A. H.; Harrity, J. P. A.; Wisser, J. S.; Gleason, J. D. *J. Am. Chem. Soc.* **1997**, *119*, 1488−1489. (g) Issa, Y.; Ramazani, A. *Synth. Commun*. **1997**, *27*, 1385−1390. (h) Bigi, F.; Carloni, S.; Maggi, R.; Muchetti, C.; Sartori, G. *J. Org. Chem.* **1997**, *62*, 7024−7027.

(6) For selected examples of biologically active 2*H*-1-benzopyrans, see: (a) Iwasaki, T.; Mihara, S.-I.; Shimamura, T.; Kawakami, M.; Masui, M.; Hayasaki-Kajiwara, Y.; Naya, N.; Ninomiya, M.; Fujimoto, M.; Nakajima, M. *J. Cardiovasc. Pharmacol*. **2001**, *37*, 471−482. (b) Mannhold, R.; Cruciani, G.; Weber, H.; Lemoine, H.; Derix, A.; Weichel, C.; Clementi, M. *J. Med. Chem.* **1999**, *42*, 981−991. (c) Tronchet, J. M. J.; Zerelli, S.; Bernardinelli, G. *J. Carbohydr. Chem.* **1999**, *18*, 343−359.

(7) Depending on the spectator ligands, alkyne insertions to the known palladacycles are often limited to reactions with dimethyl acetylenedicarboxylate (dmad). See: (a) Mateo, C.; Cardenas, D. J.; Fernandez-Rivas, C.; Echavarren, A. M. *Chem. Eur. J.* **1996**, *2*, 1596−1606. (b) Catellani, M.; Marmiroli, B.; Chiara-Fagnola, M.; Acquotti, D. *J. Organomet. Chem.* **1996**, *507*, 157−162. (c) Liu, D.-H.; Li, C.-S.; Cheng, C.-H. *Organometallics* **1994**, *13*, 18−20. For general references on alkyne insertions to group 10 metalacycles, see: (d) Campora, J.; Palma, P.; Carmona, E. *Coord. Chem. Rev.* **1999**, *193*−*195*, 207−281. (e) Bennett, M. A.; Macgregor, S. A.; Wenger, E. *Helv. Chem. Act*. **2001**, *84*, 3084−3104. (f) Campora, J.; Llebaria, A.; Moreto, J. M.; Poveda, M. L.; Carmona, E. *Organometallics* **1993**, *12*, 4032−4038.

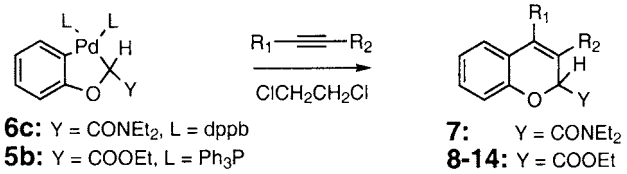
(8) Ramakrishnan, V. T.; Kagan, J. *J. Org. Chem.* **1970**, *35*, 2901−2904.

(9) Markies, B. A.; Canty, A. J.; de Graaf, W.; Boersma, J.; Janssen, M. D.; Hogerheide, M. P.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Organomet. Chem*. **1994**, *482*, 191−199.

(10) Ludwig, M.; Strömberg, S.; Svensson, M.; Åkermark, B. *Organometallics* **1999**, *18*, 970−975.

(11) An in situ monitoring of the reaction between amide **4c** and Ph_3P (2.2 equiv) via ^1H and ^{31}P NMR indicated the presence of an unreacted complex **4c**, along with low concentrations of the desired palladacycle [^{31}P NMR (202 MHz, $CDCl_3$) δ 24.5 (d, J = 27.7 Hz, 1 P), 26.7 (d, J = 27.3 Hz, 1 P)]. However, attempts to isolate this product failed.

Table 1. Reaction of Palladacycles with Alkynes



6c: Y = $CONEt_2$, L = dppb
5b: Y = COOEt, L = Ph_3P

7: Y = $CONEt_2$
8-14: Y = COOEt

	substrate	alkyne[a]	conditions: time (h)	conditions: temp (°C)	product	yield (%)	R_1	R_2
1	**6c**	$MeO_2CC{\equiv}CCO_2Me$	5[d]	80	**7**	64	CO_2Me	CO_2Me
2	**5b**	$MeO_2CC{\equiv}CCO_2Me$	1	40	**8**	95	CO_2Me	CO_2Me
3	**5b**	$MeC{\equiv}CCO_2Et$	6[d]	80	**9a**[b]	54	Me	CO_2Et
					9b		CO_2Et	Me
4	**5b**	*n*-$BuC{\equiv}CCO_2Et$	6	80	**10**	79	*n*-Bu	CO_2Et
5	**5b**	$PhC{\equiv}CCO_2Et$	5	80	**11**	76	Ph	CO_2Et
6	**5b**	$PhC{\equiv}CCOCH_3$	6[d]	80	**12**	59	Ph	$COCH_3$
7	**5b**	$C_6H_9C{\equiv}CCO_2Et$[c]	5[d]	80	**13**	57	C_6H_9[c]	CO_2Et
8	**5b**	$TMSC{\equiv}CCO_2Et$	7[d]	80	**14**	36	TMS	CO_2Et

[a] 2.2 molar equiv of alkyne was used. [b] A 6:1 mixture of products **9a** and **9b** was isolated. [c] C_6H_9 = 1-cyclohexenyl. [d] Reaction mixture was stirred for additional 20 h at room temperature.

further corroborated by X-ray crystallographic analyses of palladacycles **4a** and **5c**.

Complexes **5b** and **6c** reacted with dimethyl acetylenedicarboxylate (dmad) to afford benzopyrans **7** and **8** (Table 1, entries 1 and 2) in good to excellent yields (64−95%). The ability of palladacycle **6c** stabilized by a bidentate ligand (dppb) to undergo the insertion reaction is notable.[13] Alkyne insertions with complex **5a** had to be run under high dilution to avoid the formation of unidentified precipitates, while palladacycles **4a**−**c** and **5c** failed to react with dmad. Palladacycle **5b** inserted smoothly a variety of unsymmetrical alkynes activated by a ketone or an ester group and featuring alkyl (methyl, *n*-butyl, entries 3 and 4), phenyl (entries 5 and 6), and 1-cyclohexenyl (entry 7) substituents to afford benzopyrans **9**−**13** in 54−79% yields after chromatography (Table 1). The presence of a sterically bulky trimethylsilyl group in the alkyne reduced the yield of the corresponding benzopyran **14** to 36% (entry 8). Benzopyrans **10**−**14** were isolated as single regioisomers, and analyses of the crude reaction mixtures (entries 4−8) by ^{1}H NMR did not provide any evidence for the formation of regioisomeric products. A single exception among the unsymmetrical alkynes was noted in the reaction of ethyl 2-butynoate (entry 3). Benzopyran **9** was isolated in 54% yield as an inseparable mixture of two regioisomers in a 6:1 ratio (^{1}H NMR and GC). The major regioisomer **9a** was obtained as a pure compound in a lower yield (31%) after limiting the reaction time. The observed regioselectivity points to an electronic control exerted by the alkyne substituents.[7e] An alkyne lacking the activating substituent (PhC≡CPh) afforded only traces of the expected benzopyran. To determine the regiochemistry of the insertion reaction, long-range ^{1}H−^{13}C connectivities in the benzopyrans **9a** and **10**−**14** obtained from an HMBC 2D-NMR experiment were examined.[14]

Palladium(0) was recovered from the reaction mixture in entry 2 (Table 1) as [$(Ph_3P)_2$Pd(dmad)] in 72% yield.[15]

In conclusion, synthesis of novel palladacycles with a metal-bonded stereogenic sp^3-hybridized carbon has been described. The utility of the palladacycles as templates for the preparation of biologically significant targets has been demonstrated by a remarkably regiocontrolled synthesis of highly substituted 2*H*-1-benzopyrans. Studies of a ligand-induced asymmetry transfer are in progress, and the development of a catalytic variant is being pursued.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, to Kansas NSF EPSCoR and to Kansas Technology Enterprise Corporation for support of this research. We thank our colleague Dr. Douglas R. Powell for his assistance with X-ray crystallography.

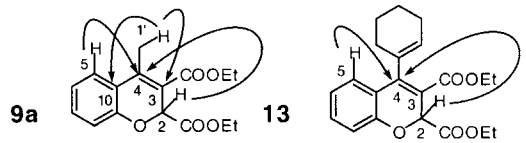
Supporting Information Available: Complete descriptions of the synthesis and characterization of all compounds prepared in this study and X-ray crystallographic studies of palladacycles **4a** and **5c**. This material is available free of charge via Internet at http://pubs.acs.org.

OL0201456

(12) Stable arylpalladium(II) enolates have been isolated. See: (a) Hartwig, J. F.; Culkin, D. A. *J. Am. Chem. Soc.* **2001**, *123*, 5816−5817. Palladium-catalyzed α-arylation of ketones, esters and amides is known. See: (b) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546−6553. (c) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261−1268.

(13) The majority of the known alkyne insertion reactions involve metalacycles bearing monodentate ligands; see refs 3a and 7.

(14) Indicative HMBC correlations for benzopyrans **9a** and **13**:



(15) Urata, H.; Suzuki, H.; Moro-oka, Y.; Ikawa, T. *J. Organomet. Chem.* **1989**, *364*, 235−244.