ORGANIC LETTERS

2010
Vol. 12, No. 8
1796−1799

Selective Synthesis of Allenes and Alkynes through Ligand-Controlled, Palladium-Catalyzed Decarboxylative Hydrogenolysis of Propargylic Formates

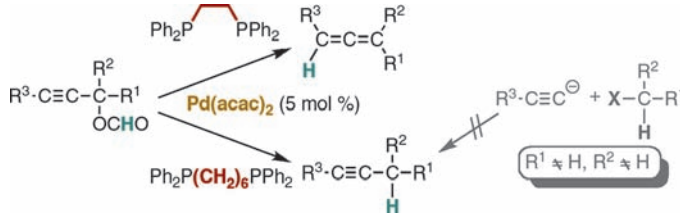
Hirohisa Ohmiya, Mingyu Yang, Yoshihiro Yamauchi, Yuhki Ohtsuka, and Masaya Sawamura*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

sawamura@sci.hokudai.ac.jp

Received February 17, 2010

ABSTRACT



Ligand-controlled regioselective palladium-catalyzed decarboxylative hydrogenolysis of propargylic formates is described. A wide range of allenes and alkynes were obtained by using either 1,2-diphenylphosphinoethane (DPPE) or 1,6-bisdiphenylphosphinohexane (DPPH) as a catalyst ligand.

Palladium-catalyzed decarboxylative hydrogenolysis of propargylic alcohol derivatives is a potentially useful method of synthesizing allenes or alkynes. Tsuji, Mandai, and coworkers disclosed effective Pd-PBu_3 catalyst systems for decarboxylative hydrogenolysis of propargylic formates and carbonates.[1,2] The catalytic reaction was selective in certain cases, forming either allenes or alkynes, but the regioselectivity was highly dependent on the structure of the substrate, limiting the synthetic utility.[3,4] Specifically, allenes were obtained only when the propargylic formates or carbonates were terminal alkynes (Scheme 1a) or primary alcohol derivatives (Scheme 1b), producing only terminal monosubstituted allenes (CH_2═C═CR^1R^2), while internal alkynes were obtained only from secondary alcohol derivatives with an internal alkyne moiety (Scheme 1c), producing disubstituted acetylenes with a primary alkyl substituent (−CH_2R^2). Thus, the Pd method is not general, as it does not afford internal allenes, and is not applicable to the reaction of tertiary alcohol derivatives to give the corresponding alkynes with a secondary alkyl substituent. Furthermore, the effect of an sp^2-substituent in the propargylic system has not been exploited.

In connection with our continuing studies on regiochemical control of metal-catalyzed allylic and propargylic substitution

(1) For reviews, see: (a) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1–24. (b) Ma, S. *Eur. J. Org. Chem.* **2004**, 1175–1183.

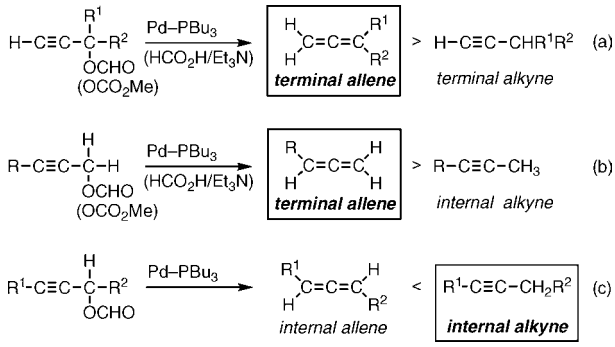
(2) (a) Tsuji, J.; Sugiura, T.; Yuhara, M.; Minami, I. *J. Chem. Soc. Chem., Chem. Commun.* **1986**, 922–924. (b) Tsuji, J.; Sugiura, T.; Minami, I. *Synthesis* **1987**, 603–606. (c) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 2161–2164. (d) Mandai, T.; Matsumoto, T.; Tsujiguchi, Y.; Matsuoka, S.; Tsuji, J. *J. Organomet. Chem.* **1994**, *473*, 343–352.

(3) Dixneuf et al. showed that a Pd$(dba)_2$-DPPE (or DPPP) catalyst system converted alkynyl cyclic carbonates into α-allenyl alcohols with excellent regioselectivity in the presence of formic acid and triethylamine, whereas homopropargylic alcohols were preferentially formed when using PBu_3 or DPPH as a ligand. These ligand effects are similar to our observations in this study. See: Darcel, C.; Bartsch, S.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1994**, 457–458.

(4) For regioselective conversion of steroidal propargylic formates to alkynes using a Pd-PMe_3 system, see: Radinov, R.; Hutchings, S. D. *Tetrahedron Lett.* **1999**, *40*, 8955–8960.

10.1021/ol100405k
Published on Web 03/19/2010

Scheme 1. Decarboxylative Hydrogenolysis of Propargylic Formates using a Pd-PBu_3 Catalyst System

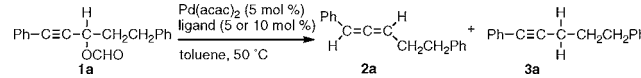


reactions, we reexamined the Tsuji−Mandai propargylic hydrogenolysis reaction.[5,6] We found interesting ligand effects that allowed selective synthesis of allenes and alkynes with a significantly expanded substrate scope.[7] Using DPPE as a ligand, internal allenes were obtained with excellent selectivity through γ-selective hydrogenolysis of internal alkynes.[3] Changing the ligand from DPPE to DPPH caused a reversal of regioselectivity, resulting in α-selective (propargylic) hydrogenolyis, which formed the corresponding alkynes with excellent selectivity in many cases.

We began by using a secondary alkyl formate (**1a**) with a phenylacetylene moiety, because the electronic effect of an aryl group at the γ-position had not been studied (Table 1).[8] Under the conditions required for the $Pd(acac)_2$-PBu_3 catalyst system based on the Tsuji−Mandai protocol, decarboxylative hydrogenolysis of **1a** afforded a mixture of alkene **2a** and alkyne **3a** in a 25:75 ratio (Table 1, entry 1).[9] Comparison of this allene/alkyne selectivity with previously reported high alkyne selectivities in the reactions of the corresponding propargylic formates with *alkyl*acetylene moieties suggests that the aryl group at the alkyne terminal exerts a significant electronic effect, inducing the formation of an allene. Almost no reaction occurred when the PPh_3 ligand was used (entry 2). Using common bisphosphine ligands of the type $Ph_2P(CH_2)_nPPh_2$ ($n = 1-6$), we observed an interesting trend in allene/alkyne selectivity (entries 3−8).[10] While DPPM inhibited the reaction completely (entry 3), the reaction with DPPE, which is generally regarded as a narrow bite-angle chelating ligand, proceeded smoothly and cleanly to give an isomeric mixture of the hydrogenolysis products in almost quantitative yield with a reaction time of 5 h at 50 °C (entry 4). More importantly, the reaction showed excellent regioselectivity (98:2), favoring the allene (**2a**) over the alkyne (**3a**). Furthermore, the regioselectivity was dramatically changed as the ligand methylene chain length increased from C2 to C5, with DPPPE ($n = 5$) giving complete selectivity toward the alkyne (**3a**) (entries 4−7). Although the rate of the alkyne-selective reaction with DPPPE was significantly lower than that of the allene formation reaction with DPPE (25 and 5 h, respectively), the reaction time was shortened to 14 h when the DPPH ligand, which contains an even longer methylene chain ($n = 6$), was used, and complete alkyne selectivity was retained (entry 8).

At first glance, the change in selectivity associated with increasing linker chain length appears to be related to the P−Pd−P bite angle, but the results of the hydrogenolysis reaction with DPPF and XANTPHOS, which are usually regarded as wide-bite-angle ligands, did not support this (Table 1, entries 9 and 10). These ligands were not useful in terms of either chemoselectivity or regioselectivity.

Table 1. Effects of Various Ligands[a]



entry	ligand	time (h)	yield (%)[b]	allene/alkyne[c] (**2a**/**3a**)
1	PBu_3	9	78	25:75
2	PPh_3	26	trace	
3	DPPM [$Ph_2PCH_2PPh_2$]	26	0	
4	DPPE [$Ph_2P(CH_2)_2PPh_2$]	5	97	98:2
5	DPPP [$Ph_2P(CH_2)_3PPh_2$]	5	99	64:36
6	DPPB [$Ph_2P(CH_2)_4PPh_2$]	5	99	15:85
7	DPPPE [$Ph_2P(CH_2)_5PPh_2$]	25	93	1:>99
8	DPPH [$Ph_2P(CH_2)_6PPh_2$]	14	96	1:>99
9	DPPF	24	—[d]	
10	XANTPHOS	26	70	85:15

[a] Conditions: $Pd(acac)_2$ (0.0125 mmol), ligand (0.0125 or 0.025 mmol, Pd/P atom 1:2), **1a** (0.25 mmol), toluene (2.0 mL), 50 °C. [b] Combined yield of **2a** and **3a**. [c] Determined by ^1H NMR of the crude product. [d] Complex mixture.

The selective synthesis of allenes and alkynes from propargylic formates with a γ-*aryl* substituent by a catalyst containing either DPPE or DPPH may be generalized in terms of electronic modification of the aryl group and the substitution pattern at the propargylic (α) carbon atom, as

(5) For our studies of regioselective reactions of propargyl alcohol derivatives, see: (a) Zhong, C.; Sasaki, Y.; Ito, H.; Sawamura, M. *Chem. Commun.* **2009**, 5850–5852. (b) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774–15775. (c) Ohmiya, H.; Ito, H.; Sawamura, M. *Org. Lett.* **2009**, *11*, 5618–5620.

(6) For our studies of regioselective reactions of allyl alcohol derivatives, see: (a) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276–17277. (b) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 879–889. (c) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895–2897. (d) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035. (e) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857.

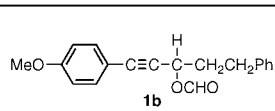
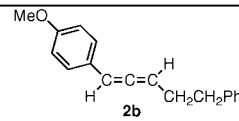
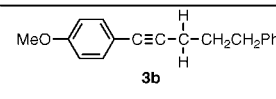
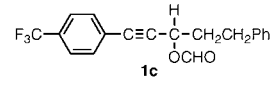
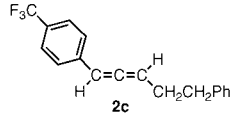
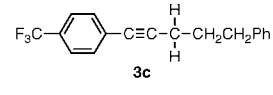
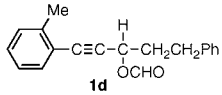
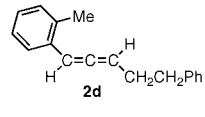
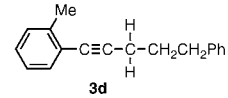
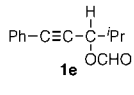
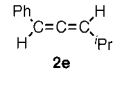
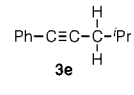
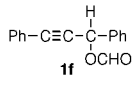
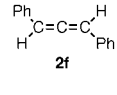
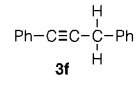
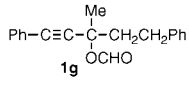
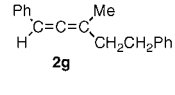
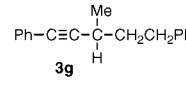
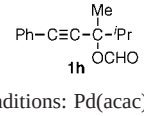
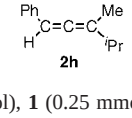
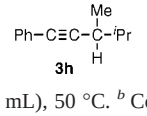
(7) For selective formation of allenes and alkynes through coupling reactions, see :(a) Ma, S.; Zhang, A.; Yu, Y.; Xia, W. *J. Org. Chem.* **2000**, *65*, 12287–12291. (b) Ma, S.; Zhang, A. *J. Org. Chem.* **2002**, *67*, 2287–2294. (c) Ma, S.; Wang, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4215–4217. (d) Zhao, J.; Yu, Y.; Ma, S. *Chem.—Eur. J.* **2010**, *16*, 74–80.

(8) A Pd-to-P atom ratio of 1:2 was crucial for reproducing catalytc activity and selectivity in all cases.

(9) The reaction of **1a** using a $Pd(acac)_2$-PBu_3 catalyst system (5 mol % Pd, Pd/P 1:1) resulted in no reaction in our hand.

(10) Similar trends in allene (**2a**)/alkyne (**3a**) selectivity were observed using DCE, THF and MeCN as a solvent. See Supporting Information for the details.

Table 2. Decarboxylative Hydrogenolysis of Propargylic Formates (**1b**−**h**) with a γ-Aryl Substituent[a]

entry	propargylic formate	ligand	time (h)	allene **2**	alkyne **3**	yield (%)[b]	allene/alkyne[c]
1	 **1b**	DPPE	4.5	 **2b**	 **3b**	84	97:3
2		DPPH	3.3			93	1:>99
3	 **1c**	DPPE	21	 **2c**	 **3c**	81	88:12
4		DPPH	21.5			88	2:98
5	 **1d**	DPPE	7.5	 **2d**	 **3d**	91	66:34
6		PBu_3	32			90	32:68
7		DPPH	12			–[d]	–
8	 **1e**	DPPE	4	 **2e**	 **3e**	97	99:1
9		PBu_3	9.5			93	6:94
10		DPPH	30			92	1:>99
11	 **1f**	DPPE	2	 **2f**	 **3f**	83	>99:1
12		PBu_3	47			–[d]	–
13		DPPH	4			96	52:48
14	 **1g**	DPPE	5	 **2g**	 **3g**	94	98:2
15		PBu_3	46			92	52:48
16		DPPH	3			96	1:>99
17	 **1h**	DPPE	2	 **2h**	 **3h**	95	>99:1
18		PBu_3	27			95	91:9
19		DPPH	6			92	5:95

[a] Conditions: $Pd(acac)_2$ (0.0125 mmol), ligand (0.0125 mmol), **1** (0.25 mmol), toluene (2.0 mL), 50 °C. [b] Combined yield of **2** and **3**. [c] Determined by ^1H NMR of the crude product. [d] Complex mixture.

summarized in Table 2. Formates (**1b**,**c**) with an electron-donating *p*-MeO or -withdrawing *p*-CF_3 group in the γ-aryl group were converted into the corresponding allenes (**2b**,**c**) and alkynes (**3b**,**c**) with high regioselectivity using DPPE and DPPH as respective ligands (entries 1−4). The *o*-Me substituent in **1d**, however, hampered the selective conversion (entries 5 and 7). A bulky alkyl substituent such as an isopropyl group was tolerated at the propargylic tertiary carbon, as shown by the highly selective conversion of **1e** to allene **2e** and alkyne **3e** (Table 2, entries 8 and 10). For the reactions of 1,3-diphenylpropargyl formate (**1f**) (entries 11−13), only the DPPE ligand was effective for regioselective conversion, affording the highly conjugated allene **2f**; this substrate seems to be electronically biased toward the formation of the more conjugated allene (**2f**) over the less conjugated alkyne (**3f**).

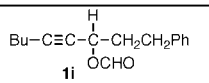
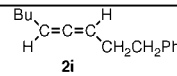
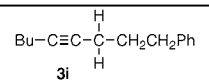
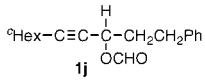
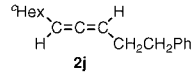
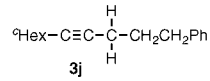
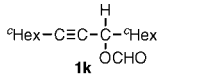
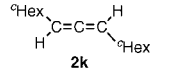
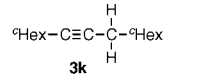
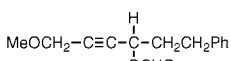
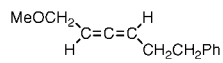
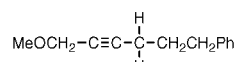
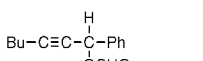
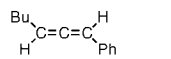
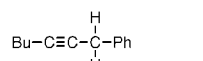
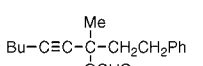
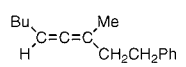
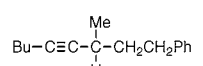
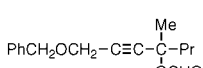
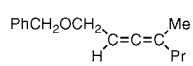
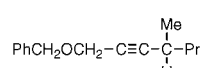
Notably, the tertiary propargylic formates **1g** and **1h** were also converted with high selectivity into trisubstituted allenes **2g**,**h** and alkynes (**3g**,**h**) with secondary alkyl substituents, using either DPPE or DPPH (Table 2, entries 14−19). Our studies also showed clearly that the Pd-PBu_3 system was less useful for both allene and alkyne synthesis from tertiary alkyl formates (entries 15 and 18).

Next, we investigated the applicability of the Pd-DPPE/DPPH system to the reaction of propargylic formates (**1i**−**o**) with an *alkyl* substituent at the alkyne terminal (γ-alkyl substituent) (Table 3). In agreement with the report by Tsuji, Mandai, and co-workers, the Pd-PBu_3 catalyst system converted a secondary alkyl formate with a γ-alkyl substituent (**1i**) to the corresponding alkyne **3i** with excellent regioselectivity (Table 3, entry 2). In contrast, Pd-catalyzed hydrogenolysis of **1i** with DPPE as a ligand afforded the allene isomer as a major product with high selectivity (entry 1). The Pd-DPPH system was not found to be useful in this case (entry 3). The selectivity trend observed for the DPPE and DPPH ligands was maintained in the reaction of the secondary alkyl formates **1j**,**k** with one or two more sterically demanding alkyl substituents (^{c}Hex) within the propargylic system (entries 4−7). Although the oxygen atom in the γ-substituent in **1l** disturbed the regioselectivity of the Pd-PBu_3 system to a considerable extent, selective synthesis of allene **2l** and alkyne **3l** using the Pd-DPPE/DPPH system tolerated the ether functional group well (entries 8−10).[11]

Upon changing the α-substituent from an alkyl group to a Ph group (formate **1m**), the regioselectivity of the Pd-PBu_3 system was reversed, with preferential formation of allene **2m** (allene/alkyne 90:10; Table 3, entry 12). As was the case for the 1,3-diphenylpropargyl formate **1f**, benzylic formate **1m** also seemed to be biased toward the formation of the

(11) The significant substituent effects of the alkoxy groups in **1l** and **1o** in favor of the allene formation in the reactions with either DPPE or PBu_3 ligands may be explained by orbital interactions between σ(C−Pd) and σ^*(C−O) orbitals in hypothetical (σ-allenyl)palladium(II) intermediates.

Table 3. Decarboxylative Hydrogenolysis of Propargylic Formates (**1i**−**o**) with a γ-Alkyl Substituent[a]

entry	propargylic formate	ligand	time (h)	allene **2**	alkyne **3**	yield (%)[b]	allene/alkyne[c]
1	 **1i**	DPPE	15	 **2i**	 **3i**	87	94:6
2		PBu_3	2			97	2:98
3		DPPH	4			94	32:68
4	 **1j**	DPPE	12	 **2j**	 **3j**	94	90:10
5		DPPH	12			95	69:31
6	 **1k**	DPPE	3	 **2k**	 **3k**	85	97:3
7		DPPH	7.5			72[d]	39:61
8	 **1l**	DPPE	2	 **2l**	 **3l**	84	98:2
9		PBu_3	21.5			91	17:83
10		DPPH	3.5			95	1:99
11	 **1m**	DPPE	1.5	 **2m**	 **3m**	89	>99:1
12		PBu_3	4			93	90:10
13		DPPH	5.5			90	1:>99
14	 **1n**	DPPE	2	 **2n**	 **3n**	95	97:3
15		PBu_3	8			99	38:62
16		DPPH	3			99	1:>99
17	 **1o**	DPPE	1	 **2o**	 **3o**	92	99:1
18		PBu_3	9			95	87:13
19		DPPH	4			84	2:98

[a] Conditions: $Pd(acac)_2$ (0.0125 mmol), ligand (0.0125 mmol), **1** (0.25 mmol), toluene (2.0 mL), 50 °C. [b] Combined yield of **2** and **3**. [c] Determined by ^1H NMR of the crude product. [d] NMR yield.

conjugated allene (**2m**) over the nonconjugated alkyne (**3m**). In agreement with this assumption, the reaction of **1m** using DPPE as a ligand afforded allene **2m** with excellent selectivity (>99:1, entry 11). Remarkably, the regioselectivity of this reaction was switched, giving complete alkyne formation (allene/alkyne 1:>99), by the use of DPPH as a ligand (entry 13).

The selective synthesis of allenes and alkynes using DPPE or DPPH, respectively, also tolerated the reactions of the tertiary propargylic formates **1n**,**o** with an *alkyl*acetylene moiety (Table 3, entries 14−19). The effect of quaternary substitution at the propargylic carbon in disturbing alkyne selectivity in the Pd-PBu_3 system is significant (entry 15), and selectivity was even reversed toward the allene when the effect overlapped with the heteroatom effect in the γ-substituent ($BnOCH_2$−) (entry 18).

In conclusion, our studies show that palladium-catalyzed decarboxylative hydrogenolysis of propargylic formates is useful in the synthesis of allenes and alkynes. The phosphine ligands DPPE, DPPH, and PBu_3 complement the palladium catalyst, covering a wide range of substrates. In most of the cases studied, DPPE and DPPH can be used for selective synthesis of allenes and alkynes, respectively, but PBu_3 is the ligand of choice for the synthesis of alkynes from secondary propargylic formates with an *alkyl*acetylene moiety. The synthesis of alkynes with a secondary alkyl substituent from tertiary propargylic formates using DPPH as a ligand is of particular interest because these alkynes are not accessible through alkylation of acetylides with the corresponding secondary alkyl halides. There are some exceptional and challenging cases, namely, the reaction of propargylic formates with a bulky aromatic γ-substituent, such as **1d**, and alkyne formation from 1,3-diarylpropargyl formates such as **1f**. At present, we have no clear explanation for the effect of the ligand on regioselectivity, but the results described here may assist future mechanistic studies of this reaction.[12] Studies of enantioselective reactions using chiral catalysts for the synthesis of chiral allenes and alkynes are ongoing in our laboratory.[13]

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology, Government of Japan. M.Y. thanks the China Scholarship Council for a fellowship.

Supporting Information Available: Experimental procedures and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100405K

(12) For mechanistic studies of palladium catalysis involving (η^3-allenyl/propargyl)palladium(II) species, see: (a) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687–2692. (b) Ogoshi, S.; Nishida, T.; Tsutsumi, K.; Ooi, M.; Shinagawa, T.; Akasaka, T.; Yamane, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 3223–3228.

(13) The reaction with the optically active propargylic formate (*S*)-**1k** in the presence of 5 mol % $Pd(acac)_2$/DPPE formed the racemic allene **2k**.