meso-Phbox-Pd(II) catalyzed tandem carbonylative cyclization of 1-ethynyl-1-propargyl acetate†

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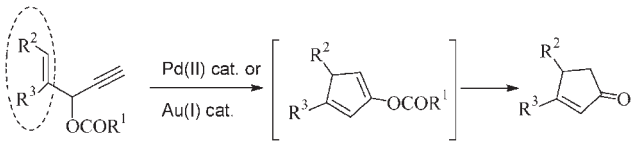
Palladium(II) catalyzed carbonylation of 1-ethynyl-1-propargyl acetate 1 is described; in the absence of the bisoxazoline (box) ligand, the second triple bond did not react, affording cyclic orthoesters 3 and 4. The use of *meso*-Phbox-Pd(II) strikingly changed the course of the reaction, yielding bicyclic lactone 2 by tandem carbonylative cyclization as a result of insertion of the second triple bond.

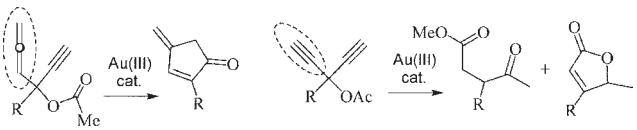
The transition metal-catalyzed reaction of unsaturated systems has recently proven to be a powerful method for the construction of a variety of carbo- and heterocycles.[1] A large number of reactions of propargylic esters mediated by transition metal catalysts have been recently reported.[2] For example, Rautenstrauch[3a] and Toste and co-workers[3b] reported palladium and gold catalyzed cycloisomerizations of propargylic acetates having a 1,4-enyne structure (Scheme 1).

Recently, we reported the gold catalyzed cycloisomerization of propargylic acetates having a 1,5-allenyne structure,[4a] and also the gold catalyzed double Wacker-type reaction[4b] of propargylic acetates having a 1,4-diyne structure (Scheme 2).

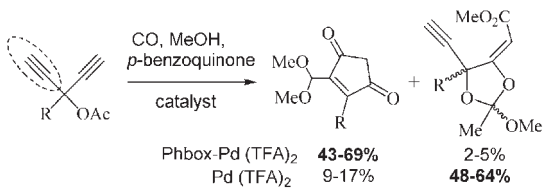
In addition, we reported the palladium complex catalyzed carbonylation of 1,4-diynes (Scheme 3).[4c] In the absence of the Phbox ligand, orthoesters are predominantly formed. However, the use of the Phbox ligand afforded functionalized 4-cyclopentene-1,3-diones as major products. Clearly, the Phbox ligand plays an important role in product selectivity. Although box ligands are among the most popular classes of chiral ligands in asymmetric chemistry, examples where the box ligand changes the course of the reaction are rare. During the course of our studies,[4a–c] we became interested in the palladium catalyzed carbonylation of propargylic acetates having a 1,5-diyne structure **1**. Herein, we report a *meso*-Phbox/$Pd(TFA)_2$ catalyzed tandem carbonylative cyclization of 1,2-diethynyl acetates **1** (Scheme 4).[5]



Scheme 1 1,4-Enynes: Rautenstrauch[3a] and Toste and co-workers.[3b]

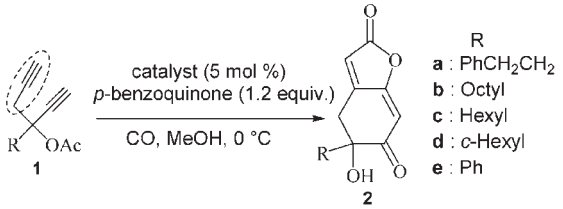


Scheme 2 1,5-Allenynes and 1,4-diynes (Au cat.): Kato *et al.*[4a,b]



Scheme 3 1,4-Diynes (Pd cat.): Kato *et al.*[4c]

Initially, we selected **1a** as a standard substrate to search for potential catalysts (Scheme 5, Table 1). The reaction of **1a** with $(CH_3CN)_2PdCl_2$ (5 mol%) in the presence of *p*-benzoquinone (1.2 equiv.) in methanol under carbon monoxide atmosphere (balloon) generated the expected[4c–e] product **3a** in 57% yield as a mixture of diastereomers (ratio = 2.5 : 1) along with a small amount (11%) of bicyclic lactone **2a** (Table 1, entry 1). As mentioned previously,[4c,f,g] the phosphine ligand seemed to be ineffective for reactions of this type, *i.e.*, a palladium complex of (*S*)-BINAP gave a complex mixture (entry 2), and $(Ph_3P)_2PdCl_2$ (entry 3) and BPPFA[6] did not show catalytic activity. In addition, the use of (2,2′-bipyridine)dichloropalladium(II) and (−)-sparteine/$Pd(TFA)_2$ resulted in no



Scheme 4 1,5-Diynes: this work.

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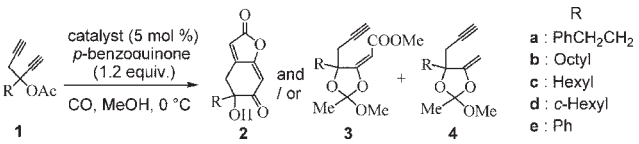


Scheme 5

reaction. In the case of $Pd(TFA)_2$, the second triple bond did not react at all, affording cyclic orthoesters **3** and **4** in 57–72% total yield (entries 4–8).

Next, we used the box ligand depicted in Fig. 1 according to our previous results (Scheme 3).[4c] Although the use of (*S*)-*i*-Prbox and (*S*)-Bnbox resulted in the formation of the bicyclic lactone **2a** in 34–43% yield together with an unidentified mixture (Scheme 4, Table 2, entries 1 and 2), (*S*)-Phbox and (±)-Phbox accelerated the reaction, and the yield improved to 86–87% (entries 3 and 4). However, the reaction of **1d** having a bulky cyclohexyl group was sluggish and the yield of **2d** was reduced to 51%. Dihydroxybenzaldehyde **5** (Fig. 1) was also produced as a by-product (entry 5). We then used the *meso*-Phbox ligand[7] depicted in Fig. 1. The yields of **2a** catalyzed by the palladium complexes of *meso*-Phbox and (±)-Phbox were almost identical (entries 4 and 6). However, the use of the *meso*-Phbox ligand improved the yield of **2d** (entry 7) and the products **2b**, **2c** and **2e** having octyl, hexyl and Ph groups were obtained in 82–86% yields (entries 8–10). Unfortunately, the internal acetylene **1f** was inert under the reaction conditions (Fig. 1). Product **2** contained a small amount of the corresponding acetate, and the structure of **2a** was determined by X-ray crystallographic analysis† after recrystallization (Fig. 2). Although the box ligands used in entries 1–3 were optically active, the products were almost racemic (2–9% ee).

A plausible mechanism for the present reaction is shown in Scheme 6. 1,2-Diethynyl acetate **1** coordinates to Pd(II) and this intermediate undergoes nucleophilic attack by MeOH to produce the vinyl palladium intermediate. This is followed by CO insertion or protonolysis to provide acyl palladium intermediate **A1** and enol ether **4**, respectively. In the absence of the Phbox ligand, the second triple bond does not react at all, suggesting that it does not coordinate to the palladium. The coordination of MeOH to **A1** leads to methoxy carbonylation to give ester product **3**. In the presence of the *meso*-Phbox ligand (Scheme 7), the bicyclic lactone **2** is the sole product, implying that the *meso*-Phbox ligand induces the coordination of the second triple bond to the palladium. As a result, the racemic substrate **1** produces two acyl palladium intermediates,

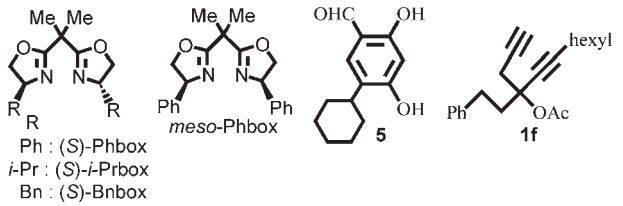


Fig. 1

Table 2 Carbonylation of **1** in the presence of box ligand (Scheme 4)

Entry	Catalyst[a]	R	*t*/h	Yield **2**[b] (%)
1	(*S*)-*i*-Prbox/$Pd(TFA)_2$	$PhCH_2CH_2$	22	**2a**: 43
2	(*S*)-Bnbox/$Pd(TFA)_2$	$PhCH_2CH_2$	20	**2a**: 34[c]
3	(*S*)-Phbox/$Pd(TFA)_2$	$PhCH_2CH_2$	4	**2a**: 87[d]
4	(±)-Phbox/$Pd(TFA)_2$	$PhCH_2CH_2$	5	**2a**: 86
5	(±)-Phbox/$Pd(TFA)_2$	*c*-Hexyl	8	**2d**: 51[e]
6	*meso*-Phbox/$Pd(TFA)_2$	$PhCH_2CH_2$	2	**2a**: 86
7	*meso*-Phbox/$Pd(TFA)_2$	*c*-Hexyl	2	**2d**: 75[f]
8	*meso*-Phbox/$Pd(TFA)_2$	Octyl	2	**2b**: 82
9	*meso*-Phbox/$Pd(TFA)_2$	Hexyl	2	**2c**: 86
10	*meso*-Phbox/$Pd(TFA)_2$	Ph	2	**2e**: 83

[a] $Pd(TFA)_2$ (5 mol%), ligand (7.5 mol%). [b] A small amount of the corresponding acetate of **2** was present (17 : 1 to 7 : 1). [c] 9% ee. [d] 2% ee. [e] Aldehyde **5** was obtained in 15% yield. [f] 5: 1 Mixture of **2d** and the corresponding acetate.

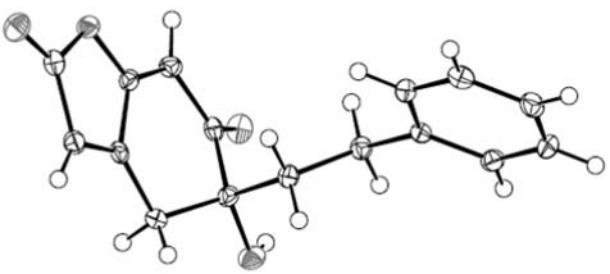


Fig. 2 X-Ray crystal structure of **2a**.

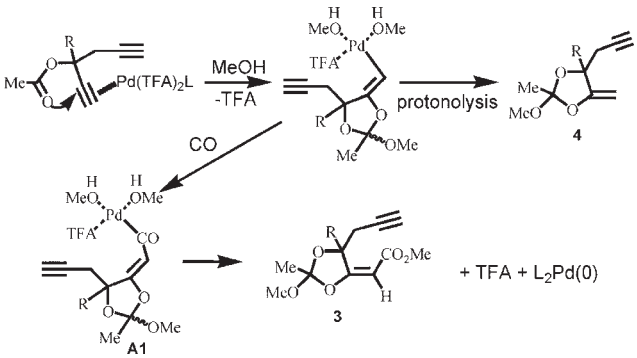
A2 and **A3**. Insertion of the second triple bond then occurs, followed by carbonylative lactonization and subsequent hydrolysis of the acetate, producing the bicyclic lactone **2**.

Although the precise mechanism of the reaction selectivity is still an open question, it might be ascribed to the different coordination sphere of palladium species **A**. The coordination

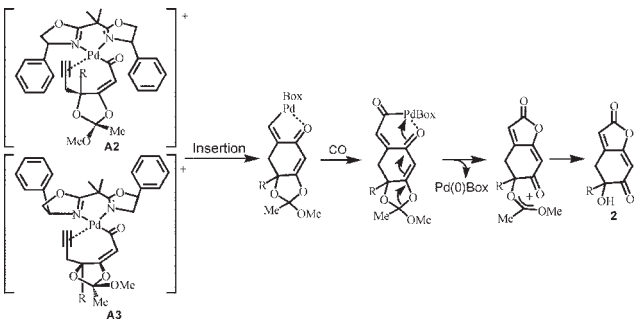
Table 1 Carbonylation of **1** in the absence of box ligand (Scheme 5)

Entry	Catalyst	*t*/h	Yield **2** (%)	Yield **3** (%) (ratio[a])	Yield of **4** (%) (ratio[a])
1	$(CH_3CN)_2PdCl_2$	10	**2a**: 11	**3a**: 57 (2.5 : 1)	—
2	(*S*)-BINAP/$Pd(TFA)_2$	48	Complex mixture		
3	$(Ph_3P)_2PdCl_2$	72	N.R.		
4	$Pd(TFA)_2$	4	—	**3a**: 22 (1.9 : 1)	**4a**: 50 (1.8 : 1)
5	$Pd(TFA)_2$	3	—	**3b**: 13 (1.9 : 1)	**4b**: 48 (1.9 : 1)
6	$Pd(TFA)_2$	1.5	—	**3c**: 15 (1.9 : 1)	**4c**: 51 (2.3 : 1)
7	$Pd(TFA)_2$	5	—	**3d**: 22 (3.1 : 1)	**4d**: 34 (6.6 : 1)
8	$Pd(TFA)_2$	27	—	**3e**: 33 (1 : 1)	**4e**: 25 (2.1 : 1)

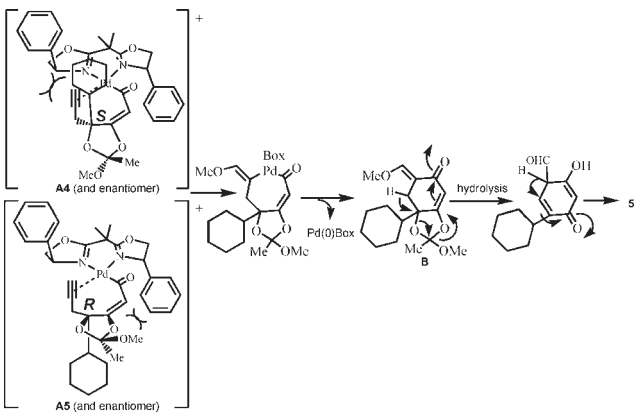
[a] Mixture of diastereomers.



Scheme 6 Plausible mechanism (I): in the absence of Phbox ligand.



Scheme 7 Plausible mechanism (II): in the presence of *meso*-Phbox ligand.



Scheme 8 Possible acyl palladium complex of (±)-Phbox and plausible mechanism for the generation of by-product **5**.

sphere of palladium in **A1** contains one acyl ligand, one TFA^-, and presumably two MeOH molecules, whereas **A2**/**A3** contain one acyl ligand and one Phbox ligand (two N-donor atoms) and the triple bond. Therefore, a cationic Pd(II) center with a C, N, N coordination will clearly be more electrophilic and thus more prone to bind the triple bond than a neutral Pd(II) center with a C, TFA^-, MeOH coordination. Moreover, the structures of **A2** and **A3** are more rigid than that of **A1** and this rigidity places the triple bond in a better position to bind to palladium than can be expected in the more flexible **A1**. Such factors may be playing an important role for the reaction selectivity. The difference in reactivity between the *meso*-Phbox and the (±)-Phbox ligands is believed to be caused by steric and/or electronic repulsion in the acyl palladium intermediates [**A2** and **A3** for *meso*-Phbox (Scheme 7) and **A4** and **A5** for (±)-Phbox (Scheme 8)].

In the case of **A4** and **A5**, steric and/or electronic repulsion between the phenyl ring and the cyclohexyl group inhibits the insertion of the second triple bond, allowing methoxy palladation of **A4** and/or **A5**, followed by reductive elimination to give intermediate **B** (Scheme 8). Hydrolysis of the enol ether moiety in intermediate **B** and subsequent aromatization afforded dihydroxybenzaldehyde **5** as a by-product. However, no considerable steric and/or electronic repulsion exists in the intermediates **A2** and **A3** (Scheme 7).

In conclusion, the *meso*-Phbox ligand strikingly changes the course of the carbonylation of 1-ethynyl-1-propargyl acetate **1**. $Pd(TFA)_2$ catalyzed single cyclization afforded cyclic orthoesters **3** and **4**, whereas the *meso*-Phbox-$Pd(TFA)_2$ complex catalyzed tandem carbonylative cyclization leading to bicyclic lactone **2**.

Notes and references

1 (*a*) *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, Wiley, New York, 2002, vol. II, p. 2309; for recent reviews, see: (*b*) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127; (*c*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (*d*) B. C. G. Soderberg, *Coord. Chem. Rev.*, 2004, **248**, 1085; (*e*) S. A. Vizer, K. B. Yerzhanov, A. A. A. A. Quntar and V. M. Dembitsky, *Tetrahedron*, 2004, **60**, 5499; (*f*) J. Muzart, *Tetrahedron*, 2005, **61**, 5955; (*g*) N. Asao, *Synlett*, 2006, 1645.

2 (*a*) N. Marion, S. Diez-Gonzalez, P. Fremont, A. R. Noble and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2006, **45**, 3647; (*b*) S. Wang and L. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 8414; (*c*) B. G. Pujanauski, B. A. B. Prasad and R. Sarpong, *J. Am. Chem. Soc.*, 2006, **128**, 6786; (*d*) L. Zhang and S. Wang, *J. Am. Chem. Soc.*, 2006, **128**, 1442; (*e*) J. Zhao, C. O. Hughes and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 7436; (*f*) L. Zhang, *J. Am. Chem. Soc.*, 2005, **127**, 16804; (*g*) M. J. Johansson, D. J. Gorin, S. T. Staben and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 18002; (*h*) K. Cariou, E. Mainetti, L. Fensterbank and M. Malacria, *Tetrahedron*, 2004, **60**, 9745.

3 (*a*) V. Rautenstrauch, *J. Org. Chem.*, 1984, **49**, 950; (*b*) X. Shi, D. J. Gorin and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 5802.

4 (*a*) K. Kato, T. Kobayashi, T. Fujinami, S. Motodate, T. Kusakabe, T. Mochida and H. Akita, *Synlett*, 2008, 1081; (*b*) K. Kato, R. Teraguchi, T. Kusakabe, S. Motodate, S. Yamamura, T. Mochida and H. Akita, *Synlett*, 2007, 63; (*c*) K. Kato, R. Teraguchi, S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin and O. V. Gusev, *Synlett*, 2007, 638; (*d*) K. Kato, Y. Yamamoto and H. Akita, *Tetrahedron Lett.*, 2002, **43**, 6587; (*e*) K. Kato, H. Nouchi, K. Ishikura, S. Takaishi, S. Motodate, H. Tanaka, K. Okudaira, T. Mochida, R. Nishigaki, K. Shigenobu and H. Akita, *Tetrahedron*, 2006, **62**, 2545; (*f*) K. Kato, C. Matsuba, T. Kusakabe, H. Takayama, S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin and O. V. Gusev, *Tetrahedron*, 2006, **62**, 9988; (*g*) T. A. Kusakabe, K. Kato, S. Takaishi, S. Yamamura, T. A. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin and O. V. Gusev, *Tetrahedron*, 2008, **64**, 319.

5 Recent examples of carbonylative cyclization: (*a*) S. Sugawara, K. Uemura, N. Tsukada and Y. Inoue, *J. Mol. Catal. A: Chem.*, 2003, **195**, 55; (*b*) A. Kamitani, N. Chatani and S. Murai, *Angew. Chem., Int. Ed.*, 2003, **42**, 1397; (*c*) R. Schiller, M. Pour, H. Fakova, J. Kunes and I. Cisarova, *J. Org. Chem.*, 2004, **69**, 6761; (*d*) Y. Harada, Y. Fukumoto and N. Chatani, *Org. Lett.*, 2005, **7**, 4385.

6 T. Hayashi, T. Mise, M. Fukushima, M. Kagotani, N. Nagashima, Y. Hamada, M. Akira, S. Kawakami, M. Konishi, K. Yamamoto and M. Kumada, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1138.

7 C. Foltz, B. Stecker, G. Marconi, S. Bellemin-Laponnaz, H. Wadepohl and L. H. Gade, *Chem.–Eur. J.*, 2007, **13**, 9912.