Synthetic Methods

DOI: 10.1002/anie.200806080

Intermolecular Methoxycarbonylation of Terminal Alkynes Catalyzed by Palladium(II) Bis(oxazoline) Complexes

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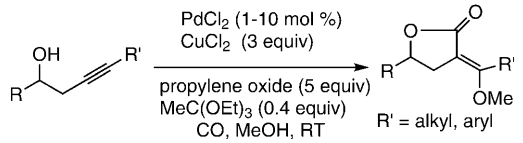
The β-methoxyacrylate system is a common structure present in biologically active natural products such as dihydrokawain[1a] (and related six-membered lactones[1b–e]), tetronic acids[2a] (and related five-membered lactones[2b–e]), and β-methoxyacrylate antibiotics.[3] Transition-metal-catalyzed reactions of unsaturated systems has recently been widely used for the construction of a variety of carbo- and heterocycles.[4] Palladium-catalyzed carbonylation of alkynes has provided several kinds of transformation.[5] In general, the intermolecular addition of alcohols to alkynes is more difficult to accomplish than the intramolecular process, thus requiring a stronger π Lewis acid catalyst.[6] Although many examples of the intramolecular oxycarbonylation of 4-alkynols,[7] 4-alkynones,[8] and propargyl acetates[9] have been reported, the intermolecular reaction is extremely rare. Tamaru and co-workers reported the palladium-catalyzed carbonylation of 4-alkyl- or 4-aryl-3-butyn-1-ols, in which MeOH attacked the C4 position of the alkyne to afford methoxycarbonylated five-membered lactones (Scheme 1).[5a] The reaction of the terminal alkyne was not described.



Scheme 1. Palladium-catalyzed carbonylation of 4-alkyl- or 4-aryl-3-butyn-1-ols by Tamaru and co-workers.[5a]

The intermolecular methoxycarbonylation of terminal alkynes is a synthetically valuable method for the direct conversion of terminal alkyne units into β-methoxyacrylate units. To our knowledge, there is no precedent for the intermolecular methoxycarbonylation of a simple terminal alkyne. Recently, we reported the ligand-controlled tandem carbonylative cyclization of propargyl acetates with 1,4-diyne[10a] and 1,5-diyne structures.[10b] In the absence of the bis(oxazoline) ligand (box), the second triple bond did not react. However, the use of the box ligand caused a significant change to the course of the reaction, and tandem carbonylative cyclization occurred as a result of insertion at the second triple bond. Although box ligands are among the most popular classes of chiral ligands in asymmetric chemistry, examples of the box ligand changing the course of the reaction are rare.[10,11] We believe that the box ligand enhances the π-electrophilicity of Pd^{II} complexes, and thus promotes coordination of the second triple bond to Pd^{II}, leading to the tandem reaction. We hypothesize that {(box)-Pd^{II}} complexes should strongly activate the alkyne, so that the intermolecular methoxycarbonylation of alkynes can be realized. Consequently, we report the [(Phbox)$Pd(tfa)_2$]-catalyzed intermolecular methoxycarbonylation of alkyne **1** (Phbox = 2,2-isopropylidenebis(4-phenyl-2-oxazoline); tfa = trifluoroacetate; Table 1).

Initially, the carbonylation of **1a** was performed under the conditions reported by Tamaru and co-workers. However, methoxyacrylate **2a** was not obtained, but instead the acetylene carboxylate[5b] (32%) and maleate derivatives[5n] (20%) were afforded, together with an unidentified mixture.[12] The reaction conditions were therefore changed to those used for our previously reported Pd^{II}/*p*-benzoquinone catalytic system.[7–10] The reaction of **1a** with $Pd(tfa)_2$ (5 mol%) and *p*-benzoquinone (2 equiv) in the absence of the ligand in methanol under a carbon monoxide atmosphere afforded the acetylene carboxylate derivative in 23% yield with a small amount of **2a** (7%).[12] The use of $[(CH_3CN)_2PdCl_2]$, $[(bpy)PdCl_2]$ (bpy = 2,2′-bipyridine), $[(Ph_3P)_2PdCl_2]$, and [{(*S*)-binap}$Pd(tfa)_2$] yielded unsatisfactory results.[12] Next, an attempt was made to use the (±)-Phbox ligand, according to our hypothetical expectation.[10] As expected, the reaction occurred smoothly in the presence of the (±)-Phbox ligand, affording methoxyacrylate **2** in moderate to good yields (Table 1). For substrates **1a–d** with hydrocarbon substituents, the reaction proceeded well (entries 1, 4–6). The use of $[(CH_3CN)_2PdCl_2]$ and $[(CH_3CN)_4Pd](BF_4)_2$ instead of $Pd(tfa)_2$ resulted in slightly decreased yields of **2a** (Table 1, entries 2 and 3).

The aryl-substituted alkynes **1e–h** and thienyl-substituted **1i** gave moderate to good yields (Table 1, entries 7–11). The reaction of protected propargyl glycosides **1j** and **1k** provided **2j** and **2k** in moderate yields (Table 1, entries 12–14). Protection of the hydroxy group was not necessary, as **1l** and **1m** (Table 1, entries 15 and 16) incorporate four hydroxy groups and reaction proceeds smoothly. The ketal protecting group was also tolerated under the reaction conditions. (Table 1, entry 17). In comparison to the terminal alkynes, internal alkynes **1o** and **1p** were less reactive (Table 1, entries 18 and 20), and 5-decyne was inactive under the

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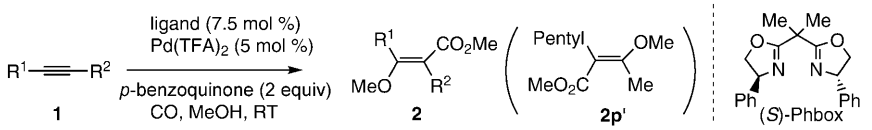
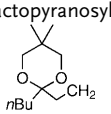
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200806080.

Table 1: [(Phbox)Pd(tfa)$_2$]-catalyzed intermolecular methoxycarbonylation of **1**.



Entry	Alkyne	R^1	R^2	Ligand	T [°C]	t [h]	Product	Yield [%]
1	**1a**	$Ph(CH_2)_3$	H	(±)-Phbox	10	24	**2a**	85
2[a]	**1a**	$Ph(CH_2)_3$	H	(±)-Phbox	26	24	**2a**	65
3[b]	**1a**	$Ph(CH_2)_3$	H	(±)-Phbox	10	21	**2a**	79
4	**1b**	$Ph(CH_2)_3$	H	(±)-Phbox	10	20	**2b**	86
5	**1c**	$CH_3(CH_2)_5$	H	(±)-Phbox	10	20	**2c**	89
6	**1d**	$CH_3(CH_2)_7$	H	(±)-Phbox	10	20	**2d**	88
7	**1e**	Ph	H	(±)-Phbox	10	48	**2e**	66
8	**1f**	4-$MeOC_6H_4$	H	(±)-Phbox	10	24	**2f**	81
9	**1g**	4-FC_6H_4	H	(±)-Phbox	10	48	**2g**	77
10	**1h**	6-MeO-2-naphthyl	H	(±)-Phbox	10	71	**2h**	60
11	**1i**	3-thienyl	H	(±)-Phbox	10	48	**2i**	64
12	**1j**	tetra-*O*-acetyl-β-D-gluco-pyranosyl–CH_2	H	(*S*)-Phbox	26	20	**2j**	75
13	**1j**	tetra-*O*-acetyl-β-D-gluco-pyranosyl–CH_2	H	(*R*)-Phbox	26	20	**2j**	59
14	**1k**	tetra-*O*-acetyl-β-D-galacto-pyranosyl–CH_2	H	(*S*)-Phbox	26	18	**2k**	67
15	**1l**	β-D-glucopyranosyl–CH_2	H	(*S*)-Phbox	26	23	**2l**	68
16	**1m**	β-D-galactopyranosyl–CH_2	H	(*S*)-Phbox	26	10	**2m**	65
17	**1n**		H	(±)-Phbox	26	4	**2n**	82
18	**1o**	$Ph(CH_2)_3$	CO_2Me	(±)-Phbox	26	40	**2o**	49[c]
19[d]	**1o**	$Ph(CH_2)_3$	CO_2Me	(±)-Phbox	26	48	**2o**	61
20[e]	**1p**	$CH_3(CH_2)_4$	CH_3	(±)-Phbox	26	48	**2p/2p'**	44[f]

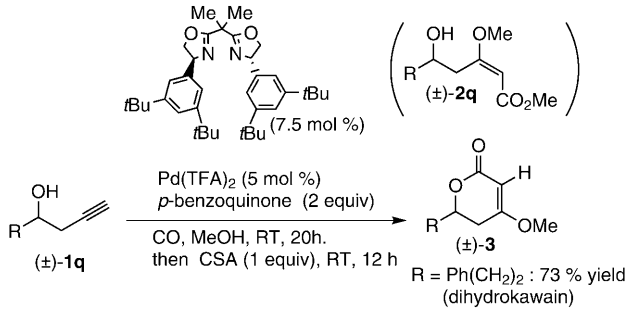
[a] $[(CH_3CN)_2PdCl_2]$ was used in place of $Pd(tfa)_2$. [b] $[(CH_3CN)_4Pd](BF_4)_2$ was used in place of $Pd(tfa)_2$. [c] **1o** was recovered (50%). [d] [{(±)-Phbox}$Pd(CH_3CN)_2](SbF_6)_2$ was used as catalyst. [e] $Pd(tfa)_2$ (10 mol%) and (±)-Phbox (12 mol%) were used as catalyst. [f] Combined yield, 1.8:1 product ratio.

reaction conditions. The use of a cationic palladium species as the catalyst resulted in slightly increased yields (Table 1, entry 19). The structures of **2o**, **2p**, and **2p′** were determined by NMR heteronuclear multiple-bond correlation (HMBC) spectroscopy experiments. The reaction was successfully applied in the one-pot synthesis of (±)-dihydrokawain **3**[1a] (Scheme 2). The reaction of homopropargyl alcohol **1q** using the [{(±)-3,5,3′,5′-tBu_4Phbox}$Pd(tfa)_2$] complex[13] afforded β-methoxyacrylate **2q** (65%) and the six-membered lactone **3** (23%) in 88% combined yield. A one-pot treatment of the carbonylation reaction mixture with (+)-10-camphorsulfonic acid (CSA), directly afforded (±)-dihydrokawain **3** in 73% yield.

To investigate the effects of the Phbox ligand, control reactions were performed. Solvolysis of the simple ketal **4** proceeded using $Pd(tfa)_2$ to afford **5** and **6** with a good combined yield (Table 2, entry 1). The ketal **4** was almost unchanged after 5 h using [(Phbox)$Pd(tfa)_2$], although **5** and **6** were obtained in 57% combined yield after 24 h (Table 2, entries 2 and 3). These results indicated that [(Phbox)$Pd(tfa)_2$] has low Lewis acidity (oxophilicity) and strong π electrophilicity (alkynophilicity) to activate the "soft" triple bond (Table 1, entry 17).

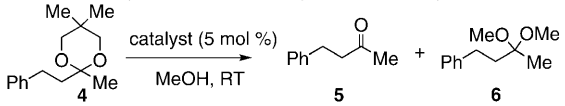
The low Lewis acidity and strong π electrophilicity of the {(box)Pd^{II}} complex is attributed to the box ligand. Density functional (DFT) calculations revealed that the ligand π orbitals, delocalized over the double bonds and periphery, lie energetically close to the lowest unoccupied molecular orbital (LUMO).[12] Thus, the box ligand increases the polarizability of the metal center, and the ligand orbitals contribute to the π electrophilicity, which leads to activation of the "soft" triple bond. In contrast, the Lewis acid character of $Pd(tfa)_2$ without the box ligand may be attributed to a lower-energy LUMO than that of the {(box)Pd^{II}} complex.

Based on the above results, a mechanism is proposed for the present reaction. This reaction is initiated by the nucleophilic attack of methanol on an alkyne coordinated to {(Phbox)Pd^{II}}, forming a vinylpalladium intermediate. The insertion of CO into the C–Pd bond, followed by methanolysis of the resulting acylpalladium complex, affords the β-methoxyacrylate **2** and the reduced {(Phbox)Pd^0} complex.



Scheme 2. One-pot synthesis of (±)-dihydrokawain. CSA = (+)-10-camphorsulfonic acid.

Table 2: Methanolysis of ketal **4** with palladium catalysts.



Entry	Catalyst	t [h]	Yield of **5** [%]	Yield of **6** [%]	Recovery [%]
1	$Pd(tfa)_2$	5	55	28	5
2	(*S*)-Phbox/$Pd(tfa)_2$	5		no reaction	
3	(*S*)-Phbox/$Pd(tfa)_2$	24	33	24	42

The {(Phbox)Pd^0} is reoxidized to {(Phbox)Pd^{II}} by *p*-benzoquinone, and thus the catalytic cycle continues.

In summary, we have reported the {(box)Pd^{II}}-catalyzed intermolecular oxycarbonylation of terminal alkynes. Acetyl and ketal protecting groups, free hydroxy groups and acid sensitive glycosidic bonds were not affected under the reaction conditions. The reaction offers a direct method for the preparation of β-methoxyacrylate species, and the one-pot synthesis of (±)-dihydrokawain **3** from the homopropargyl alcohol was achieved. The box ligand is thought to enhance the π electrophilicity of Pd^{II}. Control experiments and DFT calculations for the palladium complexes supported this hypothesis. The concept presented here should provide greater insight for the design of several new transition-metal-catalyzed reactions using alkyne substrates.

Received: December 13, 2008
Published online: February 4, 2009

Keywords: alkynes · carbonylation · homogeneous catalysis · ligand effects · palladium

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[12] See the Supporting Information.

[13] Ligand screening revealed that the use of (±)-3,3′,5,5′-*t*Bu_4Phbox as a ligand provided better yields than that of (±)-PhBox in the reaction of homopropargylic alcohols.

