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Palladium-Catalyzed Intermolecular Alkoxy-Alkoxycarbonylation of Vinylphenols in the Presence of Copper Salt: Unexpected Cooperative Effect of Tin Salt

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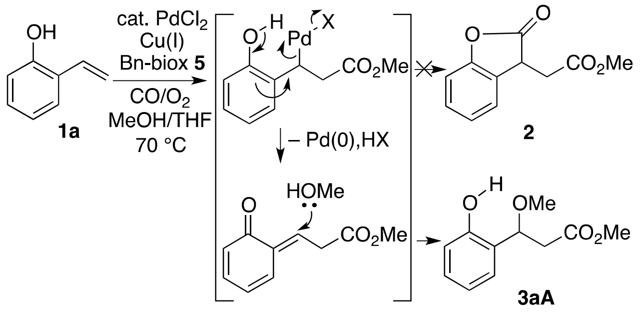
The palladium-catalyzed intermolecular alkoxy-alkoxycarbonylation of vinylphenols under normal pressure of CO and O_2 in alcohol was developed to afford the corresponding 3-alkoxy-3-arylpropanoates in good to high yields. Not only primary alcohols but also secondary alcohols were applicable to the present reaction. The presence of tin salt was crucial to realize reproducibly high yields.

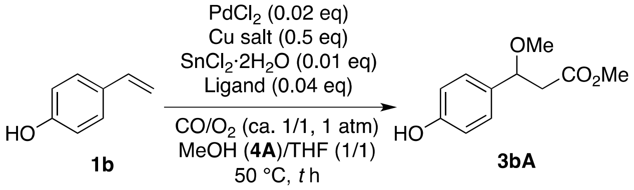
Transition metal-catalyzed carbonylation reactions of alkenes are important in organic synthesis to provide efficient entries to a variety of useful carbon-homologated compounds with oxygen functional groups.[1] The palladium-catalyzed addition of carbon monoxide to alkenes in the presence of a suitable nucleophile has received considerable attention. Concerning palladium-catalyzed carbonylation of unsaturated alcohols, intramolecular alkoxy-carbonylation often proceeds to furnish cyclic ethers, such as tetrahydrofurans or tetrahydropyrans.[2] However, the intermolecular version of the alkoxy-carbonylation of alkenes is quite limited.[3] Carbonylation of terminal alkenes in the presence of $PdCl_2$ and $CuCl_2$ under 3 atm of CO in MeOH was reported to give predominantly β-methoxy esters, while the corresponding succinates were obtained under basic conditions.[3a] A palladium-catalyzed acetoxy-carbonylation of alkenes proceeded in the presence of $CuCl_2$ in acetic anhydride and acetic acid.[4,5] We have previously reported the palladium-catalyzed intra- and intermolecular bis(alkoxycarbonylation) of homoallylic alcohols in the presence of copper (I) salt.[6] In the present manuscript, palladium-catalyzed intermolecular alkoxy-alkoxycarbonylation of vinylphenols is described to afford the corresponding 3-alkoxy-3-arylpropanoates in good to high yields.[7]

We initially attempted the asymmetric intra- and intermolecular bis(alkoxycarbonylation) of 2-vinylphenol (**1a**) in the presence of $PdCl_2$ (0.02 eq) and $[Cu(C_6H_6)_{0.5}]OTf$ (0.5 eq) under normal pressure of CO and O_2 in MeOH (**4A**)/THF using (*S*,*S*)-benzyl-substituted bioxazoline **5** as a ligand.[6b,c]



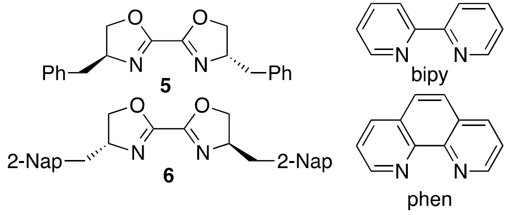
Scheme 1. Alkoxy-Alkoxycarbonylation of 2-vinylphenol

Table 1. Alkoxy-alkoxycarbonylation of 4-vinylphenol (**1b**)[a]



Entry	Cu salt	Ligand	*t*/h	Yield/%[a]
1	$[Cu(C_6H_6)_{0.5}]OTf$	**6**	7.5	99
2	CuCl	**6**	7.5	--
3	CuBr	**6**	7.5	--
4	CuI	**6**	7.5	--
5	$[Cu(MeCN)_4]BF_4$	**6**	3	99
6[b]	$[Cu(MeCN)_4]BF_4$	**6**	4.5	80
7[c]	$[Cu(MeCN)_4]BF_4$	**6**	3	96
8[d]	$[Cu(MeCN)_4]BF_4$	**6**	3	74
9	$[Cu(MeCN)_4]BF_4$	--	8	38[e]
10	$[Cu(MeCN)_4]BF_4$	**5**	8	91
11	$[Cu(MeCN)_4]BF_4$	bipy	6.5	91
12	$[Cu(MeCN)_4]BF_4$	phen	20	91
13	$[Cu(MeCN)_4]BF_4$	DABCO	8	99
14[f]	$[Cu(MeCN)_4]BF_4$	DABCO	8	5

[a]Yields were determined by the analyses of ^1H NMR spectra of the crude products based on octane as an internal standard. [b]$[PdCl_2(PhCN)_2]$ was used instead of $PdCl_2$. [c]$SnCl_4$ was used instead of $SnCl_2·2H_2O$. [d]$Sn(OAc)_4$ was used instead of $SnCl_2·H_2O$. [e]4-Hydroxyacetophenone was also isolated in 33% yield. [f]Reaction was carried out without O_2.

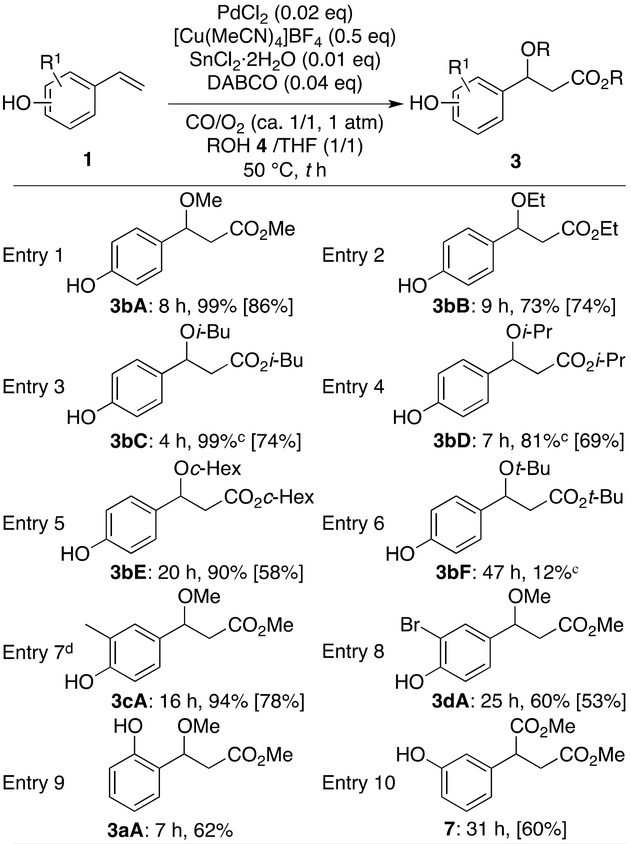


Although the carbonylation proceeded smoothly, the expected lactone **2** was not formed, but instead 3-aryl-3-methoxypropanoic acid methyl ester **3aA** was obtained in 53% yield. This ester might be derived from regioselective carbopalladation followed by reductive elimination and subsequent addition of MeOH to the resulted quinonemethide before the second carbonylation (Scheme 1). If this hypothesis is correct, 4-vinylphenol would also afford the corresponding 3-methoxypropanoate. Indeed, the alkoxycarbonylation of 4-vinylphenol (**1b**) was performed, and 3-methoxypropanoate **3bA** was obtained in good chemical yield (up to over 90% yield). Unfortunately, the chemical yield was not reproducible. After intensive examination, the chemical yield was found to fluctuate depending on the MeOH used. When MeOH purchased in an amber glass bottle was used, **3bA** was obtained in around 30% lower yields than when using MeOH purchased in 18 L tin-plates.[8] When the reaction was performed by the addition of $SnCl_2 \cdot 2H_2O$, the product **3bA** was obtained in reproducibly high yields.

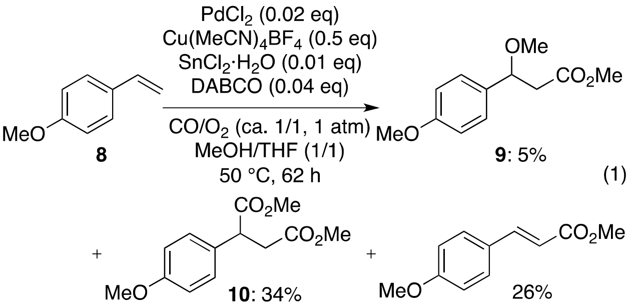
Consequently, the present intermolecular methoxy-methoxycarbonylation of 4-vinylphenol (**1b**) in the presence of a bioxazoline ligand **6**[9] was examined under various conditions (Table 1). Among the copper salts, CuCl, CuBr, and CuI were not effective (Entries 1–4). It was confirmed that cationic copper(I) salts, especially $[Cu(MeCN)_4]BF_4$, were quite effective to give the product quantitatively within 3 h (Entry 5).[10] The reaction proceeded in a similar manner by the use of $[PdCl_2(PhCN)_2]$ instead of $PdCl_2$ (Entry 6). Concerning the tin salts, $SnCl_4$ and $Sn(OAc)_4$ were interchangeable (Entries 7 and 8). In the absence of bioxazoline ligand **6**, the reaction was sluggish and a Wacker-type product, 4-hydroxyacetophenone, was formed (Entry 9). Substituents on the bioxazolines did not influence the reaction (Entry 10). Achiral ligands instead of bioxazoline compounds were examined. By the use of bidentate pyridine-type ligands, the reaction proceeded smoothly (Entries 11 and 12). DABCO was found to be comparable to bioxazoline **6** to afford 3-methoxypropanoate **3bA** in high yield (Entry 13). Oxygen was crucial to promote the present alkoxy-alkoxycarbonylation (Entry 14).

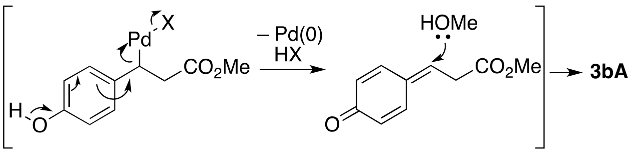
Under the optimized reaction conditions, the alkoxy-alkoxycarbonylation of vinylphenols **1** was performed in the presence of various alcohols (Table 2, Entries 1–6). By the use of not only primary alcohols but also secondary alcohols, the corresponding 3-alkoxy esters **3bA**–**3bE** were obtained in good to high yields (Entries 1–5). In the case of *t*-butyl alcohol (**4F**), the reaction was sluggish and gave the product **3bF** in poor yield (Entry 6). When H_2O was used as a nucleophile instead of alcohols for 65 h, 93% of 4-vinylphenol (**1b**) was recovered and a carbonylated 3-aryl-3-hydroxypropanoic acid was not observed in ^{1}H NMR spectrum of the crude products. Generally, isolated yields, as listed in parentheses, tended to decrease because the obtained 3-alkoxy-3-(hydroxylaryl)propanoates **3** were rather labile under purification by column chromatography on SiO_2 to often give the corresponding 3-(hydroxyphenyl)prop-2-enoates via *β*-elimination of the alcohols. In fact, purification of 3-(*t*-butoxy)propanoate **3bF** was failed. The reaction of 2-methyl-4-vinylphenol (**1c**) furnished the desired product **3cA** in high yield by the use of enhanced amount of the catalysts (Entry 7). Unfortunately, side reactions, presumably polymerization, proceeded prior to the desired alkoxy-alkoxycarbonylation resulting in unknown product mixtures when the 4-vinylphenol derivatives with rather electron donating groups, such as 2-methoxy-4-vinylphenol and 2,6-dimethyl-4-vinylphenol, were used as substrates. 2-Bromo-4-vinylphenol (**1d**) bearing an electron withdrawing bromo group afforded the corresponding 3-alkoxyesters **3dA** in 60% yield (Entry 8). The reaction of 2-vinylphenol (**1a**) afforded **3aA** in reasonable yield (Entry 9). However, the treatment of 3-vinylphenol (**1e**) modulated the carbonylation into the bis(alkoxycarbonylation) reaction to produce a succinate derivative **7** (Entry 10).[3a,6]

Table 2. Alkoxy-alkoxycarbonylation of vinylphenols **1**[a,b]



[a]Yields were determined by the analysis of ^{1}H NMR spectra of the crude products based on octane as an internal standard otherwise mentioned. [b]Yields in parentheses are isolated yields. [c]Yield was determined by the analysis of ^{1}H NMR spectrum of the crude products based on dibromomethane as an internal standard. [d]$PdCl_2$ (0.05 eq), $[Cu(MeCN)_4]BF_4$ (0.5 eq), $SnCl_2 \cdot 2H_2O$ (0.02 eq), and DABCO (0.10 eq) were used.



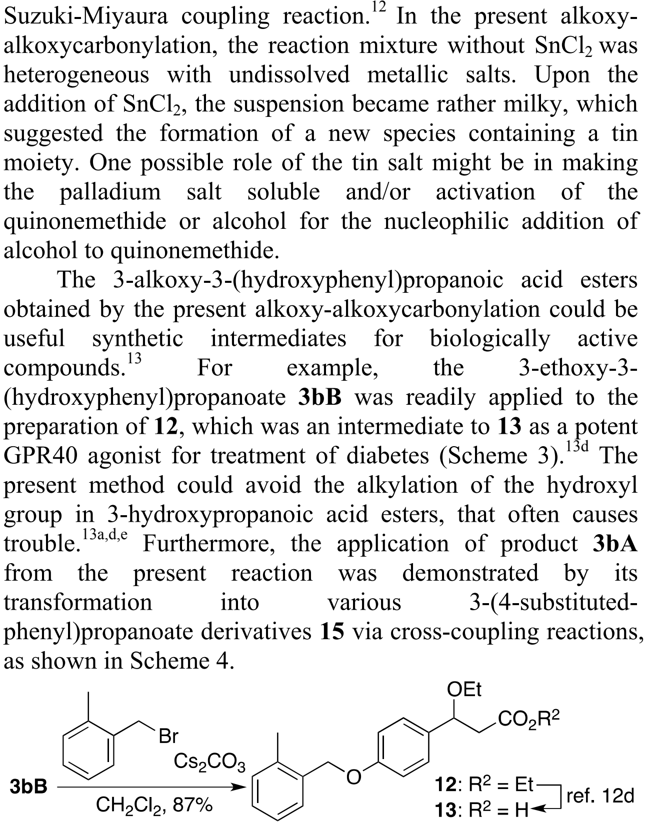


Scheme 2. Plausible reaction pathway

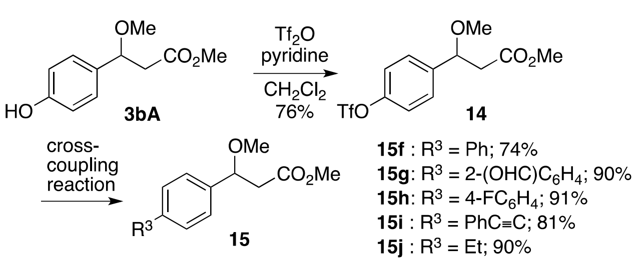
The effect of the hydroxyl group in the vinylphenol was examined next. When 1-methoxy-4-vinylbenzene (**8**) was subjected to the present carbonylation, the reaction was sluggish to give the corresponding 3-methoxypropanoate **9** in poor yield accompanied with the succinate **10** and prop-2-enoate (Eq 1). This result suggested that the electron-donating ability of the hydroxyl group might be crucial in promoting the reductive elimination from the Pd intermediate to produce quinonemethide (Scheme 2). The result of Entry 10 in Table 2 would also support the significance of the electron-donating effect of hydroxyl group on *para*- or *ortho*-position to vinyl group.

The role of the tin salt is not yet clear. In the case of palladium-catalyzed hydroformylation, SnCl$_2$ was also reported to promote the carbonylation although these reactions required high-pressure CO conditions.[11,12] Recently, the heterobimetallic Pd-Sn catalyst, PdCl(COD)SnCl$_3$, was reported to activate oxygen functional groups, resulting in promotion of the Michael reaction, nucleophilic addition, and Suzuki-Miyaura coupling reaction.[12] In the present alkoxy-alkoxycarbonylation, the reaction mixture without SnCl$_2$ was heterogeneous with undissolved metallic salts. Upon the addition of SnCl$_2$, the suspension became rather milky, which suggested the formation of a new species containing a tin moiety. One possible role of the tin salt might be in making the palladium salt soluble and/or activation of the quinonemethide or alcohol for the nucleophilic addition of alcohol to quinonemethide.

The 3-alkoxy-3-(hydroxyphenyl)propanoic acid esters obtained by the present alkoxy-alkoxycarbonylation could be useful synthetic intermediates for biologically active compounds.[13] For example, the 3-ethoxy-3-(hydroxyphenyl)propanoate **3bB** was readily applied to the preparation of **12**, which was an intermediate to **13** as a potent GPR40 agonist for treatment of diabetes (Scheme 3).[13d] The present method could avoid the alkylation of the hydroxyl group in 3-hydroxypropanoic acid esters, that often causes trouble.[13a,d,e] Furthermore, the application of product **3bA** from the present reaction was demonstrated by its transformation into various 3-(4-substituted-phenyl)propanoate derivatives **15** via cross-coupling reactions, as shown in Scheme 4.



Scheme 3. Transformation of **3bB**



Scheme 4. Transformation of **3bA** to 3-(4-substituted-phenyl)propanoate derivatives **15**. Reaction conditions for **15f-15h**: RB(OH)$_2$, cat. [Pd(PPh$_3$)$_4$], K$_2$CO$_3$, toluene/DMF (10/1). **15i**: PhC≡CH, cat. [PdCl$_2$(PPh$_3$)$_2$], Et$_3$N, DMF. **15j**: Et$_3$B, cat. [PdCl$_2$(dppf)$_2$], CsOAc, THF.

In conclusion, we have realized the palladium-catalyzed alkoxy-alkoxycarbonylation of vinylphenols in the presence of copper and tin salts to afford 3-alkoxy-3-arylpropanoic acid esters. An unexpected effect of tin salt was discovered in the present carbonylation. Further investigation of tin cooperation toward the palladium-catalyzed carbonylation reaction is now under investigation in our laboratory.

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References and Notes

1 a) H. M. Colquhoun, D. J. Thompson, M. V. Twigg, *Carbonylation*, Plenum Press, New York, **1991**. b) *Catalytic Carbonylation Reactions*, ed. by M. Beller, Springer, Berlin, **2006**. c) A. Brennführer, H. Neumann, M. Beller, *ChemCatChem* **2009**, *1*, 28.

2 a) Y. Tamaru, T. Kobayashi, S.-I. Kawamura, H. Ochiai, M. Hojo, Z.-I. Yoshida, *Tetrahedron Lett.* **1985**, *26*, 3207. b) M. F. Semmelhack, N. Zhang, *J. Org. Chem.* **1989**, *54*, 4483. c) M. McCormick, R. Monahan III, J. Soria, D. Goldsmith, D. Liotta, *J. Org. Chem.* **1989**, *54*, 4485. d) J. S. Yadav, E. S. Rao, V. S. Rao, B. M. Choudary, *Tetrahedron Lett.* **1990**, *31*, 2491. e) K. Kato, C. Matsuba, T. Kusakabe, H. Takayama, S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdinc, O. V. Gusev, *Tetrahedron* **2006**, *62*, 9988. f) L. F. Tietze, J. Zinngrebe, D. A. Spiegl, F. Steckera, *Heterocycles* **2007**, *74*, 473. g) L. M. Ambrosini, T. A. Cernak, T. H. Lambert, *Synthesis* **2010**, 870. h) O. Karlubíkova, M. Babjak, T. Gracza, *Tetrahedron* **2011**, *67*, 4980.

3 a) D. E. James, J. K. Stille, *J. Am. Chem. Soc.* **1976**, *98*, 1810. b) G. B. Bajracharya, P. S. Koranne, T. Tsujihara, S. Takizawa, K. Onitsuka, H. Sasai, *Synlett* **2009**, 310.

4 H. Urata, A. Fujita, T. Fuchikami, *Tetrahedron Lett.* **1988**, *29*, 4435.

5 For other types of oxy-carbonylations, see: a) E. K. G. Schmidt, W. Wiese, *Tetrahedron Lett.* **1980**, *21*, 4425. b) T. Taniguchi, Y. Sugiura, H. Zaimoku, H. Ishibashi, *Angew. Chem. Int. Ed.* **2010**, *49*, 10154. c) W. Liu, Y. Li, K. Liu, Z. Li, *J. Am. Chem. Soc.* **2011**, *133*, 10756.

6 a) S. Toda, M. Miyamoto, H. Kinoshita, K. Inomata, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3600. b) Y. Ukaji, M. Miyamoto, M. Mikuni, S. Takeuchi, K. Inomata, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 735. c) T. Aratani, K. Tahara, S. Takeuchi, S. Kitamura, M. Murai, S. Fujinami, K. Inomata, Y. Ukaji, *Bull. Chem. Soc. Jpn.* **2012**, *85*, 1225.

7 Examples for palladium-catalyzed carbonylation of vinylphenols, see: a) C. Dong, H. Alper, *J. Org. Chem.* **2004**, *69*, 5011. b) J. Ferguson, F. Zeng, H. Alper, *Org. Lett.*, **2012**, *14*, 5602.

8 Prof. A. Yokoyama informed that ICP-MS analysis revealed abundance of tin in MeOH stored in 18L tin-plate.

9 Y. Yonezawa, T. Furuya, T. Aratani, S. Fujinami, K. Inomata, Y. Ukaji, *Tetrahedron: Asymmetry* **2014**, *25*, 936.

10 The enantiomeric excess of the obtained **3bA** was confirmed to be 0% ee.

11 For cooperation of tin salts in palladium-catalyzed carbonylation, see: a) J. F. Knifton, *J. Org. Chem.* **1976**, *41*, 2885. b) R. Naigre, T. Chenal, I. Ciprés, P. Kalck, J.-C. Daran, J. Vaissermann, *J. Organomet. Chem.* **1994**, *480*, 91. c) G. Lenoble, M. Urrutigoïty, P. Kalck, *Tetrahedron Lett.* **2001**, *42*, 3697.

12 For cooperation of tin salts in palladium-catalyzed reactions, see: a) M. Noskowska, E. Sliwińska, W. Duczmal, *Transition Met. Chem.* **2003**, *28*, 756. b) D. Das, S. Pratihar, U. K. Roy, D. Mal, S. Roy, *Org. Biomol. Chem.* **2012**, *10*, 4537. c) D. Das, S. Pratihar, S. Roy, *Org. Lett.* **2012**, *14*, 4870. d) D. Das, S. Pratihar, S. Roy, *J. Org. Chem.* **2013**, *78*, 2430.

13 a) S. Toda, M. Yoshida, R. Takano, M. Inoue, T. Honda, K. Matsumoto, R. Nakajima, Jpn. Kokai Tokkyo Koho **2011**, 2011148774. b) S. Keil, E. Defossa, V. Dietrich, S. Stengelin, A. Herling, G. Haschke, T. Klabunde, U.S. Pat. Appl. Publ. **2012**, US 20120004187 A1. c) R. Nakashima, T. Yano, J. Ogawa, N. Tanaka, N. Toda, M. Yoshida, R. Takano, M. Inoue, T. Honda, S. Kume, K. Matsumoto, *Eur. J. Pharmacol.* **2014**, *737*, 194. d) R. Takano, M. Yoshida, M. Inoue, T. Honda, R. Nakashima, K. Matsumoto, T. Yano, T. Ogata, N. Watanabe, N. Toda, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2949. e) R. Takano, M. Yoshida, M. Inoue, T. Honda, R. Nakashima, K. Matsumoto, T. Yano, T. Ogata, N. Watanabe, M. Hirouchi, T. Kimura, N. Toda, *Bioorg. Med. Chem.* **2015**, *23*, 5546.