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Palladium Catalyzed Alkoxy- and Aminocarbonylation of Vinyl Tosylates

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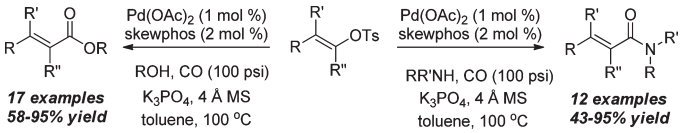
ABSTRACT



The palladium catalyzed alkoxycarbonylation and aminocarbonylation of vinyl tosylates are described. A variety of ketone and aldehyde derived vinyl tosylates may be carbonylated in the presence of primary, secondary, and tertiary alcohols, or primary and secondary amines, to provide the corresponding esters and amides in good yields. The alkoxycarbonylation was applied to a short synthesis of isoguvacine.

The palladium catalyzed alkoxy- or aminocarbonylation of vinyl electrophiles is a useful route to α,β-unsaturated esters and amides. The reactions were first described by Heck in 1974 for vinyl bromide and iodide substrates.[1] The carbonylation of vinyl triflates was later developed by Cacchi and co-workers.[2] The use of vinyl chlorides has also been investigated, though less extensively.[1b,3] Larhed and co-workers recently reported the palladium catalyzed aminocarbonylation of vinyl phosphates under microwave conditions using $Mo(CO)_6$ as the CO source.[4] The alkoxycarbonylation of aryl arenesulfonates was first reported in 2006 by Cai and co-workers.[5] Recently Buchwald and co-workers reported the alkoxycarbonylation of aryl tosylates and mesylates at atmospheric pressure of CO using a $Pd(OAc)_2$/dcpp catalyst system.[6] While various cross-coupling reactions employing vinyl tosylates have been reported, the carbonylation of these compounds has not previously been described.[7] Vinyl tosylates are attractive alternatives to conventional vinyl electrophiles due to their simple one-step synthesis from ketone or aldehyde precursors and their generally high crystallinity which simplifies isolation and handling. In addition, the reagent used to prepare vinyl tosylates (Ts_2O) is cheaper than the reagent used to prepare vinyl triflates [$PhN(Tf)_2$]. Herein we describe our results on the development of a practical process for the alkoxy- and aminocarbonylation of vinyl tosylates.

Our initial screening of reaction conditions focused on the alkoxycarbonylation of tosylate **1** with 1-pentanol to give ester **2** (Table 1). A survey of various bidentate phosphine ligands was done, as well as a comparison of commercially available preformed palladium complexes with the corresponding $Pd(OAc)_2$/ligand combination. Phosphines containing a 3-carbon tether (dppp, skewphos, dcpp) gave the best results (entries 2−5). Introducing a slight increase of steric constraint (e.g., methyl groups on the carbons adjacent to phosphorus) improves the catalyst performance (entries 3 and 5) while an increased bite angle is detrimental (entry 8). Thus the overall efficiency trend is skewphos > dcpp > dppp > dppb > dppf > dppe for the same catalyst loading (5 mol %). These observations are in agreement with previously reported data for Pd-catalyzed

(1) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.
(2) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
(3) Nicholas, P. P. *J. Org. Chem.* **1987**, *52*, 5266.
(4) Lagerlund, O.; Mantel, M. L. H.; Larhed, M. *Tetrahedron* **2009**, *65*, 7646.
(5) Cai, C.; Rivera, N. R.; Balsells, J.; Sidler, R. R.; McWilliams, J. C.; Schults, C. S.; Sun., Y. *Org. Lett.* **2006**, *8*, 5161.
(6) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754.
(7) For other Pd-catalyzed reactions of vinyl tosylates, see: (a) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, 471. (b) Baxter, J. M.; Steinhuebel, D.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215. (c) Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 670. (d) Klapars, A.; Campos, K. R.; Chen, C.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185. (e) Reeves, D. C.; Rodriguez, S.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Tetrahedron Lett.* **2009**, *50*, 2870.

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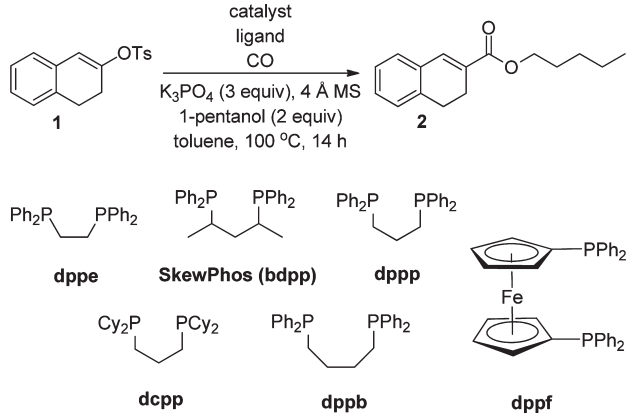
alkoxycarbonylation of alkenes[8] and carbonylation of aryl halides (dppp > dppb > dppe > dppm).[9] The commercially available complex $PdCl_2$(dppf) performed well (entry 6), although reducing the catalyst loading significantly decreased the yield (entries 7 and 11). In the case of skewphos, however, the catalyst loading could be reduced to 1 mol % without loss of performance. From a cost analysis standpoint, even in enantiopure form, skewphos is preferable to dcpp·2HBF$_4$. Finally, decreasing the CO pressure from 100 to 50 psi resulted in a slight loss in yield (entry 13).

Table 1. Catalyst and Ligand Screening Results

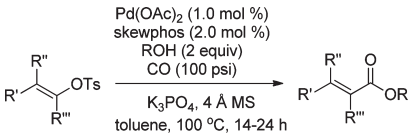


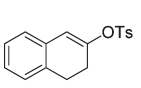
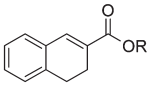
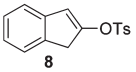
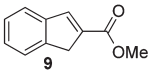
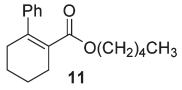
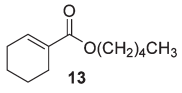
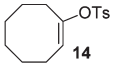
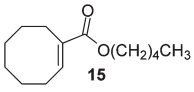
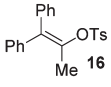
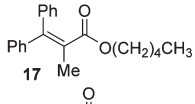
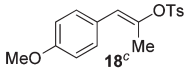
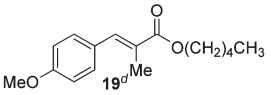
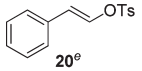
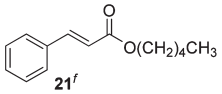
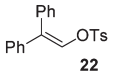
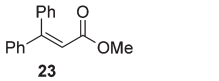
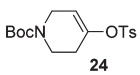
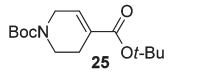
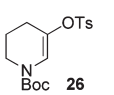
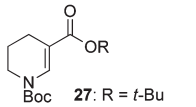
entry	catalyst	ligand[a]	Pd cat. (mol %)	press (psi)	yield (%)[b]
1	$PdCl_2$(dppe)	–	5.0	100	40
2	$PdCl_2$(dppp)	–	5.0	100	86
3	$Pd(OAc)_2$	skewphos[c]	5.0	100	99
4	$PdCl_2$	skewphos	5.0	100	97
5	$Pd(OAc)_2$	dcpp·2HBF$_4$[d]	2.5	100	95
6	$PdCl_2$(dppf)	–	10	100	92
7	$Pd(OAc)_2$	dppf	5.0	100	78
8	$PdCl_2$(dppb)	–	5.0	100	80
9	$Pd(OAc)_2$	skewphos	2.5	100	99
10	$Pd(OAc)_2$	skewphos	1.0	100	99
11	$PdCl_2$(dppf)	–	5.0	100	50
12	$PdCl_2$(dppf)	–	5.0	200	31
13	$Pd(OAc)_2$	skewphos	5.0	50	91

[a] L/Pd ratio = 2. [b] HPLC assay yield. [c] 2,4-Bis(diphenylphosphino)-pentane. [d] 1,3-Bis(dicyclohexylphosphino)propane·2HBF$_4$.

The substrate scope of the alkoxycarbonylation reaction was explored with respect to vinyl tosylate and alcohol (Table 2). Using β-tetralone derived tosylate **1**, various alcohols were surveyed (entries 1–6). Primary, secondary, and tertiary alcohols all gave good yields of ester products. Full substitution of the vinyl tosylate olefin was tolerated (entries 8 and 11). Aldehyde-derived vinyl tosylates (entries 13 and 14) were found to be competent substrates. The geometric integrity of enol tosylates was preserved during the carbonylation reaction (entries 12 and 13). The reaction could also be performed on heterocyclic substrates (entries 15–17).

Table 2. Pd-Catalyzed Alkoxycarbonylation of Vinyl Tosylates[a]



entry	vinyl tosylate	product	yield (%)[b]
1	 **1**	 **2**: R = Me	85
2		**3**: R = *n*-pentyl	72
3		**4**: R = *i*-pentyl	81
4		**5**: R = *i*-Pr	78
5		**6**: R = *c*-pentyl	90
6		**7**: R = *t*-pentyl	86
7	 **8**	 **9**	90
8	 **10**	 **11**	77
9	 **12**	 **13**	95
10	 **14**	 **15**	58
11	 **16**	 **17**	59
12	 **18**[c]	 **19**[d]	85
13	 **20**[e]	 **21**[f]	83
14	 **22**	 **23**	63
15	 **24**	 **25**	78
16	 **26**	 **27**: R = *t*-Bu	69
17		**28**: R = Me	74

[a] For experimental details see the Supporting Information. [b] Isolated yields. [c] E/Z = 10:1. [d] E/Z = 13:1. [e] E/Z = 2.4:1. [f] E/Z = 4:1.

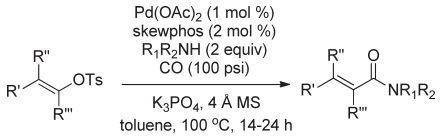
We next examined the aminocarbonylation of vinyl tosylates. Direct application of the conditions developed for alkoxycarbonylation to carbonylation in the presence

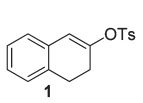
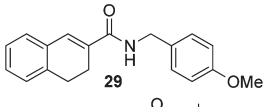
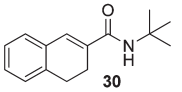
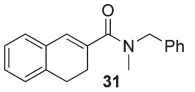
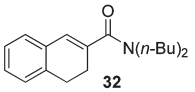
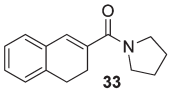
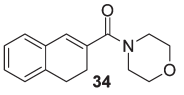
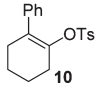
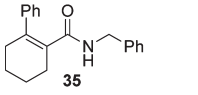
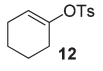
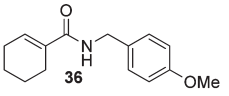
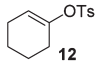
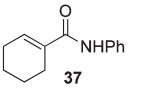
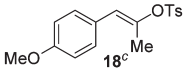
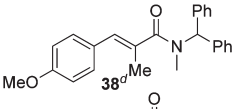
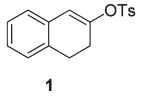
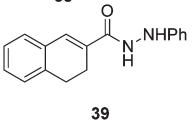
(8) (a) Dierkes, P.; Van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519. (b) Van Leeuwen, P. W. N. M.; Freixa, Z. Bite Angle Effects of Diphosphines in carbonylation Reactions. In *Modern Carbonylation Methods*; Kollar, L., Ed.; Wiley: Weinheim, 2008; pp 1–25 and references cited therein.

(9) Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P. G.; Murry, J. A. *Org. Lett.* **2004**, *6*, 2097.

of amines was found to give good yields of α,β-unsaturated amide products. The scope of the aminocarbonylation reaction is given in Table 3.

Table 3. Pd-Catalyzed Aminocarbonylation of Vinyl Tosylates[a]



entry	vinyl tosylate	product	yield (%)[b]
1	 1	 29	79
2		 30	61
3		 31	83
4		 32	95
5		 33	73
6		 34	75
7	 10	 35	75
8	 12	 36	85
9	 12	 37	91
10	 18[c]	 38[d]	73
11	 1	 39	46

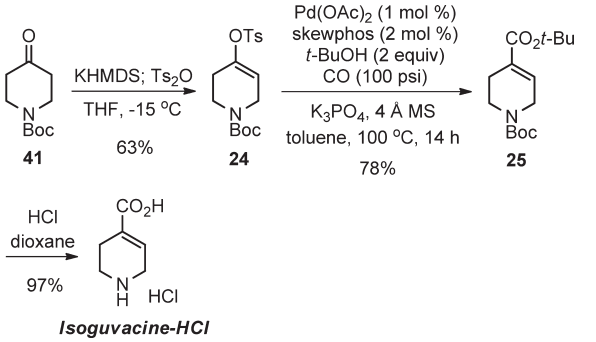
[a] For experimental details, see the Supporting Information. [b] Isolated yields. [c] E/Z = 10:1. [d] $E/Z \geq$ 10:1.

Both primary and secondary amines reacted smoothly. Full substitution of the vinyl tosylate was tolerated (entry 7).

In addition to alkyl amines, aniline could be employed to give an *N*-phenyl amide in high yield (entry 9). The reaction was also applied to a hydrazine to provide an acyl hydrazine in moderate yield (entry 11).

Isoguvacine is a potent γ-amino butyric acid (GABA) agonist which has attracted interest as a potential treatment for psychiatric and neurological disorders.[10] We applied the vinyl tosylate alkoxycarbonylation to a short synthesis of isoguvacine (Scheme 1). Beginning with commercially available *N*-Boc 4-piperidone **41**, treatment with KHMDS and subsequent trapping with Ts_2O gave the vinyl tosylate **24** in 63% yield. Carbonylation in the presence of *tert*-butanol gave the ester **25** in 78% yield. Finally, simultaneous deprotection of the *tert*-butyl ester and the Boc group was accomplished with HCl in dioxane. Isoguvacine was isolated as its HCl salt in 97% yield. This three-step synthesis of isoguvacine is an improved alternative to previous syntheses of this compound in terms of overall yield and number of steps (48% overall yield, 3 steps vs 8% overall yield, 6 steps).[11]

Scheme 1. Vinyl Tosylate Alkoxycarbonylation in the Synthesis of Isoguvacine



In summary, we have demonstrated the first alkoxy- and aminocarbonylation of vinyl tosylates, a one carbon homologation method. The simple one-step synthesis of vinyl tosylates from ketones or aldehydes makes them an attractive alternative to vinyl halides or triflates. The alkoxycarbonylation is tolerant of a diverse set of enol tosylate and alcohol reactants and provides the ester products in good yields. The same reaction conditions may be applied to aminocarbonylation. Primary, secondary, and aryl amines react to give the corresponding amides in good yields. Hydrazines may also be used and provide acyl hydrazines in moderate yields. The alkoxycarbonylation reaction was demonstrated in a three-step synthesis of the GABA agonist isoguvacine.

Supporting Information Available. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all products and unknown substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) Falch, E.; Krogsgarrd-Larsen, P. *J. Med. Chem.* **1981**, *24*, 285.
(11) (a) Chang, M.-Y.; Chen, S.-T.; Chang, N.-C. *Heterocycles* **2002**, *57*, 2321. (b) Chang, M.-Y.; Chen, C.-Y.; Tasi, M.-R.; Tseng, T.-W.; Chang, N.-C. *Synthesis* **2004**, 840.