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Enantioselective Palladium-Catalyzed Allylic Alkylation Using *E*- and *Z*-Vinylogous Sulfonates

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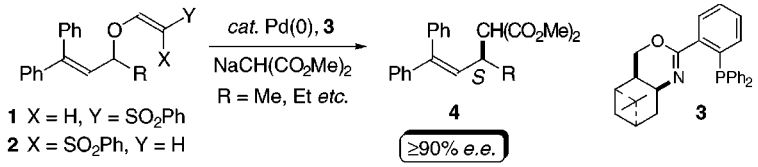
ABSTRACT

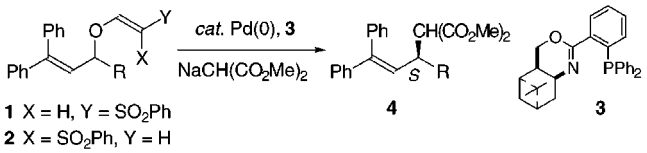


The *E*- and *Z*-vinylogous sulfonates of β-phenylcinnamyl alcohol derivatives 1 and 2 undergo rapid and enantioselective palladium-catalyzed allylic alkylation (≥90% ee) with the palladium complex of the phosphino-1,3-oxazine 3 and sodium salt of dimethyl malonate.

Transition metal-catalyzed reactions represent important methods for the construction of carbon−carbon bonds in synthetic organic chemistry. The palladium-catalyzed allylic alkylation[1,2] is representative of this reaction class and has been widely employed as the key step in an array of target-directed syntheses, with increasing emphasis on the development of new ligands for asymmetric catalysis.[3−5] However, despite an enormous amount of effort, only a limited number of ligand/substrate systems have been reported that can facilitate the enantioselective allylic alkylation (≥90% ee) of simple straight-chain alkyl-substituted allylic systems.[6]

Herein, we describe the *enantioselective* allylic alkylation of an array of vinylogous sulfonate-activated alkyl-substituted secondary β-phenylcinnamyl alcohol derivatives **1** and **2**, with the palladium complex of the *cis*-phosphino-1,3-oxazine ligand **3** (Scheme 1).

Scheme 1



The palladium-catalyzed allylic alkylation of methyl- and aryl-substituted β-phenylcinnamyl alcohol derivatives occurs

(1) Tsuji, J. In *Palladium Reagents and Catalysts*; Wiley: New York, 1996; Chapter 4, pp 290−404.

(2) For some recent reviews on the Pd(0)-catalyzed allylic alkylation, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (b) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed; VCH Publishers: New York, 1993; p 325. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(3) For some of the early conceptual contributions to Pd(0)-catalyzed allylic alkylation, see: (a) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191. (b) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228. (c) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (d) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (e) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. For a more recent Mo-catalyzed allylic alkylation procedure using aryl derivatives, see: Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.

(4) For an exhaustive citation of the literature pertaining to the asymmetric Pd(0)-catalyzed allylic alkylation reactions, see: Vyskocil, S.; Jaracz, S.; Smrcina, M.; Stícha, M.; Hanus, V.; Polásek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7727. For recent eamples, see: (a) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 2994. (b) Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, S.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1999**, 514. (c) Saitoh, A.; Misawa, M.; Morimoto, T. J. *Synlett* **1999**, 483.

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with excellent regio- and enantioselectivity.[6a] The extension of this concept to simple straight-chain alkyl substituents via the addition of the relevant organometallic reagent to commercially available β-phenylcinnamaldehyde was expected to provide a template to allow a somewhat general approach to the enantioselective allylic alkylation and to avoid the need for symmetrical substrates. The alkenyl group can then be cleaved to the aldehyde, which serves as a useful handle for further functionalization and the benzophenone adduct recycled via Wittig homologation. Bosnich[7] was the first to report the palladium-catalyzed allylic alkylation of secondary β-phenylcinnamyl alcohol derivatives, in which the trisubstituted alkene proved a particularly challenging substrate for oxidative addition.[8] Indeed, this may be the reason this substrate has not been employed in the manner described herein.

The vinylogous sulfonate was developed in our laboratory as an improved leaving group for palladium-catalyzed allylic alkylation reactions.[9] We rationalized that since the allylic vinylogous sulfonates resemble the dibenzylidene acetone ligand (dba), in that they have two proximal alkenes, the metal could more easily undergo an entropically favored oxidative addition. Furthermore, the vinylogous sulfonate becomes a β-formyl methylsulfonate upon oxidative addition, which was expected to influence both the catalytic turnover and possibly the enantioselectivity through its counterion effect.[10]

Indeed, treatment of the *E*-vinylogous sulfonate **1a**,[11] with the sodium salt of dimethyl malonate and the palladium catalyst derived from the phosphino-1,3-oxazine ligand **3**, prepared from (−)-β-pinene, furnished **4a** in 89% yield with 90% enantiomeric excess in only 80 min (Table 1, Entry 1).[12] The *Z*-isomer **2a**[11] behaved in a similar fashion, affording a slightly higher yield due to less hydrolysis.

Table 1. Asymmetric Allylic Alkylation of the *E*- and *Z*-Vinylogous Sulfonates **1** and **2**

entry	substrate **1/2**[a] R =		geom.	yield (%)[c] **4**	yield (%)[c] **5**	ee[d] (%)	abs config
1	Me	**a**	*E*	89	6	90	(*S*)
2			*Z*	94	3	91	
3	Et	**b**	*E*	73	18	94	(*S*)[e]
4			*Z*	80	11	94	
5	*n*-Pr	**c**	*E*	59	23	95	(*S*)[e]
6			*Z*	75	10	95	
7	*n*-Bu	**d**	*E*	63	24	94	(*S*)[e]
8			*Z*	78	12	93	
9	$BnOCH_2$	**e**	*E*	36	54	95	(*S*)[e]
10			*Z*	61	30	95	
11	$BnO(CH_2)_2$	**f**	*E*	59	14	97	(*S*)[e]
12			*Z*	58	10	98	
13	$TBSO(CH_2)_3$	**g**	*E*	63	30	96	(*S*)[e]
14			*Z*	78	12	95	
15	$TBSO(CH_2)_4$	**h**	*E*	65	14	93	(*S*)[e]
16			*Z*	76	9	92	

[a] All reactions were carried out on a 0.5 mmol scale with 2 equiv of the sodium salt of dimethyl malonate at 30 °C unless noted to the contrary. [b] Reaction carried out at 20 °C. [c] Isolated yields. [d] Enantioselectivities determined by 400 MHz ^{1}H NMR ($CDCl_3$) using the shift reagent (+)-$Eu(hfc)_3$. [e] Assignment made by analogy to **4a**.[5,13]

Table 1 summarizes the results with both *E*- and *Z*-vinylogous sulfonates for a range of straight-chain alkyl substituents, in which all the substrates furnished allylic alkylation products with excellent enantioselectivity in ~4 h (entries 3−16). In each case the major competitive side reaction was hydrolysis to the secondary alcohol **5a**, which was easily separated and recycled. The increased hydrolysis observed with the *E*-isomer is presumably the result of its ability to adopt antiperiplanar transition state necessary for elimination.[11] It is also particularly noteworthy that the alkene geometry of the leaving group has no appreciable effect on the enantioselectivity, indicating that enantiodiscrimination occurs after ionization. Therefore, the vinylogous sulfonates have unique properties that both facilitate facile oxidative addition to unreactive allylic systems and increase the enantioselectivity compared with the more traditional leaving groups often utilized for this transformation.[9]

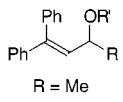
The absolute configuration of the allylic alkylation products is consistent with the model proposed by Helmchen and others[13] for 1,3-oxazoline ligands. Alkylation of the π-allyl intermediate occurs opposite the phosphine, due to its superior π-accepting character, providing two transition states in which **i** rather than **ii** is responsible for the formation of the major enantiomer (Figure 1).

(5) Evans, P. A.; Brandt, T. A. *Tetrahedron Lett.* **1996**, *37*, 9143.

(6) For examples of the enantioselective (≥90% ee) Pd(0)-catalyzed allylic alkylation of alkyl substituted allylic systems, see: (a) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2535. (b) Trost, B. M.; Radinov, R. *J. Am. Chem. Soc.* **1997**, *119*, 5962. (c) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141.

(7) Auburn, P. R.; MacKenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.

(8) Preliminary studies demonstrated that the nature of the leaving group was crucial to the success of this transformation using the phosphino-1,3-oxazine ligand **3**. Treatment of the allylic acetate **6a** with the sodium salt of dimethyl malonate and the palladium catalyst derived from the phosphino-1,3-oxazine ligand **3**, failed to give any of the desired product **4a** under a variety of reaction conditions.



5a R' = H
6a R' = MeCO
7a R' = MeOCO
8a R' = CF_3CO

This observation prompted the examination of alternative leaving groups for this system. Treatment of the allylic carbonate **7a** under similar conditions furnished the allylic alkylation product **4a** in 55% yield, albeit with modest enantiomeric excess (82% ee). The trifluoroacetate derivative **8a** proved less effective due to hydrolysis, furnishing the alcohol **5a** (68%) and the allylic alkylation product **4a** in only 28% yield with 85% ee.

(9) Evans, P. A.; Brandt, T. A.; Robinson, J. E. *Tetrahedron Lett.* **1999**, *40*, 3105.

(10) For a leading reference on the effect of the metal counterion on enantioselectivity and turnover rate, see: Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155 and pertinent references therein.

(11) For the stereospecific synthesis of *E*- and *Z*-vinylogous sulfonates, see: Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1968**, *33*, 985.

(12) The analogous reaction using **6a** and the phosphino-1,3-oxazoline palladium catalyst required 24 h.[6a] The vinylogous sulfonates of β-phenylcinnamyl alcohols with aryl substituents are however particularly unstable due to ionization of the leaving group.

(13) Spritz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523 and pertinent references therein.

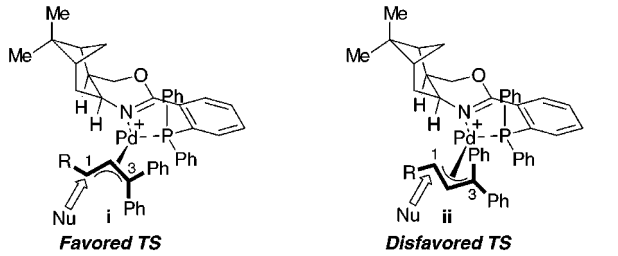


Figure 1.

Although the reaction rates were improved compared to the analogous transformation with acetates, we decided to examine the merit of microwave catalysis. Focused microwave irradiation of the *Z*-vinylogous sulfonate **2d** with the palladium complex of **3** and the sodium salt of dimethyl malonate, furnished the allylic alkylation product **4** in 78% yield with 91% ee in 4 min. This represents the first microwave accelerated asymmetric allylic alkylation with ≥90% ee and will be the subject of further investigation.[14]

In conclusion, we have developed a versatile catalytic protocol for the enantioselective synthesis of ternary stereogenic centers using the vinylogous sulfonate leaving group in conjunction with the palladium complex of *cis*-phosphino-1,3-oxazine **3**, with a variety of alkyl-substituted *β*-phenylcinnamyl alcohol derivatives. The excellent enantioselectivities and increased turnover rates, make vinylogous sulfonates attractive alternatives to existing leaving groups for the asymmetric palladium-catalyzed allylic alkylation. Furthermore, our studies suggest that this observation is not limited to the *cis*-phosphino-1,3-oxazine **3**, but analogous selectivities were obtained with the more widely utilized phosphino-1,3-oxazoline palladium catalyst.[3c−e]

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds, including details for the preparation of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For the first example of a microwave-catalyzed asymmetric palladium-catalyzed allylic alkylation, see: Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 1082.