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Highly Enantioselective Alkenylation of Glyoxylate with Vinylsilane Catalyzed by Chiral Dicationic Palladium(II) Complexes

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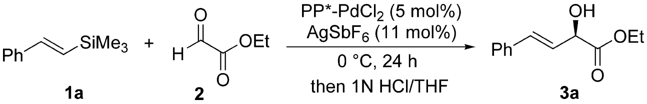
Enantiomerically enriched and highly functionalized allylic alcohol is one of the most important chiral building blocks for synthesizing many naturally occurring or synthetic products.[1] As a useful synthetic method for chiral allylic alcohols, catalytic enantioselective alkenylation using alkenylzinc species reliably achieves both high yield and enantioselectivity. However, it is necessary to use a stoichiometric amount of zinc reagents such as ZnR_2 for transmetalation in addition to prior hydroboration[2] or hydrozirconation[3,4] of terminal alkynes.[5] On the other hand, easily synthesized, storable, air- and moisture-stable vinylsilanes hold strong potential for direct synthesis of versatile chiral allylic alcohols because their geometry potentially impacts the allylic alcohol products.[6] However, vinylsilanes have been rarely utilized as nucleophiles because of their low reactivity. Shibasaki reported catalytic asymmetric alkenylation of carbonyl compounds with vinylsilanes using a chiral CuF complex.[7] It was demonstrated by mechanistic investigations that the reactive vinylcopper generated by transmetalation of vinylsilane with the CuF complex was the key species. Direct vinylsilane addition to carbonyl compounds with a chiral Lewis acid catalyst is limited to Evans's report using the Sc complex.[8] We have already reported that chiral dicationic Pd complex-catalyzed asymmetric glyoxylate− and ketoester−ene reactions produce the corresponding chiral β-hydroxy ester derivatives.[9,10] The chiral Pd complexes are air- and moisture-stable Lewis acid catalysts[11] that are easily synthesized and handled as well as catalytically very active, facilitating high yield and enantioselectivity. In this paper, we describe a chiral dicationic Pd complex-catalyzed enantioselective alkenylation employing vinylsilanes with high enantioselectivity.[12] The same approach can be extended to asymmetric dienylation and trienylation.

Initial investigations used vinylsilane **1a** as a model substrate to react with ethyl glyoxylate **2** via catalysis by chiral dicationic Pd complexes bearing C_2-symmetric biaryl ligands that have been shown to be highly efficient[9] (Table 1). The Pd complexes were simply activated in situ by adding $AgSbF_6$ in dichloromethane.[13] To find a suitable catalyst readily available chiral ligands were screened (entries 1−6), and a BINAP complex presented the best results (84% yield, 98% ee) (entry 1). Also, the catalyst loading could be reduced to 1 mol% without a deleterious effect on the enantioselectivity (97 and 98% ee), even under neat conditions (entries 9, 10). Notably, the use of ethyl glyoxylate in a polymeric form[14] instead of a freshly distilled one maintained sufficient yield and high enantioselectivity, although a higher reaction temperature of 50 °C was necessary for depolymerization of ethyl glyoxylate by the Pd catalyst (entry 11).

The scope of silyl groups in vinylsilane **1a** was explored under the optimized conditions (Scheme 1). The sterically more hindered $SiEt_3$, $SiMe_2Ph$, and Si^iPr_3 groups yielded product **3a** in high enantioselectivity (95−99% ee), although the reactivity of Si^iPr_3 was slightly lower. In contrast, vinylsilanes bearing $Si(OEt)_3$ or $SiMe(OEt)_2$ groups with alkoxy substituents were of extremely low reactivity. Vinylsilane reagent with $Si(OMe)_3$ did not undergo a similar reaction because of decomposition under the reaction conditions.

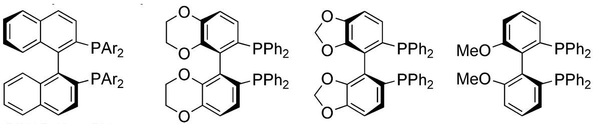
Table 1. Enantioselective Alkenylation with Vinylsilane **1a** and Ethyl Glyoxylate **2** by Chiral Dicationic Pd Catalysts



1a **2** **3a**

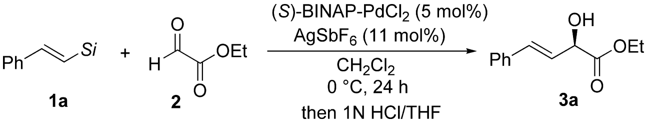
entry	PP* ligand	solvent	yield (%)[d]	ee (%)[e]
1	(*S*)-BINAP	CH_2Cl_2	84	98
2	(*S*)-tol-BINAP	CH_2Cl_2	75	98
3	(*S*)-xylyl-BINAP	CH_2Cl_2	48	75
4	(*S*)-SYNPHOS	CH_2Cl_2	72	93
5	(*S*)-SEGPHOS	CH_2Cl_2	78	96
6	(*S*)-MeO-BIPHEP	CH_2Cl_2	68	97
7	(*S*)-BINAP	toluene	11	98
8	(*S*)-BINAP	Et_2O	35	98
9[a]	(*S*)-BINAP	neat	67	97
10[b]	(*S*)-BINAP	CH_2Cl_2	53	98
11[c]	(*S*)-BINAP	CH_2Cl_2	78	95

[a] Reaction was examined with 1 mol% catalyst without solvent at 50 °C for 16 h. [b] Reaction time was 48 h with 1 mol% catalyst. [c] Ethyl glyoxylate polymer form (47% in toluene) without distillation was used at 50 °C for 12 h. [d] Isolated yield. [e] Determined by HPLC analysis.



(*S*)-BINAP (Ar = Ph)
(*S*)-tol-BINAP (Ar = 4-Me-Ph)
(*S*)-xylyl-BINAP (Ar = 3,5-Me_2-Ph)
(*S*)-SYNPHOS
(*S*)-SEGPHOS
(*S*)-MeO-BIPHEP

Scheme 1. Silyl Effects of **1a** on Enantioselective Alkenylation



1a **2** **3a**

Si =				
	$SiEt_3$	84%, 99% *ee*	$Si(OMe)_3$	0%, -
	$SiMe_2Ph$	72%, 98% *ee*	$Si(OEt)_3$	9%, 92% *ee*
	Si^iPr_3[a]	80%, 95% *ee*	$SiMe(OEt)_2$	35%, 90% *ee*

[a] Reaction proceeded at 50 °C for 12 h.

Under optimized conditions, the substrate scope of the reactions was examined using dicationic BINAP−Pd complexes (Table 2). Alkenyl products were obtained with greater than 90% ee. The palladium catalyst facilitated the alkenylation of glyoxylate with vinylsilanes **1b**−**d** bearing an electron-donating MeO substituent on the aromatic ring, regardless of its position (94−97% ee) (entries 2−4). An electron-withdrawing CF_3 substituent led to high enantioselectivity (97% ee) but lower reactivity (55% yield) (entry 5). The different rate of 4-CF_3 versus MeO styryl substrates even partially obeys a β-Si cationic description. With aliphatic substituents, high enantioselectivity was consistently obtained (91% ee) (entry 6). 2,2′-Disubstituted vinylsilanes **1g** and **1h** were applicable as well, with higher enantioselectivity (99% ee) (entries 7, 8). Significantly, sterically more demanding 1,2,2′-trisubstituted vinylsilane **1i** could be employed, resulting in the corresponding product **3i** in a 73% yield and 99% ee (entry 9). The use of 2-monosubstituted (*Z*)-vinylsilanes **1j** and **1k** produced the corresponding (*Z*)-allylic alcohols with high enantioselectivity (96 and 95% ee) (entries 10, 11). Product **3j** was a mixture of

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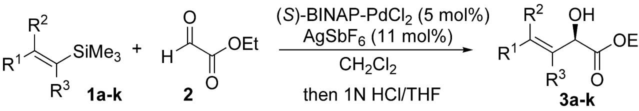
geometrical isomers (96:4 *Z*/*E*), but in the case of **3k**, complete retention of the geometry was observed.[6]

Table 2. Enantioselective Alkenylation with Various Vinylsilanes **1a**−**k** and Ethyl Glyoxylate **2**

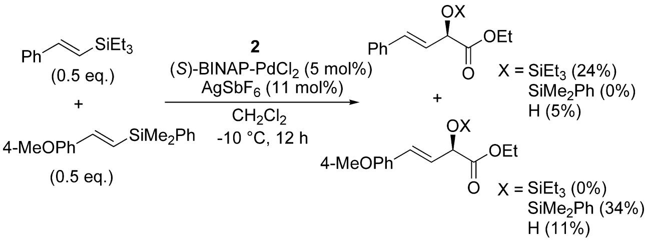


entry	R^1	R^2	R^3	*T* (°C)	time (h)	yield (%)[b]	ee (%)[d]
1	Ph (**1a**)	H	H	0	24	84	98
2	4-OMe-C_6H_4 (**1b**)	H	H	0	18	83	95
3	3-OMe-C_6H_4 (**1c**)	H	H	0	18	85	97
4	2-OMe-C_6H_4 (**1d**)	H	H	0	18	91	94
5[a]	4-CF_3-C_6H_4 (**1e**)	H	H	r.t.	48	55	97
6[a]	^{n}Bu (**1f**)	H	H	r.t.	48	64	91[e]
7	Ph (**1g**)	Me	H	0	24	75	99
8	*n*-C_6H_{11} (**1h**)	Me	H	0	24	83	99
9	Me (**1i**)	Me	Me	r.t.	24	73	99
10	H (**1j**)	Ph	H	0	24	79[c]	96[f]
11[a]	H (**1k**)	^{n}Bu	H	r.t.	48	60	95[e]

[a] Using 10 mol% catalyst. [b] Isolated yield. [c] A 96:4 *Z*/*E* mixture. [d] Determined by HPLC analysis. [e] Determined by ^{1}H and ^{19}F NMR analyses after MTPA esterification. [f] Enantiopurity of the *Z* product.

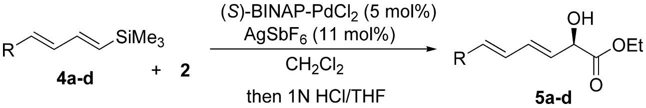
Additionally, a crossover experiment was examined to clarify whether silicon transfer proceeds via an intra- or intermolecular process (Scheme 2). Only the intramolecular silicon transfer was observed, ruling out a vinylpalladium intermediate, although Pd is well-known to engage in transmetalation. The alcohol products were produced after desilylation under the reaction conditions.

Scheme 2. Crossover Experiment for Silyl Substituents



With these successes in terms of high yield and enantioselectivity, we attempted dienylation of ethyl glyoxylate **2** with dienylsilanes **4** (Table 3). Use of (*E*,*E*)-dienylsilane **4a** gave the corresponding (*E*,*E*)-dienyl alcohol product **5a** in 95% ee with exclusive retention of *E*,*E* geometry (entry 1). Both electron-donating MeO and electron-withdrawing CF_3 substituents also led to high yield and enantioselectivity (97 and 96% ee) (entries 2, 4). The low catalyst loading of 1 mol% slightly reduced the enantioselectivity (96% ee) (entry 3). Dienylsilane **4d** with an aliphatic isovaleryl group gave high enantioselectivity (92% ee) (entry 5). Moreover, (*E*,*E*,*E*)-trienylsilane **6** afforded the corresponding trienyl product **7** with high enantioselectivity and geometrical purity in good yield (Scheme 3).

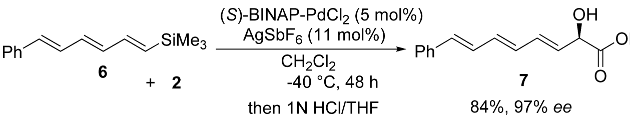
Table 3. Enantioselective Dienylation with Dienylsilanes **4a**−**d**



entry	R	*T* (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	Ph (**4a**)	−20	30	84	95
2	4-OMe-C_6H_4 (**4b**)	−20	30	83	97
3[a]	4-OMe-C_6H_4 (**4b**)	0	48	61	96
4	4-CF_3−C_6H_4 (**4c**)	0	24	81	96
5	$(CH_3)_2CHCH_2$ (**4d**)	−20	30	76	92.

[a] Using 1 mol% catalyst. [b] Isolated yield. [c] Determined by HPLC analysis.

Scheme 3. Enantioselective Trienylation



In summary, we have achieved dicationic Pd complex-catalyzed alkenylation to give highly optically active allylic alcohols. The reaction is applicable to dienylation and trienylation. Attempts to construct more sterically demanding structures (e.g., quaternary carbon centers) are ongoing.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Whether AgCl was filtered or not, the conditions of 10 mol% $AgSbF_6$ to 5 mol% BINAP-$PdCl_2$ complex produced the same result. It was also observed that $AgSbF_6$ did not catalyze the reaction.
(14) TCI ethyl glyoxylate polymer form in 47% toluene solution.

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