Communications to the Editor

Enantioselective Addition of Enol Silyl Ethers to Imines Catalyzed by Palladium Complexes: A Novel Way to Optically Active Acylalanine Derivatives

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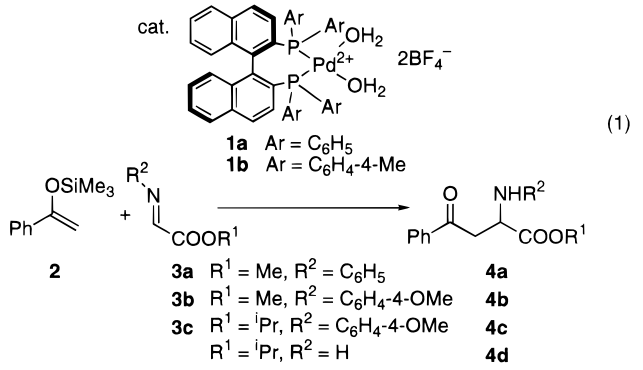
Carbon−carbon bond-forming reactions that involve the addition of resonance-stabilized nucleophiles such as enols and enolates to iminium salts and imines, so-called Mannich-type reactions, comprise one of the most important classes of reaction in organic synthesis.[1] Recently, the potential utility of these reactions for the synthesis of optically active compounds has been recognized, and a number of methods for the diastereoselective reaction of imines with enolates of carboxylic acid derivatives or silyl ketene acetals have been reported.[2] However, examples of enantioselective variants of this reaction are quite limited,[3] and to our knowledge, there are only two examples of a catalytic, enantioselective method.[4] The addition of metal enolates of ketone or enol silyl ethers to imines appears to be even more difficult,[5] and no method for the enantioselective addition of a ketone to an imine has been reported. Thus, the development of a catalytic asymmetric variant of this reaction would be a significant contribution to synthetic chemistry. Here, we report the first example of a Pd(II)-catalyzed asymmetric addition of enol silyl ethers to imines.

The difficulty of the ketone−imine addition compared to the ester/thioester−imine addition may be due to the relatively high reactivity of ketones, a property that may cause undesired side reactions. Thus, our strategy involved the use of a less nucleophilic transition-metal enolate instead of a highly nucleophilic metal enolate and/or strong Lewis acid catalyst. Recently we reported the catalytic asymmetric addition of enol silyl ethers to aldehydes with the chiral palladium(II) diaquo complexes, [Pd((*R*)-binap)$(H_2O)_2$]$^{2+}$(BF_4^-)$_2$ (**1a**) or [Pd((*R*)-tol-binap)$(H_2O)_2$]$^{2+}$-(BF_4^-)$_2$ (**1b**). This reaction is believed to proceed via a chiral Pd(II) enolate.[6] As palladium is believed to have a high affinity for nitrogen, we suspected that this chiral palladium catalyst system might be useful for reactions with imines, at least in a stoichiometric sense.



(1)

There has been an increasing interest in the development of a method for the preparation of nonnatural α-amino acid derivatives, building blocks for many therapeutic agents and for combinatorial chemistry. Thus, we focused on the reaction of iminoacetic acid derivatives **3**. To a mixture of enol silyl ether **2** (1.5 equiv) and the Pd diaquo complex **1a** (10 mol %) in DMF was added a solution of imine **3a** in DMF, and the mixture was stirred at 0 °C for 24 h. Contrary to our expectations, the simple application of reaction conditions suitable for the aldol reaction completely failed. Although the desired product **4a** was obtained in reasonable chemical yield (60%), *the optical yield of the product was 0%*. Similar results were obtained for imines **3b** and **3c**.[7] Furthermore, negligible asymmetric induction was observed using even a stoichiometric amount of **1a**.

After extensive experimentation, we found that **4c** could be obtained in 67% enantiomeric excess (ee) and 85% yield using the following rather complicated procedure. A solution of Pd diaquo complex **1a** (10 mol %) and **2** (1.5 equiv) in DMF was stirred at 25 °C for 1 h, after which time the solution was warmed to 60 °C, and a solution of imine **3c** was added over 4 h using a syringe pump. During the addition of **3c** additional **2** (3 × 0.5 equiv at 1 h intervals) was supplied to the reaction mixture. The whole mixture was stirred at the same temperature for an additional 2 h. Three aspects of these conditions were found to be critical for asymmetric induction: (1) preincubation of **2** with the Pd diaquo complex **1a**,[8] (2) control of the imine concentration,[9] and (3) reaction temperature. It is particularly interesting that increase of the reaction temperature from 25 to 60 °C improved the enantiomeric excess of the product (**4c**) from 3% to 67% ee. This temperature-dependent improvement of enantioselectivity was also observed with methyl ester **3b** (0 °C, 1% ee; 25 °C, 28% ee; 35 °C, 41% ee; 60 °C, 65% ee). The unusual temperature dependence and the sensitivity of the reaction conditions strongly suggest the existence of an undesired competitive reaction pathway that affords the racemic product.

If the reaction to produce highly optically active **4** proceeds via the palladium enolate **5**, one plausible route to racemic **4** would be a proton-catalyzed one (Figure 1). Upon generation of the palladium enolate from **2** and the diaquo complex **1**, an equivalent amount of tetrafluoroboric acid should be generated, and this strong protonic acid could catalyze the unselective

(1) For review, see: Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 893−951, and references therein.

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(7) For preparation of imines **3**, and determination of optical purity of the products, see the Supporting Information.

(8) As the preincubation time was reduced, the enantiomeric excess decreased significantly. See the Supporting Information.

(9) The imine concentration should be kept low during the reaction. When imine **2** was added in one portion, the enantioselectivity of **4** was drastically decreased.

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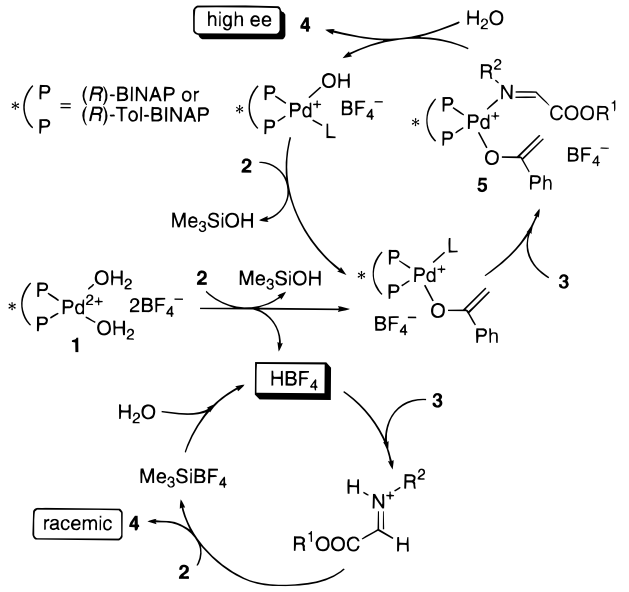
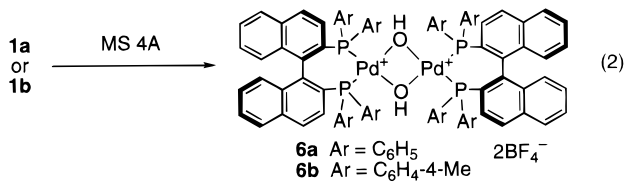


Figure 1.

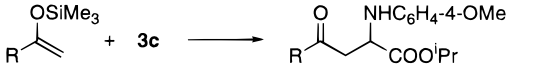
addition of **2** to **3**.[10] If this is the case, higher asymmetric induction might be attained by suppressing the undesired production of HBF_4. Thus, we attempted to prepare a catalyst which would give a similar palladium enolate without undesired formation of HBF_4. After examination of a variety of possibilities, we found that the binuclear μ-hydroxo complex, [{Pd((*R*)-tol-binap)-(μ-OH)}$_2$]$^{2+}$(BF_4^-)$_2$ (**6b**), could be made by the treatment of the diaquo complex **1b** with 4A molecular sieves in acetone. The ^{1}H NMR spectrum of **6b** contains a singlet at −3.03 ppm which is typical for a μ-hydroxo group.[11] Presumably, this dimeric form of the hydroxo complex is generated by the removal of 1 equiv of HBF_4 from the diaquo complex **1b**. The (*R*)-BINAP complex **6a** was also prepared in a similar manner.



(2)

Using the novel chiral complex **6b** (5 mol %) as a catalyst, reaction of **2** with **3c** proceeded smoothly at 25 °C to give **4c** in 95% yield. As expected, *the optical yield increased to 90% ee!* It is noteworthy that the troublesome reaction procedure described above is no longer necessary. Furthermore, decomposition of **2** was slow under these "less acidic" conditions making 1.5−2 equiv of **2** sufficient for the completion of the reaction. Solvent effects were also reexamined, and amide or urea solvents have been found to be suitable. Reaction of the enol silyl ethers **7**−**11** was also carried out to afford the corresponding optically active acylalanine derivatives with good asymmetric induction (Table 1).[12]

Table 1. Enantioselective Mannich-Type Reaction of **3c** Catalyzed by Binuclear μ-OH Pd Complex **6**



entry[a]	silyl ether	R =	solvent	yield, %	% ee
1	**2**	C_6H_5	DMF	95	90
2[b]	**2**	C_6H_5	DMF	83	81
3[c]	**2**	C_6H_5	DMF	87	83
4[b]	**2**	C_6H_5	NMP	79	83
5[b]	**2**	C_6H_5	DMI	75	81
6[b]	**2**	C_6H_5	TMU	59	82
7[b]	**2**	C_6H_5	CH_2Cl_2	45	53
8[b]	**2**	C_6H_5	THF	60	67
9	**7**	2-naphthyl	DMF	82	83
10	**8**	3,4-Cl_2-C_6H_3	DMF	80	84
11	**9**	2-MeO-C_6H_4	DMF	87	71
12[d,e]	**10**	3-NO_2-C_6H_4	DMF	62	60
13[d,f]	**11**	CH_3	DMF	79	53

[a] Reaction was carried out using a catalyst **6b** (5 mol %) and enol silyl ether (2 equiv) at 28 °C for 17−24 h. Imine **3c** was added in one portion. [b] 3 mol % of **6b** was used. [c] **6a** (3 mol %) was used as a catalyst. [d] Syringe pump was used for the addition of **3c** (over 4 h). [e] 1.5 equiv of enol silyl ether was used. [f] 3 equiv of enol silyl ether was used.

Simple recrystallization of **4c** (90% ee) gave the optically pure sample (75% yield of recovery). The absolute stereochemistry of **4c** was determined to be (*S*) after deprotection of methoxyphenyl group (cerium ammonium nitrate (CAN), CH_3CN-H_2O, 0 °C, 54%) and comparison with an authentic sample of **4d** prepared according to the literature procedure.[13] Benzoylalanine and its substituted derivatives are known as potent inhibitors of kynurenine 3-hydroxylase and kynureninase, potential drugs for the treatment of neurodegenerative disorders that function by controlling the toxic quinolinic acid concentration in the brain.[14]

In summary, we have found that highly optically active acylalanine derivatives (up to 90% ee) can be obtained by the enantioselective Mannich-type reaction of enol silyl ethers with imines catalyzed by the novel chiral binuclear μ-hydroxo palladium(II) complex. Since the acylalanine derivatives are not only themselves therapeutically useful compounds but also important synthetic intermediates for a wide variety of nonnatural amino acids, the methodology described above should prove to be extremely useful. Further mechanistic studies of this novel C−C bond-forming reaction are in progress.

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Supporting Information Available: Experimental procedure and selected spectral data (13 pages). See any current masthead page for ordering information and Web access instructions.

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(10) Indeed, HBF_4 (10 mol %) prepared from $AgBF_4$ and trimethylsilyl chloride in DMF (containing a trace amount of water) did catalyze the reaction of **2** with **3c** to give **4c** in 76% yield after 3 h at 25 °C. Effects of bases on the **1a**-catalyzed reaction were also examined, and $CaCO_3$ (1 equiv to **3c**) was found to improve the optical yield from 67% to 79% ee.

(11) Similar binuclear μ-hydroxo Pd complexes of 1,2-bis(diphenylphosphino)propane (DPPP) and 1,1′-bis(diphenylphosphino)ferrocene (DPPF) have been reported to show the OH signal at −2.3 and −2.32 ppm respectively in the ^{1}H NMR. See: (a) Pisano, C.; Consiglio, G.; Sironi, A.; Moret, M. J. *J. Chem. Soc., Chem. Commun.* **1991**, 421−423. (b) Longato, B.; Pilloni, G.; Valle, G. Corain, B. *Inorg. Chem.* **1988**, *27*, 956−958.

(12) Preliminary results of reaction of **2** with imines derived from benzaldehyde under similar conditions suggested the possible applicability of this reaction to various other imines. Although the reaction is slow, desired optically active amine was obtained (for $C_6H_5CH{=}NTs$, 144 h, 55%, 30% ee; for $C_6H_5CH{=}NC_6H_4$-4-OMe, 70 h, 54%, 16% ee). Further optimization of reaction conditions is in progress. In contrast, reaction of silyl ketene acetals such as $CH_2{=}C(OSiMe_3)(OC_6H_5)$ with **3c** also gave low chemical yield of the desired products, but negligible asymmetric induction was observed.

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