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Catalytic, Enantioselective Alkylation of α-Imino Esters Using Late Transition Metal Phosphine Complexes as Catalysts

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Over the past several years, highly effective methods for enantioselective aldol additions catalyzed by Lewis acids have been developed.[1] Analogous alkylations of imines, however, have not been nearly as well studied nor as successful.[2] α-Imino esters are almost unstudied in Lewis acid-catalyzed reactions,[3] but are especially attractive imine substrates for the efficient syntheses of natural product precursors,[4] pharmaceutically active compounds,[5] and nonnatural amino acids;[6] the last category has recently received much attention as peptidomimetics[7] and in site-directed mutagenesis studies.[8] In a recent report, we demonstrated that select late transition metals can catalyze the cis−trans isomerization of prolyl peptides through simultaneous coordination of the metal to the amide nitrogen (N_a) and the side chain carbonyl group (Figure 1, **a**).[9] Catalysis fails to occur on simple amides that do not contain an additional binding site. These results prompted us to investigate whether analogous coordination of a transition metal to the nitrogen of a functionalized imine and a chelating carbonyl group could activate the substrate toward a highly enantioselective addition of nucleophiles (Figure 1, **b**).

From our point of view, activated α-imino esters **1** seemed ideal substrates for Lewis acid catalyzed asymmetric alkylations for several reasons: (1) alkylation occurs readily at the imine carbon with a variety of nucleophiles, (2) the electron-withdrawing α-ester group provides additional activation of the imino group to nucleophilic attack, (3) the imine N and carbonyl O can form a stable five-membered chelate ring with a chiral Lewis acid catalyst (eq 1),[10] providing additional rigidity to an activated

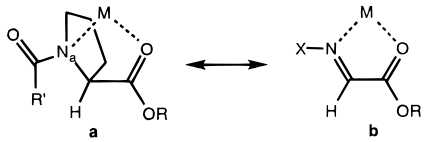
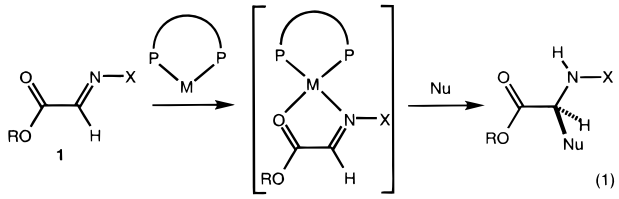
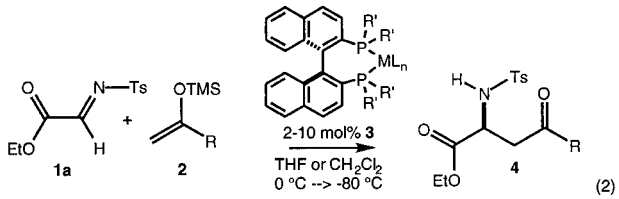


Figure 1. Chelate coordination of amide and imine nitrogens.



(1)

complex and potentially enhanced product selectivity, and (4) alkylation of imine derivatives **1** with enol silane nucleophiles can lead to substituted γ-oxo α-amino acids (aspartic acid analogues) that comprise a class of interesting and useful biologically active natural compounds.[11] We report herein a means to alkylate α-imino esters enantioselectively in up to 98% ee and in high chemical yields with enol silanes using chiral catalytic late transition metal phosphine complexes selected from Ag(I), Cu(I), Ni(II), and Pd(II) (eq 2).



(2)

2a, 4a R = phenyl
2b, 4b R = 4-methoxyphenyl
2c, 4c R = t-butyl
2d, 4d R = 4-(dimethylamino)phenyl
2e, 4e R = 4-fluorophenyl
2f, 4f R = 4-chlorophenyl
2g, 4g R = 4-(trifluoromethyl)phenyl
2h, 4h R = β-naphthyl

3a R' = C_6H_5, ML_n = $AgSbF_6$
3b R' = C_6H_5, ML_n = $Pd(ClO_4)_2$
3c R' = 4-MeC_6H_4, ML_n = $CuClO_4$
3d R' = C_6H_5, ML_n = $Ni(SbF_6)_2$

We turned our attention to readily available tosyl imine **1a**,[12] although slight uncatalyzed reaction in THF solution at −50 °C between **1a** and **2a** was initially a cause for concern. Surprisingly, however, slow addition of 1.1 equiv enol silane **2a** over the course of 2 h into a solution of the α-imino ester **1a** containing 10 mol % of (*R*)-BINAP-$AgSbF_6$[13] (**3a**) at −80 °C gave the protected amino acid **4a**[14] in 95% yield and 90% ee[15] (eq 2, entry 1, Table 1) after a quench with MeOH at −80 °C. Use of 1 equiv of catalyst led to identical selectivity (90% ee) and suggested that uncatalyzed reaction plays a minor role in affecting asymmetric induction under these conditions. When we conducted the said reaction at −40 °C the selectivity decreased to 67% ee. The Ag(I)-catalyzed reaction at −80 °C is complete after 12 h; a noteworthy feature is that enol silanes, which are usually too

(1) For notable recent examples of asymmetric aldol reactions, see: (a) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. (b) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319. (c) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.*, **1993**, *33*, 6907. (d) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648. (e) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649.

(2) For examples of Lewis acid catalyzed enantioselective imine alkylation, see: (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (c) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773. (d) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195.

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(4) α-Imino esters are attractive precursors to the synthesis of γ-hydroxy amino acid fragments that are found in a number of biologically active peptides, including the antifungal agents theonellamide (Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Walchi, M. *J. Am. Chem. Soc.* **1989**, *111*, 2582), and the nikkomycins and the neopolyoxins (Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298). Neopolyoxins are a group of nucleoside di- and tripeptide antibiotics (Barrett, A. G. M.; Dhanak, D.; Lebold, S.; Russell, M. A. *J. Org. Chem.* **1991**, *56*, 1894 and references therein).

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(10) Structural evidence exists for the chelate binding of α-imino esters and Zn(II): Van Vliet, R. P.; Van Koten, G.; Modder, J. F.; Van Beek, J. A. M.; Klaver, W. J. *J. Organomet. Chem.* **1987**, *319*, 285.

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(14) Analysis of compound **3a** (see Supporting Information) establishes the sense of induction as *S* by comparison with a product derived from natural aspartic acid, see: Wessig, P.; Steiner, A.; Posborn, K. *Helv. Chim. Acta* **1996**, *79*, 1843. Stereoregularity is inferred over the range of products.

(15) Enantiomeric excesses (ee's) were measured by HPLC employing a Chiralcel OD column, with EtOH/hexane as eluent.

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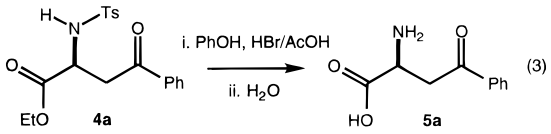
Table 1. Enantioselective Alkylation of **1a** by Enol Silanes **2a**−**h** Catalyzed by **3a**−**d**

entry	Nu	cat.[a]	*T* (°C)	%yield$_1$	%ee$_1$[d]	%yield$_2$[e]	%ee$_2$[f]
1	**2a**	**3a**	−80	95	90	66	99
2	**2a**	**3b**[b]	−80	91	80	63	90
3	**2a**	**3c**	0	91	98	80	>99
4	**2a**	**3c**[c]	0	92	96	60	>99
5	**2a**	**3d**	−80	89	30		
6	**2b**	**3a**	−80	94	86	63	95
7	**2b**	**3b**[b]	−80	89	73	51	90
8	**2b**	**3c**	0	90	98	76	>99
9	**2c**	**3a**	−80	70	75		
10	**2c**	**3c**	0	65	90		
11	**2d**	**3c**	0	91	92	65	99
12	**2e**	**3a**	−80	85	86	66	95
13	**2e**	**3c**	0	91	96	80	99
14	**2f**	**3a**	−80	92	88	61	96
15	**2f**	**3c**	0	93	95	82	99
16	**2g**	**3c**	25	75	89		
17	**2g**	**3a**[b]	25	87	61		
18	**2h**	**3c**	0	91	92	68	99

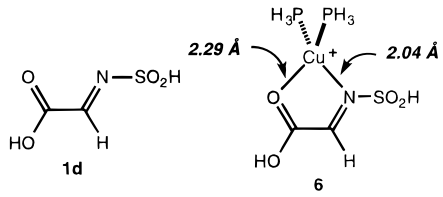
[a] Reactions with catalysts **3a**,**b**,**d** were run with 0.4 mmol of imine **1c**, 0.43 mmol of enol silane, and 0.04 mmol of catalyst (10 mol % metal salt, 10.5 mol % (*R*)-BINAP), and 0.02 mmol of catalyst (5 mol % metal salt, 5.2 mol % (*R*)-Tol-BINAP) for catalyst **3c** at the specified temperature for 24 h. [b] Reactions run in CH_2Cl_2 solvent. [c] Reaction run with 2 mol % ligand, 1.9 mol % metal. [d] ee$_1$ represents enantiomeric excess before product recrystallization. [e] Yield$_2$ represents yield after one recrystallization from ether/hexane. [f] ee$_2$ represents enantiomeric excess after recrystallization from ether/hexane.

unreactive for applications in Lewis acid-based asymmetric catalysis, react with good selectivity, whereas silyl ketene acetals, classic substrates of aldol methodology, appear to possess high uncatalyzed rates at the temperatures we screened. The complex (*R*)-BINAP·Pd$(ClO_4)_2$ (**3b**) afforded lower ee (80%, entry 2), whereas the straw-yellow complex (*R*)-Tol-BINAP·$CuClO_4$·$(MeCN)_n$ (**3c**)[16] performed the best, giving high yield (91%) and selectivity at 0 °C (98% ee, entry 3). Demonstrating the utility of our process, *similarly good ee was obtained even when this reaction was conducted at 0 °C in the presence of only 2 mol % catalyst (96% ee, entry 4).* At this temperature, the reaction is complete after only 1 h. To our knowledge, this is the first use of a phosphine−Cu(I) complex as a effective chiral Lewis acid.[17] In our hands, red (*R*)-BINAP·Ni$(SbF_6)_2$ (**3d**) is the least selective catalyst of those screened (30% ee, entry 5).

Use of slightly more reactive nucleophile **2b** led to 86% ee at −80 °C with 10 mol % Ag(I)-based catalyst **3a** (entry 6) and 98% ee with Cu(I)-based catalyst **3c** (entry 8). Other enol silanes (**2c**−**h**, Table 1) were also examined. For example, the enol silane derived from pinacolone (**2c**) gave 90% ee with catalyst **3c** (entry 10), although with lower chemical yield (65%). Of the nucleophiles derived from para-substituted acetophenones, rates of product formation[18] correlate well with the electron-donating ability of the para substituent. For example, in the presence of 10 mol % catalyst **3c**, nucleophile **2d** reacted the fastest (92% ee, entry 11), whereas **2g** reacted the slowest (89% ee, entry 16) and also afforded a lower chemical yield (75%). The enol silane **2h** derived from *β*-naphthyl methyl ketone gave high ee (92%) with catalyst **3c** (entry 18). Overall, THF appears to be the best solvent, although with Pd(II)-based catalysts, CH_2Cl_2 proved most effective. The products of the reaction (eq 2) were often highly crystalline, and in some cases, one recrystallization from ether/hexane afforded virtually enantiomerically pure materials (>99% ee, Table 1). The tosyl and ethyl groups were removed from product **4a** by treatment with phenol in a refluxing solution of HBr/AcOH, followed by addition of water, to yield substituted amino acid **5a** in 75% chemical yield with no detectable racemization (eq 3).[19]



Evidence for chelate formation in the activated complex of the catalyzed reaction (eqs 1 and 2) was obtained by FTIR spectroscopy. Upon addition of 1 equiv of catalyst **3c**, the ester carbonyl band of **1a** at 1735 cm^{-1} shifted by −38 cm^{-1}, to 1697 cm^{-1}, and the C=N absorption shifted from 1630 to 1618 cm^{-1} (−12 cm^{-1}). The *carbonyl band* underwent the greater frequency shift, as would be expected for chelate formation.[20] Theoretical calculations of model imine **1d** and Cu(I) complex **6** employing the DFT protocol pBP/DN* were undertaken.[21] The activated complex **6** is calculated to be approximately tetrahedral, in line with other complexes of Cu(I).[22] A vibrational analysis of **6** indicates a greater shift (−90 cm^{-1}) for the carbonyl group than the imino group (−45 cm^{-1}) relative to precursor **1d**, consistent with our experimental observations.



In summary, we have developed a high-yielding, enantioselective method for the alkylation of α-imino esters in up to 98% ee, with ee's of >99% obtainable after simple recrystallization in some cases. This method provides access to a variety of nonnatural amino acids as well as to precursors for natural products. We plan to expand the scope of these reactions to include other nucleophiles and other activated imines, as well as to explore mechanistic details in the near future.

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Supporting Information Available: General procedures for the conduct of catalytic reactions, spectroscopic details for all new compounds, and proof of absolute configuration (4 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(21) MO calculations were performed using the Spartan program (version 5.0.3).

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