Diastereo- and Enantioselective Alkylation of α-Imino Esters with Enol Silanes Catalyzed by (*R*)-Tol-BINAP−$CuClO_4$·$(MeCN)_2$

Dana Ferraris, Brandon Young, Christopher Cox, William J. Drury III, Travis Dudding, and Thomas Lectka*

Department of Chemistry, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218

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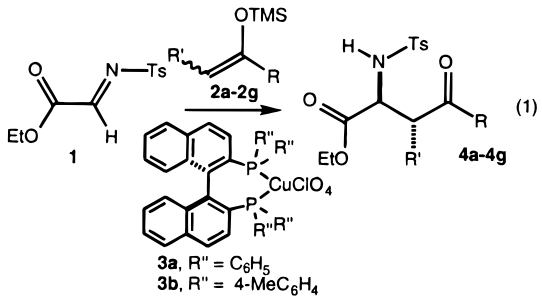
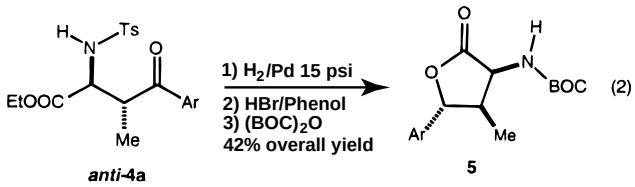
The past few years have witnessed a profusion of highly efficient, catalytic, enantio- and diastereoselective alkylations of carbonyl compounds.[1] At the present time, the alkylation of the imino functional group presents a timely challenge in asymmetric catalysis, and recent work has focused on enol silanes, silyl ketene acetals, and TMSCN as carbon-based nucleophiles.[2] We recently reported a means to alkylate α-imino ester **1** in up to 98% ee with enol silanes using chiral catalytic late-transition-metal phosphine complexes based on Ag(I), Cu(I), Ni(II), and Pd(II) (eq 1, R′ = H).[3] The best results were obtained with the easy-to-prepare catalyst (*R*)-Tol-BINAP−$CuClO_4$·$(MeCN)_2$. In this paper, we extend the utility of our reaction to include diastereo- and enantioselective variants that yield precursors for a number of pharmacologically active classes of compounds.[4] Regardless of the geometry of the enol silane, in many cases, excellent anti diastereoselectivity as well as enantioselectivity (up to 99% ee) can be obtained in the reaction (eq 1).[5] In fact, the precise nature of the chiral phosphines we employ is responsible for the diastereoselectivity, as certain achiral bis(triphenylphosphine)−Cu(I) complexes lead to equal amounts of anti and syn products.



Initial screening focused on the reaction of *Z*-enol silane **2a** (R′ = Me)[6] with α-imino ester **1**.[7] A pale straw yellow solution of the active catalyst **3b** can be made simply by mixing 5 mol % of $CuClO_4$·$(MeCN)_4$[8] with 5.5 mol % of commercially available (*R*)- or (*S*)-Tol-BINAP in CH_2Cl_2. This catalyst solution is stirred for 30 min, at which time 1 equiv of imino ester **1** is added at room temperature. As part of our standard procedure, slow addition of a CH_2Cl_2 solution of 1.1 equiv of **2a** over 1 h to the catalyst−imine mixture at 0 °C afforded product **4a** with good yield (86%), excellent ee (98%), and diastereoselection (anti/syn = 25:1; Table 1, entry 1). The yield, enantioselectivity, and diastereoselectivity all decreased slightly with the use of (*S*)-BINAP−$CuClO_4$·$(MeCN)_2$ **3a**, an unexpected result that mirrors the recent findings of Carreira in a Cu(II) phosphine-catalyzed asymmetric aldol reaction.[9] Not surprisingly, the enol silane **2b**[10] reacted under these conditions to yield 75% of **4b** in 95% ee and a 25:1 anti/syn ratio (entry 2). The absolute and relative stereochemistries of **4a** and **4b** were determined by diastereoselective reduction/cyclization to yield an intermediate lactone which was converted to known compound **5** (eq 2).[11] This methodology provides a convenient way to synthesize asymmetrically trisubstituted lactones that are building blocks for many natural products.[12]



We were interested in whether an *E*-enol silane could reverse the stereochemistry at the *β*-carbon leading to the syn product. Simple *E*-enol silanes, however, are difficult to synthesize isomerically pure without laborious purification.[13] One way to approach the problem of diastereoselective enolization is to enforce *E*-geometry by using a cyclic framework. The cyclic enol silane **2e** affords a 20/1 anti/syn ratio of product **4e** in >99% ee (entry 5).[14] Enol silane **2f**, derived from the corresponding known ketone,[15] can be viewed as a masked equivalent of *E*-enol silane **2b**. The silyl tetralone **2f** afforded the product **4f** with anti stereochemistry in 99% ee at −78 °C (15:1 anti/syn, entry 6, Table 1).[16] We found that higher reaction temperatures drastically eroded the enantio- and diastereoselectivity of **4f** due to an appreciable nonselective background rate between **1** and **2f**. Other cyclic enol silanes yielded somewhat lower enantio- and diastereoselectivities. For example, the enol silane **2c**

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(14) The absolute and relative stereochemistry of product (2*S*,1′*R*)-**4e** was determined by X-ray crystallography as shown in the Supporting Information. Stereoregularity was inferred for the cyclic products **4c**, **4d**, and **4f**.

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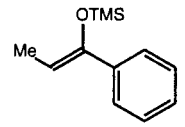
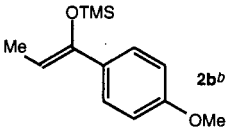
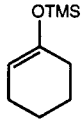
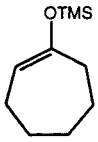
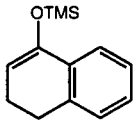
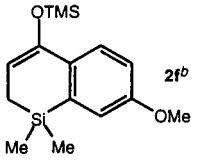
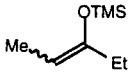
Table 1. Diastereoselective Alkylations of α-Imino Ester 1

entry	enol silane	catalyst	yield	ee %	anti/syn
1	 2a[a]	3a	80	92[c]	10/1
		3b	86	98[c]	25/1
2	 2b[b]	3b	75	95[c]	25/1
3	 2c[b]	3a	75	78[c]	7/1
		3b	71	88[c]	11/1
4	 2d[b]	3b	71	46[d]	7/1
5	 2e[a]	3b	82	>99[c]	20/1
6	 2f[b]	3b	75	99[c]	15/1
7	 2g (Z)[a]	3b	77	75[d]	3/1
	2g (E/Z 2/1)[a]	3b	76	61[d]	2/1

[a] Reactions carried out at 0 °C → rt. [b] Reactions carried out at −78 °C. [c] %ee determined by Chiralcel OD chiral HPLC column. [d] %ee determined by chiral shift reagent (+)-Pr(hfc)$_3$.

derived from cyclohexanone affords product **4c** in 71% yield (88% ee, 11:1 anti/syn, entry 3) with catalyst **3b**. Once again, both the enantioselectivity and diastereoselectivity diminished slightly with the use of catalyst **3a** (78% ee, 7:1 anti/syn ratio). The cycloheptanone-derived enol silane **2d** led to a lower ee and anti/syn ratio (entry 4). Not surprisingly, the aliphatic enol silane **2g** led to similar diastereoselectivity and enantioselectivity regardless of the purity of enol silane (entry 7).

Intriguing reports on the intermediacy of Pd(II)- and Cu(II)-based enolates in catalytic asymmetric imine additions and aldol reactions[2b,9] prompted us to examine whether they might be involved in our system. Treatment of a 1 mM solution of enol silane **2h** (R = Ph, R′ = H) in CD_2Cl_2 with 1 equiv of catalyst produced no discernible change in the ^{13}C and ^1H NMR spectra of the enolate over the course of 2 days, whereas previously we had demonstrated a chelate-based interaction between imino ester **1** and the catalyst **3b** by IR spectroscopy.[3] Thus, our results are consistent with the catalyst **3b** working as a classical Lewis acid. We were also aware of the potential ease of interconversion between Cu(I) and Cu(II).[17] To our surprise, a similar, although somewhat less effective, catalyst could also be generated by mixing $Cu(ClO_4)_2$ with (*R*)- or (*S*)-BINAP in THF. This catalyst afforded product **4h** (R = Ph, R′ = H) in 85% ee under the conditions of our screen. In addition, a major ligand-based byproduct of this reaction was identified as the bis(phosphine) oxide of BINAP (BINAPO).[18] To determine the source of oxygen in this phosphine oxidation, $Cu(ClO_4)_2$ was added to (*S*)-BINAP in a THF solution to which a slight excess of water enriched in $H_2{}^{18}O$ had been added. Workup and MS analysis of the BINAPO byproduct showed corresponding isotopic incorporation of ^{18}O into the phosphine oxide moiety,[19] implying that a small amount of adventitious water is the oxygen source when BINAP is oxidized by $Cu(ClO_4)_2$.[20] Consequently, the use of Cu(I)− or Cu(II)−BINAPO complexes in the alkylation of **1** led to racemic products **4h** (R = Ph, R′ = H), implying that only Cu(I)−BINAP is the active catalyst in our system, albeit present in reduced amounts when a Cu(II) salt is employed as a starting material.

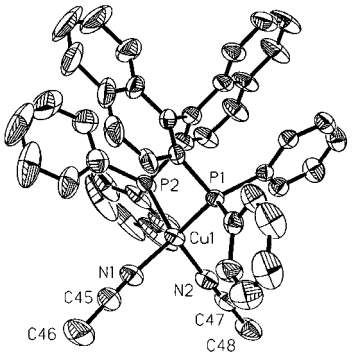


Figure 1. Crystal structure of (*S*)-BINAP−$CuClO_4$·$(MeCN)_2$ (50% ellipsoids).

The UV spectra of catalysts derived from either Cu(I) or Cu(II) salts appeared virtually identical, with features characteristic of Cu(I), including the lack of d−d absorption bands indicative of Cu(II).[17] Similarly, NMR spectra showed none of the expected paramagnetic broadening associated with the use of Cu(II), even when $Cu(ClO_4)_2$ was the starting copper salt. The catalyst's composition was determined by an X-ray crystal structure of the catalyst (*S*)-BINAP−$CuClO_4$·$(MeCN)_2$ (Figure 1), showing conclusively that a tetrahedral complex of Cu(I) is involved in our reactions.[21] Some interesting structural features of the crystal include one of the largest bite angles (P−Cu−P = 98.98°) of any BINAP−M complex,[22] apparently due to its approximate tetrahedral geometry. When single crystals of catalyst **3a** were redissolved in THF or CH_2Cl_2, a fully competent catalyst solution was formed.

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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 (37 pages).

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(21) Crystals of **3a** were obtained by slow evaporation of THF. Crystal data for **3a**: monoclinic, *C*2; a = 39.263(2), b = 10.8841(4), c = 11.0147 Å; V = 4705.4(3) Å^3; Z = 4; d_{calcd} = 1.225 Mg/m^3; $F(000)$ = 1792; μ(Mo Kα) = 0.120 mm^{-1}; μ(Mo Kα) = 0.710 73 Å; 17 316 reflections measured, 8125 observed; ($I > 2\sigma(I)$) = 6800; 107 variables; R = 0.0570, R_W = 0.1015, GOF = 1.045.

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