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Catalytic Asymmetric Addition of Alcohols to Imines: Enantioselective Preparation of Chiral *N,O*-AminalsGuilong Li,[†] Frank R. Fronczek,[‡] and Jon C. Antilla^{*,†}Department of Chemistry, University of South Florida, 4202 East Fowler Avenue CHE205A, Tampa, Florida 33620,
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The use of nonmetal based asymmetric catalysis has witnessed an extremely rapid advancement since 2000.¹ Led by the independent pioneering studies of Akiyama and Terada in 2004, a variety of chiral phosphoric acids were first shown to be excellent nonmetal chiral catalysts for the asymmetric activation of imines.² In relatively rapid succession numerous methodological studies have recently shown that the addition of nucleophiles to imines could provide potentially synthetically useful amines with excellent enantioselectivity.³

Chiral *N,O*-aminals are structural motifs found in a number of interesting natural products and pharmaceuticals. For example, chiral *N,O*-aminal subunits are found in important natural products like zampanolide,^{4a,b} echinocandin B, spergualin, the tallsomycins, mycalamide A,^{4c} and other compounds in the pederin^{4d} family along with important targets like psymberin^{4e–h} (Figure 1). The stereochemical importance of this motif to biological activity is significant and well-known as evidenced through cytotoxicity studies against various human tumor cell lines in studies by De Brabander with psymberin^{4g} and by others in the pederin/mycalamide series.⁵ Another important aspect of the chiral *N*-acyl hemiaminal subunit was that it represents a particularly difficult synthetic challenge that had to be addressed in the previous preparative studies.^{4d}

Although some elegant methods were developed to construct *N,O*-aminals, the preparation of chiral *N,O*-aminals via asymmetric catalysis is still unknown.⁶ In 2005, we reported a highly enantioselective amidation of imines^{7a} catalyzed by VAPOL-phosphoric acid as part of our ongoing studies involving asymmetric catalysis with chiral Brønsted acids.⁷ We envisioned that because of this prior work the addition of an alcohol to an activated imine could reasonably present a direct approach to chiral *N,O*-aminal products (Figure 2). Herein, we would like to report our preliminary results, the first highly enantioselective synthesis of *N,O*-aminals utilizing catalytic methodology.

The development of methodology that can construct chiral *N,O*-aminals was initially believed to be challenging to us due to their presumed instability under basic, acidic, and other relatively harsh conditions. Another significant issue arises from the fact that the addition of alcohols to *N*-acyl imines can take place smoothly even without catalytic promotion. We initiated our studies by running the reactions under low temperature, believing that we could slow this competitive background reaction. Using toluene as the solvent, we treated imine **1** with methanol in the presence of catalyst (*R*)-**A1**. However, upon addition a very low enantioselectivity was obtained for product **3a**. For example, in toluene at –30 °C the yield of **3a** was 84%, but the ee, while nonzero, was still quite low (12% ee). Unexpectedly at ambient temperature the ee value of **3a** increased to 30%, albeit in a lower yield (Table 1, entry 1). A significant solvent effect was found, with higher polarity solvents giving improved ee.

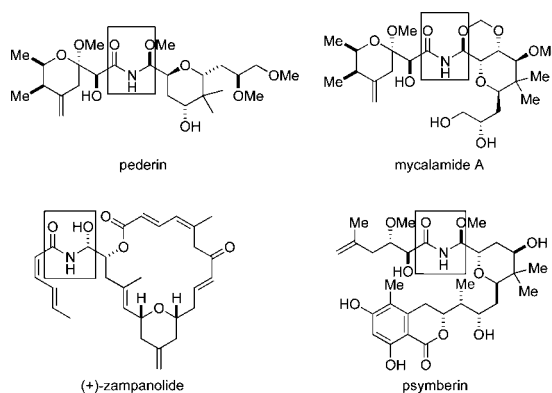
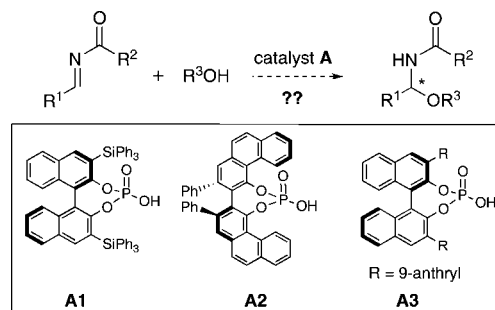
Figure 1. Natural products containing chiral *N*-acyl hemiaminals.

Figure 2. Chiral phosphoric acid catalysts.

Our best solvent was determined to be ethyl acetate, with the reaction providing **3a** in 52% ee in that case (entry 5).

The result of our catalyst screening showed that VAPOL-phosphoric acid (**A2**) was a poor enantioselective catalyst for this reaction (entry 6). However, catalyst **A3** provided for a 93% isolated yield of **3a** with a 94% ee (entry 7).⁸ Surprisingly lowering (entry 8) or slightly raising the temperature (entry 9) had a deleterious effect on the enantioselectivity. As indicated above, the reaction was found to proceed smoothly even without adding any catalyst (entry 10). At this time, it is not entirely clear how our catalytic reaction dominated the obvious background reaction to provide such high enantioselectivities for the desired product. Finally, it should be mentioned that anhydrous alcohols and solvents are necessary to achieve high enantioselectivity.

It is clear that the chiral phosphoric acid-catalyzed addition of alcohols to *N*-acyl imines is quite general (Table 2). For instance, the use of primary alcohols like methanol, ethanol, and longer chain varieties provide excellent yield and ee of the respective chiral aminal (90–95% ee, entries 1–2 and 5–10) as determined by chiral HPLC. Secondary alcohols, such as isopropanol, allowed for slightly lower enantioselectivity (88% ee, entry 3). It is noteworthy that relatively sterically hindered *tert*-butanol still afforded a high enantioselectivity

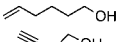
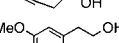
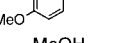
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Table 1. Optimized Conditions for the Addition of Methanol to *N*-Acyl Imine **1**

$\text{Ph}-\text{CH}=\text{N}-\text{COPh} + \text{MeOH} \xrightarrow[\text{solvent, temp. 24h}]{\text{catalyst (5 mol\%)}} \text{Ph}-\text{CH}(\text{NHCOPh})(\text{OMe})$					
entry ^a	solvent	catalyst	temp, °C	yield, % ^b	ee, % ^d
1	toluene	A1	rt	49	30
2	CHCl ₃	A1	rt	37	30
3	THF	A1	rt	41	30
4	CH ₃ CN	A1	rt	37	32
5	EtOAc	A1	rt	74	52
6	EtOAc	A2	rt	83	0
7	EtOAc	A3	rt	99(93) ^c	94
8	EtOAc	A3	0	99	86
9	EtOAc	A3	35	97	87
10	EtOAc	none	rt	>95	0

^a The reaction employed a molar ratio of **1**:**2** = 1:2 (equiv), with a concentration of **1** being 0.17 M. ^b Yield determined by ¹H NMR. ^c 93% Isolated yield. ^d Determined by chiral-HPLC analysis.

Table 2. Asymmetric Addition of Alcohols to *N*-Acyl Imines^a

$\text{R}^1-\text{CH}=\text{N}-\text{COPh} + \text{R}^2\text{OH} \xrightarrow[\text{EtOAc, rt, 24h}]{\text{A3 (5 mol\%)}} \text{R}^1-\text{CH}(\text{NHCOPh})(\text{OR}^2)$					
entry ^a	R ¹	R ² OH	product	yield, % ^b	ee, % ^c
1	Ph	MeOH	3a	93	94
2	Ph	EtOH	3b	95	90
3	Ph	ⁱ PrOH	3c	81	88
4	Ph	^t BuOH	3d	81	92
5	Ph	ClCH ₂ CH ₂ OH	3e	87	92 (R)
6	Ph	<i>c</i> -C ₆ H ₁₁ OH	3f	84	81
7	Ph	BnOH	3g	92	93
8	Ph		3h	92	91
9	Ph		3i	94	95
10	Ph		3j	85	93
11	4-BrC ₆ H ₄	MeOH	3k	99	92
12	4-FC ₆ H ₄	MeOH	3l	76	88
13	4-ClC ₆ H ₄	MeOH	3m	96	93
14	4-CF ₃ C ₆ H ₄	MeOH	3n	93	89
15	4-MeC ₆ H ₄	MeOH	3o	95	91
16	4-MeOC ₆ H ₄	MeOH	3p	91	83
17	3-MeC ₆ H ₄	MeOH	3q	91	84
18	2-MeC ₆ H ₄	MeOH	3r	96	91
19	4-ClC ₆ H ₄	BrCH ₂ CH ₂ CH ₂ OH	3s	82	90
20	CH ₃ CH ₂	MeOH	3t	62	65

^a Molar ratio of **1**:**2** = 1:2 (equiv). ^b Isolated yield. ^c Determined by chiral-HPLC analysis.

for product **3d** (92% ee, entry 4). With the cyclic secondary cyclohexanol substrate, a slightly lower enantioselectivity was found presumably due to its rigid structure (81% ee, entry 6). In addition, the reaction was found to tolerate alcohols with double and triple bond functionality, which could provide a synthetic handle for further useful transformations (entries 8 and 9). This methodology was also shown to be quite efficient for a variety of *N*-acyl imines. All of the aromatic *N*-acyl imines evaluated could provide the desired chiral *N,O*-aminals in high yields and enantioselectivities. For instance, the reactions of *N*-acyl imines derived from *p*-halogenated aromatic aldehydes afforded 88–93% ee values (Table 2, entries 11–13). The *N*-acyl imine bearing a strong EWG such as a trifluoromethyl group also provided a product with an excellent yield and high enantioselectivity (89% ee, entry 14). Use of *N*-acyl imines substituted with a *p*-methoxy group on the phenyl

ring gave a lower enantioselectivity (83% ee, entry 16). While the imine with *m*-methyl substitution gave slightly low selectivity (84% ee, entry 17), the *o*-substituted (2-methyl) imine provided the same ee with that of *p*-substituted (4-methyl) substrate (91% ee, entries 15 and 18). A lower enantioselectivity for an aliphatic imine was noted (65% ee, entry 20). This was believed to be due to the level of imine purity that could be obtained due to isomerization to the corresponding enamine.

The absolute stereochemistry of the chiral *N,O*-aminal products was determined by the single crystal X-ray diffraction of **3e** (entry 5). This unambiguously shows that the absolute configuration to be (*R*)-**3e**.⁹

In conclusion, we have successfully developed the first catalytic asymmetric addition of alcohols to *N*-acyl imines catalyzed by chiral phosphoric acids. The chiral *N,O*-aminal could be prepared in a straightforward procedure in high yields with excellent enantiomeric excess under mild reaction conditions. Future work will be directed toward the extension of substrate scope, mechanistic studies, and synthetic application.

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Supporting Information Available: Experimental procedures, X-ray details, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) Note that *N*-Boc substitution on the imine gave lower yields with good selectivity (61% yield, 84% ee) while the corresponding *N*-3,5-dimethoxybenzoyl imine gave similar results (83% yield, 86% ee).
- (9) Please see Supporting Information for X-ray crystallographic details.

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