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Chiral Phosphoric Acid-Catalyzed Addition of Thiols to *N*-Acyl Imines: Access to Chiral *N*,*S*-Acetals

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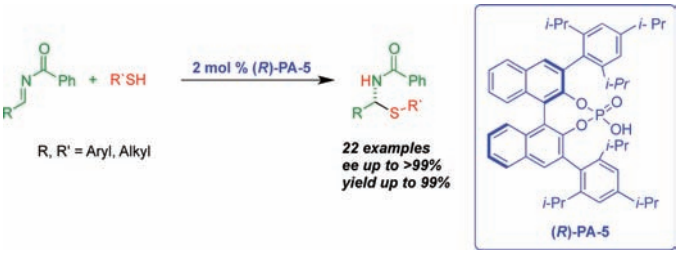
ABSTRACT



The first catalytic asymmetric method to prepare enantioenriched *N*,*S*-acetals using chiral BINOL phosphoric acids is reported. The reaction combines *N*-acyl imines with thiols to generate products in excellent yield and enantioselectivity. The addition reaction could also be achieved with an exceptional substrate to catalyst (S/C) molar ratio. Electron-rich and electron-deficient aromatic *N*-acyl imines, as well as a broad range of aliphatic and aromatic thiols, showed excellent reactivity.

Chiral sulfur compounds have been utilized as ligands for metal-based catalysis,[1] as organocatalysts,[2] and as chiral auxiliaries.[3] The most versatile method to generate chiral sulfur-containing molecules is via conjugate addition of sulfur nucleophiles to α,β-unsaturated compounds (sulfa-Michael addition) using chiral metal complexes[4] or organocatalysts.[5] Other methods to synthesize chiral sulfur-containing compounds include desymmetrization of *meso*-epoxides[6] and *meso*-aziridines[7] by sulfur nucleophiles as well as thiol additions to allenoates.[8]

Chiral *N*,*S*-acetals are biologically important molecules present in numerous natural products such as β-lactam antibiotics,[9] the natural product fusaperazine, and the

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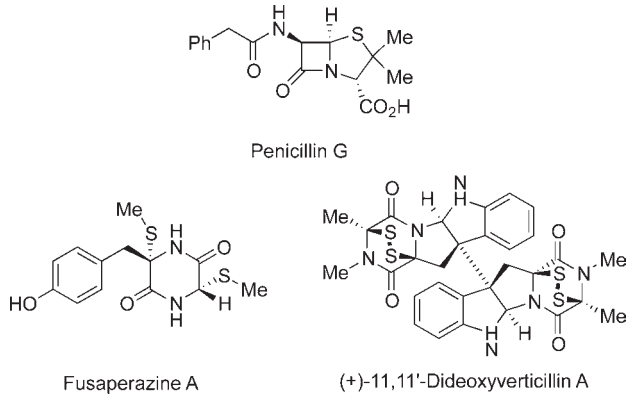


Figure 1. Natural products with chiral *N*,*S*-acetal functionality.

fungal metabolite (+)-11,11′-dideoxyverticillin, an epidithioketopiperazine alkaloid (Figure 1).[10]

Recently, Rai et al. synthesized novel tricyclic β-lactams from hydrazone imines, which were screened for their antibacterial properties.[11] Few cyclic *N*,*S*-acetals have been explored for their therapeutic potential.[12] In some analogs of 2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one, an *N*,*S*-acetal containing compound, the "*R*" enantiomer was found to be 50 times more potent than the "*S*" enantiomer for antiviral activity.[13] Recently, lithiated *N*,*S*-acetals of chiral auxiliaries were used as chiral formylating reagents.[14] However, in spite of their promising biological and chemical properties, there are no existing methods for the direct synthesis of acyclic[15] or cyclic *N*,*S*-acetals in a catalytic enantioselective manner.

Chiral BINOL phosphoric acids have been utilized as catalysts for many organic transformations (Figure 2).[16] In continuation of our investigation into chiral phosphoric acid/phosphate salt-catalyzed addition of heteroatoms to imines,[17] we wish to report a highly enantioselective addition of thiols to *N*-acyl imines providing chiral *N*,*S*-acetals in excellent yields and enantioselectivities. The reaction was extremely efficient affording high asymmetric induction

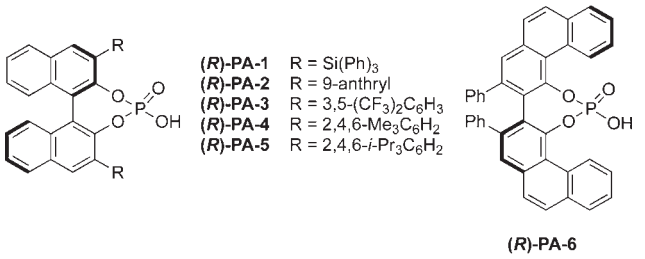
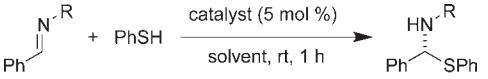


Figure 2. Chiral phosphoric acids.

even at 0.005 mol % of catalyst loading. To the best of our knowledge, this is the first enantioselective synthesis of *N*,*S*-acetal using a chiral catalyst.

Table 1. Catalytic Reaction Condition Optimization for the Enantioselective Addition of Thiophenol to Imine **1a**



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

entry[a]	R	catalyst (*R*)	solvent	yield (%)[b]	ee (%)[c]
1	COPh	**PA-1**	ether	47	11
2	COPh	**PA-2**	ether	45	30
3	COPh	**PA-3**	ether	42	43
4	COPh	**PA-4**	ether	54	36
5	COPh	**PA-5**	ether	72	91
6	COPh	**PA-6**	ether	79	0
7	COPh	**PA-5**	THF	86	44
8	COPh	**PA-5**	MTBE	65	92
9	COPh	**PA-5**	toluene	95	99
10	Boc	**PA-5**	toluene	85	80
11	$CHPh_2$	**PA-5**	toluene	0	0

[a] General conditions: 1.0 equiv of imine and 1.2 equiv of thiophenol. [b] Isolated yields. [c] ee determined by chiral HPLC analysis.

We began our investigation by examining the catalytic asymmetric addition of thiophenol **2a** to *N*-acyl imine **1a** in ether (Table 1). To our delight, **PA-5** was found to be the best catalyst for this transformation (entry 5). Toluene was the most suitable solvent for product formation, allowing a 95% yield and 99% ee (entry 9). Boc-protected imine gave chiral *N*,*S*-acetal product, albeit with lower yield and enantioselectivity (entry 10), while a benzhydryl-protected imine did not undergo the addition reaction (entry 11).

During the optimization studies (Table 2), we observed that the addition reaction was extremely fast (entry 1) and was complete within 30 s. In the absence of catalyst, the racemic product was obtained in approximately 5 min with excellent yield as identified by ^{1}H NMR (entry 8). With this unexpected reactivity, we decided to examine the efficiency of the Brønsted acid as a function of catalyst loading. Five mol % and 2 mol % catalyst loading essentially obtained the same enantioselectivity. (entry 1 and 2). Lowering the

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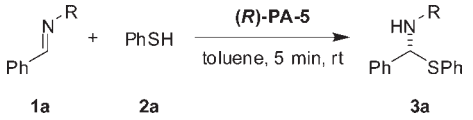
Table 2. Catalytic Loading Data for the Enantioselective Addition of Thiophenol to Imine **1a**



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

entry[a]	catalyst (mol %)	yield(%)[b]	er[c]
1	5	95	99.5:0.5
2	2	96	99.6:0.4
3	1	91	99.4:0.6
4	0.5	95	99.4:0.6
5	0.1	96	98.5:1.5
6	0.01	96	95.4:4.6
7	0.005	96	93.8:6.2
8	0	96	1:1

[a] General conditions: 1.0 equiv of imine and 1.2 equiv of thiophenol. [b] Isolated yields. [c] Er determined by chiral HPLC analysis.

catalyst loading to 1 mol % and to 0.5 mol %, only a slight decrease in the enantioselectivity was observed respectively (entry 3 and 4). Catalyst loading as low as 0.005 mol %, gave the product with 88% enantiomeric excess (entry 7).[18] Asymmetric induction was not observed when **1a** was treated with thiophenol in the presence of 10 mol % of chiral product **3a**. This verified the Brønsted acid as the sole source of chiral induction in the resulting product, with no autoinduction observed. Many of the existing organocatalytic reactions reported in the literature are performed at 10 mol % or higher catalyst loading and this can represent a limitation of this type of catalysis. There are only two examples of chiral phosphoric acid catalysts with significantly lower catalyst loading reported in literature;[19] by far this is the most noteworthy illustration of catalyst efficiency observed to date with these catalysts.[20]

The scope of nucleophilic addition of thiophenol **2a** to various *N*-acyl imines was explored using 2 mol % of **PA-5** (Table 3). Note that in each case we could optimize further in terms of lower catalyst loadings but chose 2 mol % for the general study. To our satisfaction, aromatic imines with electron withdrawing substituents (**3b-e**), as well as electron donating substituents (**3f** and **3g**) were tolerated under the reaction conditions. Sterically demanding imines such as a 1-napthyl analogue led to excellent yield and ee (**3h**). Aliphatic imines were discovered to be poor substrates, with products being obtained in low yields and ee.[21]

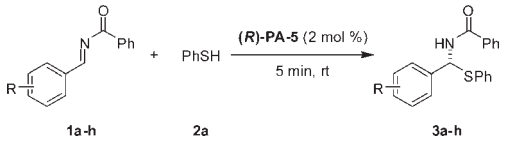
(18) To ensure complete conversion to the product, all of the reactions were stirred for 5 min.

(19) For an aza ene type reaction using BINOL Phosphoric acid, 0.05 mol % of catalyst loading and a 93% ee was reported; for details, see: (a) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254–2257. For an enantioselective protonation, a reaction using *N*-triflyl phosphoramides, with 0.05 mol % catalyst loading and a 86% ee, was reported; for details, see:(b) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246–9247.

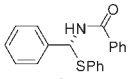
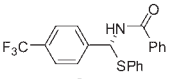
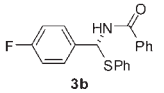
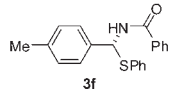
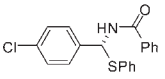
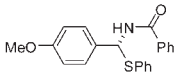
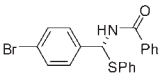
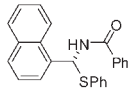
(20) See Supporting Information for HPLC traces and catalyst loading data.

(21) For example, with a *t*-butyl *N*-acyl substrate, 2.0 equiv of imine and 1.0 equiv of **2a** were used, and the resulting product **3i** was isolated in 51% yield and 31% ee (see Supporting Information).

Table 3. The Catalytic Asymmetric Addition of Thiophenol to *N*-Acyl Imines



1a-h **2a** **3a-h**

product[a]	yield (%)[b]	ee (%)[c]	product[a]	yield (%)[b]	ee (%)[c]
 **3a**	95	99	 **3e**	77	93
 **3b**	96	97	 **3f**	80	98
 **3c**	93	99	 **3g**	98	97
 **3d**	99	99	 **3h**	96	98

[a] General conditions: 1.0 equiv of imine and 1.2 equiv of thiophenol. [b] Isolated yields. [c] ee determined by chiral HPLC analysis.

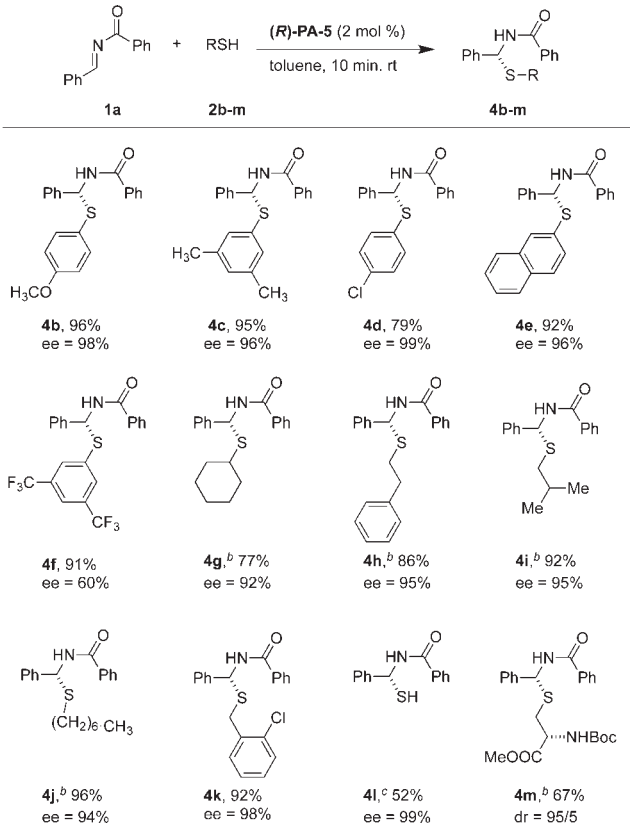
Encouraged by the excellent reactivity of aromatic imine substrates, we evaluated the scope of the addition reaction with respect to thiol nucleophiles. The results are summarized in Scheme 1. Under the optimum reaction conditions, thiophenols bearing electron donating (**4b** and **4c**) as well as electron withdrawing (**4d**) substituents led to the formation of *N*,*S*-acetal products in excellent yields and enantioselectivities. Napthyl-2-thiol was also found to be an excellent nucleophile for the addition reaction (**4e**). However, aromatic thiols with strong electron withdrawing groups such as 3,5-bis(trifluoromethyl)thiophenol yielded *N*,*S*-acetal with lower asymmetric induction (**4f**).

In the case of aliphatic thiols 5 mol % of catalyst was needed in order to achieve high levels of selectivity. Cyclohexyl, hydrocinnamyl, *iso*-butyl and *n*-heptyl thiols were found to be excellent nucleophiles furnishing the *N*,*S*-acetals in good yields and ee (**4g**–**j**). 2-Chlorobenzylthiol was found to be an exceptionally active nucleophile, achieving excellent enantioselectivity even at 2 mol % catalyst loading (**4k**).

The substrate scope is very broad with respect to the thiols. We successfully synthesized a chiral amido-thiol using liquefied H_2S in greater than 99.0% ee (**4l**). Boc protected L-cysteine ester gave the addition product in 95/5

(22) (a) For a review on selenium containing β-lactams, see: (a) Garud, D. R.; Ninomiya, M.; Koketsu, M. *Heterocycles* **2010**, *81* (24), 39–2463. For an example of chiral organoselenium compound synthesis, see:(b) Yang, M.; Zhu, C.; Yuan, F.; Huang, Y.; Pan., Y. *Org. Lett.* **2005**, *7*, 1927–1930.

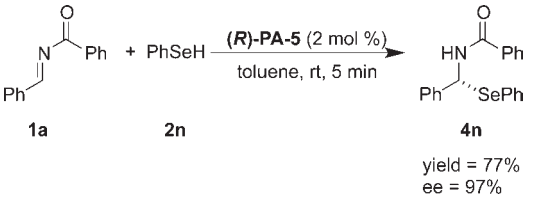
Scheme 1. Catalytic Asymmetric Addition of Thiols to *N*-Acyl Imines[a]



[a] General conditions: 1.0 equiv of imine and 1.2 equiv of thiophenol, isolated yields and ee determined by chiral HPLC analysis. [b] 5 mol % catalyst loading. [c] Reaction was performed at −78 °C.

dr (**4m**). Selenophenol yielded the expected result, forming the addition product with 97% ee[22] (Scheme 2). The absolute configuration of the *N*,*S*-acetals was determined unambiguously to be "*R*" using single X-ray crystallographic

Scheme 2. Catalytic Asymmetric Addition of Seleophenol to Imine **1a**



analysis of compound **4b**, and the stereochemistry of all other products was assigned by analogy (see Supporting Information).

To summarize, we have developed the first method to synthesize chiral *N*,*S*-acetals catalyzed by a BINOL phosphoric acid. This addition reaction has a broad substrate scope and the resulting *N*,*S*-acetals were obtained in high yields and excellent enantioselectivities. The BINOL phosphoric acid was found to be an extremely efficient catalyst for the transformation, resulting in asymmetric induction at extremely low catalyst loading. This methodology has given access to new chiral sulfur compounds, which have the potential to be used as synthetic building blocks. Moreover, these new sulfur compounds themselves could also be exploited for potential therapeutic benefit.

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Supporting Information Available. Characterization, chiral HPLC conditions, experimental preparation and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.