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# Chiral Brønsted acid-catalysed enantioselective synthesis of isoindolinone-derived *N*(acyl),*S*-acetals†

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The first organocatalytic asymmetric addition of thiols to *N*-acyl ketimines, which are generated *in situ* from 3-hydroxy isoindolinones, is described. The reaction proceeds smoothly with a broad range of ketimines and thiols using a chiral Brønsted acid catalyst to afford *N*(acyl),*S*-acetals comprising a tetrasubstituted stereocenter in high yields and enantioselectivities (up to 98.5:1.5 e.r.). The usefulness of the developed protocol is demonstrated in the synthesis of a known HIV-1 reverse transcriptase inhibitor.

*N*(Acyl),*S*-acetals are important structural motifs in numerous natural products and are present as a key functional group in pharmacologically active compounds (Fig. 1). For example, the chiral *N*(acyl),*S*-acetal structural motif is found within the penicillin family of  $\beta$ -lactam antibiotics (**I**),<sup>1</sup> as well as in the natural product fusaperazine A (**II**).<sup>2</sup> This functional group has also been observed in drugs that have been investigated for their cell growth inhibitory (**III**)<sup>3</sup> and sedative (**IV**)<sup>4</sup> properties.

Over the past decade, various efficient strategies for the organocatalytic synthesis of chiral sulfur-containing molecules have been developed.<sup>5</sup> These processes mostly entail sulfa-Michael addition to  $\alpha,\beta$ -unsaturated compounds using chiral organocatalysts,<sup>6</sup> while alternative methods rely on the desymmetrization of *meso*-aziridines<sup>7</sup> and thiol additions to allenates.<sup>8</sup> On the other hand, *N,S*-acetals are usually prepared by the 1,2-addition of thiols to imines, however enantioselective variants of this method are scarcely known.

In 2011, Antilla and co-workers first reported the chiral Brønsted acid-catalyzed addition of thiols to *N*-acyl imines with high enantioselectivities.<sup>9</sup> In a different approach, Wang and co-workers employed cinchona-derived squaramides to control the highly enantioselective addition of thiols to trifluoromethylated aldimines.<sup>10</sup> Zhao and co-workers reported the enantioselective

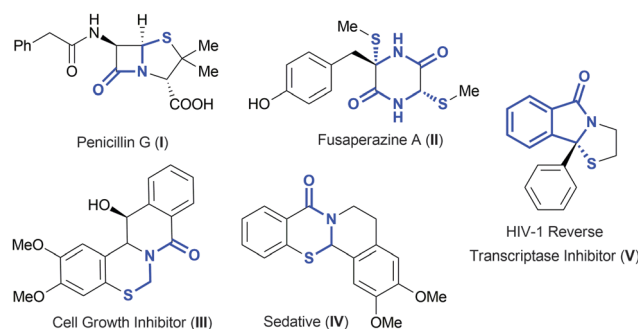


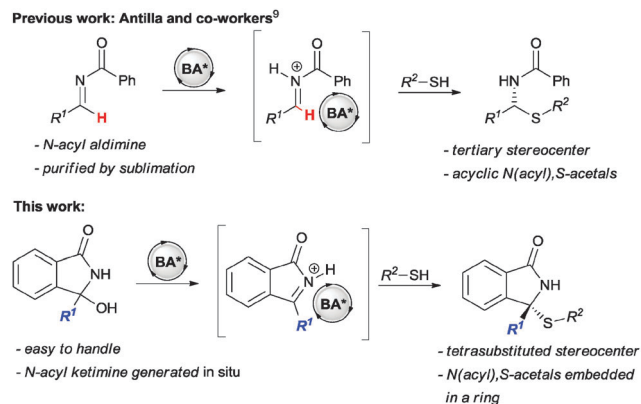
Fig. 1 Examples of natural products and bioactive compounds that possess a *N*(acyl),*S*-acetal motif.

addition of thiols to imines derived from aldehydes with thiourea-quaternary ammonium salts under phase-transfer conditions.<sup>11</sup> More recently, Sun and Qian reported the asymmetric assembly of thiazolidine scaffolds with cinchona alkaloid catalysts through a formal [3+2] annulation.<sup>12</sup> In 2015, the enantioselective additions of thiols to isatin-derived ketimines were reported by Enders and co-workers, utilizing chiral phosphoric acids,<sup>13</sup> and by Nakamura and co-workers, employing cinchona alkaloids.<sup>14</sup> To the best of our knowledge, the seminal work by Antilla and co-workers is the only reported addition of thiols to *N*-acyl imines. Although it is a beautiful example of *N*(acyl),*S*-acetal synthesis, their method entails certain drawbacks. The substrate scope includes only *N*-aldimines, which have to be prepared beforehand by sublimation and are difficult to handle. Moreover, the obtained *N*(acyl),*S*-acetals are limited to acyclic systems with tertiary stereocenters (Scheme 1).

Considering the abundance of *N*(acyl),*S*-acetal motifs embedded in the cyclic systems of bioactive molecules and natural products, as well as the lack of methods available to generate chiral variants that bear a tetrasubstituted stereocenter, a new synthetic route towards this building block would be broadly useful. Herein, we report the enantioselective chiral phosphoric acid catalyzed addition of thiols to *N*-acyl ketimines generated *in situ* from 3-hydroxy isoindolinones. These heterocycles have been successfully employed as substrates in asymmetric hydrogenolysis,<sup>15</sup> Friedel-Crafts<sup>16</sup> and

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Scheme 1

arylation<sup>17</sup> reactions, and generating the isoindolinone cores of drugs and natural products. Moreover, isoindolinone-derived *N*(acyl),*S*-acetals are well-known HIV-1 reverse transcriptase inhibitors (Fig. 1, V).<sup>18</sup>

We started our investigations by combining thiophenol with 3-hydroxy isoindolinone **27** in the presence of various chiral Brønsted acids (**BA\***) (Table 1).

Our initial attempt with phenyl-substituted chiral phosphoric acid **BA1** in dichloromethane led to the complete conversion to *N*(acyl),*S*-acetal **1** within 2 hours; however, at room temperature no enantioselectivity was observed (entry 1). By reducing the temperature to  $-10\text{ }^{\circ}\text{C}$ , a low enantioselectivity (58:42 e.r.) was

Table 1 Enantioselective reaction optimization<sup>a</sup>

Entry	Catalyst	Solvent	Temperature	e.r.
1	<b>BA1</b>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	51:49 <sup>b</sup>
2	<b>BA1</b>	CH <sub>2</sub> Cl <sub>2</sub>	$-10\text{ }^{\circ}\text{C}$	58:42
3	<b>BA2</b>	CH <sub>2</sub> Cl <sub>2</sub>	$-10\text{ }^{\circ}\text{C}$	53:47
4	<b>BA3</b>	CH <sub>2</sub> Cl <sub>2</sub>	$-10\text{ }^{\circ}\text{C}$	89:11
5	<b>BA4</b>	CH <sub>2</sub> Cl <sub>2</sub>	$-10\text{ }^{\circ}\text{C}$	<b>94:6</b>
6	<b>BA5</b>	CH <sub>2</sub> Cl <sub>2</sub>	$-10\text{ }^{\circ}\text{C}$	73:27 <sup>c</sup>
7	<b>BA4</b>	CH <sub>2</sub> Cl <sub>2</sub>	$-30\text{ }^{\circ}\text{C}$	94.5:5.5 <sup>d</sup>
8	<b>BA4</b>	THF	$-10\text{ }^{\circ}\text{C}$	No reaction
9	<b>BA4</b>	Et <sub>2</sub> O	$-10\text{ }^{\circ}\text{C}$	91:9
10	<b>BA4</b>	Toluene	$-10\text{ }^{\circ}\text{C}$	91:9
11	<b>BA4</b>	MTBE	$-10\text{ }^{\circ}\text{C}$	88:12
12	<b>BA4</b>	CH <sub>3</sub> Cl	$-10\text{ }^{\circ}\text{C}$	90:10
13	<b>BA4</b>	MeNO <sub>2</sub>	$-10\text{ }^{\circ}\text{C}$	88:12
14	<b>BA4</b>	CH <sub>2</sub> Cl <sub>2</sub>	$-10\text{ }^{\circ}\text{C}$	94:6 <sup>e</sup>

<sup>a</sup> Reactions performed on a 10 mg scale. Conversions monitored by TLC.<sup>19</sup> e.r. determined by chiral HPLC from crude mixture. <sup>b</sup> 2 h. <sup>c</sup> 12 h. <sup>d</sup> 96 h. <sup>e</sup> Catalyst (5 mol%), 96 h, incomplete conversion.

observed and the reaction time was prolonged to 16 hours (entry 2). The introduction of electron-donating groups on the phenyl ring of the acid (**BA2**) did not lead to an increase in enantioselectivity (entry 3). However, the introduction of bulkier substituents on the catalyst resulted in substantially higher enantiomeric ratios (entries 4 and 5). In order to accelerate the reaction, the acidity of the catalyst was increased by placing electron-withdrawing substituents on the flanking aromatic rings of the chiral phosphoric acid (**BA5**). This catalyst demonstrated an improved reaction rate, but at the expense of enantioselectivity (entry 6).

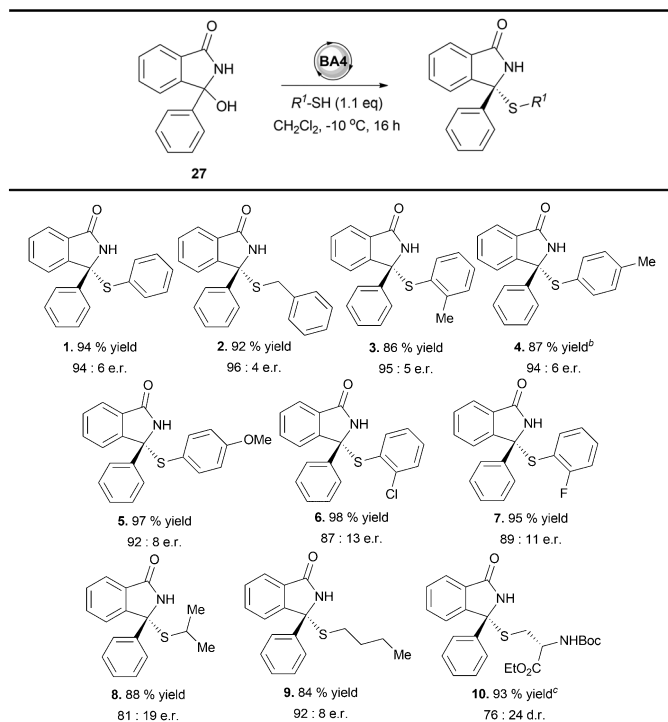
After identifying (*R*)-TRIP (**BA4**) as the optimal catalyst for the transformation, the influence of temperature, solvent and catalyst loading was investigated. Cooling the reaction to  $-30\text{ }^{\circ}\text{C}$  prolonged the reaction time to 4 days with virtually no increase in enantioselectivity (entry 7). Next, we investigated the influence of solvent and discovered that the reaction did not occur when THF was used (entry 8). In other common solvents, the product was obtained with slightly lower enantioselectivities (entries 9–13). In addition, we examined the chiral catalyst loading, which when lowered to 5 mol% led to the same enantioselectivity as with 10 mol% loading, but the reaction time was substantially longer (entry 14). Hence, the optimized procedure employed 10 mol% of **BA4** catalyst in dichloromethane at  $-10\text{ }^{\circ}\text{C}$ .

With optimized reaction conditions in hand, we turned our attention to investigate the substrate scope and reaction limitations. Initially, we examined asymmetric *N*(acyl),*S*-acetal formation with various thiols (Table 2).

3-Hydroxy isoindolinone **27** reacted efficiently with several different thiols and provided high enantioselectivities. When benzyl mercaptan, along with *ortho*- and *para*-methyl substituted thiophenols were employed, the reaction maintained its high efficiency and furnished *N*(acyl),*S*-acetals **2**, **3** and **4** in very good yields and enantioselectivities. An electron donating substituent on the thiol led to a slight decrease in selectivity (**5**, 92:8 e.r.), while halogens on the aromatic ring further decreased the enantiomeric ratios (**6**, 87:13 e.r. and **7**, 89:11 e.r.). The introduction of aliphatic thiols yielded products with both moderate (isopropyl thiol-**8**, 81:19 e.r.) and very good selectivities (butanethiol-**9**, 92:8 e.r.). When Boc-Ser-OEt was employed, the reaction did not occur under the optimized reaction conditions. When heated to reflux, the reaction furnished the desired *N*(acyl),*S*-acetal **10** with a substantial drop in enantioselectivity (76:24 e.r.).

Furthermore, we turned our attention to investigating the scope and limitations of the reaction with various 3-hydroxy isoindolinones (Table 3).

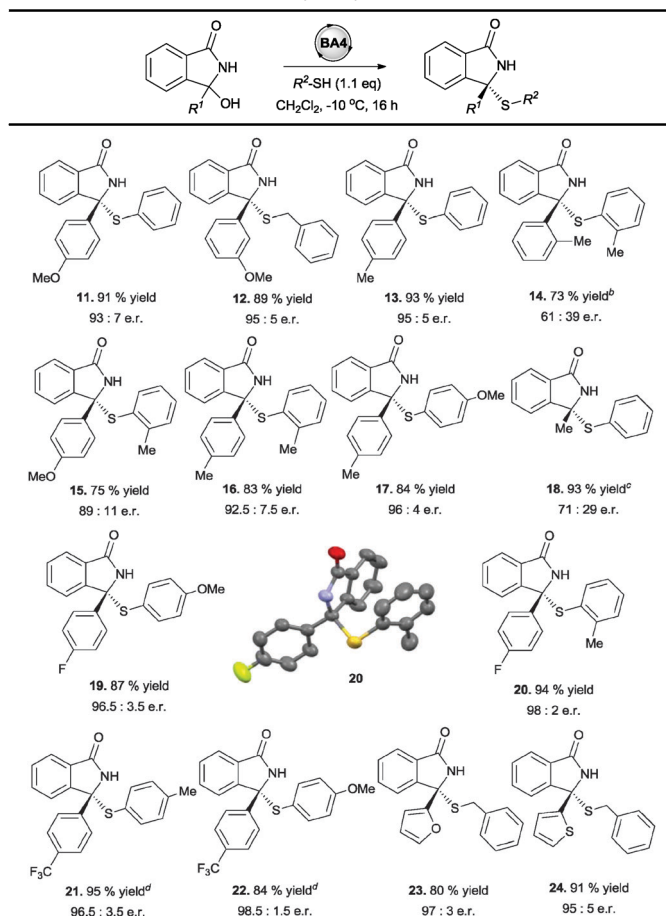
The introduction of electron-donating groups at different positions on the 3-hydroxy isoindolinone resulted in high yields and enantiomeric ratios (**11**, 91% yield, 93:7 e.r. and **12**, 89% yield, 95:5 e.r.). The substrate bearing a *para*-substituted methyl group was also well tolerated and it furnished product **13** in 93% yield with a 95:5 e.r. When *ortho*-methyl substituted 3-hydroxy isoindolinone and *ortho*-methyl substituted thiophenol were combined, the reaction time was prolonged to 48 h to give

Table 2 Substrate scope I: thiols<sup>a</sup>

<sup>a</sup> Isolated yields. Reactions performed on a 0.2 mmol scale. <sup>b</sup> 48 h. <sup>c</sup>  $-40^\circ\text{C}$ . Combined yields of both diastereomers.

a moderate yield and enantioselectivity (**14**, 73% yield, 61:39 e.r.). The most probable rationalization for this observation is that the increased steric hindrance around the reaction center overrides the steric influence of the chiral phosphoric acid catalyst. In general, the reaction maintained its effectiveness when substituents were introduced at different sites around the aromatic ring of both the 3-hydroxy isoindolinone and thiol, with enantioselectivities ranging from 89:11 e.r. (**15**) to 96:4 e.r. (**17**). Employing methyl substituted 3-hydroxy isoindolinone under the optimized reaction conditions furnished *N*(acyl),*S*-acetal **18** in high yield, but as a racemate. Moderate enantioselectivity was observed only when the temperature was lowered to  $-40^\circ\text{C}$ . The reason for the moderate enantioselectivity is most likely due to the size of the substituent; the methyl group is probably not big enough to successfully create differentiation between the enantiotopic faces of the iminium intermediate when binding to the catalyst.

The introduction of a fluorine substituent on the 3-hydroxy isoindolinone resulted in excellent enantioselectivities, regardless of the nature and position of the substituents on the thiophenol (**19**, 96.5:3.5 e.r. and **20**, 98:2 e.r.). Reactions performed with trifluoromethyl substituents on the aromatic ring of 3-hydroxy isoindolinone maintained high yields and enantioselectivities despite warming to room temperature, with **22** providing the highest enantiomeric ratio of 98.5:1.5 e.r. Heterocyclic substituents were also well tolerated: *N*(acyl),*S*-acetals with furan **23** and thiophene **24** substituents were obtained in very good yields and high enantioselectivities (97:3 e.r. and 95:5 e.r., respectively).

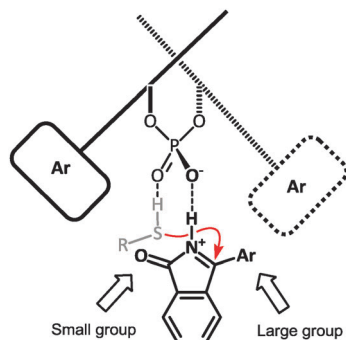
Table 3 Substrate scope II: 3-hydroxy isoindolinones<sup>a</sup>

<sup>a</sup> Isolated yields. Reactions performed on a 50 mg scale of the 3-hydroxy isoindolinone derivative. <sup>b</sup> 48 h. <sup>c</sup>  $-40^\circ\text{C}$ , 48 h. <sup>d</sup> Room temperature.

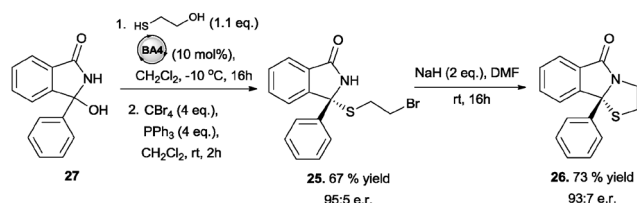
The absolute configuration of the isoindolinone *N*(acyl),*S*-acetal **20** was unambiguously assigned to be (*R*) by X-ray structure analysis. The absolute configurations of the remaining products were assigned by analogy. By considering the absolute configuration of the products, we propose the following stereochemical model of asymmetric induction, based on reports by Simón and Goodman (Scheme 2).<sup>21</sup>

Following the protonation of 3-hydroxy isoindolinone, water is eliminated to generate a reactive ketimine intermediate. The resulting cation forms an ion pair with the anionic phosphate catalyst, which blocks the *si* face of the substrate. The approaching thiol then attacks the planar ketimine from the opposite side to yield products with a (*R*) configuration. At this point, it remains unclear whether probable hydrogen bonding between thiol and the catalyst<sup>22</sup> influences the stereochemical outcome. To fully examine the role of non-bonding interactions in this asymmetric transformation, DFT calculations and additional experiments are currently under way.

To demonstrate the usefulness of the novel protocol, we prepared HIV-1 reverse transcriptase inhibitor **V** (Scheme 3). Employing 2-mercaptoethanol as a nucleophile under the optimized reaction conditions, followed by an *in situ* Appel reaction, 3-hydroxy isoindolinone **27** was successfully converted



Scheme 2 Proposed transition state.



Scheme 3 Synthesis of the HIV-1 reverse transcriptase inhibitor V.

into bromide **25** with 67% yield over two steps and excellent enantioselectivity (95:5 e.r.). 5-Exo tet cyclization with sodium hydride yielded HIV-1 reverse transcriptase inhibitor **V** (**26**) in good yield and with a slight loss in enantioselectivity in the final product (73% yield, 93:7 e.r.).

In conclusion, we developed a chiral Brønsted acid-catalyzed asymmetric addition of thiols to *in situ* generated ketimines from 3-hydroxy isoindolinones. This approach is the first example of an enantioselective synthesis of *N*(acyl),*S*-acetals from ketimines to generate tetrasubstituted stereocenters. This transformation proceeds smoothly with a broad range of thiols and isoindolinone alcohols to afford products with great yields and high enantioselectivities. This newly developed reaction might support the discovery of novel bioactive compounds and prove useful for the synthesis of natural product analogues, as demonstrated in the synthesis of HIV-1 reverse transcriptase inhibitor **V**. Further elucidation of the stereochemical model of the reaction is currently under investigation and will be reported in due course.

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- In entries 1 and 2, when TLC showed complete consumption of starting material, crude NMR was taken to confirm disappearance of the –OH signal in <sup>1</sup>H NMR at 4.17 ppm. Conversion in both entries amounted to >98%, and the remaining entries were monitored only by TLC.
- When the reaction was performed on 0.8 mmol scale, reaction time was prolonged to 36 h, with a loss of enantioselectivity observed in the product (91% yield, 91:9 e.r.).
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