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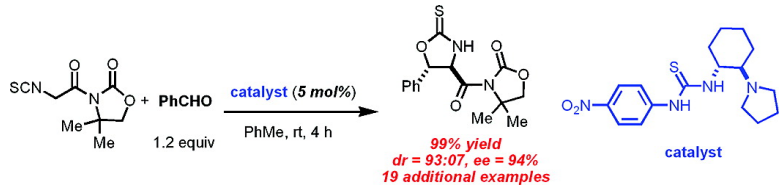

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Catalytic Enantioselective Aldol Additions of α-Isothiocyanato Imides to Aldehydes

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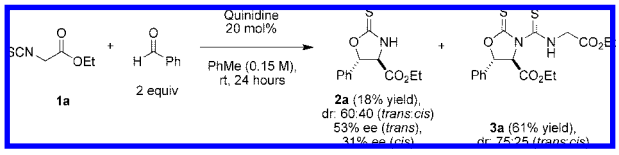
Many biologically active natural products such as biphenomycin A,[1] cyclomarins,[2] exochelins,[3] polyoxins,[4] ustiloxins,[5] and vancomycin[6] contain β-hydroxy-α-amino acids within their structural frameworks. The majority of methods currently available to synthesize β-hydroxy-α-amino acids rely on diastereoselective approaches, e.g., the use of chiral auxiliaries.[7,8] The development of highly efficient catalytic enantioselective variants remains challenging[9−15] with some methods requiring the use of preformed enolate equivalents.[16] Here we report a direct catalytic and highly diastereo- and enantioselective approach to protected *syn* β-hydroxy-α-amino acids using a bifunctional thiourea catalyst that operates under mild reaction conditions.[17,18]

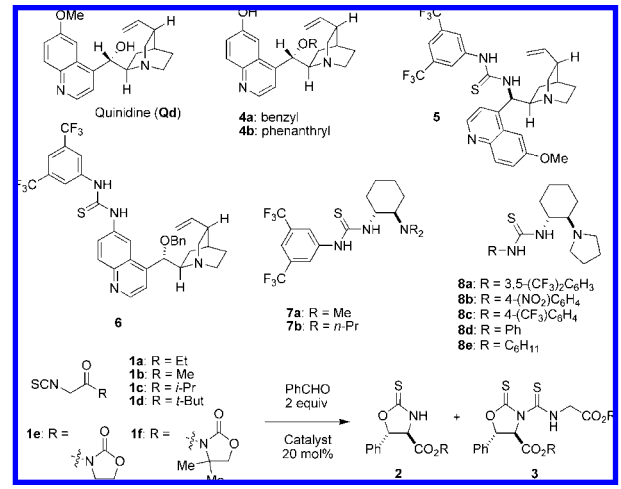
Scheme 1



With the goal of developing an organocatalytic approach to β-hydroxy-α-amino acids, we initiated our studies by evaluating the reaction between commercially available ethyl α-isothiocyanato acetate (**1a**) and benzaldehyde using quinidine as the catalyst (Scheme 1). In addition to the desired product **2a** (obtained in low diastereo- and enantioselectivity), compound **3a** was obtained as the major product resulting from the addition of primary product **2a** to another equivalent of **1a**. Other readily available organocatalysts[18] were subsequently evaluated (Table 1). Stereoselectivities were promising in some cases (e.g., Table 1, entry 8), but **3a** was consistently obtained as the major product. Control experiments revealed that the presence of catalyst is required for the formation of **3a** from **2a** and **1a**. We speculated that the reverse reaction may also be catalyzed by **8a**. Entries 8−10 (Table 1) support the assumption that longer reaction times will increase the yield of **2a** at the expense of **3a**, but this process was found to be too slow to be practical. With other α-isothiocyanato esters (Table 1, entries 11−13), **3** was again obtained as the major product. The yield of **2** could be dramatically increased with imide **1e**, the substrate previously used by Willis and co-workers in their enantioselective metal catalyzed approach.[10] Formation of undesired **3** was almost completely suppressed, but **2** was obtained in low diastereoselectivity slightly favoring the *cis* isomer (Table 1, entries 14−16). A poorly defined enolate geometry might be responsible for the low levels of diastereoselectivity. Greatly enhanced diastereomeric ratios were observed with the dimethyl analogue **1f**.[19] Evaluation of different catalysts revealed that **8b** provides product **2** in excellent yield and with high levels of selectivity in a relatively short reaction time (Table 1, entry 18).

Further optimization allowed for reducing the catalyst loading to 5 mol% and the equivalents of aldehyde to 1.2. Virtually no difference was seen between reactions performed under anhydrous conditions and reactions run simply in capped flasks with HPLC grade toluene and without rigorous exclusion of air or moisture. The substrate scope was evaluated using these operationally convenient conditions (Table 2).

Table 1. Optimization of Reaction Parameters[a]



entry	sm	catalyst	time [h]	**2** [% yield][b]	dr[c]	**2** [% ee][d]	**3** [% yield][e]
1	**1a**	**Qd**	24	18	60:40	53	61
2	**1a**	**4a**	48	39	65:35	59	58
3	**1a**	**4b**	48	26	60:40	61	62
4	**1a**	**5**	72	24	65:35	69	68
5[f]	**1a**	**6**	30	18	80:20	40	nd[h]
6	**1a**	**7a**	24	29	65:35	79	65
7	**1a**	**7b**	72	37	65:35	81	51
8	**1a**	**8a**	12	33	80:20	89	61
9	**1a**	**8a**	48	44	75:25	87	53
10	**1a**	**8a**	96	50	80:20	89	43
11	**1b**	**8a**	12	24	80:20	89	71
12	**1c**	**8a**	12	31	80:20	87	64
13[g]	**1d**	**8a**	120	25	80:20	91	39
14	**1e**	**8a**	4	97	45:55	75	−
15	**1e**	**Qd**	8	82	35:65	59	8
16	**1e**	**7a**	8	92	35:65	73	<5
17	**1f**	**8a**	2	98	80:20	85	−
18	**1f**	**8b**	1	99	93:07	93	−
19	**1f**	**8c**	1	98	90:10	91	−
20	**1f**	**8d**	8	98	93:07	91	−
21	**1f**	**8e**	48	87	83:17	61	7
22	**1f**	**Qd**	48	18	80:20	49	nd[h]
23	**1f**	**7a**	7	99	75:25	81	−

[a] Reactions were performed at rt on a 1 mmol scale in toluene (0.15 M) and were run to full conversion as judged by TLC analysis. The enantiomeric excess was determined by HPLC analysis. [b] Combined yield of both diastereomers. [c] *trans*/*cis*, determined by ^{1}H NMR. [d] *trans* isomer. [e] Mixture of *trans* and *cis* isomers. [f] Run on a 0.16 mmol scale. [g] 64% conversion after 120 h. [h] Not determined.

Several electron-rich and -poor aromatic aldehydes with different substitution patterns gave rise to products that were generally obtained in good yields and with high levels of diastereo- and enantioselectivity. Heteroaromatic systems were also viable substrates as were α,β-

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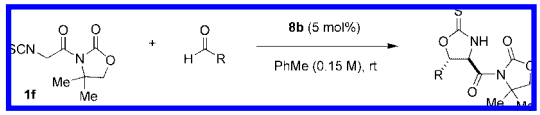
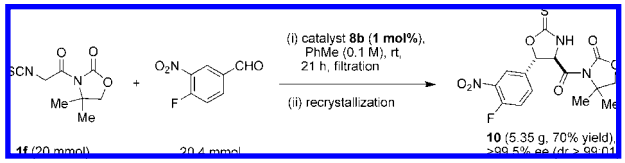
Table 2. Scope of the Reaction[a]



entry	R	product	time [h]	yield [%][b]	dr[c]	ee [%]
1	Ph	**2f**[ppt]	4	99	93:07	94
2	4-NO_2−C_6H_4	**9a**[ppt]	2	97	95:05	93
3	4−Br-C_6H_4	**9b**[ppt]	2	91	95:05	94
4	4−F-C_6H_4	**9c**[ppt]	8	97	95:05	94
5	4-MeO-C_6H_4	**9d**[ppt]	3	76	97:03	96
6	4-Me-C_6H_4	**9e**[ppt]	16	94	94:06	94
7	3−Br-C_6H_4	**9f**[ppt]	3	88	88:12	92
8	3-Me-C_6H_4	**9g**[ppt]	12	90	94:06	93
9	3-MeO-C_6H_4	**9h**[ppt]	6	87	93:07	92
10[d]	2-NO_2−C_6H_4	**9i**[ppt]	24	97	98:02	90
11[d,e]	2−Cl-C_6H_4	**9j**	48	86	89:11	93
12	2−F-C_6H_4	**9k**	20	80	86:14	90
13	2-Me-C_6H_4	**9l**	48	80	83:17	90
14	1-naphthyl	**9m**	72	60	93:07	94
15	2-naphthyl	**9n**[ppt]	2	97	94:06	91
16	2-thiophenyl	**9o**[ppt]	12	86	87:13	91
17	C_6F_5	**9p**[ppt]	2	83	90:10	90
18	cinnamyl	**9q**[ppt]	24	85	85:15	93
19	CH_2CH_2Ph	**9r**[ppt]	24	70	90:10	81
20	*n*-Bu	**9s**[ppt]	72	55	82:18	82

[a] Reactions were run on a 1 mmol scale using 1.2 equiv of aldehyde. The enantiomeric excess was determined by HPLC analysis following conversion of the products into their corresponding ethyl esters (see Supporting Information). ppt: product partially precipitated in course of the reaction. [b] Combined yield of both diastereomers. [c] *trans*/*cis*, determined by ^{1}H NMR. [d] Reaction was performed at 0 °C. [e] Performed at 0.1 M concentration.

Scheme 2



unsaturated aldehydes. Aliphatic aldehydes were found to be less reactive and gave rise to products in lower yields and selectivities.

We observed that reaction times are significantly reduced in instances where products (partially) precipitate in the course of the reaction. The minimization of nonproductive product−catalyst interactions could account for this finding which provides an opportunity for practical product recovery. A reaction between benzaldehyde and **1f** gave rise to analytically pure product **2f** in 67% yield (dr > 99:01, 98% ee) when worked up through a simple filtration rather than by the usual chromatographic purification. Additional product **2f** was isolated from the filtrate in 27% yield (dr = 78:22, 77% ee).

To evaluate the applicability of our method, compound **10** was prepared on a larger scale (Scheme 2). Using only 1 mol% of catalyst **8b**, product **10** was obtained in good yield and with excellent levels of diastereo- and enantioselectivity without the need for chromatographic purification. The protected β-hydroxy-α-amino acid **10** is related to intermediates previously used in the synthesis of vancomycin[20] and ristocetin.[21]

In summary, we have introduced a mild and facile method for catalytic enantioselective aldol additions of α-isothiocyanato imides to aldehydes. Low catalyst loadings and operationally convenient conditions make this method attractive for the synthesis of various protected *syn* β-hydroxy-α-amino acids.

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Supporting Information Available: Experimental procedures and characterization data including X-ray crystal structures of **1f**, *cis*-**3a**, and the ethyl ester derived from **9h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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