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Direct Catalytic Asymmetric Aldol Reactions of Thioamides: Toward a Stereocontrolled Synthesis of 1,3-Polyols

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The 1,3-polyol system is a frequently occurring structural motif found in a plethora of biologically active natural products, most prominently represented by the macrolide antibiotics.[1] The importance of this particular class of compounds has prompted chemists to pursue efficient methodologies for the stereocontrolled synthesis of 1,3-oriented hydroxy group arrays,[2] but there remains much room for the development of a general and rapid protocol via catalytic asymmetric C−C bond formation.[2,3] In nature, multifunctional enzymes called polyketide synthases are harnessed to enable efficient, iterative elongation of a thioester-activated C2 unit through a decarboxylative Claisen condensation coupled with an enzymatic stereoselective reduction of ketones to provide 1,3-polyol arrays (Scheme 1a).[1,4] Herein, we report a comparably efficient approach using thioacetamide **1** as the C2 unit, which was iteratively installed via a direct catalytic asymmetric aldol reaction in conjunction with the construction of enantioenriched secondary alcohols by catalyst-controlled stereoselection (Scheme 1b).

The direct catalytic asymmetric aldol reaction has gained increasing attention as an atom-economical proton-transfer C−C bond-forming process,[5,6] where an active enolate is catalytically generated in situ and integrated into the subsequent enantioselective addition to aldehydes. Whereas recent advances in this field have allowed for the implementation of various aldol donors in this efficient process, those in the carboxylic acid oxidation state have yet to be exploited because of the intrinsic difficulty of deprotonative activation.[7−9] To consolidate the iterative direct aldol reaction outlined in Scheme 1b while allowing further elaboration of the aldol products, an aldol donor in the carboxylic acid oxidation state is desirable.[10] We envisioned the use of thioamides as the C2 aldol donor for this purpose,[11] as these would be chemoselectively activated to generate thioamide enolates under soft Lewis acid/hard Brønsted base cooperative catalysis.

We began this study with the reaction of *N*,*N*-diallylthioacetamide (**1a**) and isobutyraldehyde (**2a**) in THF at −20 °C in the presence of 10 mol % (*R*,*R*)-Ph-BPE/$[Cu(CH_3CN)_4]PF_6$/Li(OC_6H_4-*o*-OMe) catalyst (Table 1, entry 1), which is effective in direct Mannich-type reactions of thioamides.[12] The reaction, however, was very sluggish, and the desired product **3aa** was obtained in only 5% yield after 60 h, albeit with encouraging enantioselectivity (79% ee). Thin-layer chromatography, NMR, and electrospray ionization mass spectrometry analyses indicated that **3aa** was tightly bound to the (*R*,*R*)-Ph-BPE/Cu catalyst, suggesting that the catalytic cycle was arrested by product inhibition.[13] The addition of pyridine somewhat improved the yield without affecting the enantioselectivity, likely because of the competitive coordination of the pyridine to copper to liberate the product (entries 2 and 3). The use of a Lewis basic solvent effectively circumvented the product inhibition to afford **3aa** in good yield, despite concomitant β-elimination (entries 4−6), which was mostly prevented by decreasing the temperature to −60 °C (entry 7). Use of the stronger Brønsted base 2,2,5,7,8-pentamethylchromanol lithium salt (**4**) compensated for the reduced catalytic activity at the lower temperature, affording **3aa** in 91% yield and 95% ee (entry 8).[13] The reaction reached completion with as little as 3 mol % catalyst (entry 9).

Scheme 1. Biosynthetic and Direct Aldol Approaches to 1,3-Polyols

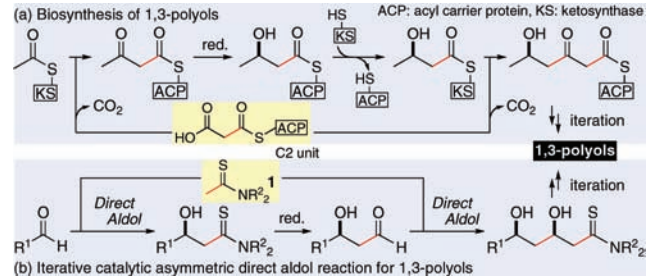
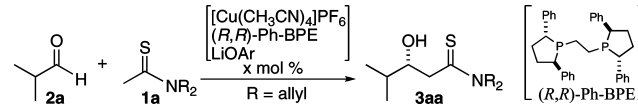
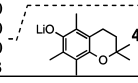


Table 1. Direct Catalytic Asymmetric Aldol Reaction of Thioamide **1a**[a]



entry	x	LiOAr	additive (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)	ee (%)
1	10		—	THF	−20	60	5	79
2	10		pyridine (10)	THF	−20	80	51	81
3	10		pyridine (100)	THF	−20	80	62	82
4	10		—	DMF	−20	100	62 (14)	87
5	10		—	DMA	−20	40	73 (3)	80
6	10		—	NMP	−20	40	60 (11)	82
7	10		—	DMF	−60	40	10 (trace)	89
8	10		—	DMF	−60	40	91 (4)	95
9	3		—	DMF	−60	40	91(trace)	91

[a] **1a**, 0.24 mmol; **2a**, 0.2 mmol. [b] Determined by ^{1}H NMR analysis. Yields of dehydrated products are provided in parentheses.

The scope of the direct catalytic asymmetric aldol reaction was then examined (Table 2).[14] Commercially available thioamide **1b** gave better enantioselectivity in the reaction with **2a**, although with a marginal loss in the chemical yield (entries 1 and 2). Other branched aldehydes **2b**−**d** were well-suited for the present catalytic system and exhibited high enantioselectivity (entries 3−5). Non-branched aldehydes **2e**−**i**, which are susceptible to self-condensation under basic conditions, afforded the desired products without the formation of self-aldols (entries 6−10). An ester functionality was also tolerated in the reaction of **2i**, confirming the mild basic conditions (entry 10). The aldol reaction of **2a** in the presence of acetophenone, which is more prone to form an enolate than **1a** in terms of the pK_a of the α-proton, afforded only **3aa**, further highlighting the highly chemoselective nature of the present catalytic

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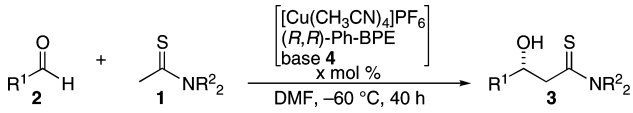
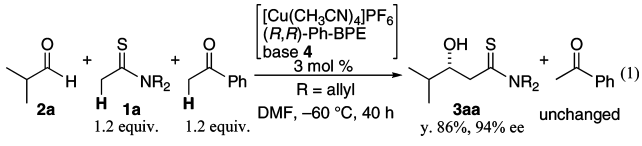
Table 2. Substrate Scope of the Direct Catalytic Asymmetric Aldol Reaction of Thioamides **1**[a]



entry	x	aldehyde R^1CHO		thioamide R^2 =		product	yield[b] (%)	ee (%)
1	3	^{i}PrCHO	**2a**	allyl	**1a**	**3aa**	87	91
2	3	^{i}PrCHO	**2a**	Me	**1b**	**3ba**	76	94
3	3	^{c}C$_6$H$_{11}$CHO	**2b**	allyl	**1a**	**3ab**	98	92
4	3	^{t}BuCHO	**2c**	allyl	**1a**	**3ac**	90	92
5	9		**2d**	Me	**1b**	**3bd**	84	84
6	3	$CH_3(CH_2)_6CHO$	**2e**	allyl	**1a**	**3ae**	80	89
7	3	$(^cC_6H_{11})CH_2CHO$	**2f**	allyl	**1a**	**3af**	81	90
8	3	$(CH_3)_2CHCH_2CHO$	**2g**	allyl	**1a**	**3ag**	90	90
9	3	$PhCH_2CH_2CHO$	**2h**	allyl	**1a**	**3ah**	63	88
10	3	$BzO(CH_2)_7CHO$	**2i**	allyl	**1a**	**3ai**	82	90

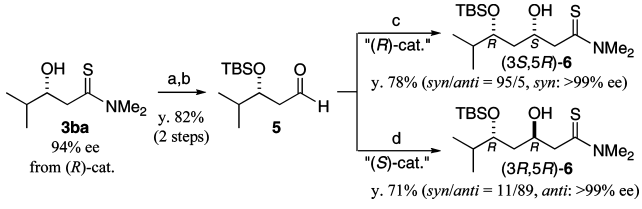
[a] **1**, 0.48 mmol; **2**, 0.4 mmol. [b] Isolated yield based on **2**.

system for nucleophilic activation of the thioamide functionality (eq 1).



Having developed the direct catalytic asymmetric aldol reaction of thioamides, we applied the protocol to 1,3-diol synthesis (Scheme 2). TBS protection followed by reduction of the thioamide functionality with the Schwartz reagent converted **3ba** to aldehyde **5** in 82% yield (two steps),[15] and **5** was then subjected to another direct aldol reaction with either the *R*- or *S*-configured catalyst. The reaction proceeded stereoselectively to afford diol (3*S*,5*R*)-**6** or (3*R*,5*R*)-**6**, respectively, indicating that the catalyst largely controlled the newly formed stereogenic center.[16]

Scheme 2. Catalyst-Controlled Direct Catalytic Asymmetric Aldol Reaction for the Synthesis of 1,3-Diols[a]



[a] Conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2; (b) $Cp_2Zr(H)Cl$, toluene, rt; (c) **1b**, $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE/**4** (10 mol %), DMF, −60 °C, 40 h; (d) **1b**, $[Cu(CH_3CN)_4]PF_6$/(*S*,*S*)-Ph-BPE/**4** (10 mol %), DMF, −60 °C, 40 h.

In summary, we have documented a direct catalytic asymmetric aldol reaction of thioamides. The soft Lewis acid/hard Brønsted base cooperative catalysis exerted by (*R*,*R*)-Ph-BPE/$[Cu(CH_3CN)_4]PF_6$/**4** enables highly chemoselective deprotonative activation of thioamides over aldehyde and ketone functionalities. Facile reduction of thioamide regenerates the aldehyde functionality, and a second direct aldol reaction proceeds stereoselectively in a catalyst-controlled manner. Future work will be dedicated to applying the present protocol to the asymmetric synthesis of natural products bearing a 1,3-polyol motif.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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