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Direct Catalytic Enantio- and Diastereoselective Aldol Reaction of Thioamides

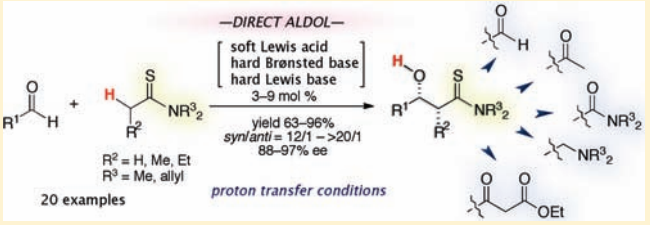
Mitsutaka Iwata,[†] Ryo Yazaki,[†,‡] I-Hon Chen,[†] Devarajulu Sureshkumar,[†] Naoya Kumagai,*[,†] and Masakatsu Shibasaki*[,†]

[†]Institute of Microbial Chemistry, Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

[‡]Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Supporting Information

ABSTRACT: A direct catalytic asymmetric aldol reaction of thioamides using a soft Lewis acid/hard Brønsted base cooperative catalyst comprising (*R*,*R*)-Ph-BPE/[$Cu(CH_3CN)_4$]PF_6/LiOAr is described. Exclusive enolate generation from thioacetamides through a soft−soft interaction with the soft Lewis acid allowed for a direct aldol reaction to α-nonbranched aliphatic aldehydes, which are usually susceptible to self-condensation under conventional basic conditions. A hard Lewis basic phosphine oxide has emerged as an effective additive to constitute a highly active ternary soft Lewis acid/hard Brønsted base/hard Lewis base cooperative catalyst, enabling a direct enantio- and diastereoselective aldol reaction of thiopropionamides. Strict control of the amount of the hard Lewis base was essential to drive the catalytic cycle efficiently with a minimized retro-aldol pathway, affording *syn*-aldol products with high stereoselectivity. Divergent transformation of the thioamide functionality is an obvious merit of the present aldol methodology, allowing for a facile transformation of the aldol product into the corresponding aldehyde, ketone, amide, amine, and ketoester. An aldehyde derived from the direct aldol reaction was subjected to a second direct aldol reaction, which proceeded in a catalyst-controlled manner to provide 1,3-diols with high stereoselectivity.



INTRODUCTION

The past decade has witnessed considerable advances in direct catalytic asymmetric aldol methodology[1,2] with increasing attention to the development of atom-economical[3] and environmentally benign transformations in organic synthesis.[4] Because catalytic in situ generation of enolates is central to triggering this process, aldol donors such as ketones and aldehydes that are prone to form enolates through facile deprotonation are commonly employed.[5] Despite the prospective synthetic utility, however, the use of aldol donors in the carboxylic acid oxidation state in a direct catalytic asymmetric aldol reaction is limited due to reluctant enolate formation resulting from the intrinsic low acidity of the α-proton in this class of pronucleophiles.[5,6] In this context, we focused on thioamides **1** as potential pronucleophiles in the catalytic asymmetric direct aldol reaction,[7−9] because (1) they are in the carboxylic acid oxidation state, (2) the soft Lewis basic character of thioamide functionality is expected to allow for chemoselective activation by a soft Lewis acid in the presence of aldehydes, and (3) divergent transformation of thioamide functionality is advantageous for the further elaboration of the aldol products.[10] During our efforts to design a soft Lewis acid/hard Brønsted base cooperative catalyst,[11] specifically designed for in situ chemoselective activation/deprotonation of soft Lewis basic carbon pronucleophiles such as allylic cyanides,[12] we identified that a soft Lewis acid/hard Brønsted base cooperative binary catalyst was effective for direct catalytic asymmetric aldol reactions of thioamides **1** and aldehyde **2**, delivering enantiomerically enriched β-hydroxythioamides **3** under proton transfer conditions (Scheme 1a).[9b,c] The addition of a hard Lewis basic additive to constitute a soft Lewis acid/hard Brønsted base/hard Lewis base ternary catalyst enhanced the catalytic activity, allowing for the facile enolate generation from thiopropionamides to afford the aldol product in a highly enantio- and diastereoselective manner (Scheme 1b). Exquisite control of the aldol/retro-aldol process by the appropriate choice and amount of hard Lewis base was crucial to enhance the catalytic efficiency, affording the desired *syn*-aldol products with high stereoselectivity. Divergent transformation of the thioamide functionality highlights the synthetic utility of the present protocol.

RESULTS AND DISCUSSION

The central issue of the present catalysis is a chemoselective enolate formation from thioamides in the presence of more acidic aldehydes and subsequent enantioselective addition to aldehydes. By exploiting specific soft−soft interactions between thioamides and a soft Lewis acid catalyst, we anticipated that a hard Brønsted base cocatalyst would chemoselectively deprotonate the activated

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Scheme 1. Direct Catalytic Asymmetric Aldol Reaction of Thioamides

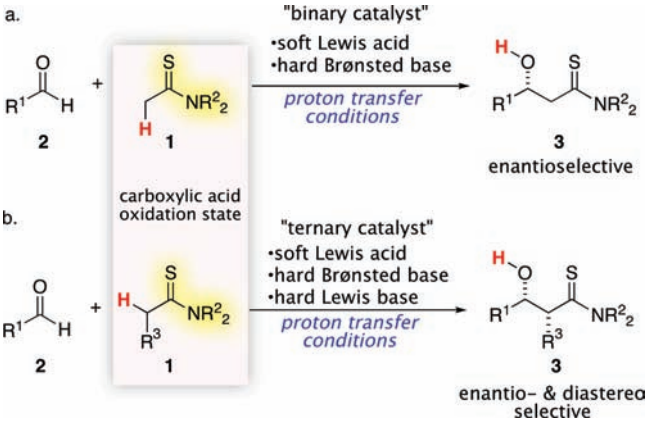
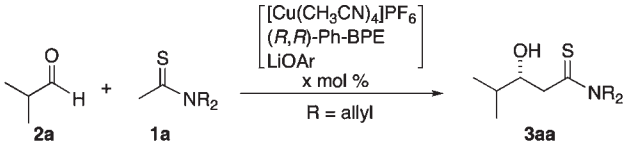
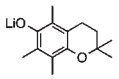
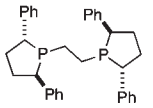
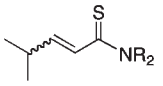


Table 1. Direct Catalytic Asymmetric Aldol Reaction of Thioacetamide 1a[a]



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
10[c]	3		—	DMF	–60	40	0	—
11[d]	3	Li salt of **5**	—	DMF	–60	40	0	—





[a] **1a**, 0.24 mmol; **2a**, 0.2 mmol. [b] Determined by ^{1}H NMR analysis. Yield of dehydrated product **4aa** is provided in parentheses. [c] The reaction without $[Cu(CH_3CN)_4]PF_6$ and (*R*,*R*)-Ph-BPE. [d] The reaction without the Li salt of **5**.

thioamides to generate thioamide enolates, and subsequent addition to aldehyde/proton transfer would complete the catalytic cycle without generating any waste. 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 % of a soft Lewis acid/hard Brønsted base cooperative catalyst comprising (*R*,*R*)-Ph-BPE/$[Cu(CH_3CN)_4]PF_6$/Li(OC_6H_4-*o*-OMe) (Table 1, entry 1), which is effective for direct Mannich-type reactions of thioamides.[9a,13] The reaction was very sluggish, however, and the desired product **3aa** was obtained in only 5% yield after 60 h of stirring albeit with encouraging

Scheme 2. Competitive Direct Aldol Reaction of Thioacetamide 1a and Acetophenone 6

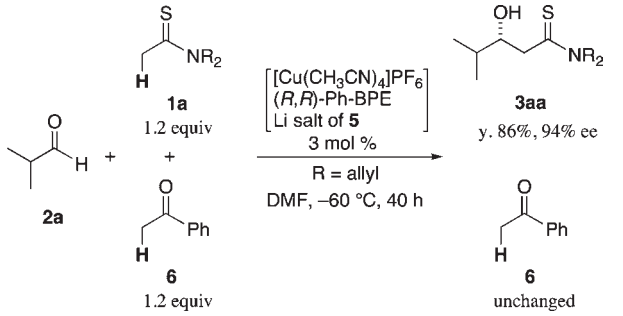
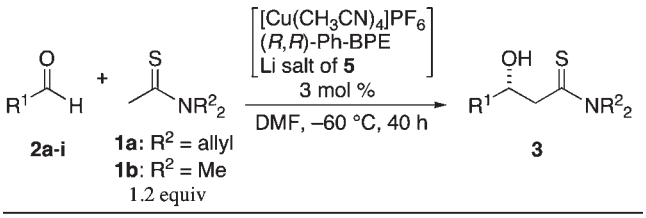
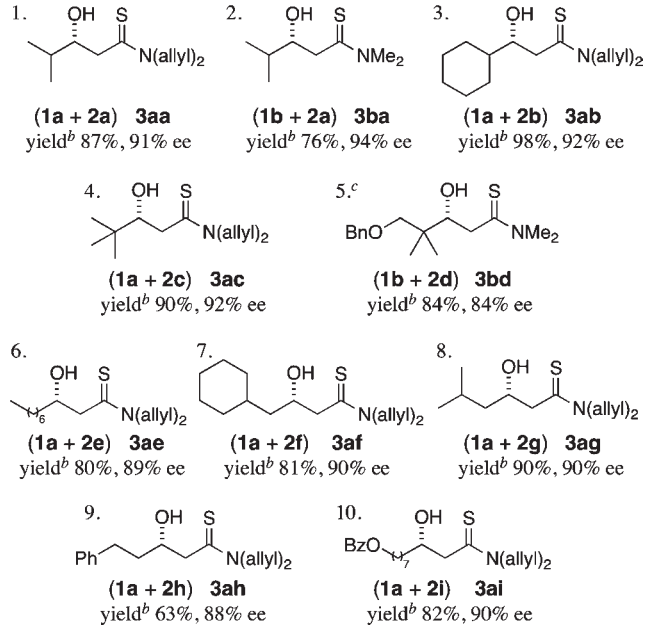


Table 2. Direct Catalytic Asymmetric Aldol Reaction of Thioacetamides[a]





[a] **1a**, 0.48 mmol; **2a**, 0.4 mmol. [b] Isolated yield. [c] 9 mol % of catalyst was used.

enantioselectivity (79% ee). Collective data obtained from TLC, ^{1}H NMR, and ESI-MS analyses indicated that **3aa** was tightly bound to the soft Lewis acid part of the catalyst (*R*,*R*)-Ph-BPE/Cu, suggesting that the catalytic cycle was arrested by product inhibition.[14] The addition of the Lewis basic additive pyridine somewhat improved the yield without affecting enantioselectivity, likely because of the competitive coordination of the pyridine to copper to liberate the product (entries 2, 3). The use of a Lewis basic solvent such as DMA, DMF, or NMP more effectively

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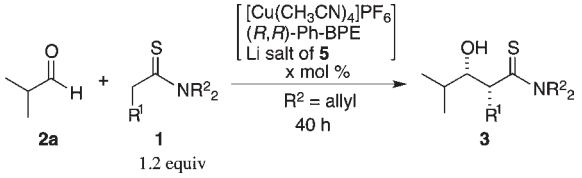
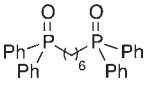
Table 3. Direct Catalytic Enantio- and Diastereoselective Aldol Reaction of Thiopropionamides[a]



entry	x	R^1	solvent	additive (mol %)	3	temp (°C)	yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	10	H **1a**	DMF		**3aa**	−60	91		95
2	10	Me **1c**	DMF		**3ca**	−60	86	4.7/1	0
3[e,f]	10	Me **1c**	THF		**3ca**	−60	18	>20/1	97
10[f]	10	Me **1c**	THF/DMF (9/1)		**3ca**	−60	89	>20/1	86
10[f]	10	Me **1c**	THF/DMF (19/1)		**3ca**	−60	65	>20/1	97
10[f]	10	Me **1c**	THF/NMP (19/1)		**3ca**	−60	80	>20/1	90
7[f]	10	Me **1c**	THF/HMPA(19/1)		**3ca**	−60	93	1/1.2	6[h]
8[e]	10	Me **1c**	THF	Pyr (30)	**3ca**	−60	83	9.4/1	54
9	10	Me **1c**	THF	7 (20)[g]	**3ca**	−60	90	>20/1	81
10	10	Me **1c**	THF	7 (20)[g]	**3ca**	−70	90	>20/1	94
11	3	Me **1c**	THF	7 (1.5)	**3ca**	−70	79	>20/1	95
12[f]	3	Me **1c**	THF	7 (1.5)	**3ca**	−70	7	>20/1	97
13	3	Me **1c**	THF	7 (1.5) **5**(2)	**3ca**	−70	94	>20/1	95



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[a] **1**, 0.24 mmol; **2a**, 0.2 mmol. [b] Determined by ^{1}H NMR of the crude mixture with toluene as an internal standard. [c] Determined by ^{1}H NMR of the crude mixture. [d] ee of the *syn* diastereomer. [e] Reaction time was 60 h. [f] Li(OC_6H_4-*p*-OMe) was used as the Brønsted base instead of the Li salt of **5**. [g] A large part of **7** was crystallized upon cooling of the reaction mixture. [h] The major enantiomer obtained was (2*S*,3*R*)-*syn*-**3ca**. Pyr = pyridine.

circumvented the product inhibition, affording **3aa** in more than 60% yield, despite concomitant formation of dehydrated product **4aa** through β-elimination of the desired product **3aa** (entries 4−6), which was effectively prevented by running the reaction at a lower temperature (−60 °C) (entry 7). A stronger Brønsted base, the Li salt of 2,2,5,7,8-pentamethylchromanol **5**, was identified to compensate for the reduced catalytic activity at the lower temperature, affording **3aa** in 91% yield and 95% ee (entry 8).[15] Under the optimized reaction conditions, the reaction was completed with as little as 3 mol % of catalyst and there was only a marginal loss of enantioselectivity (entry 9). The crucial nature of the soft Lewis acid/hard Brønsted base catalysis was delineated by the following control experiments. In the absence of a soft Lewis acid $[Cu(CH_3CN)_4]PF_6$ or hard Brønsted base Li salt of **5**, the reaction afforded no product at all under otherwise identical conditions (entries 10, 11). The competitive aldol reaction in the presence of two aldol donor substrates thioamide **1a** and acetophenone (**6**), whose α-proton is more acidic than that of thioamides, proceeded with the cooperative catalyst to exclusively afford the aldol product derived from **1a**, showcasing the highly chemoselective nature of the present catalysis (Scheme 2).

Next, we explored the substrate generality of the direct aldol reaction of thioacetamides and various aldehydes (Table 2).[16,17] *N*,*N*-Dimethylthioacetamide (**1b**), which is commercially available, served as a suitable nucleophile to exhibit better enantioselectivity in the reaction with isobutyraldehyde (**2a**), albeit with a marginal loss of the chemical yield (entries 1, 2). The aldol reaction with α-branched aldehydes **2b**−**d** proceeded smoothly in the present catalytic system to give the desired β-hydroxythioamides in a highly enantioselective manner (entries 3−5). Particularly noteworthy examples are the reactions with α-nonbranched aldehydes **2e**−**i**, which are susceptible to self-condensation under conventional basic conditions, affording the desired aldol products without the formation of self-aldols (entries 6−10). An ester functionality of aldehyde **2i** was tolerated during the aldol reaction, confirming the mild basic conditions of the present catalysis (entry 10).

The direct catalytic asymmetric aldol reaction of thiopropionamide offers efficient access of the enantioenriched propionate unit, which is a common structural motif of a wide range of natural products. The control of both enantio- and diastereoselectivity in the thiopropionamide aldol reaction is an obvious next challenge in our continuing studies of the direct aldol reaction. Initial attempts to perform an enantio- and diastereoselective direct aldol reaction of *N*,*N*-diallylthiopropionamide (**1c**) and isobutyraldehyde (**2a**) in DMF at −60 °C under

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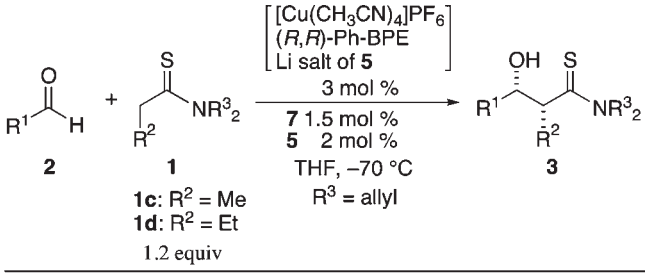
Table 4. Direct Catalytic Enantio- and Diastereoselective Aldol Reaction of Thiopropionamides[a]



1. **(1c + 2a) 3ca** — 40 h, *syn*/*anti*[b] = >20/1, yield[c] 93%, 95% ee[d]
2. **(1d + 2a) 3da** — 96 h, *syn*/*anti*[b] = 19/1, yield[c] 71%, 94% ee[d]
3. **(1c + 2b) 3cb** — 40 h, *syn*/*anti*[b] = >20/1, yield[c] 93%, 90% ee[d]
4. **(1c + 2e) 3ce** — 96 h, *syn*/*anti*[b] = >20/1, yield[c] 95%, 97% ee[d]
5. **(1c + 2g) 3cg** — 96 h, *syn*/*anti*[b] = >20/1, yield[c] 96%, 96% ee[d]
6. **(1c + 2h) 3ch** — 96 h, *syn*/*anti*[b] = >20/1, yield[c] 80%, 97% ee[d]
7. **(1c + 2i) 3ci** — 48 h, *syn*/*anti*[b] = >20/1, yield[c] 96%, 97% ee[d]
8. **(1c + 2j) 3cj** — 96 h, *syn*/*anti*[b] = 20/1, yield[c] 74%, 95% ee[d]
9. [e,f] **(1c + 2k) 3ck** — 48 h, *syn*/*anti*[b] = 12/1, yield[c] 63%, 94% ee[d]
10. [f,g] **(1c + 2l) 3cl** — 48 h, *syn*/*anti*[b] = 20/1, yield[c] 76%, 92% ee[d]

[a] **1**, 0.48 mmol; **2**, 0.4 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Isolated yield. [d] ee of the *syn* diastereomer. [e] Catalyst, 6 mol %; **5**, 4 mol %; **7**, 3 mol %; −60 °C. Potassium salt of **5** was used as a Brønsted base. [f] **1**, 0.24 mmol; **2**, 0.2 mmol. [g] Catalyst, 9 mol %; **5**, 6 mol %; **7**, 3 mol %; −60 °C. The potassium salt of **5** was used as a Brønsted base.

optimal conditions[9b] for the aldol reaction of thioacetamides resulted in the formation of aldol product **3ca** with unexpectedly poor stereoselectivity (Table 3, entries 1, 2). In marked contrast, excellent *syn*-selectivity and enantioselectivity were observed when the same reaction was run in THF, albeit with low catalytic efficiency (entry 3). A plausible rationale for this observation is that (1) the reaction intrinsically proceeded in a highly stereoselective manner; (2) a rapid retro-aldol reaction of **3ca** occurred in DMF, affording the aldol product in low stereoselectivity after an extended reaction time; and (3) a Lewis basic species such as DMF was essential to efficiently drive the catalytic cycle; otherwise, the cycle was halted by the formation of a stable Cu aldolate. The binary solvent system of THF and Lewis basic solvent was then examined (entries 4−7). As the DMF content increased, a higher catalytic efficiency was observed at the expense of enantioselectivity (entry 4 vs 5). NMP exhibited better performance to promote the reaction with a marginal loss of enantioselectivity (entry 6), whereas the use of the stronger Lewis basic HMPA resulted in poor stereoselectivity (entry 7). In pursuit of a more efficient catalytic system, we next focused on the use of hard Lewis basic additives (entries 8−13). Whereas the addition of pyridine eroded the stereoselectivity (entry 8), 1, 6-bis(diphenylphosphino)hexane dioxide (**7**) facilitated the catalytic cycle with an attenuated flux of the retro-aldol pathway (entry 9),[18] which was further reduced by decreasing the reaction temperature to −70 °C (entry 10). With this soft Lewis acid/hard Brønsted base/hard Lewis base ternary catalytic system,[9d] the reaction could be performed with 3 mol % catalyst loading (entry 11) and the use of Li(OC_6H_4-*p*-OMe) instead of the Li salt of **5** showed poor conversion (entry 12), indicating the particular effectiveness of **5** in this catalysis. All of the components, including the soft Lewis acid, hard Brønsted base, and hard Lewis base, were essential to promote the desired aldol reaction.[14] The use of 2 mol % of **5** as a proton source was beneficial for higher catalytic efficiency and suppression of the retro-aldol pathway (entry 13).

The scope of the direct catalytic *syn*-selective asymmetric aldol reaction is summarized in Table 4.[16,19] Thioamide **1d** derived from butyric acid was applicable in this process to afford *syn* aldol product **3da** in a highly stereoselective manner (entry 2). The reaction with other α-monosubstituted aldehydes proceeded efficiently (entry 3). The reaction with α,α-disubstituted aldehydes resulted in low conversion likely due to an exceedingly high steric demand in the transition state. The reaction with α-nonbranched aldehydes, which readily undergo self-aldol reactions under simple Brønsted basic conditions, highlights the utility of the present catalytic system where chemoselective activation of intrinsically less acidic thioamide functionality through a soft−soft interaction ensures exclusive enolate formation from thioamide **1c** (entries 4−10). Aldehydes bearing a pendant benzoate group afforded the corresponding product **3ci** without removal or migration of the benzoyl group, showcasing the mild basic nature of the present catalysis (entry 7). TBS ether hardly interfered with the desired aldol pathway (entry 8), whereas the reaction of α-benzyloxyacetaldehyde (**2k**) required 6 mol % of catalyst with the potassium salt of **5** as a Brønsted base and lower diastereoselectivity was observed, likely because chelate formation negatively impacted both the catalytic efficiency and diastereoselectivity (entry 9). The use of an aldehyde **2l** with a pyridyl group, which may coordinate to copper to impair the catalytic function, revealed the robustness of the present catalysis (entry 10).

The mechanistic aspects of the effect of hard Lewis base **7** in the present catalytic system are intriguing. ^{1}H and ^{31}P NMR analysis of the $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE/$LiPF_6$/**7** solution in THF-d_8 indicated the preferential coordination of **7** to the Li cation over the Cu cation through a hard−hard interaction.[14] The Li salt of **5** acquired enhanced basicity upon coordination with **7**,[12c,20,21] facilitating the deprotonation step to accelerate the reaction. The observations that (1) the $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE complex was indispensable to promote the aldol reaction and (2) the catalyst seemed to be arrested at Cu aldolate **A** in the absence of **7** (Figure 1) suggested that the role of **7** was not fully due to the activation of the Brønsted base. The likely scenario for another role of **7** would be the destabilization of Cu aldolate A, although the coordination of **7** to the Cu cation was not predominant in the presence of a Li cation. The coordination of **7** to Cu destabilized the Cu aldolate **A**, inducing a cation exchange to give the Li aldolate **B**, and the

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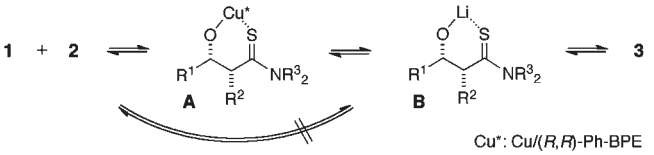
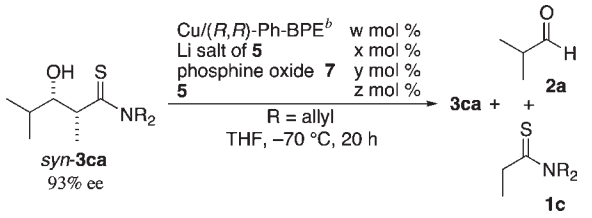


Figure 1. Competitive aldol/retro-aldol reaction via Cu aldolate **A** and Li aldolate **B**.

Table 5. Examination of Retro-Aldol Reaction[a]

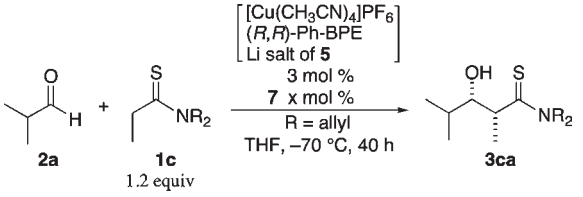


					recovered **3ca**			recovered **1c**
entry	w	x	y	z	(%)[c]	*syn*/*anti*[d]	ee (%)[e]	(%)[c]
1	0	3	0	0	100	*syn* only	93	0
2	0	3	1.5	0	100	*syn* only	93	0
3	3	3	1.5	0	89	88/1	81	11
4	3	3	1.5	2	89	88/1	89	11

[a] **3ca**, 0.1 mmol. [b] Prepared from $[Cu(CH_3CN)_4]PF_6$ and (*R*,*R*)-Ph-BPE. [c] Determined by ^{1}H NMR analysis of the crude mixture with toluene as an internal standard. [d] Determined by ^{1}H NMR analysis of the crude mixture. [e] ee of the *syn* diastereomer.

subsequent rapid protonation of **B** afforded aldol product **3**.[22] In the present catalysis, all the processes are virtually in equilibrium, and the flux of the retro-aldol pathway needs to be considered. The aldol product **3ca** (93% ee) was intact under basic conditions with the Li salt of **5**, irrespective of the presence of **7** (Table 5, entries 1, 2). In contrast, the attempted resubjection of **3ca** to the catalyst solution induced a retro-aldol reaction, resulting in erosion of the enantioselectivity with concomitant recovery of thioamide **1c**, confirming that the retro aldol reaction proceeds through Cu aldolate **A** (entry 3). Coexistence of **5** as a proton source retarded the retro-aldol reaction likely due to the decreased mole fraction of **B** (entry 4). The coordination of **7** would destabilize intermediates **A** and **B** while the basicity of the Li salt of **5** increased, which virtually enhanced all of the forward and backward processes delineated in Figure 1. Indeed, a balance of the aldol/retro-aldol process is of prime importance for stereoselectivity and is quite sensitive to the amount of **7** in the solution (Table 6). Lower loading of **7** limited the reaction efficiency (entry 1) and higher loading led to a substantial decrease in enantioselectivity at the expense of a high yield due to the iterative aldol/retro-aldol reaction (entries 3–5); the effect was significantly leveraged by a small deviation from the optimum amount of **7** (entry 2). An increase in the amount of **7** enhanced both aldol and retro-aldol processes, narrowing the range of the optimal reaction time in which the aldol product was obtained with high stereoselectivity.[23] Stringent control of a hard Lewis basic additive allowed for the efficient production of kinetic aldol products with high stereoselectivity.

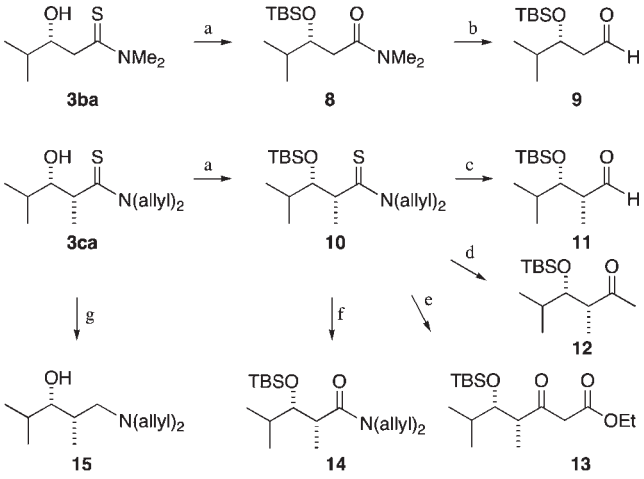
Table 6. Re-examination of Phosphine Oxide Effect[a]



entry	x	concn[b]	yield[c] (%)	*syn*/*anti*[d]	ee[e] (%)
1	1	0.1	54	>20/1	97
2	1.5	0.1	79	>20/1	95
3	2	0.1	87	>20/1	87
4	3	0.067	93	>20/1	62
5	4	0.05	93	18/1	42

[a] **1c**, 0.24 mmol; **2a**, 0.2 mmol. [b] At the designated concentration, no crystallization of **7** was detected. [c] Determined by ^{1}H NMR analysis of the crude mixture with toluene as an internal standard. [d] Determined by ^{1}H NMR analysis of the crude mixture. [e] ee of *syn* diastereomer.

Scheme 3. Transformation of Aldol Products[a]



[a] Conditions: (a) TBSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, rt, yield 98% for **8**, yield 98% for **10**; (b) $Cp_2Zr(H)Cl$ (2 equiv), toluene, rt, yield 84%; (c) (i) MeOTf (2 equiv), ether, rt, (ii) $LiAlH(O^tBu)_3$ (2 equiv), 0 °C–rt, yield 89%; (d) (i) MeOTf (2 equiv), ether, rt, (ii) MeLi (3 equiv), −78 °C, yield 84%; (e) (i) MeOTf (2 equiv), ether, rt, (ii) CH_2=C(OLi)OEt (3 equiv), −78 °C, yield 84%; (f) TFAA (5 equiv), CH_2Cl_2, rt, yield 81%; (g) Red-Al (3 equiv), ether, rt, yield 89%.

From a synthetic point of view, the meritorious feature of the present aldol methodology is the divergent transformation of the thioamide functionality (Scheme 3). The aldol product **3ba** derived from thioacetamide was converted to TBS ether **8** by treatment with TBSOTf/2,6-lutidine, and subsequent reduction of the thioamide functionality with the Schwartz reagent afforded aldehyde **9** in 84% yield.[24] This single-operation reduction protocol was not effective for the TBS-protected thioamide **10** derived from thiopropanamide likely due to increased steric demand at the thiocarbonyl moiety. *S*-Methylation of the thioamide functionality with MeOTf effectively enhanced the electrophilicity,[25] allowing for facile hydride reduction with $LiAlH(O^tBu)_3$ to give aldehyde **11** in 89% yield. This single-flask protocol was valid for other

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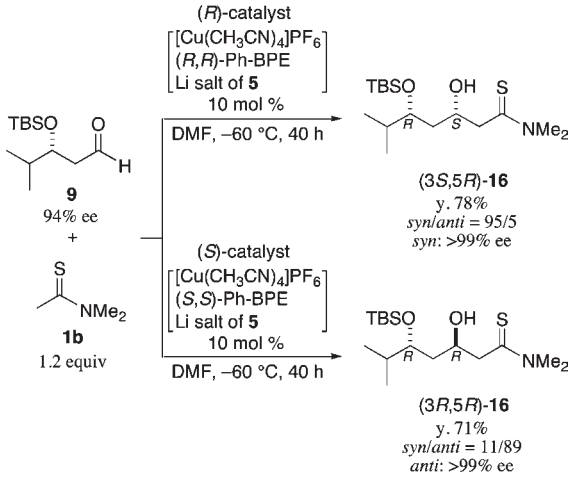
Scheme 4. Catalyst-Controlled Stereoselective Synthesis of 1,3-Diols



nucleophiles, affording the corresponding ketone **12** and ketoester **13** by treatment with MeLi and Li ester enolate at −78 °C, respectively. Activation of the thiocarbonyl moiety with TFAA gave the corresponding amide **14**.[26] It is worth noting that no epimerization proceeded during the activation of thioamide in these transformation reactions. Amino alcohol **15** was obtained by directly subjecting the aldol product **3ca** to the reduction with Red-Al in ether at room temperature. The second aldol reaction of the thus-obtained sample with 94% ee aldehyde **9** demonstrates the application of the present aldol methodology to the enantioselective synthesis of 1,3-diols via catalyst-controlled stereoselection (Scheme 4).[27,28] A second aldol reaction with thioacetamide **1b** was attempted using 10 mol % (*R*)-catalyst in DMF at −60 °C, affording predominantly *syn*-diol (3*S*,5*R*)-**16** with excellent enantioselectivity. On the other hand, subjecting the same substrate set to (*S*)-catalyst delivered *anti*-diol (3*S*,5*R*)-**16** with high stereoselectivity, indicating that stereoselectivity of the newly constructed stereogenic center was largely controlled by chirality of the catalyst.

CONCLUSIONS

In conclusion, we developed a direct catalytic asymmetric aldol reaction of thioacetamides promoted by a soft Lewis acid/hard Brønsted base cooperative catalyst. As a result of the highly chemoselective deprotonation of thioamide through a soft−soft interaction, the desired aldol products were produced in a highly stereoselective manner, even with α-nonbranched enolizable aldehydes. The addition of phosphine oxide to the above-mentioned catalyst constituted a soft Lewis acid/hard Brønsted base/hard Lewis base ternary catalyst, enhancing the catalytic activity in THF to enable the *syn*-selective direct catalytic asymmetric aldol reaction of thiopropionamides. Because of the substantial effect of phosphine oxide and the presence of the retro-aldol reaction, stringent control of the phosphine oxide was essential to achieve high stereoselectivity. Divergent transformation of the thioamide functionality showcases the synthetic utility of the present catalysis, culminating in the catalyst-controlled stereoselective synthesis of both *syn* and *anti* 1,3-diols via iterative direct aldol reactions.

ASSOCIATED CONTENT

Supporting Information. Characterization of new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
nkumagai@bikaken.or.jp; mshibasa@bikaken.or.jp

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(16) For the determination of absolute configuration, see Supporting Information.

(17) The aldol reaction of aromatic aldehydes was partially successful due to retro-aldol reaction and β-elimination. For the reference, see ref 9c.

(18) The phosphine oxide effect at −60 °C with 10 mol % of catalyst loading is summarized in Supporting Information.

(19) An aromatic aldehyde seemed to require more delicate optimization due to a greater tendency toward a retro-aldol reaction. The reaction of thioamide **1c** with benzaldehyde (**2m**) was specifically optimized: $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE/Li(OC_6H_4-*p*-OMe) 3 mol %, THF/DMF = 1/7, −75 °C, 48 h, the aldol product **3cm** was obtained in 76% yield, *syn*/*anti* = 13/1, 84% ee (*syn*).

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(22) The possibility of a direct protonation of Cu aldolate **A** cannot be ruled out.

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