Asymmetric Catalysis

Direct Catalytic Asymmetric Mannich-Type Reaction of Thioamides**

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Thioamides are widely utilized as useful precursors for the synthesis of a broad range of heterocyclic compounds by exploiting their ambident nucleophilic character at both the sulfur and nitrogen atoms.^[1] They are, however, rarely recognized as carbon pronucleophiles in enantioselective C-C bond-forming reactions. Yoshida and co-workers disclosed that the exposure of thioamides to a stoichiometric amount of strong base selectively generated a Z enolate, thus affording syn-aldol products upon the addition of aldehydes.^[2] Lithium thioamide enolates and thioketene S-silyl N,S-acetals were successively reported as activated nucleophiles for Michael,^[3] aldol,^[4] and Mannich-type reactions.^[5] Later the aldol reaction was rendered asymmetric under stoichiometric conditions, although only one example with benzaldehyde was described.^[6] In this context, there are no reports on the catalytic generation of active carbon nucleophiles from thioamides and their integration into enantioselective C-C bond-forming processes. Such an approach would be more advantageous than the preceding stoichiometric reactions in terms of both atom and step economy.^[7] Herein, we report a direct catalytic asymmetric Mannich-type reaction of thioamides and N-diphenylphosphinoyl (Dpp) imines^[8] under proton-transfer conditions by soft Lewis acid/hard Brønsted base cooperative catalysis, to afford enantiomerically enriched β-amino thioamides. Divergent transformation of the thioamides ensures the synthetic utility of the product.

The direct catalytic asymmetric Mannich-type reaction has attracted much attention as a useful protocol to provide optically active β -amino carbonyl units under proton-transfer conditions.^[9] We recently reported a catalytic system comprising [Cu(CH₃CN)₄]ClO₄/(*R*,*R*)-Ph-BPE/LiOAr that was particularly effective for catalytic generation of nucleophiles from otherwise unreactive pronucleophiles bearing soft Lewis basic functionality.^[10] We envisioned employing thioamides as carbon pronucleophiles in this catalytic system. The thioamide functionality has an even larger rotational barrier and dipole moment than the corresponding amides, although the C=S bond, unlike the C=O bond, is intrinsically not polar-

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ized.^[11] A commonly accepted interpretation is the greater contribution of the canonical structure B in Scheme 1, where more pronounced charge transfer from N to S is antici-



Scheme 1. Catalytic generation of the thioamide enolate by soft Lewis acid/hard Brønsted base cooperative catalysis.

pated.^[12] Higher acidity of the α proton of thioamides compared to that of amides may also be ascribed to better accommodate the negative charge at the sulfur atom. $^{\left[13\right] }$ We hypothesized that chemoselective coordination of the sulfur atom to a cationic soft Lewis acid would accommodate the partial negative charge and enhance the acidity of the α proton of thioamides, thus leading to a facile catalytic generation of thioamide enolates by a mild Brønsted base (Scheme 1). Initially, we selected N,N-dimethylthioacetamide (2a), which is a commercially available thioamide pronucleophile,^[14] and it was subjected to a direct Mannich-type reaction with N-Dpp imine 1a (Table 1). The catalyst prepared from $[Cu(CH_3CN)_4]PF_6$, (R,R)-Ph-BPE, and Li(OC₆H₄-p-OMe) showed better catalytic turnover than that prepared from [Cu(CH₃CN)₄]ClO₄, and afforded **3aa** with encouraging enantioselectivity (Table 1, entries 1 and 2). The reaction in CH₂Cl₂ or DME resulted in a lower yield despite the higher solubility of **1a** (Table 1, entries 3 and 4). Toluene offered a suitable reaction medium for the present catalysis in terms of both catalytic turnover and ee value (Table 1, entry 5). The reaction in the absence of the Cu¹ salt or base did not proceed at all, thus verifying the crucial cooperative nature of the soft Lewis acid and hard Brønsted base to generate the active nucleophile from 2a (Table 1, entries 6 and 7). The reaction can be carried out in the presence of 1 mol % of catalyst at -20 °C without any loss of enantioselectivity (Table 1, entry 8).

The investigation of the substrate scope with the present system was our next focus. *N*,*N*-diallyl **2b** and *N*,*N*-bisPMB **2c** variants, whose nitrogen substituents can be removed at the product elaboration stage, were used as thioamide pronucleophiles. In the reaction using **2b**, β elimination of the *N*-Dpp group occurred occasionally at 0 °C, which was circumvented by lowering the reaction temperature to -20 °C and using Li(OC₆H₄-*o*-OMe) as the base.^[15] The reaction of **1a** and **2b** proceeded smoothly with 3 mol% of the catalyst, and



Table 1: Direct catalytic asymmetric Mannich-type reaction of *N*-Dpp imine **1 a** and thioamides **2 a** with soft Lewis acid/hard Brønsted base cooperative catalysis.^[a]

	O N Ph H 1a	+N 2a	soft Le (<i>R</i> , <i>R</i>)-F base; x mol % 0	wis acid Ph-BPE 6 of each °C	O Ph-" Ph' NH Ph' 3a	S N a		
Entry	Soft Lewis acid	Base		Solvent	x [mol%]	<i>t</i> [h]	Yield [%] ^[b]	ee [%]
1	[Cu(CH₃CN)₄]ClO₄	Li(OC ₆ H₄- <i>p</i> -O	Me)	THF	10	20	60	87
2	[Cu(CH ₃ CN) ₄]PF ₆	Li(OC ₆ H₄-p-O	Me)	THF	10	20	72	89
3	[Cu(CH ₃ CN) ₄]PF ₆	Li(OC ₆ H₄-p-O	Me)	DME	10	20	60	93
4	[Cu(CH ₃ CN) ₄]PF ₆	Li(OC ₆ H₄-p-O	Me)	CH_2CI_2	10	20	46	88
5	[Cu(CH ₃ CN) ₄]PF ₆	Li(OC ₆ H₄-p-O	Me)	toluene	10	20	95	95
6 ^[c]	-	Li(OC ₆ H₄-p-O	Me)	toluene	10	20	0	-
7 ^[c]	[Cu(CH₃CN)₄]PF ₆	_	-	toluene	10	20	0	-
8 ^[d]	[Cu(CH ₃ CN) ₄]PF ₆	Li(OC ₆ H ₄ -p-O	Me)	toluene	1	72	88 ^[e]	96

[a] **1a** (0.2 mmol), **2a** (0.24 mmol). [b] Determined by ¹H NMR with Bn₂O as an internal standard. [c] In the absence of (*R*,*R*)-Ph-BPE. [d] Run with 1.5 equivalents of **2a** at -20 °C. [e] Yield of isolated product. THF = tetrahydrofuran, DME = 1,2-dimethoxyethane.

(*R*,*R*)-Ph-BPE

the reaction also reached completion with as little as 1 mol% of catalyst over an extended period of time (Table 2, entries 1 and 2).^[16] The methyl group at the *ortho* position of the imine did not interfere with the enantioselectivity (Table 2, entry 3), whereas an imine derived from 1-naphthaldehyde gave a



lower enantioselectivity (Table 2, entry 4). Excellent enantioselectivity was maintained with imines bearing either bromide or methoxy substituents in the para position (Table 2, entries 5 and 6). Notably, enantioselectivity high was observed even for imines bearing soft Lewis basic 2-thienyl or 2pyridyl groups (Table 2, entries 8 and 9). Although the yield was moderate with 1h likely owing to a competitive coordination to Cu^I. In view of the synthetic utility of the product, a Mannich-type reaction was conducted with imines bearing aliphatic or alkenyl substituents and reasonable enantioselectivities were observed (Table 2, entries 10 and 11). Thioamide 2c also served as a suitable pronucleophile to afford 3ac in excellent yield and enantioselectivity (Table 2, entry 12). The reactions using thio-

amides **2d,e** derived from propionic or butyric acids were sluggish and required Li(OC₆H₄-*p*-OMe) as a stronger base, and afforded the product in high *anti*-diastereoselectivity and in moderate to good enantioselectivity (Table 2, entries 13– 16). A plausible transition state model is depicted in Scheme 2. The (*R*,*R*)-Ph-BPE/Cu(OC₆H₄-*o*-OMe) complex, which would be formed by mixing (*R*,*R*)-Ph-BPE, [Cu-(CH₃CN)₄]PF₆, and Li(OC₆H₄-*o*-OMe),^[17] serve as a soft Lewis acid and a hard Brønsted base to generate thioamide enolates, which would be in equilibrium between *E*/*Z* isomers through protonation/deprotonation. Taking severe steric constraint into account, the reaction would proceed through the transition state where the *N*,*N*-dialkyl and *C*-alkyl groups



Scheme 3. Transformation of the Mannich products. TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride.

Scheme 2. Proposed transition state.

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R³

(2S,3R)-3

Communications

		$ \begin{array}{c} $		Cu(CH ₃ CN) ₄]PF ₄ 7, <i>R</i>)-Ph-BPE (OC ₆ H ₄ - <i>o</i> -OMe); mol % of each bluene, -20 °C		$ \begin{array}{c} O \\ Ph_{-}P \\ Ph' \\ Ph' \\ R^{1} \\ 3 \\ R^{2} \end{array} $ NR ³ ₂					
Entry	Imine 1	R ¹	T	nioamide 2	x [mol %]	Produc	ct <i>T</i> [°C]	t [h]	anti/syn ^[b]	Yield [%] ^[c]	ee [%]
1	1a		2 b	S N N	3	3 ab	-20	20	-	95	97
2	la	Ме	2 b	~	1	3 ab	-20	72	-	99	95
3	16	3	2 b		3	3 bb	-20	48	-	88	95
4	1c	i i i i i i i i i i i i i i i i i i i	2 b		3	3 cb	-20	20	-	96	84
5	1 d	Br	2 b		3	3 db	-20	20	-	94	95
6	le	MeO	2 b		3	3 eb	-20	48	-	89	95
7	1 f	O YY	2 b		3	3 fb	-20	48	-	95	93
8	1g	S ví	2 b		3	3 gb	-20	48	-	90	90
9	1 h	N XY	2 b		3	3 hb	-20	48	-	54	88
10	1i	V [*] *	2 b		3	3 ib	-20	48	_	60	78
11	1j	Ph	2 b		3	3 jb	-20	48	-	66	81
12	1a		2c	N(PMB)₂	3	3 ac	-20	48	-	99	94
13 ^[d,e]	1a		2 d	S N	10	3 ad	-20	72	89/11	57	88 ^[f]
14 ^[d,e]	1a		2 d	I	10	3 ad	0	72	90/10	89	74 ^[f]
15 ^[d,e]	1a		2e	S N	10	3 ae	0	72	90/10	84	53 ^[f]
16 ^[d,e]	1d		2 d	1	10	3 dd	0	42	89/11	89	71 ^[f]

Table 2: Direct catalytic asymmetric Mannich-type reaction of N-Dpp imine 1 and thioamides 2.^[a]

[a] 1 (0.2 mmol), 2 (0.3 mmol). [b] Determined by ¹H NMR analysis. [c] Yield of isolated product. [d] Li(OC₆H₄-p-OMe) was used instead of Li(OC₆H₄-o-OMe). [e] THF was used as the solvent. [f] Enantioselectivity of the *anti* diastereomer. PMB = p-methoxybenzyl.

of the *E* enolate and the *P*,*P*-diphenyl groups of **1** occupy the vacant space of the asymmetric architecture provided by (R,R)-Ph-BPE, thereby affording (2S,3R)-**3** predominantly.

The rich chemistry of thioamides enabled functional group manipulation of the Mannich product (Scheme 3). Treatment of **3ab** with MeI in the presence of H₂O under acidic conditions gave methyl thioester **4a** in quantitative yield.^[18] Meanwhile, anhydrous conditions and the addition of HCl·NH₂OBn provided benzyloxyamidine **5ab** as a single geometric isomer. Facile conversion into amide **6ab** was achieved by TFAA in CH₂Cl₂.^[19] Desulfurization of **3ac** with Raney-Ni generated the *N*,*N*-bisPMB-protected diamine **7ac** in 75 % yield.

the resulting residue was purified by column chromatography on silica gel to give Mannich product **3ab** as a colorless solid (87.5 mg, 0.19 mmol, 95% yield). The enantioselectivity was determined by HPLC on a chiral stationary phase using a Daicel Chiralcel OD-H column (ϕ 0.46 × 25 cm); eluent: *n*-hexane/2-propanol = 4/1; flow rate: 0.5 mLmin⁻¹; detection at 254 nm; $t_{\rm R}$ = 12.0 min ((*S*) minor), 16.6 ((*R*) major).

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In summary, we have developed a direct catalytic asymmetric Mannich-type reaction of N-Dpp imines and thioamides. A soft Lewis acid/hard Brønsted base cooperative system worked efficiently to generate the active carbon nucleophile from thioamides by exploiting the soft Lewis basic nature of the sulfur atom. The reaction can be performed with as little as 1 mol% of catalyst and excellent enantioselectivity as well as high anti-diastereoselectivity was observed. Divergent transformation of thioamide functionality highlights the utility of the methodology presented here.

Experimental Section

A typical procedure for the direct catalytic asymmetric Mannich-type reaction of N-Dpp imine 1a and thioamide 2b described in Table 2, entry 1: A flame-dried 20 mL test tube equipped with a magnetic stirring bar was charged N-Dpp imine 1a (61.1 mg, 0.2 mmol) and was dried under vacuum for 10 min. The test tube was back-filled with argon and dry toluene (2.0 mL) was added in an argon atmosphere. Then a premixed solution of $[Cu(CH_3CN)_4]PF_6$ and (R,R)-Ph-BPE in THF (60 µL, 0.006 mmol, 0.1M) was added at room temperature. After cooling the reaction mixture to -20°C, $Li(OC_6H_4-o-OMe)$ (30 µL, 0.006 mmol, 0.2 M/THF) and thioamide 2b (47.7 µL, 0.3 mmol) were subsequently added. After stirring at the same temperature for 20 h, 1N HCl (1.0 mL) was added and the resulting biphasic mixture was extracted with AcOEt three times. The combined organic layers were washed with saturated aqueous NaHCO3 and brine, then dried over Na₂SO₄. The volatiles were removed under reduced pressure and



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