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Direct Catalytic Asymmetric Intramolecular Conjugate Addition of Thioamide to α,β-Unsaturated Esters

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Catalytic asymmetric conjugate addition of carbon pronucleophiles to electron-deficient olefin is one of the most reliable and well-developed enantioselective C–C bond-forming reactions.[1] In situ generation of carbon nucleophiles offers an efficient entry to this process, allowing for the construction of stereogenic carbon with perfect atom economy.[2] Historically, active methylene compounds are widely used as pronucleophiles due to their high enolization aptitude,[1] followed by the successful application of aldehydes and ketones as pronucleophiles by metal-based catalysis[3] and enamine catalysis.[4] Catalytic generation of active enolates from carbonyl-type pronucleophiles in the carboxylic acid oxidation state is a formidable task and thus their use in this catalytic process is largely limited.[5] Our recent investigations of soft Lewis acid/hard Brønsted base cooperative catalysis[6] revealed that thioamides are viable pronucleophiles, because they are in the carboxylic acid oxidation state, allowing for further manipulation of the product; specific soft–soft interaction of thioamides and soft Lewis acids allows for facile deprotonation with the aid of mild base to generate thioamide enolates in a catalytic manner.[7–9] As part of our continuing effort to pursue the utility of thioamides as pronucleophiles, herein we report the direct catalytic asymmetric intramolecular conjugate addition of thioamide to α,β-unsaturated ester, providing enantiomerically enriched five- and six-membered carbocycles bearing ester and thioamide functions in an *anti* fashion.

We have previously reported that $[Cu(CH_3CN)_4]^+X^-$/chiral bisphosphine ligand/LiOAr served as an effective soft Lewis acid/hard Brønsted base cooperative catalyst for activating soft Lewis basic pronucleophiles.[10] For the 1,2-type addition of in situ generated thioamide enolates, such as aldol and Mannich-type reactions, a catalyst composed of $[Cu(CH_3CN)_4]PF_6$/Ph-BPE/LiOAr (Ph-BPE = 1,2-bis(2,5-diphenylphospholano)ethane) exhibits high performance in terms of catalytic efficiency and stereoselectivity. In this context, we attempted to apply the cooperative catalyst to a catalytic asymmetric intermolecular 1,4-type conjugate addition of thioamides to electron-deficient olefins. Despite several trials, however, the reaction was unsuccessful,[11] presumably due to a different transition-state structure from 1,2-type addition, which would be unfavorable in the asymmetric environment provided by the $[Cu(CH_3CN)_4]PF_6$/Ph-BPE/LiOAr catalyst. To compensate for the entropic factor for an intermolecular reaction, we turned our attention to intramolecular conjugate addition of the thioamide functionality to an α,β-unsaturated ester.

An initial trial was conducted with substrate **1a**; *N*,*N*-dibenzylthiopropionamide and ethyl acrylate were tethered by benzene, which was then exposed to 10 mol% of the $[Cu(CH_3CN)_4]PF_6$/(*S*,*S*)-Ph-BPE/Li(OC_6H_4-*p*-OMe) catalyst in THF at 0°C; and the desired product *anti*-**2a** was obtained in >99% yield and >20:1 *anti* selectivity, albeit with moderate enantioselectivity (60% *ee*; Table 1, entry 1).[12] Nonpolar (toluene) and aprotic polar (DMF) solvents were tested and the reaction in DMF afforded the highest enantioselectivity (entries 1–3). The reaction proceeded smoothly even at −40°C and enantioselectivity increased to 79% *ee* (entry 4). The ligand (*S*)-Xyl-P-Phos (Xyl-P-Phos = 2,2′,6,6′-tetramethoxy-4,4′-bis(di(3,5-xylyl)phosphino)-3,3′-bipyridine) outperformed (*S*,*S*)-Ph-BPE exhibiting higher enantioselectivity with a marginal decrease in chemical yield (entry 5), which was recovered by the use of $[Cu(CH_3CN)_4]SbF_6$ as a cationic soft Lewis acid (entry 6). Intriguingly, the intramolecular conjugate addition of **1a** was catalyzed solely by 10 mol% of Li(OC_6H_4-*p*-OMe) in DMF with diastereoswitching, affording the *syn* product **2a** in >99% yield and 1:9.1 *syn* selectivity (entry 7), whereas no reaction proceeded with 10 mol% of Li(OC_6H_4-*p*-OMe) in THF, even at room temperature (entry 8). This observation suggested that DMF significantly enhanced the Brønsted basicity of Li(OC_6H_4-*p*-OMe) to induce enolization of the thioamide and that the Li cation of Li thioamide enolate would be in near proximity to the ester at the transition state to give *syn*-**2a** preferentially. With the Cu–bisphosphine complex, the intermediate is likely a Cu thioamide enolate with a large bisphosphine ligand and conjugate addition in an *anti*-fashion would be favorable.

With a suitable catalyst in hand, we next examined the substrate scope of the intramolecular conjugate addition

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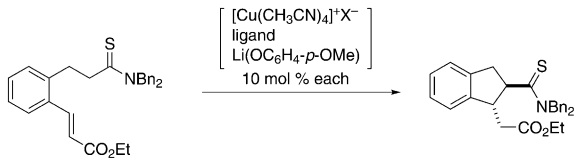
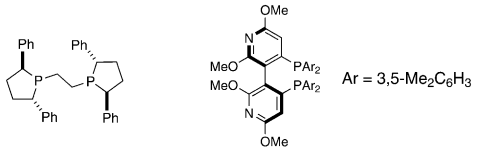
Table 1. Initial screening.

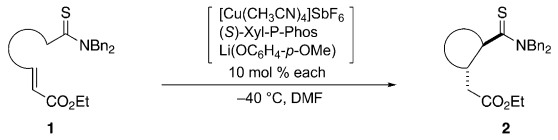


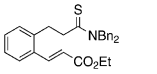
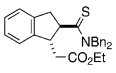
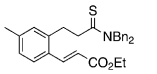
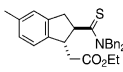
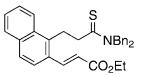
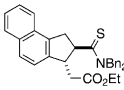
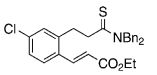
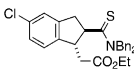
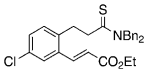
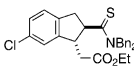
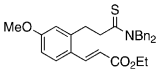
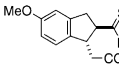
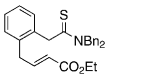
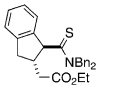
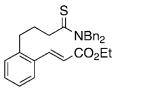
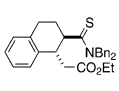
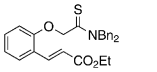
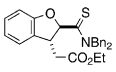
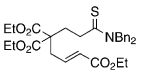
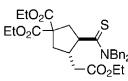
	X^-	Ligand	Solvent	T [°C]	t [h]	Yield[a] [%]	*anti*/*syn*[a]	*ee*[b] [%]
1	PF_6^-	(*S*,*S*)-Ph-BPE	THF	0	16	>99	>20:1	60
2	PF_6^-	(*S*,*S*)-Ph-BPE	toluene	0	16	>99	>20:1	61
3	PF_6^-	(*S*,*S*)-Ph-BPE	DMF	0	16	>99	>20:1	69
4	PF_6^-	(*S*,*S*)-Ph-BPE	DMF	−40	16	91	>20:1	79
5	PF_6^-	(*S*)-Xyl-P-Phos	DMF	−40	20	72	20:1	86
6	SbF_6^-	(*S*)-Xyl-P-Phos	DMF	−40	20	90	>20:1	86
7[c]	–	–	DMF	−40	8	>99	1:9.1	–
8[c]	–	–	THF	RT	20	0	–	–



[a] Determined from ^{1}H NMR spectroscopy of the crude mixture. [b] Enantiomeric excess of *anti* isomer. [c] The reaction without [Cu(CH_3CN)$_4$]$^+$X$^-$ and chiral phosphine ligand.

Table 2. Direct catalytic asymmetric intramolecular conjugate addition of thioamide to α,β-unsaturated ester.

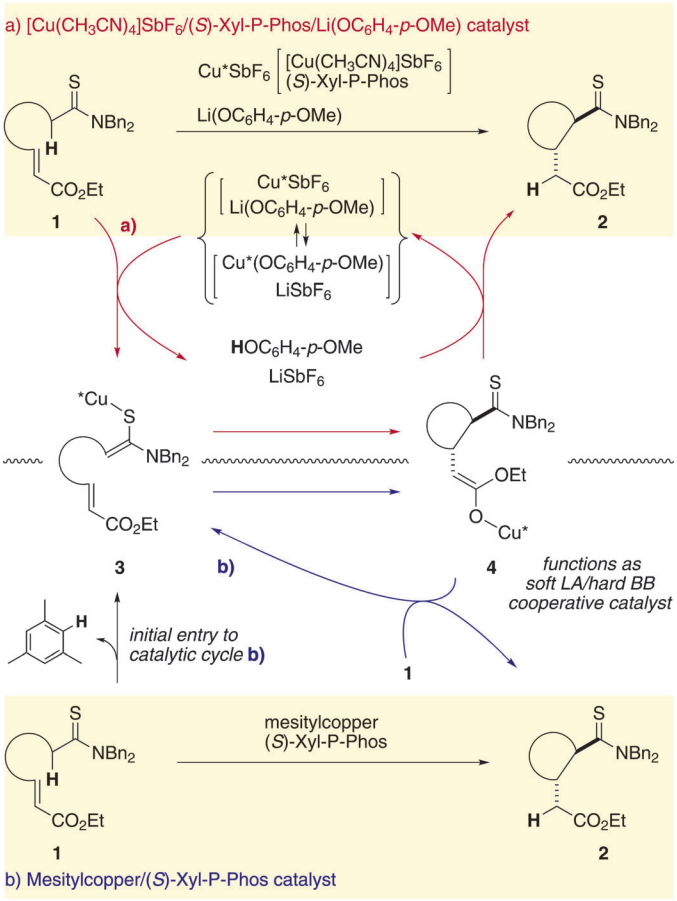


	Substrate		Product		t [h]	Yield[a] [%]	*anti*/*syn*[b]	*ee*[c] [%]
1		**1a**		**2a**	20	90	20:1	86
2		**1b**		**2b**	96	50	20:1	83
3		**1c**		**2c**	72	87	4.4:1	87
4		**1d**		**2d**	20	66	15:1	84
5		**1e**		**2e**	72	86	7.7:1	78
6		**1f**		**2f**	20	4	10:1	81
7		**1g**		**2g**	20	64	2.6:1	64
8		**1h**		**2h**	20	28	20:1	96
9		**1i**		**2i**	20	90	4.4:1	28
10		**1j**		**2j**	96	99	3.1:1	65

[a] Isolated yield. [b] Determined from ^{1}H NMR spectroscopy of crude mixture. [c] Enantiomeric excess of *anti* isomer.

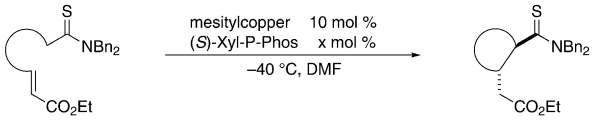
(Table 2). Steric and electronic factors of a benzene-type tether, as well as the tethering pattern, impacted the reactivity and stereoselectivity (entries 1–9). Substrates bearing tolyl or naphthyl tether **1b** and **1c** afforded the corresponding product with comparable enantioselectivity as in the reaction of **1a**, whereas **1b** exhibited low reactivity, and only moderate *anti* selectivity was observed with **1c** (entries 2 and 3). The position of the chloro substituent on the benzene tether led to remarkable difference in the diastereoselectivity (entries 4 and 5). Introduction of an electron-donating methoxy substituent considerably retarded the reaction (entry 6). The reaction of substrates with a different tethering pattern to the benzene ring, **1g** and **1h**, exhibited lower reactivity than **1a**, albeit with high *anti*- and enantioselectivity of **2h** (entries 7 and 8). The reaction with a substrate bearing oxa-tether **1i** for the construction of the functionalized benzofuran derivative proceeded smoothly, but the stereoselectivity was significantly decreased (entry 9). Alkyl-tethered substrate **1j** was applicable and the desired product **2j** was obtained in high yield with moderate *anti*- and enantioselectivity (entry 10).

In the catalytic system of [Cu(CH_3CN)$_4$]SbF_6/(*S*)-Xyl-P-Phos/Li(OC_6H_4-*p*-OMe), {[Cu/(*S*)-Xyl-P-Phos]SbF_6 + Li(OC_6H_4-*p*-OMe)} and {Cu(OC_6H_4-*p*-OMe)/(*S*)-Xyl-P-Phos + $LiSbF_6$} are likely to be in equilibrium based on previous studies.[10c,13] Both Li(OC_6H_4-*p*-OMe) and Cu(OC_6H_4-*p*-OMe)/(*S*)-Xyl-P-Phos would be operative as an actual Brønsted base for the deprotonation of thioamide to generate Cu thioamide enolate **3** and protonation of the intermediate ester enolate **4** (Scheme 1a). We assumed that intermediate **4** functions as a soft Lewis acid/hard Brønsted base cooperative catalyst to directly generate thioamide enolate **3** upon proton exchange with substrate **1** (Scheme 1b). With the mesitylcopper/(*S*)-Xyl-P-Phos catalytic system, initial entry to Cu thioamide enolate **3** is achieved with the liberation of mesitylene, and the subsequent catalytic cycle would be driven by **4**.[14] Based on this assumption, the mesitylcopper/(*S*)-Xyl-P-Phos catalyst was evaluated with several substrates (Table 3). For substrate **1a**, a catalyst prepared from mesitylcopper (10 mol%) and (*S*)-Xyl-P-Phos (7.5 mol%) promoted the conjugate addition with comparable yield and stereoselectivity, confirming that Cu ester enolate **4** functioned as a soft Lewis acid/hard Brønsted base cooperative catalyst (entry 1).[15] Higher catalytic performance over the [Cu(CH_3CN)$_4$]SbF_6/(*S*)-Xyl-P-Phos/Li(OC_6H_4-*p*-OMe) catalytic system was observed with less reactive substrates, likely due to direct proton transfer between intermediate **4** and substrate **1** (entries 2–6). The



Scheme 1. Proposed catalytic cycle for: a) $[Cu(CH_3CN)_4]SbF_6$/(*S*)-Xyl-P-Phos/$Li(OC_6H_4$-*p*-OMe) catalyst, and b) mesitylcopper/(*S*)-Xyl-P-Phos catalyst.

Table 3. Direct catalytic asymmetric intramolecular conjugate addition promoted by mesitylcopper/(*S*)-Xyl-P-Phos catalyst.

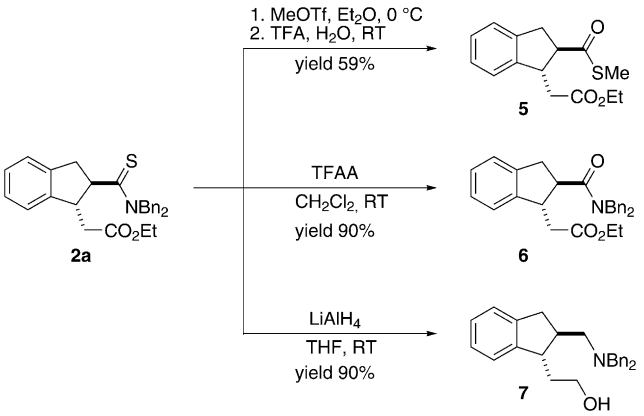


	x	Substrate	Product	*t*[d] [h]	Yield[a,d] [%]	*anti*/*syn*[b,d]	*ee*[c,d] [%]
1	7.5	**1a**	**2a**	20 (20)	99 (90)	14:1 (20:1)	83 (86)
2	7.5	**1b**	**2b**	20 (96)	80 (50)	13:1 (20:1)	85 (83)
3	7.5	**1d**	**2d**	20 (20)	99 (66)	4.6:1 (15:1)	81 (84)
4	7.5	**1e**	**2e**	20 (72)	99 (86)	8:1 (7.7:1)	78 (78)
5	10	**1f**	**2f**	92 (20)	92 (4)	14:1 (10:1)	86 (81)
6	10	**1h**	**2h**	20 (20)	87 (28)	20:1 (20:1)	93 (96)

[a] Isolated yield. [b] Determined from ^{1}H NMR spectroscopy of crude mixture. [c] Enantiomeric excess of *anti* isomer. [d] Result in parentheses is obtained from $[Cu(CH_3CN)_4]SbF_6$/(*S*)-Xyl-P-Phos/$Li(OC_6H_4$-*p*-OMe) catalyst (Table 2).

most notable example was the 92% yield observed in the reaction of substrate **1f** bearing a methoxy substituent, affording only 4% yield of **2f** with the $[Cu(CH_3CN)_4]SbF_6$/(*S*)-Xyl-P-Phos/$Li(OC_6H_4$-*p*-OMe) catalyst (entry 5). For **1b** and **1d**, the decrease in diastereoselectivity was detected and any attempts to enhance the diastereoselectivity resulted in failure (entries 2 and 3).

Different manipulations of the thioamide and ester functionality of the product are advantageous from a synthetic point of view. The thioamide functionality of **2a** was chemoselectively converted to thioester **5** or amide **6** by treatment with MeOTf followed by TFA/H_2O[16] or TFAA,[17] respectively (Scheme 2). Reduction with $LiAlH_4$ provided N-protected amino alcohol **7** in 90% yield.



Scheme 2. Transformation of the product.

In summary, we have developed a direct catalytic asymmetric intramolecular conjugate addition of thioamide to α,β-unsaturated esters. Catalytic generation of a thioamide enolate with a soft Lewis acid/hard Brønsted base cooperative catalyst was key to the efficient catalysis. A mesitylcopper/(*S*)-Xyl-P-Phos catalyst exhibited high catalytic performance, in which the reaction intermediate functioned as catalyst. Further investigation of the application of the present catalytic system to C–C bond-forming reactions using other soft Lewis basic pronucleophiles is ongoing.

Acknowledgements

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Keywords: atom economy · conjugate addition · cooperative catalysis · proton transfer · thioamides

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