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Direct Catalytic Asymmetric Conjugate Addition of Terminal Alkynes to α,β-Unsaturated Thioamides

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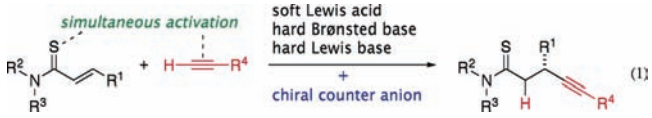
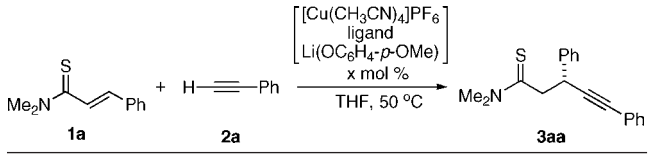
Abstract: Direct catalytic asymmetric conjugate addition of terminal alkynes to α,β-unsaturated thioamides under proton transfer conditions is described. Soft Lewis acid/hard Brønsted base cooperative catalysis is crucial for simultaneous activation of terminal alkynes and thioamides, affording the β-alkynylthioamides in a highly enantioselective manner. Control experiments suggested that the intermediate copper thioamide enolate can work as Brønsted base to drive the catalytic cycle via proton transfer. The divergent transformation of the thioamide functionality highlights the synthetic utility of the alkynylation products.

Catalytic enantioselective conjugate addition of active carbon nucleophiles generated in situ via proton transfer is an attractive protocol for C−C bond-forming reactions[1] in terms of atom and step economy.[2] Direct use of readily available terminal alkynes as pronucleophiles in this class of reaction offers an efficient approach affording chiral building blocks that are amenable to diverse transformations. Despite the prospects for synthetic utility, catalytic generation of metal alkynylides coupled with a subsequent enantioselective conjugate addition has been limited because of the low nucleophilicity of transition-metal alkynylides.[3,4] Pioneering work on copper-catalyzed enantioselective conjugate addition of terminal alkynes employing highly reactive olefins and compensating for the inherent low nucleophilicity of Cu alkynylides was reported by Carreira.[5] Subsequently, Hayashi[6] and Fillion[7] showed that rhodium catalysis is effective for enantioselective conjugate addition to enones and enals. However, conjugate addition to α,β-unsaturated carboxylate derivatives remains uncovered because of their attenuated electrophilicity. Herein, we describe the direct asymmetric conjugate addition of alkynes to α,β-unsaturated thioamides possessing the same oxidation state as carboxylic acid derivatives, catalyzed by soft Lewis acid/hard Brønsted base/hard Lewis base cooperative catalysis[8] reinforced by a chiral counteranion (eq 1).[9]

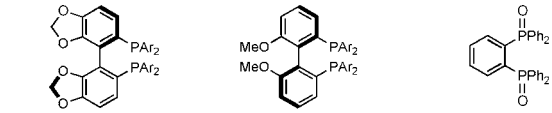


We envisioned that simultaneous activation of both the terminal alkyne and the electrophile would hold promise for overcoming any low reactivity to engage the enantioselective coupling under proton transfer conditions. Soft metal alkynylides can be catalytically generated using a soft Lewis acid/hard Brønsted base cooperative catalytic system.[10] In this context, we focused on the employment of soft Lewis basic α,β-unsaturated thioamides as electrophiles that would have enhanced electrophilicity upon activation in proximity to a soft metal alkynylide through a soft−soft interaction.[11]

Table 1. Initial Screening[a]



entry	ligand	4	x	time (h)	yield (%)[b]	ee (%)
1	(*S*)-tol-BINAP	(*S*)-**4a**	5	12	30	0
2	(*R*)-DTBM-Segphos	(*R*)-**4b**	5	12	88	89
3	(*R*)-3,5-^{t}Bu-4-MeO-MeOBIPHEP	(*R*)-**4c**	5	12	88	93
4	(*R*)-3,5-^{i}Pr-4-Me$_2$N-MeOBIPHEP	(*R*)-**4d**	5	24	81	94
5	(*R*)-3,5-^{i}Pr-4-Me$_2$N-MeOBIPHEP	(*R*)-**4d**	2	24	43	94
6[c]	(*R*)-3,5-^{i}Pr-4-Me$_2$N-MeOBIPHEP	(*R*)-**4d**	2	24	86	94



[a] **1a**/**2a** = 0.2 mmol/0.4 mmol. [b] Determined using ^{1}H NMR analysis with 2-methoxynaphthalene as an internal standard. [c] Using 4 mol % **5**.

An initial attempt to carry out a reaction using α,β-unsaturated thioamide **1a** and phenylacetylene (**2a**), conducted in THF at 50 °C with a 5 mol % loading of the soft Lewis acid/hard Brønsted base catalyst prepared from $[Cu(CH_3CN)_4]PF_6$, (*S*)-tol-BINAP, and $Li(OC_6H_4$-*p*-OMe), delivered the desired adduct **3aa**, albeit in a low yield with no enantioselection (Table 1, entry 1). After evaluation of several chiral bisphosphine ligands (entries 2−4), MeO-BIPHEP (*R*)-**4d** was identified as a ligand producing a high yield and enantioselectivity (entry 4). The combined use of bisphosphine oxide **5** as a hard Lewis base that coordinates to lithium through a hard−hard interaction enhances the Brønsted basicity of $Li(OC_6H_4$-*p*-OMe), allowing for the completion of the reaction using 2 mol % catalyst without a detrimental effect on the enantioselectivity (entry 6).[8d]

Table 2 outlines the scope of the reaction under the optimized reaction conditions. The use of *n*-hexane instead of THF increased both the yield and the enantioselectivity with as little as 1 mol % catalyst, presumably because the formation of an intimate Cu alkynylide/thioamide association was enhanced in the nonpolar reaction medium (entry 1). The direct asymmetric addition of **2a** to a range of β-aryl-α,β-unsaturated thioamides (**1b**−**f**) proceeded smoothly with 1 mol % catalyst to afford the corresponding products **3ba**−**fa** with high enantioselectivity (entries 3−7). The catalyst loading could be reduced to 0.25 mol % to afford **3fa** while maintaining a high enantioselectivity (entry 8). A catalyst loading of 5 mol % was required in order to ensure a satisfactory yield of

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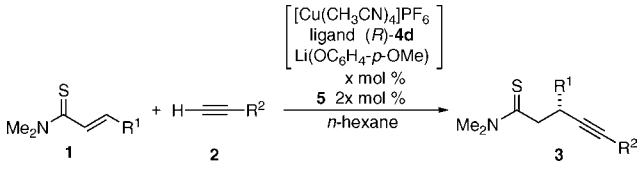
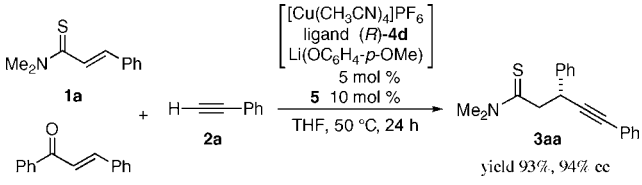
Table 2. Substrate Scope[a]



entry	R^1	1	R^2	2	x	temp (°C)	product	yield (%)[b]	ee (%)
1	Ph	**1a**	Ph	**2a**	1	50	**3aa**	98	98
2	Ph	**1a**	Ph	**2a**	0.5	50	**3aa**	72	98
3	*o*-Me-C_6H_4	**1b**	Ph	**2a**	1	50	**3ba**	97	98
4	*p*-Me-C_6H_4	**1c**	Ph	**2a**	1	50	**3ca**	74	97
5[c]	*m*-OMe-C_6H_4	**1d**	Ph	**2a**	1	80	**3da**	77	95
6[c]	*p*-OMe-C_6H_4	**1e**	Ph	**2a**	1	80	**3ea**	81	94
7	*p*-Br-C_6H_4	**1f**	Ph	**2a**	1	50	**3fa**	98	97
8	*p*-Br-C_6H_4	**1f**	Ph	**2a**	0.25	50	**3fa**	83	97
9	Me	**1g**	Ph	**2a**	5	50	**3ga**	97	80
10	^{i}Pr	**1h**	Ph	**2a**	5	50	**3ha**	63	92
11	Ph	**1a**	1-cyclohexenyl	**2b**	1	50	**3ab**	58	96

[a] **1**/**2** = 0.2 mmol/0.4 mmol, 24 h. [b] Isolated yield. [c] *n*-Heptane was used as the solvent instead of *n*-hexane.

Scheme 1. Chemoselective Activation of Thioamide



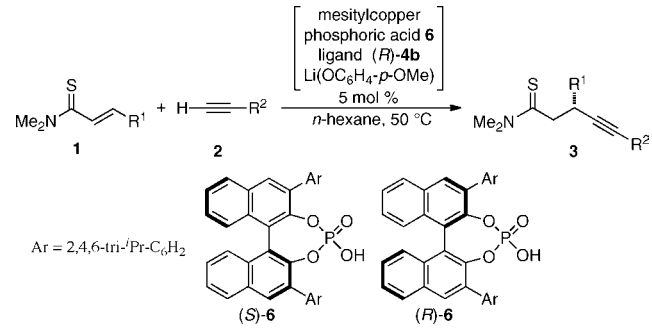
β-alkyl-α,β-unsaturated thioamides **1g** and **1h** (entries 9 and 10). The conjugated enyne **2b** was also applicable to this catalysis, affording the desired product **3ab** in high enantioselectivity, albeit with a moderate yield (entry 11).

In a competition experiment with 1 equiv of chalcone, which has a higher electrophilicity than α,β-unsaturated thioamide **1a**, the conjugate addition proceeded with **1a** exclusively while the chalcone remained unchanged, highlighting the highly chemoselective nature of the present catalytic system, which exploits the soft−soft interaction (Scheme 1).

Saturated aliphatic terminal alkynes afforded moderate enantioselectivity, even after ligand screening[12] (as exemplified in Table 3, entry 1), prompting us to implement an additional stereocontrolling element in the catalyst. We endowed the copper counteranion with chirality using mesitylcopper[13] and chiral phosphoric acid[14,15] (*S*)-**6** as the copper source, generating a catalyst armed with a chiral bulky phosphate anion in proximity to the Cu cation. Chiral phosphate was also expected to act as a hard Lewis base (similar to **5**) to enhance the reaction rate. Indeed, the developed soft Lewis acid/hard Brønsted base/chiral counteranion catalyst improved the enantioselectivity to 89% ee (entry 2). Intriguingly, the use of antipode (*R*)-**6** terminated the catalysis (entry 3), suggesting that the phosphate anion is closely involved at the transition state.[16] High enantioselectivity was observed in the series of aliphatic alkynes **2d**−**g** (entries 4−7). The yield and enantioselectivity remained moderate in the reaction with β-alkyl thioamide **1g** (entry 8).

A series of control experiments was performed to probe the reaction mechanism. Neither a soft Lewis acid copper nor a Brønsted base lithium aryloxide independently promoted the desired reaction, verifying the crucial cooperative nature of the soft Lewis acid and hard Brønsted base (Scheme 2a). In contrast to our previous observation that Li-free Cu(OC$_6$H$_4$-*p*-OMe) prepared from mesitylcopper[13] and *p*-methoxyphenol was not an efficient catalyst in the addition of allylic cyanides to ketoimines and ketones,[8d] the present reaction proceeded smoothly with Cu(OC$_6$H$_4$-*p*-OMe) to afford a reaction outcome comparable to that obtained using Li(OC$_6$H$_4$-*p*-OMe) (Scheme 2b vs Table 1, entry 4). Furthermore, using both copper phenylacetylide and (*R*)-**4d** at 5 mol % exhibited efficient catalytic performance, providing **3aa** in 92% yield with 95% ee, which suggests that the Cu thioamide enolate formed by the addition of the alkyne directly deprotonates the terminal proton of the alkyne as a Brønsted base, liberating the product with concomitant regeneration of the copper alkynylide that engaged in the enantioselective addition to **1a** (Scheme 2c). *These control experiments indicate that the use of a soft Lewis basic nucleophile/electrophile substrate set allows for an exceedingly efficient proton*

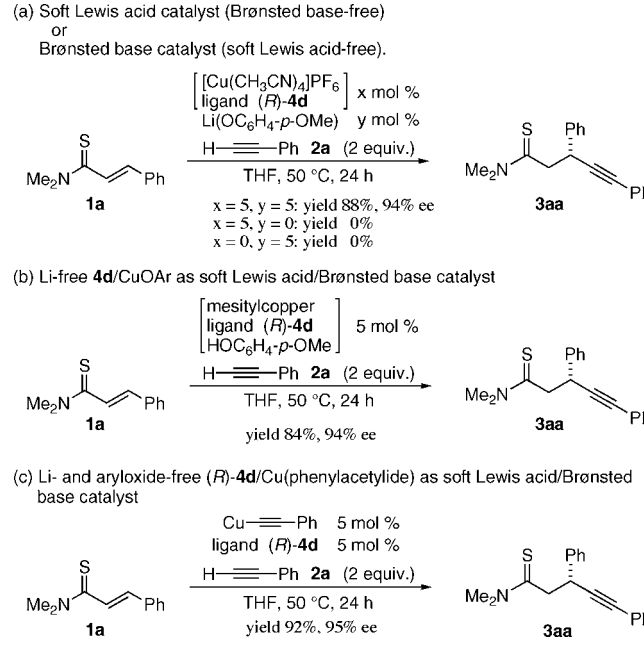
Table 3. Chiral Counteranion Catalysis[a]



entry	R^1	1	R^2	2	6	product	yield (%)[b]	ee (%)
1[c]	Ph	**1a**	^{n}C$_5$H$_{11}$	**2c**	−	**3ac**	90	82
2	Ph	**1a**	^{n}C$_5$H$_{11}$	**2c**	*S*	**3ac**	90	89
3	Ph	**1a**	^{n}C5H$_{11}$	**2c**	*R*	**3ac**	0	ND
4	Ph	**1a**	^{c}C$_3$H$_5$	**2d**	*S*	**3ad**	88	83
5	Ph	**1a**	^{c}C$_6$H$_{11}$	**2e**	*S*	**3ae**	63	91
6	Ph	**1a**	$(CH_3)_2CHCH_2$	**2f**	*S*	**3af**	63	87
7	Ph	**1a**	$PhCH_2CH_2$	**2g**	*S*	**3ag**	72	90
8	Me	**1g**	^{n}C$_5$H$_{11}$	**2c**	*S*	**3gc**	43	69

[a] **1**/**2** = 0.2 mmol/0.4 mmol, 24 h. [b] Isolated yield. [c] The catalytic system was identical to those described in Table 2 ([Cu(CH$_3$CN)$_4$]PF$_6$/(*R*)-**4b**/Li(OC$_6$H$_4$-*p*-OMe), 5 mol %; phosphine oxide **5**, 10 mol %).

Scheme 2. Control Experiments



transfer in which the reaction intermediate pendant on the soft Lewis acid works as a Brønsted base for the next catalytic cycle (Figure 1).

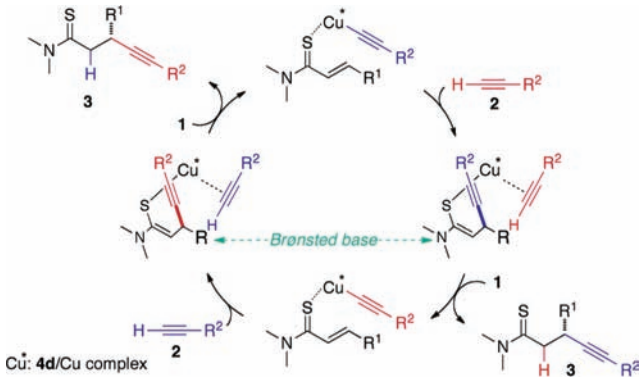
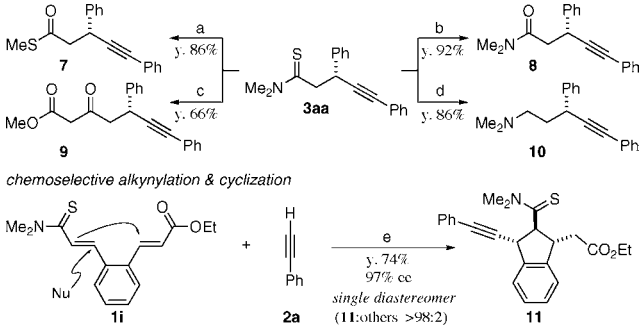


Figure 1. Plausible catalytic cycle with (*R*)-**4d**/Cu alkynylide catalyst.

The divergent functional group transformation of the thioamide highlights the synthetic utility of the products (Scheme 3). Facile conversion into other carbonyl derivatives was achieved by the activation of the thioamide functionality with MeI/H_2O or TFAA, affording the corresponding thioester **7** and amide **8**, respectively.[17,18] The Eschenmoser reaction and a following acidic hydrolysis of the resulting enaminoester allowed the installation of the β-ketoester unit.[19] Treatment with MeI and subsequent reduction with $NaBH_4$ furnished amine **10**.[20] Subjection of **1i** bearing both an ester and a thioamide-conjugated olefin to the alkynylation conditions afforded **11** in a highly stereoselective manner via chemoselective alkynylation to the unsaturated thioamide and subsequent intramolecular conjugate addition of the thioamide enolate to the unsaturated ester.

Scheme 3. Transformation of the Product[a]



[a] Reaction conditions: (a) MeI, TFA, THF/H_2O, rt, 12 h, y. 86%. (b) TFAA, CH_2Cl_2, H_2O, rt, 3 h, y. 92%. (c) MeOC(O)CH_2Br, Ph_3P, 2,6-lutidine, NaI, CH_3CN, 50 °C, 18 h, y. 66%. (d) MeI, reflux, 1 h, then $NaBH_4$, MeOH, 0 °C to rt, 30 min, y. 86%. (e) **2a** (2 equiv), copper phenylacetylide/(*R*)-**4d** (5 mol %), *n*-hexane, 50 °C, 24 h, y. 74%, **11**/other diastereomers > 98:2, 97% ee.

In summary, we have developed a direct catalytic asymmetric conjugate addition of terminal alkynes to α,β-unsaturated thioamides under proton transfer conditions, allowing efficient access to optically active β-alkynyl carboxylate derivatives. Simultaneous activation of soft Lewis basic thioamides and terminal alkynes via a soft−soft interaction enables high chemoselectivity and efficient catalytic turnover. The combined use of chiral counteranions improved the enantioselectivity in the reaction with alkyl acetylenes. The transient thioamide enolate was shown to function as a Brønsted base that drives the efficient proton transfer. The divergent transformation of the thioamide functionality contributes to the synthetic application of the present catalysis. Further effort will be dedicated to the implementation of other soft Lewis basic substrate sets.

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Supporting Information Available: Experimental procedures, characterization of new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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