Homogeneous Catalysis

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Asymmetric Synthesis of Isothiazoles through Cu Catalysis: Direct Catalytic Asymmetric Conjugate Addition of Allyl Cyanide to α,β-Unsaturated Thioamides**

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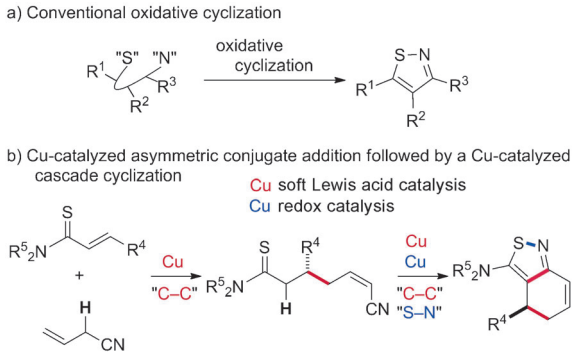
Heterocycles are frequently used in pharmaceutical sciences owing to their wide range of biological activities. A number of isothiazole derivatives manifest specific biological activities,[1] e.g. antiproliferative,[2] antiviral,[3] and antipsychotic,[4] and are applicable as bioisosteric replacements of isoxazoles to enhance lipophilicity. The common synthetic protocol for isothiazoles is a halogen-mediated oxidative coupling of a sulfur atom and a nitrogen atom that are tethered by a three-carbon unit (Scheme 1 a).[1] Herein, we document a distinct approach through a cascade C–C and S–N bond formation promoted by Cu catalysis to furnish the isothiazole nucleus (Scheme 1 b). The requisite substrates, containing thioamide and nitrile functionalities, were synthesized by a Cu-catalyzed asymmetric conjugate addition of allyl cyanide to α,β-unsaturated thioamides under proton-transfer conditions.



Scheme 1. Formation of isothiazoles.

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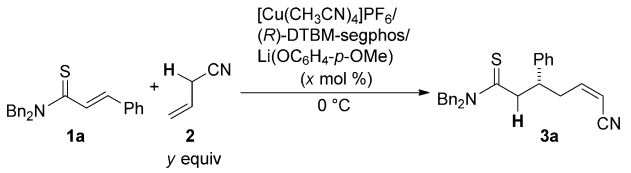
The process not only represents an unprecedented route to the isothiazole nucleus, but also demonstrates the power of Cu catalysis; all three bond-forming events were promoted by a Cu catalyst which is a soft Lewis acid and exhibits redox characteristics.

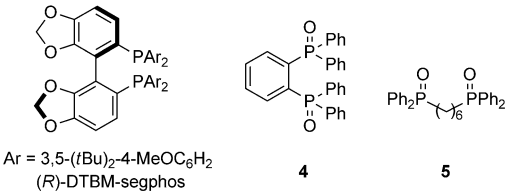
We have been engaged in a program aimed at the development of soft Lewis acid/hard Brønsted base cooperative catalysis, specifically for the activation of soft Lewis basic substrates.[5,6] Recently, we reported the simultaneous activation of soft Lewis basic pronucleophiles and electrophiles, represented by the catalytic asymmetric conjugate addition of terminal alkynes to α,β-unsaturated thioamides **1** under proton-transfer conditions.[7] Although α,β-unsaturated thioamides **1** have received little attention in asymmetric catalysis,[8] their specific activation by a soft Lewis acid and divergent transformation of the thioamide functionality highlight their potential utility. In this context, we envisaged the catalytic asymmetric conjugate addition of other soft Lewis basic pronucleophiles to α,β-unsaturated thioamides **1**. We selected allyl cyanide (**2**) as the soft Lewis basic pronucleophile.[6a,b,d,9,10] Initial studies based on a soft Lewis acid/hard Brønsted base cooperative catalyst[6,7] comprised of a cationic Cu^{I} salt/chiral bisphosphine ligand/Li aryloxide revealed that a $[Cu(CH_3CN)_4]PF_6$/(*R*)-DTBM-segphos/Li(OC_6H_4-*p*-OMe) catalytic system promoted the asymmetric conjugate addition of **2** to **1** (Table 1). Although the catalytic efficiency was not satisfactory with 5 mol% of the catalyst, **2** underwent exclusive γ addition to **1a** to afford the *Z*-configured α,β-unsaturated nitrile **3a** in 83% *ee* (Table 1, entry 1). The use of a catalytic amount of phosphine oxide as a hard Lewis base was previously found to enhance the Brønsted basicity of Li(OC_6H_4-*p*-OMe) through a hard–hard interaction with the Li cation,[11] thus facilitating the deprotonation of the relatively weakly acidic pronucleophile **2** to trigger the reaction.[6d,12] The soft Lewis acid/hard Brønsted base/hard Lewis base ternary catalytic system was successful in the present reaction, as evidenced by the significant improvement in the yield (Table 1, entries 2–6). Bisphosphine oxides **4** and **5** exhibited higher conversion, albeit with the concomitant formation of unidentified by-products. The reaction with $Ph_3P{=}O$ in EtOAc was determined to be optimal, with minimal formation of by-products (Table 1, entry 6).[13] Decreasing either the catalyst loading or the amount of **2** led to a marginally lower conversion (Table 1, entries 7 and 8). When either Cu^{I} or Li aryloxide was removed from the catalytic system, this impaired catalyst failed to promote the reaction (Table 1, entries 9 and 10), thus confirming the cooperative nature of a soft Lewis acid and hard Brønsted

Table 1: Initial screening.[a]



Entry	*x*	*y*	Phosphine oxide [mol%]	Solvent	*t* [h]	Yield[b] [%]	*ee* [%]
1	5	5	–	toluene	24	9	83
2	5	5	**4** (5)	toluene	24	76	95
3	5	5	**5** (5)	toluene	24	81	95
4	5	5	$Ph_3P{=}O$ (5)	toluene	24	74	95
5	5	5	**5** (5)	AcOEt	24	77	97
6	5	5	$Ph_3P{=}O$ (5)	AcOEt	24	84	97
7	5	2	$Ph_3P{=}O$ (5)	AcOEt	22	77	96
8	2	5	$Ph_3P{=}O$ (5)	AcOEt	22	54	97
9[c]	5	5	$Ph_3P{=}O$ (5)	AcOEt	24	0	–
10[d]	5	5	$Ph_3P{=}O$ (5)	AcOEt	24	0	–

[a] Used 0.2 mmol of **1a**. [b] Determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard. [c] The reaction was performed without $[Cu(CH_3CN)_4]PF_6$/(*R*)-DTBM-segphos. [d] The reaction was performed without $Li(OC_6H_4$-*p*-OMe). DTBM = 3,5-di-*tert*-butyl-4-methoxy.



base. The exclusive *Z*-olefin formation is intriguing and can be ascribed to the simultaneous activation of **1a** and **2** (Figure 1). The initially formed α-C-copper nucleophile proceeds to the eight-membered transition state upon coordination of **1a**; in this transition state the terminal olefin is located *s-cis* to the nitrile group and overlaps with the β position of **1a** from the *Re* face. The reaction through the γ-C-copper nucleophile by 1,3-transposition[14] would be unlikely because of the anticipated formation of the *E*,*Z* mixture of the γ-C-copper nucleophile. The intermediary copper thioamide enolate **6** functioned as a Brønsted base to generate the active nucleophile, as revealed by the control experiments outlined in Scheme 2. A mesitylcopper[15] catalyst initiated the reaction by irreversible deprotonation of **2**, followed by enantioselective addition to **1a**, and the thus formed **6** deprotonated **2** to drive the subsequent catalytic

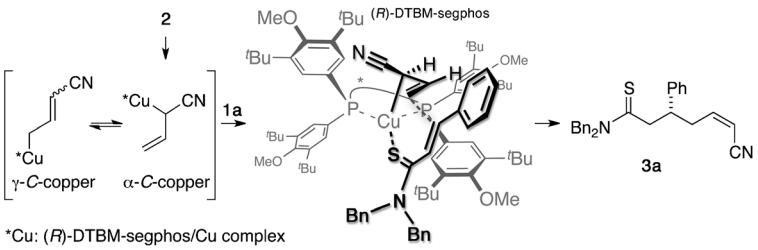
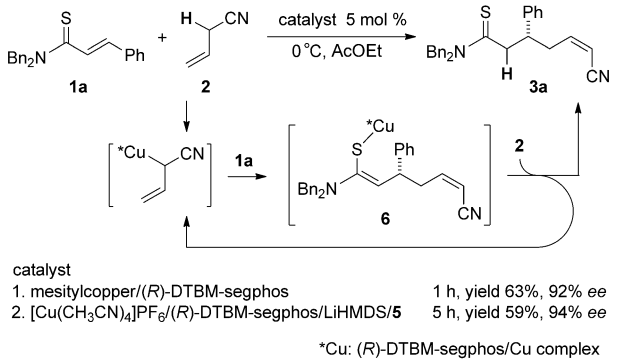


Figure 1. Plausible transition state.

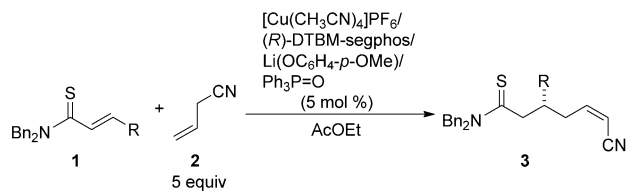


Scheme 2. Cu-thioamide enolate as a Brønsted base.

cycle, thereby demonstrating efficient proton-transfer catalysis. The more convenient $[Cu(CH_3CN)_4]PF_6$/LiHMDS system provided a similar reaction outcome. The present catalyst system failed to promote the reaction of the corresponding *N*,*N*-dibenzylcinnamamide, thus indicating that simultaneous activation of both the pronucleophile and the electrophile is crucial.

The γ and *Z* selectivity are consistent in the reaction of a range of thioamides **1**, as summarized in Table 2.[16] The reaction can be performed on a gram scale without any detrimental effects (Table 2, entry 2). The *ortho* substituent had a negative impact on the enantioselectivity (Table 2, entry 3). The reactivity of the α,β-unsaturated thioamide **1** was dependent on its electronic nature; the reaction with halogenated substrates **1d–f** proceeded rapidly (Table 2, entries 5–7), whereas the methoxy-substituted substrates required an elevated temperature to complete the reaction (Table 2, entries 8 and 9). The reaction with β-3-pyridyl thioamide **1i** proceeded with a mesitylcopper catalyst to afford **3i** with high enantioselectivity, albeit with moderate yield (Table 2, entry 10).[17] β-Alkyl thioamides **1j–1l** were also suitable substrates, thus affording the corresponding products with excellent enantioselectivity for the *Z* product (Table 2, entries 11–13). A careful inspection of the by-products in the reaction of **1a** and **2** revealed that a small amount of isothiazole **7a** was formed (Figure 2).[18] The comparable enantiomeric purity of **7a** indicated that **7a** was produced through the conjugate addition product **3a** by the proposed mechanism delineated in Table 3. When the isolated **3a** was subjected to CuOTf/$Li(OC_6H_4$-*p*-OMe), in 50 mol% and 1.1 equiv, respectively, isothiazole **7a** was obtained in 98% yield (entry 1). CuOTf/$Li(OC_6H_4$-*p*-OMe) generated the copper thioamide enolate of **3a**, which would subsequently undergo 6-*exo*-dig cyclization to give Cu^I imide **8a**. The oxidation or disproportionation[19] of **8a** along with a deprotonation would lead to Cu^{II} complex **9a**, and the subsequent reductive elimination would form a S–N bond to afford **7a** and Cu^0.[20] Re-oxidation of Cu^0 was reluctant, and a substoichiometric amount of Cu^I salt was essential to reach completion, even in an oxygen atmosphere (Table 3, entries 2 and 3). Oxidant screening revealed that TEMPO functioned as an effective oxidant in the presence of a catalytic

Table 2: Catalytic asymmetric conjugate addition of allyl cyanide (**2**) to α,β-unsaturated thioamide **1**.[a]



Entry	Thioamide **1** R		Product	*T* [°C]	*t* [h]	Yield[b] [%]	*ee* [%]
1	Ph	**1a**	**3a**	0	2	81	97
2[c]	Ph	**1a**	**3a**	0	3	87	97
3	*o*-MeC_6H_4	**1b**	**3b**	0	9	77	87
4	*p*-MeC_6H_4	**1c**	**3c**	0	3.5	85	97
5	*p*-FC_6H_4	**1d**	**3d**	0	1.5	81	98
6	*p*-ClC_6H_4	**1e**	**3e**	0	3	82	97
7	*p*-BrC_6H_4	**1f**	**3f**	0	3	82	97
8	*o*-MeOC_6H_4	**1g**	**3g**	40	24	63	89
9[d]	*p*-MeOC_6H_4	**1h**	**3h**	40	24	43	99
10[e]	3-pyridyl	**1i**	**3i**	0	3	40	93
11	Me	**1j**	**3j**	0	21	83	99
12[d]	*i*Pr	**1k**	**3k**	40	20	80	99
13[d]	*c*Hex	**1l**	**3l**	40	21	64	98

[a] Used 0.2 mmol of **1** and 1.0 mmol of **2**. [b] Yield of the isolated product. [c] 1.20 g of **1** was used. [d] Yield was determined by ^{1}H NMR spectroscopic analysis using 2-methoxynaphthalene as an internal standard. [e] 5 mol% of mesitylcopper/(*R*)-DTBM-segphos was used as the catalyst.

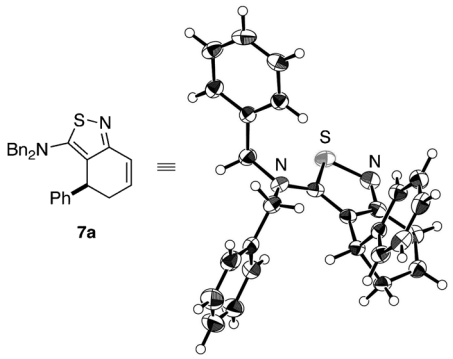
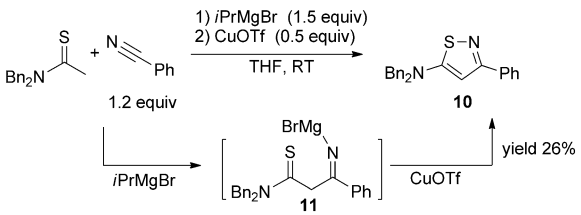


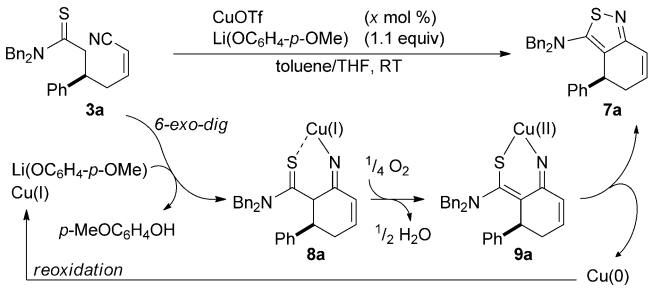
Figure 2. Ortep drawing of isothiazole **7a**.

amount of Cu to afford **7a** from **3a** (Table 3, entries 4–6).[21] The amount of TEMPO could be reduced to 0.1 equiv and no reaction proceeded in the absence of CuOTf (Table 3, entries 7 and 8).[22] Although intermediate **8a** (or its protonated form) was not isolated, a two-step reaction sequence using *i*PrMgBr and then CuOTf for the reaction of *N*,*N*-dibenzylthioacetamide and benzonitrile afforded isothiazole **10** via intermediate **11**,[23] thus suggesting that isothiazole **7a** was likely formed through **8a** [Eq. (1)].[24] The Cu-catalyzed



(1)

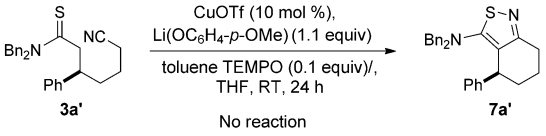
Table 3: A proposed mechanism of isothiazole formation and optimization.[a]



Entry	CuOTf (*x* mol%)	Oxidant	*t* [h]	Yield[b] [%]
1	50	–	16	98
2	10	–	16	16
3	30	O_2 atmosphere (1 atm)	16	6
4	10	TEMPO (1.1 equiv)	24	73[c]
5	10	NMO (1.1 equiv)	24	36
6	10	pyridine *N*-oxide (1.1 equiv)	24	33
7	10	TEMPO (1.1 equiv)	24	69[c]
8	0	TEMPO (1.1 equiv)	24	0

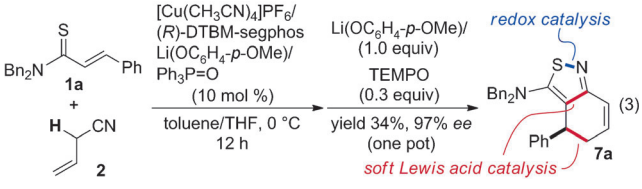
[a] Used 0.2 mmol of **3a**. [b] Determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard. [c] Yield of the isolated product. Bn = benzyl, NMO = *N*-methylmorpholine *N*-oxide, TEMPO = 2,2,6,6-tetramethylpiperidine-N-oxyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

isothiazole-forming reaction was applicable to other conjugate addition products (**3**) to furnish enantioenriched fused isothiazoles (Scheme 3). However, the hydrogenated substrate **3a′** did not provide the corresponding isothiazole **7a′**, thus suggesting that the conformational restriction by a *Z*-configured olefin is indispensable to the initial 6-*exo*-dig cyclization [Eq. (2)]. The catalytic asymmetric conjugate



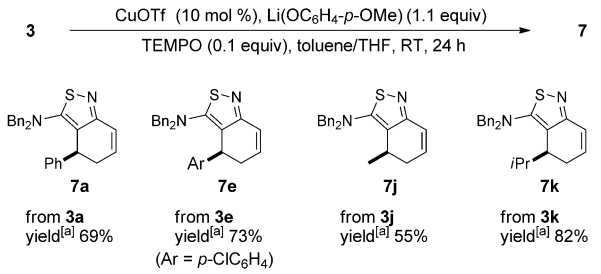
(2)

addition and isothiazole formation could be performed in a one-pot Cu-based catalysis, thus showcasing the dual roles of Cu as a soft Lewis acid and redox catalyst [Eq. (3)].



(3)

In summary, we have developed a new route to enantioenriched fused isothiazoles. The substrates for a Cu-catalyzed cascade cyclization were obtained by a catalytic



Scheme 3. Cu-catalyzed isothiazole formation. [a] Yield of the isolated product.

asymmetric conjugate addition of allyl cyanide (**2**) to α,β-unsaturated thioamides **1** by soft Lewis acid/hard Brønsted base/hard Lewis base cooperative catalysis. The soft Lewis acidic nature and redox characteristics of copper were successfully coupled to form three covalent bonds in a catalytic manner. Application of the present protocol to the synthesis of biologically active compounds is ongoing.

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Keywords: allyl cyanides · asymmetric catalysis · cyclization · homogeneous catalysis · isothiazoles

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[12] Other possibilities that cannot be ruled out at this stage: 1) phosphine oxide accelerated the conversion of the initially formed lithiated allyl cyanide into an α-C-copper nucleophile or 2) shifted the equilibrium between {$CuPF_6$ + LiOAr} and {CuOAr + $LiPF_6$} to the latter.

[13] The solvent effect was thoroughly studied. See the Supporting Information.

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[16] The reaction with pent-3-enenitrile (γ-methyl allyl cyanide) did not proceed under the optimized reaction conditions. In entries 9, 12, and 13, the chromatographic separation of the substrate and the product was difficult and the chemical yield determined by ^{1}H NMR was reported.

[17] The reaction using a $[Cu(CH_3CN)_4]PF_6$/(*R*)-DTBM-segphos/$Li(OC_6H_4$-*p*-OMe) catalyst (5 mol%) resulted in low yield (5%), probably because of the competitive coordination of the pyridine moiety of **1i**, thus disturbing the effective deprotonation of **2**. The mesitylcopper/(*R*)-DTBM-segphos system, in the absence of aryloxide and protonated *p*-methoxyphenol, appeared to partially circumvent the low reaction efficiency owing to the more efficient deprotonation of **2** through Cu thioamide enolate **6**.

[18] The absolute configuration of **7a** was determined by X-ray crystallographic analysis. CCDC 820988 (**7a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Summary of crystallographic analysis and the crystal structure was provided in Supporting Information.

[19] $2\,Cu^{I} \rightleftharpoons Cu^{0} + Cu^{II}$ is assumed.

[20] The possibility of reductive elimination via a Cu^{III} intermediate to give Cu^{I} and **7a** cannot be ruled out. See the Supporting Information for further discussion.

[21] The oxidation of **8a** to **9a** was likely mediated by TEMPO as well as O_2.

[22] TEMPO would be regenerated by O_2 dissolved in the solvent. For the reoxidation of TEMPO-OH to TEMPO by oxygen, see: P. Gamez, I. W. C. E. Arends, R. A. Sheldon, J. Reedijk, *Adv. Synth. Catal.* **2004**, *346*, 805.

[23] The enamine derived from **11** was characterized by NMR spectroscopy and X-ray crystallographic analysis. See the Supporting Information for details. CCDC 820989 (**11**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Summary of crystallographic analysis and the crystal structure was provided in Supporting Information.

[24] Recently, the concomitant formation of benzoisothiazole was reported in the Cu^{I}-catalyzed alkylation of *S*-acyl 2-mercaptoacetophenone oxime with arylboronic acid or arylstannanes, see: Z. Zhang, M. G. Lindale, L. S. Liebeskind, *J. Am. Chem. Soc.* **2011**, *133*, 6403.

