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Cooperative Activation of Alkyne and Thioamide Functionalities; Direct Catalytic Asymmetric Conjugate Addition of Terminal Alkynes to α,β-Unsaturated Thioamides

Ryo Yazaki,[a, b] Naoya Kumagai,*[a] and Masakatsu Shibasaki*[a]

On the occasion of the 150th anniversary of Department of Chemistry, The University of Tokyo

Abstract: A detailed study of the direct catalytic asymmetric conjugate addition of terminal alkynes to α,β-unsaturated thioamides is described. A soft Lewis acid/hard Brønsted base cooperative catalyst, comprising $[Cu(CH_3CN)_4]PF_6$, bisphosphine ligand, and $Li(OC_6H_4$-*p*-OMe) simultaneously activated both substrates to compensate for the low reactivity of copper alkynylide. A series of control experiments revealed that the intermediate copper-thioamide enolate functioned as a Brønsted base to generate copper alkynylide from the terminal alkyne, thus driving the catalytic cycle through an efficient proton transfer between substrates. These findings led to the identification of a more convenient catalyst using potassium hexamethyldisilazane (KHMDS) as the Brønsted base, which was particularly effective for the reaction of silylacetylenes. Divergent transformation of the thioamide functionality and a concise enantioselective synthesis of a GPR40 receptor agonist AMG-837 highlighted the synthetic utility of the present catalysis.

Keywords: alkynes · asymmetric catalysis · copper · proton transfer · thioamide

Introduction

Cooperative catalysis has gained increasing attention in asymmetric catalysis as an effective strategy to simultaneously activate multiple substrates with explicit control of the stereochemical course of the reaction.[1] In particular, the significance of this strategy is highlighted in so-called direct catalytic asymmetric C–C bond-forming reactions,[2] in which the enantioselective intermolecular C–C bond formation proceeds in a catalytic manner by proton transfer through the activation of both reaction partners. Recently, in pursuit of direct-type catalytic asymmetric reactions, we devoted much effort to exploiting the soft Lewis basic character of a thioamide functionality, which can be activated as a nucleophile by a soft Lewis acid/hard Brønsted base cooperative catalyst. Although thioamides are widely utilized in organic synthesis, especially for the construction of sulfur-containing heterocyclic compounds,[3] their use in asymmetric catalysis has been limited. Chemoselective activation through soft–soft interaction allows for in situ catalytic generation of thioamide enolates, thereby leading to the development of direct catalytic asymmetric Mannich-type and aldol reactions of thioamides (Scheme 1 a).[4] In our continuing program on thioamide chemistry, we turned our attention to incorporating electrophilic activation of a thioamide functionality in direct-type catalytic asymmetric reactions. In the nucleophilic activation of thioamides, our primary focus was on chemoselective activation in the presence of hard Lewis basic substrates. In this study, we envisioned simultaneous activation of both reaction partners by using the soft Lewis acid/hard Brønsted base cooperative catalyst, which can be represented by a catalytic asymmetric conjugate addition of soft Lewis basic α,β-unsaturated thioamides as the

[a] R. Yazaki, Dr. N. Kumagai, Prof. Dr. M. Shibasaki
Institute of Microbial Chemistry, Tokyo
3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021 (Japan)
Fax: (+81) 3-3447-7779
E-mail: mshibasa@bikaken.or.jp
nkumagai@bikaken.or.jp
Homepage: http://www.bikaken.or.jp/research/group/shibasaki/shibasaki-lab/index.html

[b] R. Yazaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

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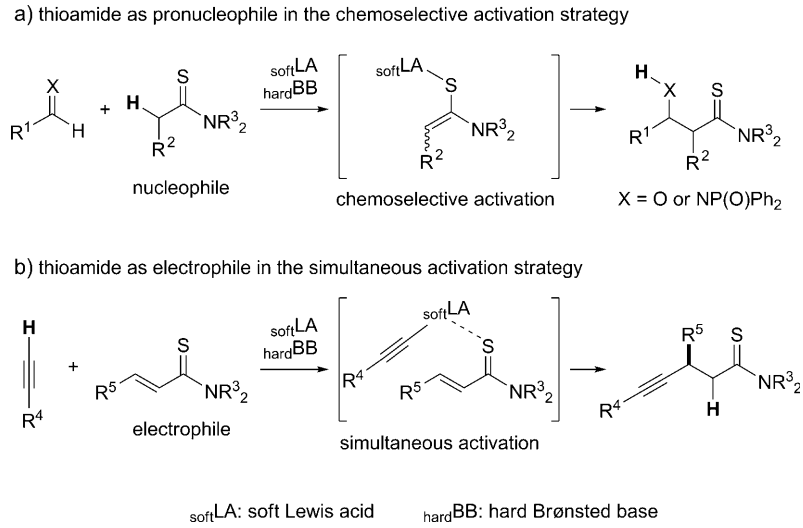
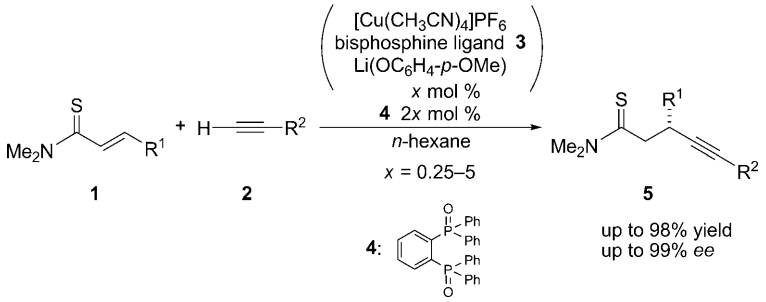


Scheme 1. Two modes of activation strategy with the soft Lewis acid/hard Brønsted base cooperative catalytic system.

electrophile and soft Lewis basic terminal alkynes as the pronucleophile (Scheme 1 b).

Catalytic asymmetric conjugate addition to an electron-deficient olefin is one of the most efficient methodologies to synthesize useful chiral building blocks for biologically active compounds.[5] Terminal alkynes have established their utility as carbon pronucleophiles in carbon–carbon bond-forming reactions,[6] including catalytic asymmetric 1,2-additions[7] and C(sp^2)–C(sp) coupling reactions such as the Sonogashira reaction,[8] but catalytic asymmetric conjugate addition of terminal alkynes suffers from limited substrate scope. Although preformed metal alkynylides are effective nucleophiles in catalytic asymmetric conjugate addition,[9] in situ generation of active metal alkynylides is more desirable in terms of both atom and step economy.[10] Pioneering work on a direct catalytic asymmetric conjugate addition of terminal alkynes was reported by Carreira et al.; this involved employing highly electron-deficient olefins as electrophiles to compensate for the inherent low nucleophilicity of copper alkynylides.[11] Indeed, the inert nature of copper alkynylides is exploited in organocuprate additions, in which alkynes function as dummy ligands.[12] Hayashi and co-workers[13] and Fillion and Zorzitto[14] subsequently showed that rhodium catalysis is effective for enantioselective conjugate addition to enones, enals, and nitro olefins. Conjugate addition to α,β-unsaturated carboxylic acid derivatives, however, has remained elusive because of their attenuated electrophilicity, despite the synthetic utility of enantioenriched β-alkynylcarboxylic acid derivatives.

In this context, our attention was directed toward the development of the direct catalytic asymmetric addition of terminal alkynes to α,β-unsaturated thioamides **1**,[15] which addresses the above-mentioned drawback and proves the effectiveness of a simultaneous activation strategy. Despite the similar electronegativity of sulfur and carbon atoms, the C=S bond of thioamides shows a higher dipole moment than that of the C=O bond of the corresponding amides.[16,17] In conjunction with the soft Lewis basic nature of sulfur atoms, the electrophilicity at the β-position of α,β-unsaturated thioamides **1** can be enhanced by activation with a soft Lewis acid. The combined use of a hard Brønsted base would allow for the facile deprotonation of soft Lewis acid-activated terminal alkynes **2** to generate a metal-alkynylide, which would engage in an enantioselective coupling, with **1** activated in close proximity. On the basis of this hypothesis, we identified that the soft Lewis acid/hard Brønsted base/hard Lewis base cooperative catalyst comprising [Cu(CH_3CN)$_4$]PF_6, biaryl-type chiral bisphosphine ligands **3**, Li(OC_6H_4-*p*-OMe), and phosphine oxide **4** efficiently promoted the desired conjugate addition of **2** to **1** under proton-transfer conditions (Scheme 2).[18] Herein, we report



Scheme 2. Direct catalytic asymmetric conjugate addition of terminal alkynes **2** to α,β-unsaturated thioamides **1** under proton-transfer conditions.

a comprehensive study on this synthetically versatile transformation, which delivers enantiomerically enriched β-alkynyl thioamides **5**. Control experiments and kinetic studies revealed mechanistic insights of the efficient proton-transfer process. The utility of the present protocol culminated in the concise enantioselective synthesis of AMG-837, a potent agonist of the G-protein coupled receptor GPR40.

Results and Discussion

Mechanistic Elucidation

Recently our group reported a soft Lewis acid/hard Brønsted base cooperative catalytic system comprising cationic copper(I), chiral bisphosphine ligand, and lithium aryloxide to promote several direct-type C–C bond-forming reactions with high enantioselectivity under proton-transfer conditions.[19] The application of 5 mol% of a cooperative catalyst prepared from $[Cu(CH_3CN)_4]PF_6$, 2,2′-bis(diphenylphosphino)-1,1′-biphenyl (BIPHEP)-type ligand (*R*)-**3a**, and $Li(OC_6H_4$-*p*-OMe) to the attempted reaction of phenylacetylene (**2a**) and α,β-unsaturated thioamide **1a** delivered the desired β-alkynylthioamide **5aa** in 81% yield and 94% *ee* (Scheme 3a, entry 1).[18,20] In the absence of either the hard Brønsted base $Li(OC_6H_4$-*p*-OMe) or the soft Lewis acid $[Cu(CH_3CN)_4]PF_6$, the reaction did not proceed at all, thereby verifying that both the soft Lewis acid and hard Brønsted base were essential for catalysis (Scheme 3a, entries 2 and 3). In ^{1}H NMR analysis of the tetrahydrofuran solution of $[Cu(CH_3CN)_4]PF_6$ and $Li(OC_6H_4$-*p*-OMe), coalescing peaks were observed derived from *para*-methoxyphenoxide at various temperatures;[21] this suggests that ([Cu/(*R*)-**3a**]PF_6+$Li(OC_6H_4$-*p*-OMe)) and ([$Cu(OC_6H_4$-*p*-OMe)]/(*R*)-**3a**+$LiPF_6$) were in equilibrium (Figure 1).[19j,22,23] The lithium-free catalyst prepared from mesitylcopper,[24] *para*-methoxyphenol, and (*R*)-**3a**, in which $Cu(OC_6H_4$-*p*-OMe)/(*R*)-**3a** was produced, exhibited almost identical catalytic activity to promote the desired alkynylation reaction (Scheme 3b). In the absence of lithium salt, $Li(OC_6H_4$-*p*-OMe) was never formed, thereby indicating that both $Li(OC_6H_4$-*p*-OMe) and $Cu(OC_6H_4$-*p*-OMe)/(*R*)-**3a** would function as a Brønsted base in this catalytic system to generate copper alkynylide. This is in marked contrast to the catalytic asymmetric addition of allyl cyanide to ketones promoted by a similar catalytic system, in which $Li(OC_6H_4$-*p*-OMe) is the actual Brønsted base and lithium-free $Cu(OC_6H_4$-*p*-OMe) failed to promote the reaction.[19j] To gain more insight in this crucial deprotonation step, in which the active nucleophile copper alkynylide was formed, the kinetic profile of the reaction was traced by using deuterated phenylacetylene [D_1]**2a**. By comparing the initial rate of the reaction with that of **2a** revealed a kinetic isotope effect of $k_H/k_D = 1.9$, thus suggesting that copper alkynylide formation, rather than the nucleophilic addition step of copper alkynylide is likely the rate-determining step (Figure 2).[25] Higher catalytic efficiency was observed owing to the presence of hard Lewis basic bisphosphine oxide **4**, which coordinated to the lithium cation to enhance the basicity of $Li(OC_6H_4$-*p*-OMe).[26] With a catalyst loading of 2 mol%, the combined use of 4 mol% of **4** was effective for accelerating the deprotonation step to complete the reaction without a detrimental effect on enantioselectivity (Scheme 4).[19j,27,28] The smooth conjugate addition to thioamides would be explained by assuming that the copper-activated thioamide was located in close proximity to copper alkynylide, with a favorable topology for carbon–carbon bond

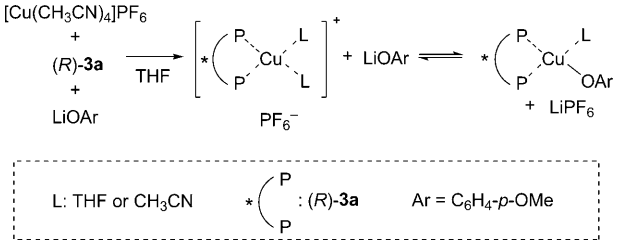
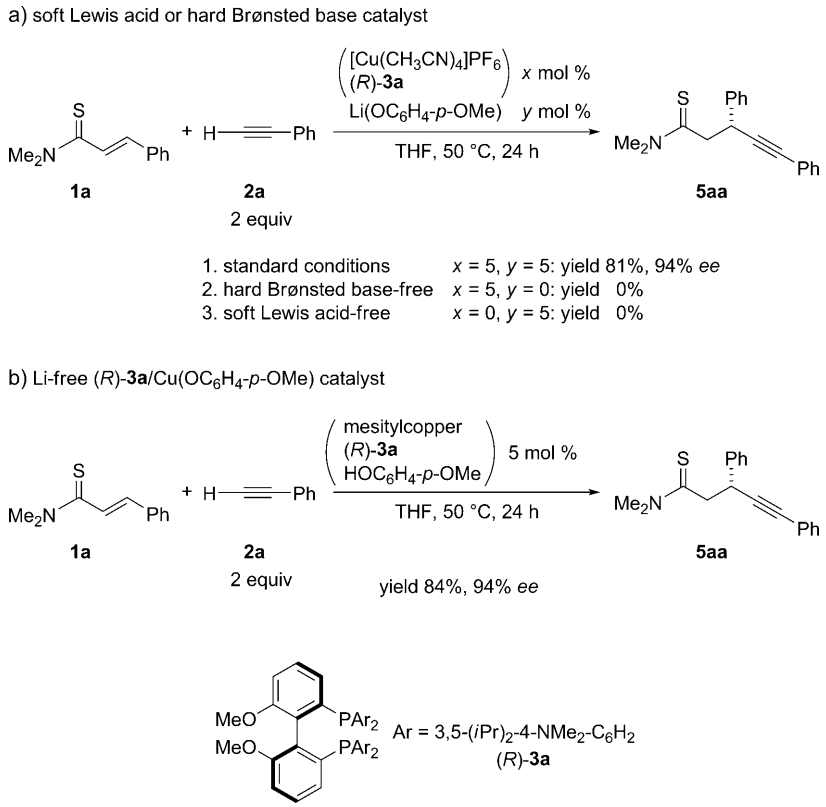
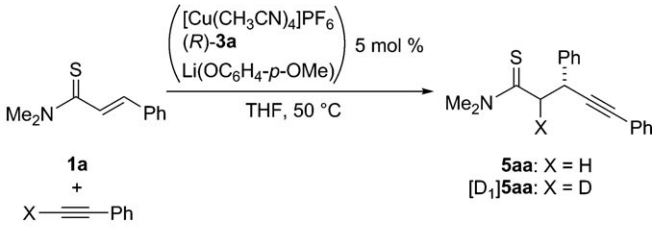


Figure 1. Equilibrium of the catalyst components.



Scheme 3. Control experiments of direct catalytic asymmetric conjugate addition of phenylacetylene (**2a**) to α,β-unsaturated thioamides (**1a**).



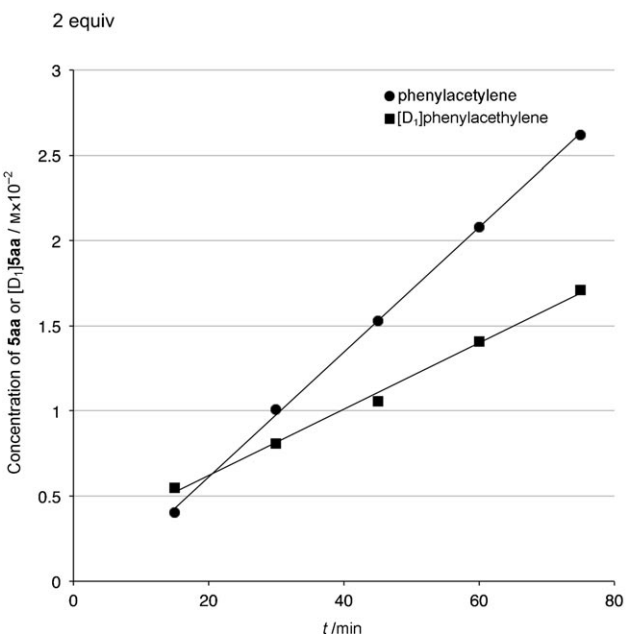
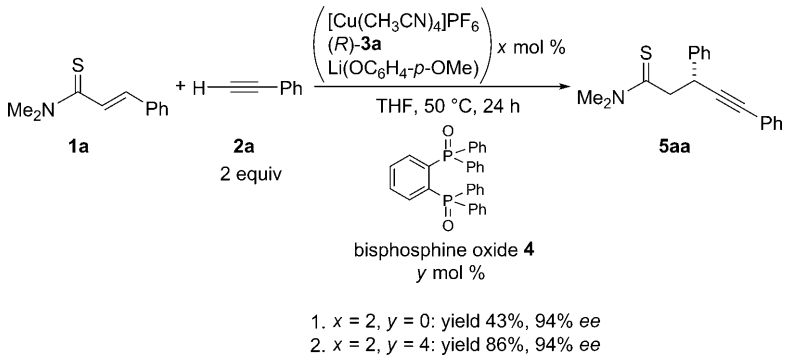


Figure 2. Kinetic isotope effect.



Scheme 4. Effect of phosphine oxide **4** as hard Lewis basic additive.

formation at the β-position through the six-membered transition state, thereby highlighting the benefit of simultaneous activation (Figure 3). This assumption was consistent with the observation that the attempted reaction using α,β-unsaturated thiolactam **1b** and **1c**, the locked *s-trans* conformation of which disrupted the formation of the six-membered transition state, resulted in no reaction at all, even in the presence of **4** (Scheme 5).[29,30] The linear relationship between the enantiopurity of (*R*)-**3a** and the enantioselectivity of **5aa** implied that the monomeric Cu/(*R*)-**3a** complex was involved in the enantiodiscrimination step (Figure 4).[31]

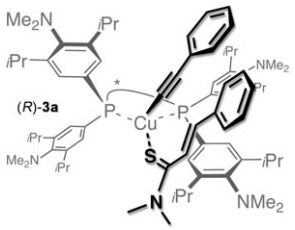
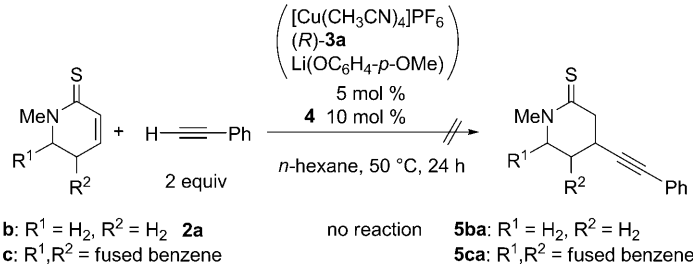


Figure 3. Proposed six-membered transition state.



Scheme 5. The reaction with α,β-unsaturated thiolactams.

After the addition of copper alkynylide to thioamide, the possible proton source for protonation of the intermediary copper-thioamide enolate is HOC_6H_4-*p*-OMe or the terminal alkyne. If the protonation with HOC_6H_4-*p*-OMe is operative, the first catalyst set is regenerated with liberation of the product. If the proton exchange between the intermediary copper-thioamide enolate and the terminal alkyne occurs, the copper-alkynylide nucleophile for the next catalytic cycle is directly formed and the reaction system can be simplified by omitting the alkali metal aryloxide base. The attempted reaction of **1a** and phenylacetylene (**2a**) using a catalyst prepared from copper alkynylide of phenylacetylene (**2a**) and (*R*)-**3a** proceeded smoothly to afford **5aa**, thus indicating the efficient proton transfer from **2a** to the copper-thioamide enolate to generate the copper alkynylide of **2a** (Scheme 6a). The catalyst prepared from mesitylcopper[24] and (*R*)-**3a** was also effective, and is applicable to the reaction with any terminal alkynes (Scheme 6b). These experimental results together clearly revealed that the catalytic cycle efficiently drives the proton transfer between terminal alkyne and copper-thioamide enolate after the initial formation of copper alkynylide. We sought a more operationally simple catalyst set and identified a catalyst comprising $[Cu(CH_3CN)_4]PF_6$, (*R*)-**3a**, and KHMDS that was effective, and all of the necessary materi-

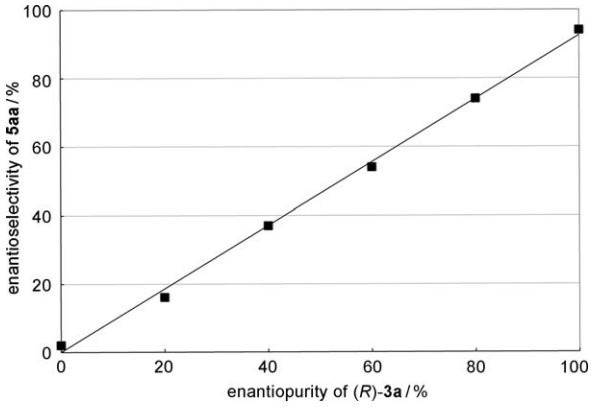
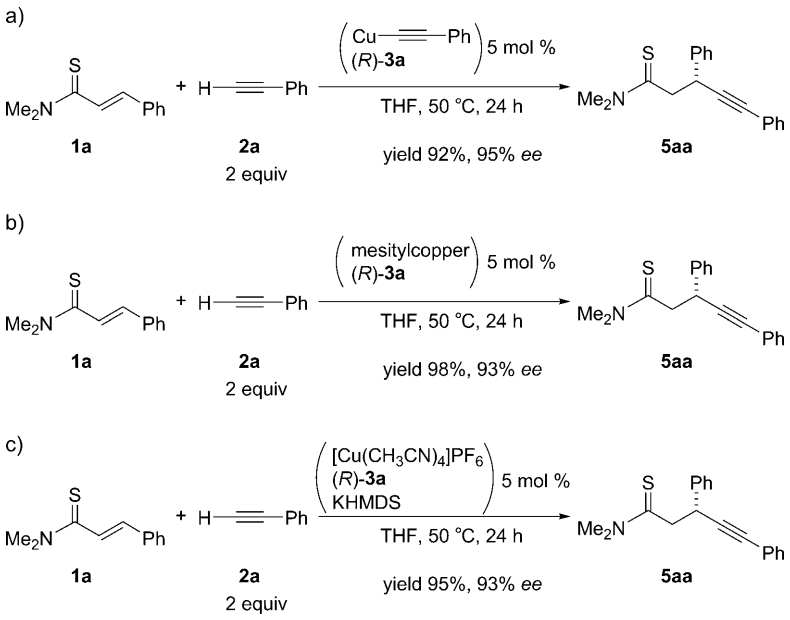


Figure 4. Linear relationship between the enantioselectivity of **5aa** and enantiopurity of (*R*)-**3a**.

als are commercially available and storable (Scheme 6c).[32] Potassium alkynylide generated at the first cycle was converted to copper alkynylide by transmetallation and the copper alkynylide drove the following catalytic cycle. The proton-transfer process was further investigated by using *N*,*N*-dimethylthiomethacrylamide (**1d**) as a probe. The α-methyl group of **1d** is expected to provide information on the stereoselection at the protonation step. Under the standard conditions using (*R*)-DTBM-Segphos (*R*)-**3b** and Li(OC_6H_4-*p*-OMe) as the Brønsted base, the alkynylation product **5da** was obtained with only 9% *ee* (Scheme 7a; DTBM = 3,5-di-*tert*-butyl-4-methoxy). On the other hand, the copper alkynylide/(*R*)-**3b** catalyst delivered **5da** in 60% *ee*; this suggests that a different protonation pathway was operative (Scheme 7b); in the presence of HOC_6H_4-*p*-OMe, copper-thioamide enolate underwent proton transfer preferentially with HOC_6H_4-*p*-OMe with poor enantioselection; in the absence of HOC_6H_4-*p*-OMe, partial enantioselective proton transfer with copper-coordinated phenylacetylene (**2a**) occurred under the influence of the asymmetric environment provided by ligand (*R*)-**3b**. This result is consistent with the observed similar enantioselectivity (59% *ee*) of **5da** with the $[Cu(CH_3CN)_4]PF_6$/(*R*)-**3b**/KHMDS catalytic system, in which the proton transfer proceeded between copper-thioamide enolate and phenylacetylene (**2a**; Scheme 7c).

On the basis of the experimental results mentioned above, the proposed catalytic cycle is illustrated in Figure 5. When a catalyst comprising $[Cu(CH_3CN)_4]PF_6$, (*R*)-**3a**, Li(OC_6H_4-*p*-OMe) (referred to as catalyst **1**) is used, both [$CuPF_6$/(*R*)-**3a**+Li(OC_6H_4-*p*-OMe)] and [Cu(OC_6H_4-*p*-OMe)/(*R*)-**3a**+$LiPF_6$] states under equilibrium are catalytically active to deprotonate phenylacetylene (**2a**) to give copper alkynylide **A**. Bisphosphine oxide **4** enhances the basicity of Li(OC_6H_4-*p*-OMe) and facilitates the deprotonation. Thioamide **1a** then coordinates to copper through a soft–soft interaction, and this leads to a six-membered transition state **B** for enantioselective carbon–carbon bond formation, in which both of the substrates are activated in close proximity and overcome the intrinsic low reactivity of copper alkynylide **A**. Indeed, the reaction with more electrophilic α,β-unsaturated ketone (chalcone) **6** does not proceed at all with this catalytic system, thus highlighting the significance of the simultaneous activation of **1a** and **2a** (Scheme 8). The thus-obtained copper-thioamide enolate **C** is protonated preferentially with HOC_6H_4-*p*-OMe, which is formed in the initial deprotonation step, liberating the desired product **5aa** with regeneration of the catalyst. In the case of catalyst **2**, comprising the copper alkynylide of **2a** and (*R*)-**3a**, coordination of **1a** affords the key transition state structure **B**. Subsequent proton transfer directly proceeds with the copper-activated phenylacetylene (**2a**) as shown in **D**, and the coordination of **1a** leads to the transition state **B**, thereby completing the catalytic cycle. Therefore, once the copper alkynylide is formed, these two substrates engage in the carbon–carbon bond formation catalytically through efficient proton transfer. Other catalyst sets, such as mesitylcopper and (*R*)-**3a** (catalyst **3**), [Cu($CH_3CN)_4$]PF_6, (*R*)-**3a**, and KHMDS (catalyst **4**), also generate copper alkynylide at the first stage of the reaction, and the following catalytic cycle is the same as that of catalyst **2**.



Scheme 6. Control experiments using different types of copper catalyst. KHMDS = potassium hexamethyldisilazane.

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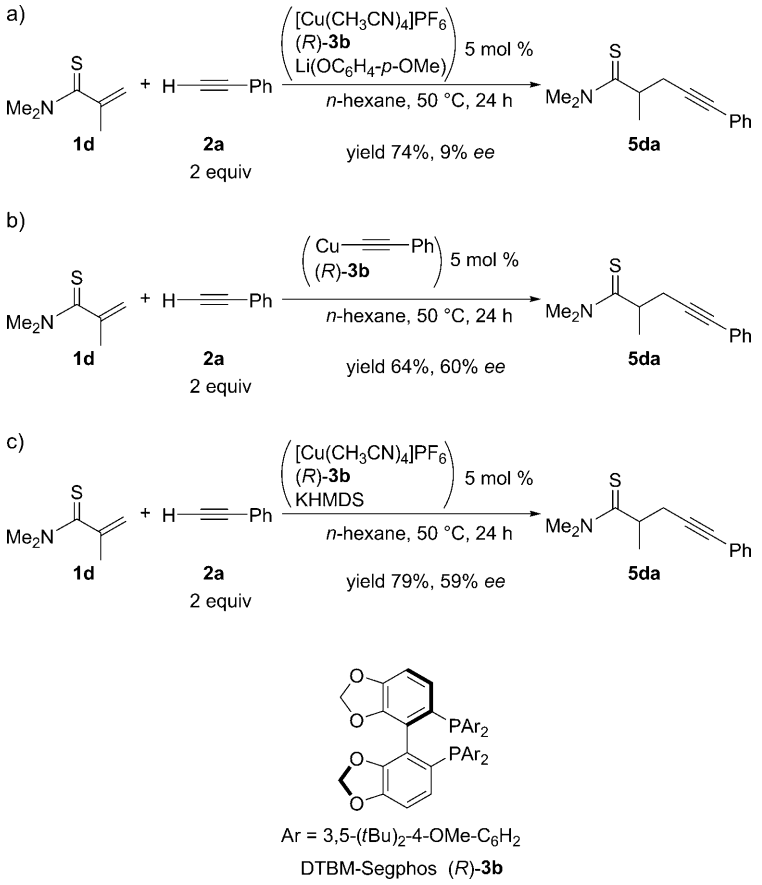
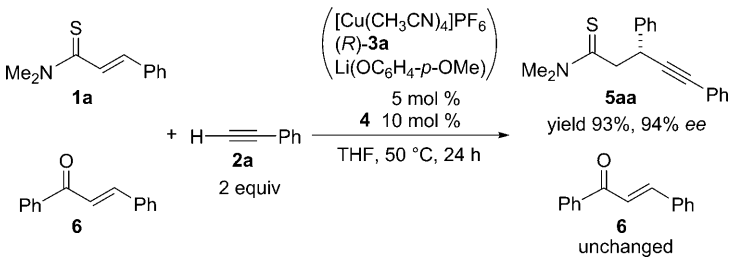


Scheme 7. Catalytic asymmetric conjugate alkynylation of thiomethacrylamide **1d**.

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

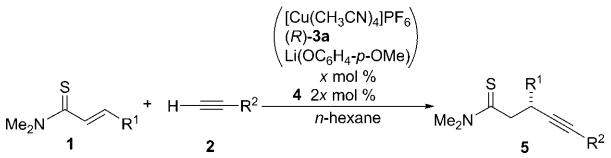
The substrate scope of the direct catalytic asymmetric conjugate alkynylation of α,β-unsaturated thioamide with catalyst **1** ([Cu(CH$_3$CN)$_4$]PF$_6$+(*R*)-**3a**+Li(OC$_6$H$_4$-*p*-OMe)) reinforced with a hard Lewis base **4** is summarized in Table 1. Further reduction in the catalyst loading to 1 mol% was achieved by changing the solvent from tetrahydrofuran to *n*-hexane, presumably because the formation of an intimate copper alkynylide/thioamide association was enhanced in the nonpolar reaction medium (entry 1 vs 2). A morpholine thioamide other than *N*,*N*-dimethylthioamide was a suitable substrate to achieve high enantioselectivity, albeit 5 mol% of catalyst was required (entry 4). Substituents at the *ortho*- or *para*-position did not interfere with enantioselection (entries 5 and 6). The present catalysis is sensitive to the electronic nature of the β-substituent of thioamide; thioamides **1h** and **1i** bearing methoxy substituents required 80°C to promote the reaction efficiently and thioamide **1j** with a 3,4-methylenedioxy group afforded the desired product in 56% yield and high enantioselectivity with 5 mol% of catalyst (entries 7–9). Thioamides **1a** and **1k** bearing *para*-bromine substituents exhibited high reactivity in the present catalytic system and trials to reduce catalyst loading conducted with these substrates led to the reaction with a catalyst loading of 0.5 and 0.25 mol%, respectively, without any loss of enantioselectivity (entries 2, 3, 10, and 11). The conjugate alkynylation of α,β,γ,δ-unsaturated thioamide **1l** derived from sorbic acid proved that the alkynylation proceeded exclusively at the β-position with high enantioselectivity (entry 12). Thioamides **1m** and **1n** having β-alkyl substituents were applicable with 5 mol% of the catalyst (entries 13 and 14), and the 1,3-enyne **2b** afforded the product in 96% *ee*, albeit in moderate yield.



Scheme 8. Direct catalytic asymmetric conjugate alkynylation in the presence of chalcone (**6**).

Conjugate addition using saturated aliphatic terminal alkynes proved elusive even after ligand screening. Using 1-heptyne (**1c**) as a model substrate, catalyst **1** using (*R*)-**3a** with phosphine oxide **4** exhibited poor catalytic activity in tetrahydrofuran, and this produced the product **5ac** in less than 10% yield with 60% *ee* (Scheme 9, entry 1).[33] The other biaryl-type ligand (*R*)-DTBM-Segphos (*R*)-**3b** increased the yield but the stereoselectivity remained unsatisfactory (entry 2). None of the reactions using other phospholane-type ligands **7** and **8** and ferrocene-conjugated ligands **9** and **10** improved enantioselectivity (entries 3–6). These results prompted us to focus on other strategies to solve this problem. We turned our attention to the counter anion, located near the copper cation, which we expected could be used to influence the asymmetric environment. We planned to endow the counter anion with chirality as an additional stereocontrolling element to reinforce stereodiscrimination at the transition state.[34,35] Various chiral phosphoric acids were used with mesitylcopper and ligand (*R*)-**3b**,[36] generating the copper/(*R*)-**3b** phosphate as a new soft Lewis

Table 1. Direct catalytic asymmetric conjugate alkynylation.[a]



Entry	Thioamide **1** R^1		Alkyne **2** R^2		x	T [°C]	Product	Yield[b] [%]	*ee* [%]
1[c]	Ph	**1a**	Ph	**2a**	1	50	**5aa**	51	94
2	Ph	**1a**	Ph	**2a**	1	50	**5aa**	98	98
3	Ph	**1a**	Ph	**2a**	0.5	50	**5aa**	72	98
4[d]	Ph	**1e**	Ph	**2a**	5	50	**5ea**	84	94
5	*o*-Me-C_6H_4	**1f**	Ph	**2a**	1	50	**5fa**	97	98
6	*p*-Me-C_6H_4	**1g**	Ph	**2a**	1	50	**5ga**	74	97
7[e]	*m*-MeO-C_6H_4	**1h**	Ph	**2a**	1	80	**5ha**	77	95
8[e]	*p*-MeO-C_6H_4	**1i**	Ph	**2a**	1	80	**5ia**	81	94
9	3,4-methylenedioxy	**1j**	Ph	**2a**	5	50	**5ja**	56	99
10	*p*-Br-C_6H_4	**1k**	Ph	**2a**	1	50	**5ka**	98	97
11	*p*-Br-C_6H_4	**1k**	Ph	**2a**	0.25	50	**5ka**	83	97
12	(*E*)-$CH_3CH{=}CH$	**1l**	Ph	**2a**	5	50	**5la**	51	94
13	Me	**1m**	Ph	**2a**	5	50	**5ma**	97	80
14	*i*Pr	**1n**	Ph	**2a**	5	50	**5na**	63	92
15	Ph	**1a**	1-cyclohexenyl	**2b**	1	50	**5ab**	58	96

[a] **1**: 0.2 mmol; **2**: 0.4 mmol. [b] Isolated yield. [c] THF was used as the solvent instead of *n*-hexane. [d] Morpholine thioamide was used instead of *N*,*N*-dimethylthioamide. [e] *n*-Heptane was used instead of *n*-hexane.

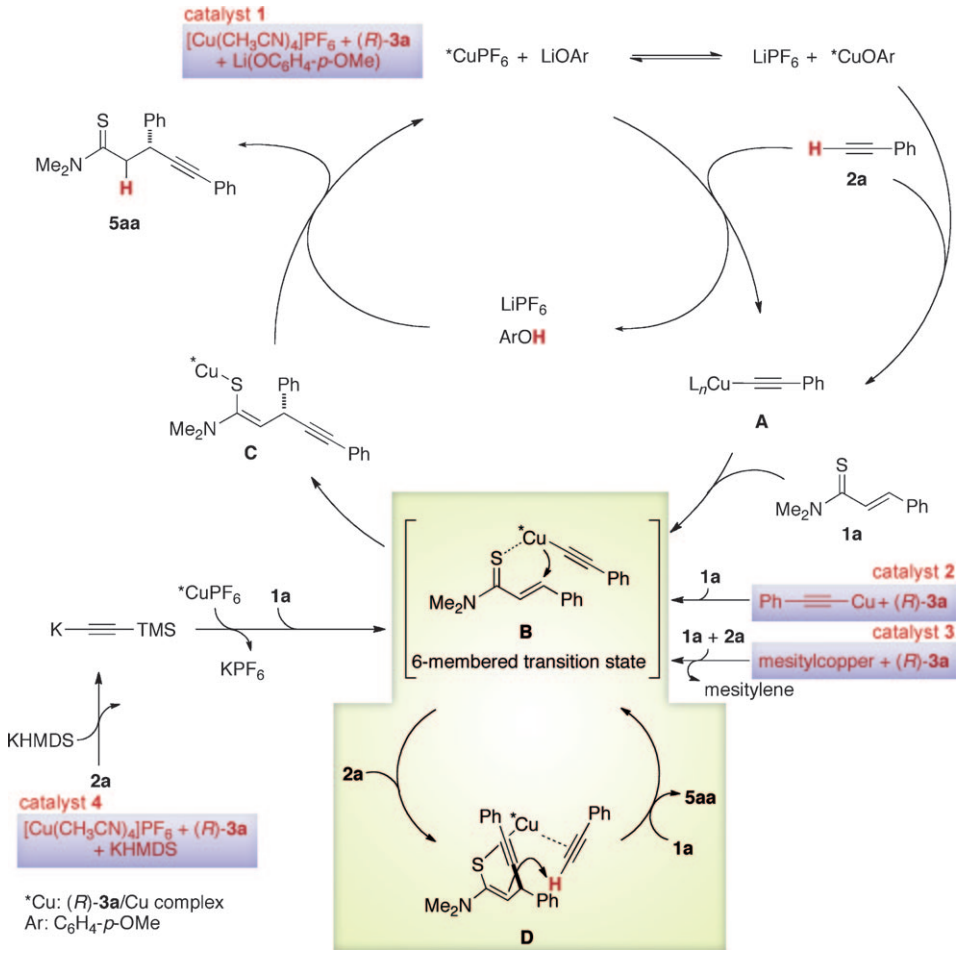


Figure 5. Proposed catalytic cycle.

acid entity bearing a chiral phosphate anion.[37] In this catalyst design, a hard Lewis basic phosphate would function as a hard Lewis base in the same manner as phosphine oxide **4**. The screening of the chiral phosphoric acid is summarized in Table 2. In the absence of chiral counter anion, the ([Cu(CH_3CN)$_4$]PF_6/(*R*)-**3b**/Li(OC_6H_4-*p*-OMe)) catalyst performed better in *n*-hexane and gave **5ac** in 90% yield with 82% *ee*. The use of the parent nonsubstituted binaphthyl-type phosphoric acid **11a** hardly affected the stereochemical course of the reaction irrespective of its chirality (entries 2 and 3). In contrast, bulkier phosphoric acid (*S*)-**11b**, in which the 2,4,6-triisopropylphenyl groups were installed at the 3,3′-positions, improved enantioselectivity to 89% *ee* (entry 5). Intriguingly, its antipode (*R*)-**11b** completely shut down the reaction, thus suggesting that the chiral phosphate anion is involved in the enantioselective carbon–carbon bond formation. Other even bulkier phosphoric acids **11c–e** with (*S*)-axial chirality were examined, and (*S*)-**11b** proved optimal for this purpose (entries 6–8). The thus-identified optimal reaction conditions for aliphatic terminal alkynes were evaluated in the reaction of various alkynes (Table 3). Although 5 mol% of catalyst was required, branched and nonbranched aliphatic terminal alkynes **2c–g** provided the desired alkynylation product in moderate to high yield with up to 91% *ee* (entries 1–5). The combination of aliphatic terminal alkyne and a thioamide bearing β-alkyl substituent remained difficult to achieve high enantioselectivity, thereby giving the alkynylation product **5mc** with 69% *ee* (entry 6). The use of silylacetylenes in alkyny-

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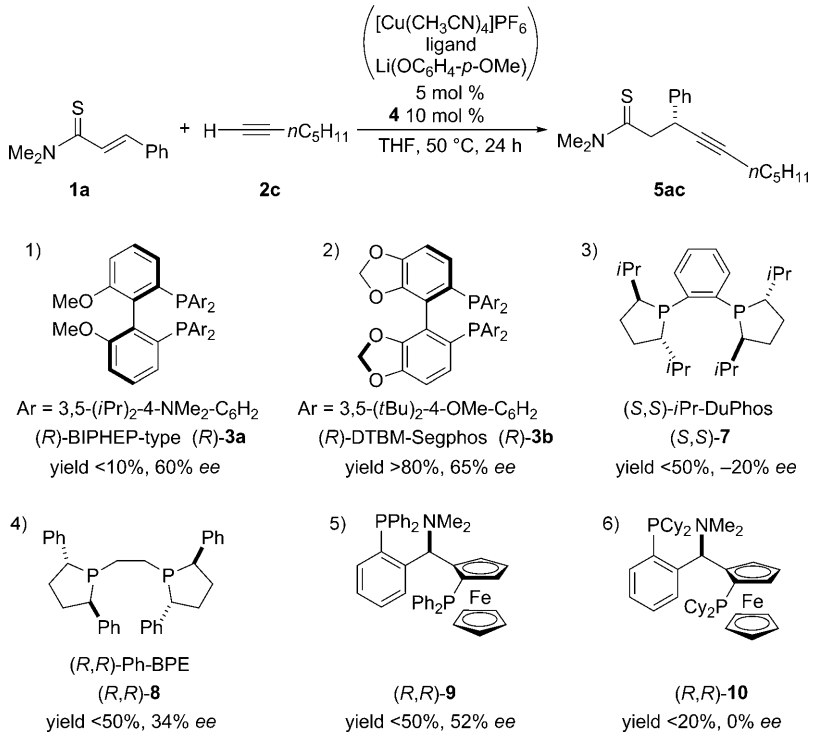
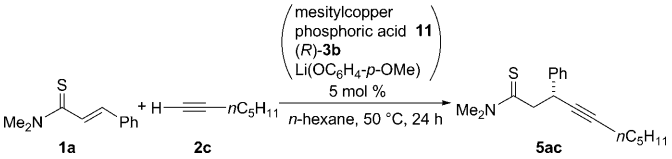


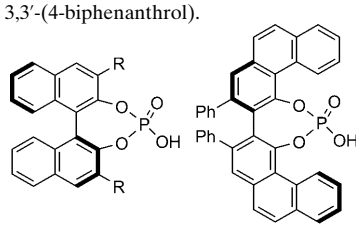
Scheme 9. Direct catalytic asymmetric conjugate alkynylation of 1-heptyne (**2c**). DTBM = 3,5-di-*tert*-butyl-4-methoxy, Ph-BPE = 1,2-bis(2,5-diphenylphospholano)ethane.

Table 2. Direct catalytic asymmetric conjugate alkynylation of 1-heptyne (**2c**) using a chiral counter anion.[a]



Entry	Chiral phosphoric acid **11**		Yield[b] [%]	*ee* [%]
1[c]	–	–	90	82
2	(*R*), R = H	(*R*)-**11a**	88	81
3	(*S*), R = H	(*S*)-**11a**	90	81
4	(*R*), R = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$	(*R*)-**11b**	0	–
5[d]	(*S*), R = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$	(*S*)-**11b**	90	89
6	(*S*), R = SiPh$_3$	(*S*)-**11c**	89	81
7	(*S*), R = 9-anthracenyl	(*S*)-**11d**	83	87
8	(*S*)-VAPOL phosphoric acid	(*S*)-**11e**	74	84

[a] **1**: 0.2 mmol, **2**: 0.4 mmol. [b] Determined by ^{1}H NMR analysis with 2-methoxynaphthalene as an internal standard. [c] The reaction conditions were identical to those described in Table 1 except for phosphine ligand ((*R*)-**3b** instead of (*R*)-**3a**). ([Cu(CH$_3$CN)$_4$]PF$_6$/(*R*)-**3b**/Li(OC$_6$H$_4$-*p*-OMe)): 5 mol %, **4**: 10 mol %. [d] Isolated yield. VAPOL = 2,2′-diphenyl-3,3′-(4-biphenanthrol).



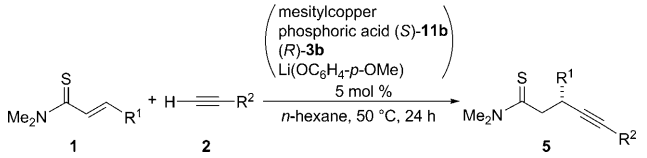
(*S*)-**11a-d** (*S*)-**11e**

lation is of particular significance because they are generally regarded as acetylene equivalents.[38] The direct application of catalyst **1** in the reaction of trimethylsilylacetylene (**2h**) produced only trace amounts of the desired product (entry 1). On the basis of the mechanistic studies, the key to the present catalysis is the generation of copper alkynylides. We envisioned applying catalyst **4** with a strong HMDS-type base to the reaction of silylacetylenes, thereby generating alkali metal alkynylides to trigger the alkynylation reaction. In entries 2–4, the HMDS-type base proved effective and the HMDS-type base of the more electropositive alkali metal performed even better. The bulkier triethylsilylacetylene (**2i**) displayed diminished reactivity to afford the product in 63% yield, even with the KHMDS base (entry 5), and no products were obtained with *tert*-butyldimethylsilyl (TBS) or triisopropylsilyl (TIPS) substituted acetylenes **2j** and **2k** (entries 6 and 7). Increasing the amount of **2h** led to a higher chemical yield (entry 8). Under these optimal conditions, (trimethylsilyl)methylacetylene (**2l**) and TMS-protected propargyl alcohol (**2m**) furnished the desired alkynylation product with 86% *ee* and 87% *ee*, respectively (entries 9 and 10). The involvement of copper alkynylide was confirmed by the reaction using catalyst **3** comprising mesitylcopper and (*R*)-**3b**, and this exhibited a similar reaction outcome. The ineffectiveness of catalyst **1**, in which Li(OC$_6$H$_4$-*p*-OMe) was used as the base and HOC$_6$H$_4$-*p*-OMe existed in the reaction mixture, can be explained by assuming that the copper silylacetylide has higher aptitude for reprotonation with HOC$_6$H$_4$-*p*-OMe, thereby reducing the concentration of active copper silylacetylide. In the absence of Li(OC$_6$H$_4$-*p*-OMe) with catalyst **3** or catalyst **4**, reprotonation of copper acetylide with HMDS or silylacetylenes would be slower (Table 4).

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

The utility of the present catalysis is due to the highly chemoselective nature of the reaction and divergent transformation of thioamide functionality.[3] The reaction using substrate **1p** bearing both α,β-unsaturated thioamide and α,β-unsaturated ester moieties showcased the stringent chemoselectivity (Scheme 10). By using catalyst **2** comprising copper alkynylide of phenylacetylene (**2a**) and (*R*)-**3a**, the

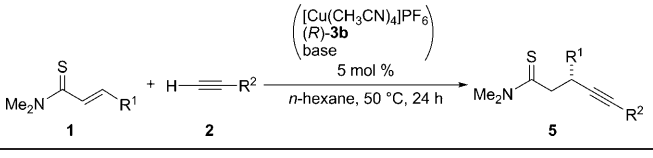
Table 3. Direct catalytic asymmetric conjugate alkynylation of aliphatic terminal alkynes using a chiral counter anion.[a]



Entry	Thioamide **1** R^1		Aliphatic alkyne **2** R^2		Product	Yield[b] [%]	*ee* [%]
1	Ph	**1a**	nC_5H_{11}	**2c**	**5ac**	90	89
2	Ph	**1a**	cC_3H_5	**2d**	**5ad**	88	83
3	Ph	**1a**	cC_6H_{11}	**2e**	**5ae**	63	91
4	Ph	**1a**	$(CH_3)_2CHCH_2$	**2f**	**5af**	63	87
5	Ph	**1a**	$PhCH_2CH_2$	**2g**	**5ag**	72	90
6	Me	**1m**	nC_5H_{11}	**2c**	**5mc**	43	69

[a] **1**: 0.2 mmol, **2**: 0.4 mmol. [b] Isolated yield.

Table 4. Direct catalytic asymmetric conjugate alkynylation of silylacetylenes using $[Cu(CH_3CN)_4]PF_6$, (*R*)-**3b**, and HMDS-type bases.[a]

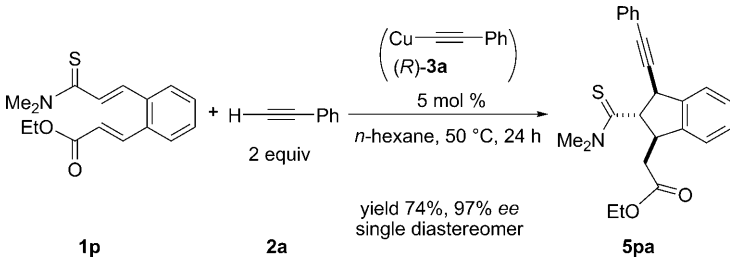


Entry	Thioamide **1** R^1		Aliphatic alkyne **2** R^2		Equiv	Base	Product	Yield[b] [%]	*ee* [%]
1[c]	Ph	**1a**	TMS	**2h**	2	Li(OC$_6$H$_4$-*p*-OMe)	**5ah**	trace	–
2	Ph	**1a**	TMS	**2h**	2	LiHMDS	**5ah**	32	89
3	Ph	**1a**	TMS	**2h**	2	NaHMDS	**5ah**	59	88
4[d]	Ph	**1a**	TMS	**2h**	2	KHMDS	**5ah**	74	92
5	Ph	**1a**	TES	**2i**	2	KHMDS	**5ai**	63	92
6	Ph	**1a**	TBS	**2j**	2	KHMDS	**5aj**	0	–
7	Ph	**1a**	TIPS	**2k**	2	KHMDS	**5ak**	0	–
8[d]	Ph	**1a**	TMS	**2h**	5	KHMDS	**5ah**	85	91
9[d]	*p*-I-C$_6$H$_4$	**1o**	$TMSCH_2$	**2l**	5	KHMDS	**5ol**	72	86
10[d]	Ph	**1a**	$TMSOCH_2$	**2m**	5	KHMDS	**5am**	79	87

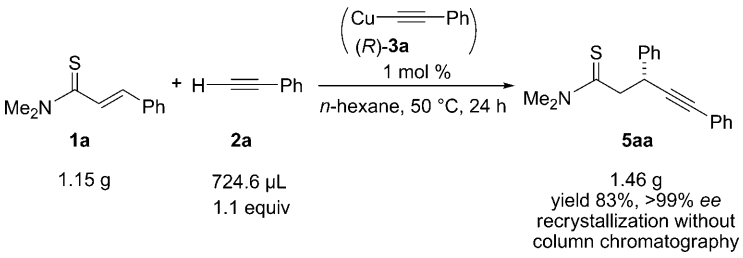
[a] **1**: 0.2 mmol. [b] Determined by ^{1}H NMR analysis with 2-methoxynaphthalene as an internal standard. [c] 10 mol% of phosphine oxide **4** was used. [d] Isolated yield.

enantioselective conjugate addition of **2a** proceeded exclusively at the β-position of α,β-unsaturated thioamide and the intermediate copper-thioamide enolate underwent diastereoselective intramolecular conjugate addition to the α,β-unsaturated ester to give rise to cyclopentane **5pa** with three continuous stereogenic centers as a single diastereomer with 97% *ee*. The present catalysis can be performed with a catalyst loading of 1 mol% on the gram scale without any problem and facile recrystallization provided an operationally simple procedure to produce the enantioenriched β-alkynyl thioamide entity (Scheme 11). Transformation of the thioamide functionality of the alkynylation product is outlined in Scheme 12. Conversion into other carboxylic acid derivatives is useful from a synthetic point of view; activation of thioamide with MeI/H_2O[39] or trifluoroacetic anhydride (TFAA) [40] provided the corresponding thioester **12** and amide **13**, respectively. *S*-Methylation with MeOTf[41] followed by alkylation with MeLi gave methyl ketone **14** in 88% yield. Treatment with MeI and subsequent hydride reduction with $NaBH_4$ afforded tertiary amine **15** in 86% yield.[42] An Eschenmoser reaction using methyl bromoacetate promoted by PPh_3 and 2,6-lutidine furnished β-ketoester **16** in 66% yield.[43]

We envisioned applying the present catalysis to the concise enantioselective synthesis of the G-protein coupled receptor GPR40 agonist AMG-837. GPR40 has received growing attention as a potential therapeutic target for insulin-derived disorders, such as type-2 diabetes.[44] Recently, the β-alkynyl acid derivative AMG-837 was documented to be a potent GPR40 agonist at Amgen (Applied Molecular Genetics).[45] In their report, the introduction of chirality to a β-alkynyl acid entity was achieved using a stoichiometric amount of Me_2Zn and cinchonidine.[46] Considering the clinical potency of AMG-837, it would be a viable synthetic target to demonstrate the utility of the present catalysis. We began our study by examining the direct catalytic asymmetric conjugate alkynylation of trimethylsilylacetylene (**2h**) of thioamides bearing a *para*-oxygen functionalized β-



Scheme 10. Direct catalytic asymmetric conjugate alkynylation followed by intramolecular diastereoselective conjugate addition.



Scheme 11. Direct catalytic asymmetric conjugate alkynylation performed on the gram scale.

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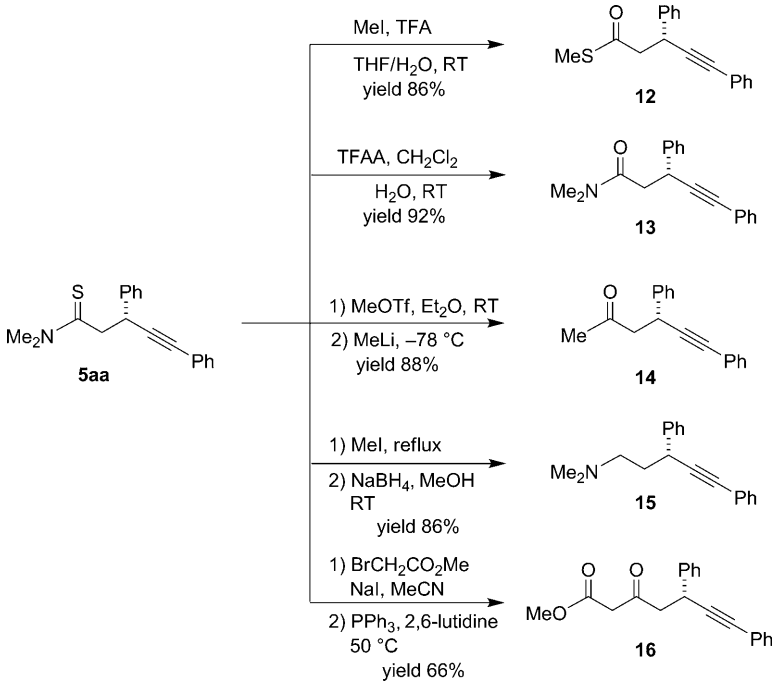
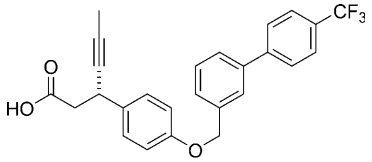


Scheme 12. Divergent transformation of the alkynylation product.

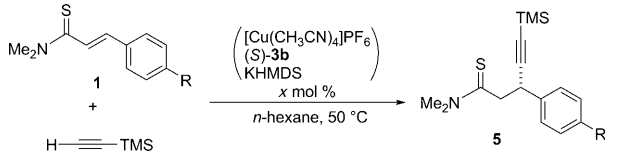


AMG-837

potent GPR40 receptor agonist

aryl substituent (Table 5).[47] As described in Table 1, the present catalysis is sensitive to the electronic nature of the β-aryl substituent, and only trace amounts of product **1ih** were obtained in the reaction with thioamide **1i** bearing a *para*-methoxy group, even with catalyst **4** using KHMDS (entry 1). Thioamides **1q** and **1r** with a *para*-acyloxy group improved the chemical yield (entries 2 and 3), while thioamide **1s** with a more electron-withdrawing *para*-mesylate group resulted in no reaction (entry 4). The reaction of thioamide **1q** was further improved by extending the reaction time to afford the product **5qh** in 80% yield and 90% *ee* (entry 5). The catalyst loading could be reduced to 5 mol% (entry 6). Although the alkynylation using propyne (**2n**) significantly simplified the enantioselective synthesis of AMG-837, the desired alkynylation product **5qn** was obtained in 24% yield with 81% *ee* under the same reaction conditions. The absolute configuration of **5qh** was unequivocally determined by single crystal X-ray crystallographic analysis (Figure 6).[48]

Table 5. Direct catalytic asymmetric conjugate alkynylation of trimethylsilylacetylene (**2h**).[a]



Entry	R		*x*	Product	*t* [h]	Yield[b] [%]	*ee* [%]
1	OMe	**1i**	10	**5ih**	18	trace	–
2	OAc	**1q**	10	**5qh**	18	58	92
3	OPiv	**1r**	10	**5rh**	18	31	–
4	OMs	**1s**	10	**5sh**	18	ND	–
5	OAc	**1q**	10	**5qh**	40	80	90
6	OAc	**1q**	5	**5qh**	40	83[c]	91

[a] **1**: 0.2 mmol, **2h**: 1.0 mmol. [b] Determined by ^{1}H NMR analysis with 2-methoxynaphthalene as an internal standard. [c] Isolated yield.

The highly crystalline character of **5qh** allowed for a facile recrystallization in a dichloromethane/*n*-hexane binary solvent system to give **5qh** in enantiomerically pure form (Scheme 13). The synthesis was initiated with **5qh**, which has the requisite stereogenic center for the synthesis of AMG-837. The protocol for thioester formation was used with MeI in the presence of H_2O under an acidic medium,[39] followed by methanolysis of the acetyl group and thioester moiety with Cs_2CO_3/MeOH as well as removal of TMS group, affording methy lester **18**. Without purification, an ether side chain was installed using aryl bromide **19**, and this afforded **20** in 48% yield over 3 steps from **5qh**. Introduction of a methyl group at the terminal alkyne was achieved by Sonogashira coupling with MeI, using a bulky carbene ligand generated from precursor **21**, to give **22** in 63% yield.[49] Finally, conventional basic hydrolysis of methyl ester delivered AMG-837, a potent GPR40 agonist.

Conclusions

In summary, we have developed a catalytic asymmetric conjugate addition of terminal alkynes to thioamides based on a simultaneous activation strategy. A prototype soft Lewis acid/hard Brønsted base cooperative catalyst comprising $[Cu(CH_3CN)_4]PF_6$, bisphosphine ligand, and $Li(OC_6H_4$-*p*-OMe) was effective. A series of control experiments revealed that the copper-thioamide enolate intermediate functioned as a Brønsted base to generate copper alkynylides

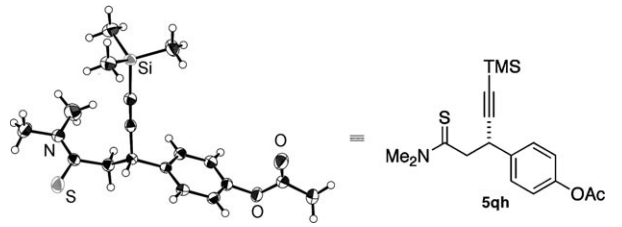
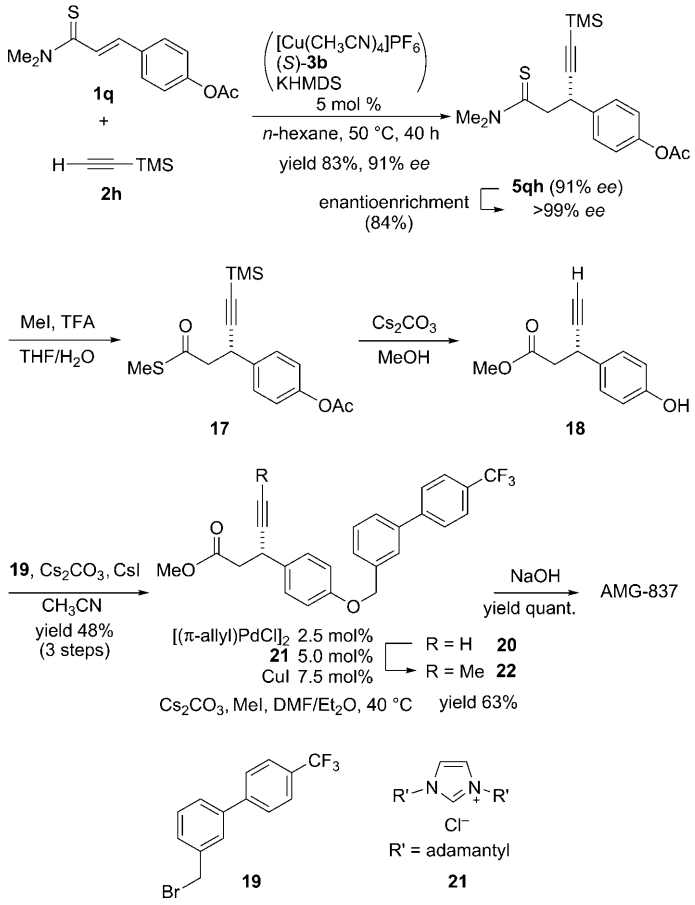


Figure 6. Ortep drawing of a single crystal of **5qh**.



Scheme 13. Enantioselective synthesis of AMG-837.

for the subsequent catalytic cycle, thus achieving highly efficient proton transfer between substrates to promote enantioselective carbon–carbon bond formation. Examination of the catalytic cycle indicated that the copper alkynylide was an entry point into the catalytic cycle, allowing for the identification of a more operationally simple catalyst comprising $[Cu(CH_3CN)_4]PF_6$, bisphosphine ligand, and KHMDS, all of which are commercially available. Divergent transformation of the thioamide functionality of the alkynylation product is of particular importance for the synthetic utility of the present catalysis. The production of an enantioenriched β-alkynyl carboxylic acid derivative through the present alkynylation methodology was successfully applied to a concise enantioselective synthesis of AMG-837, a potent GPR40 receptor agonist.

Experimental Section

See the Supporting Information for characterization data, experimental procedures, and NMR spectra.

Acknowledgements

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