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Synthesis of trifunctional thioureas bearing 1,5-disubstituted triazole tether by Ru-catalyzed Huisgen cycloaddition

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ABSTRACT

Synthesis of trifunctional thiourea catalysts tethered with a variety of functional group is described. 1,5-Triazole tether in the catalysts was constructed by ruthenium-catalyzed Huisgen cycloaddition. We demonstrate the utility of the synthetic thioureas as an asymmetric catalyst for Michal addition of nitrostyrene with cyclohexanone.

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A variety of enzymes act as efficient asymmetric catalysts in biotransformations in living cells as well as chemical reactions. An enzyme pocket, in which reaction substrates are activated giving a desired product efficiently and selectively, is built as a well-organized chiral space in a secondary/tertiary structure of proteins. In many cases, the combination of several functional groups within a chiral space of the enzyme leads to synergistic effects on the activation of substrates, providing high stereoselectivity and/or acceleration of the reaction rate. Since this past decade, organocatalysts have emerged as promising chiral catalysts because of their ready accessibility and high efficiency in various asymmetric transformations.[1] Taking lessons in a catalyst design from natural enzymes, a class of bifunctional catalysts has been developed as organocatalytic system as well as transition and typical metallic systems.[2–4] The bifunctional catalysts possess two functional groups which can activate both reacting substrates (moieties) synergistically. For example, thiourea-based bifunctional catalyst **1**,[3a] which was developed by our group, has isolated acidic and basic functional groups in the same molecule (Fig. 1). In the case, two functional moieties are placed at neighboring position so as to entropically activate the bimolecular reaction. Thioureas bearing another activating site at a comparably remote position have been less explored.[4d,5] One of the important and challenging tasks would be adequate design of the tether, which must display conformational flexibility/rigidity appropriately to afford an organized reaction space. With the interest in developing new organocatalysts for asymmetric reactions, an easily tunable design of the catalyst candidates and synthetic accessibility to them would be valuable.

1,3-Dipolar cycloaddition of alkynes with alkyl- or arylazides, which is called as Huisgen cycloaddition,[6] affords substituted 1,2,3-triazole compounds. Cu(I)-catalyzed Huisgen cycloaddition giving 1,4-disubstituted triazoles has been paid much attention as 'click chemistry'[7] on account of several synthetic advantages, such as wide tolerance for various functional groups, high chemical yield, simple reaction operation, and easy purification. Ruthenium(II) catalysts are also known to activate Huisugen cycloaddition, but the catalysts result in the formation of 1,5-disubstituted triazoles exclusively.[8] Both the substituents of 1,5-triazoles direct at the same side, whereas those of 1,4-triazoles orient at the opposite sides. We envisioned that 1,5-triazole core would be suitable for the tether of our catalyst candidates on account of the following reasons; (1) conformational rigidity of aromatic ring, (2) both substituents of 1,5-traizoles directing to the same side, and (3) synthetic convenience. Herein we wish to report the synthesis of chiral thioureas bearing acidic or basic functional group at a remote position by using Ru-catalyzed Huisgen cycloaddition.

At the out of our study, we examined compatibility of a variety of functional groups with ruthenium catalysts ($Cp^*Ru(PPh_3)_2Cl$ and $[RuCp^*Cl]_4$), which have been reported as highly active ones. As the result, it was found that various functionalities, such as phenol, amine, amide, carbamate, imide, and ester groups, are tolerant in Ru-catalyzed Huisgen cycloaddition. On the other hand, almost no formation of triazole was observed in the reaction of substrates

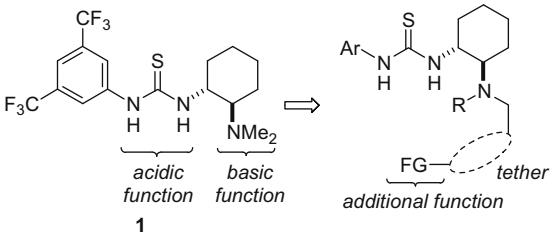

Figure 1. Design of a trifunctional thiourea catalyst.

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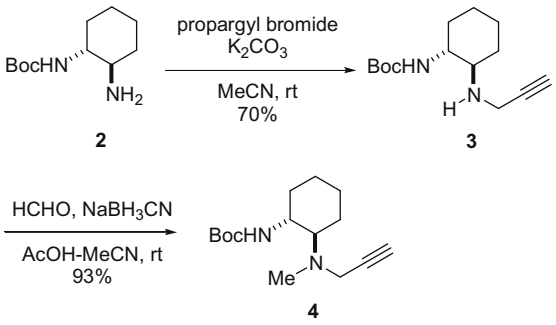
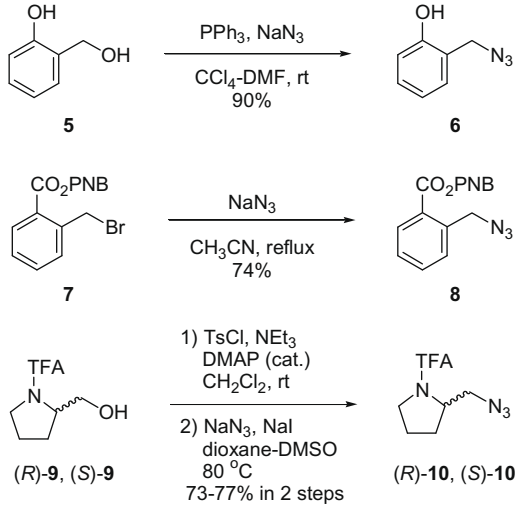


Scheme 1. Preparation of propargyl amine **4**.

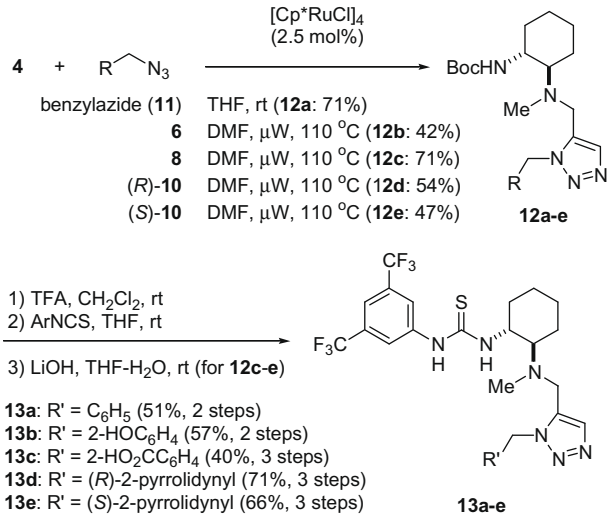


Scheme 2. Preparation of azides. PNB = *p*-nitrobenzyl, TFA = trifluoroacetyl.

having a thiourea moiety. Ruthenium catalyst would be inactivated by undesired ligation with the sulfur atom of thiourea. As the result, we planned a synthetic route toward desired thioureas as follows: (i) Ru-catalyzed Huisgen cycloaddition of alkynyl substrates and azide partners and (ii) installation of thiourea moiety.

Alkyne **4** and azides **6, 8, and 10** for the substrates of Huisgen cycloaddition were prepared (Schemes 1 and 2). Starting from mono-Boc 1,2-diaminocyclohexane (**2**), alkylation with propargyl bromide afforded secondary amine **3**. N-Methylation of **3** was accomplished by reductive amination with formaldehyde to give **4**. Azide bearing phenolic function **6** was synthesized from alcohol **5** according to the reported procedure.[9] Precursor of carboxylic acid **8** was prepared from bromide **7**. Both enantiomers of proline derivative **10** were obtained from the corresponding enantiomeric alcohols **9**.

With both substrates in hand, Ru-catalyzed Huisgen cycloaddition and further transformation into desired functionalized thioureas were accomplished (Scheme 3). Cycloaddition of **4** with benzylazide (**11**) was smoothly activated by $[Cp^*RuCl]_4$ in THF at ambient temperature giving 1,5-disubstituted triazole **12a** in good yield (71%). On the contrary, reaction with phenol **6** under the same conditions resulted in poor conversion into desired triazole **12b**. It was found that microwave irradiation in DMF (110 °C) was effective for the cycloaddition giving **12b** in 42% yield. Huisgen cycloaddition of **4** with **8**, (*R*)-**10**, and (*S*)-**10** under the same conditions afforded **12c–e**, respectively, in moderate yield. The regioselectivity in the cycloaddition was completely controlled to furnish 1,5-disubstituted 1,2,3-triazoles exclusively. Deprotection of Boc group of **12**, followed by treatment with 3,5-bis(trifluoromethyl)-

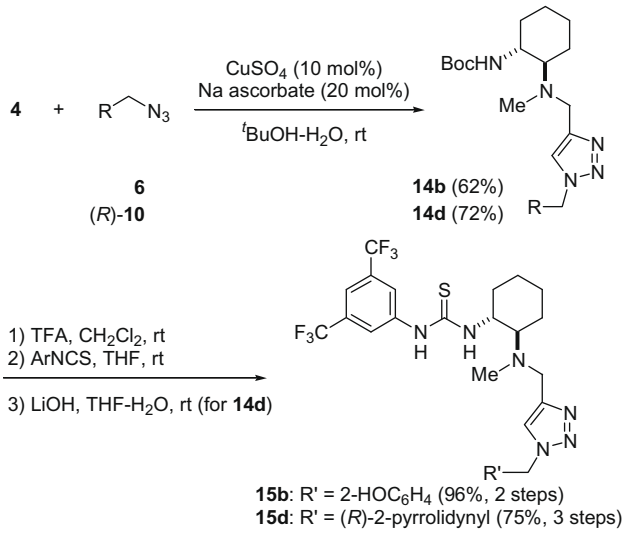


Scheme 3. Synthesis of thioureas bearing a 1,5-disubstituted triazole tether **13**. Ar = 3,5-$(CF_3)_2C_6H_3$–.

isothiocyanate and hydrolysis (only for **12c–e**), furnished thiourea 13a–**e** in fair yield.[10] The synthetic sequence involving Huisgen cycloaddition would be a facile and new methodology to prepare new classes of functional thiourea catalysts. Although thiourea moiety is intolerant of ruthenium catalysts, trifunctional thiourea catalysts having a triazole tether would be readily accessible in short steps.

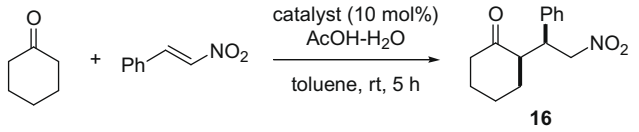
Thiourea catalysts having regioisomeric 1,4-disubstituted triazole tether were also synthesized by using Cu(I)-catalyzed cycloaddition (Scheme 4). 1,3-Dipolar cycloaddition of alkyne **4** with **6** and (*R*)-**10** in the presence of a catalytic amount of Cu(II) salt with a eductant[11] furnished 1,4-disubstituted 1,2,3-triazole **14b** and **14d**, respectively. According to the same method as mentioned above, thioureas **15b** and **15d** were obtained in good overall yield.

We next examined the effect of the remote functional group in synthetic thiourea catalysts. Asymmetric Michael addition is one of the representative C–C bond formation reactions in organocatalysis. In particular, extensive efforts for enantioselective Michael reaction of ketones to nitroalkenes have been devoted,[12] since



Scheme 4. Synthesis of thioureas bearing a 1,4-disubstituted triazole tether **15**. Ar = 3,5-$(CF_3)_2C_6H_3$–.

Table 1
Enantioselective addition of cyclohexanone to trans-β-nitrostyrene catalyzed by trifunctional thiourea[a]



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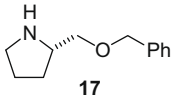
Entry	Catalyst	% Yield of **16**[b]	dr (*syn*/*anti*)[c]	% ee of *syn*-**16**[d]
1	**13d**	91	91: 9	92
2	**13e**	93	91: 9	82 (*ent*)
3	**15d**	32	93: 7	87
4[e]	**17**	10[f]	91: 9	93 (*ent*)

[a] The reaction was conducted with nitrostyrene (0.34 mmol) and cyclohexanone (3.4 mmol, 10 equiv) in the presence of catalyst (10 mol %), AcOH (15 mol %), and H_2O (1.0 equiv) in toluene (0.5 mL) at ambient temperature.
[b] Isolated yield as a mixture of *syn*/*anti* isomers.
[c] Determined by HPLC analysis and ^{1}H NMR.
[d] Determined by HPLC analysis (Daicel Chiralpak AS-H, hexane–^{i}PrOH = 90:10).
[e] The reaction result was cited from Kilburn's study (Ref. 4d).
[f] Conversion yield after the reaction was carried out for 720 h.



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the producible nitroalkanes bearing contiguous stereogenic centers would be versatile synthetic intermediates. Several pyrrolidine-based derivatives have been reported to catalyze the reaction with good to high diastereo- and enantioselectivities. Chiral thiourea-pyrrolidine-based bifunctional catalysts have also been found to give excellent enantioselectivities.[4] However, some problems such as the slow reaction rate still remain in most of the pyrrolidine-based organocatalysts. During the course of our study, Kilburn et al reported thiourea-pyrrolidine-based bifunctional catalysts,[4d] in which both functions are placed at considerably distant positions tethering with simple alkyl chain. Some of the bifunctional catalysts demonstrated excellent rate acceleration with good stereoselectivity in the reaction of cyclohexanone with *trans*-β-nitrostyrene. They made clear that the tether length between thiourea and pyrrolidine of the optimized catalyst is 5 atoms.

Under the same conditions as Kilburn's study, catalytic activity of thiourea-pyrrolidine catalyst **13d**, **13e**, and **15d** was evaluated (Table 1). The tether lengths between thiourea and pyrrolidine of **13** and **15** are 7 and 8 atoms, respectively. Catalysts **13d** and **13e** having 1,5-disubstituted triazole tether gave nitroalkane **16** in high chemical yield with good diastereo- and enantioselectivities. The stereochemistry of the major isomer **16** was determined as *syn* isomer by comparison with reported ones. Chirality of **16** from **13d** was opposite to one from **13e**. Thus, the enantioselection in the reaction would be mainly dominated by the chirality of pyrrolidinyl moiety. Although the difference of a value of enantiomeric excess is not so significant, it was observed that the chirality of 1,2-diaminocyclohexyl moiety somewhat effects on the selectivity (entries 1 and 2). In contrast, the rate of reaction with **15d** having 1,4-disubstituted triazole tether was much slower than that with **13d, e** although the enantioselectivity was comparable (entry 3). The results clearly indicated that relative position of the thiourea and pyrrolidine moieties would be a critical factor for the rate acceleration in the reaction of the Michael addition. As Kilburn reported that the reaction rate drastically decreased in the reaction with monofunctional pyrrolidine catalyst **17** (entry 4), it made clear that the thiourea function of the catalyst system would positively participate in the activation of the substrate.

The absolute configuration of the major enantiomer *syn*-**16** in the reaction with **13d** was determined to be (2*R*,1′*S*) by comparison of HPLC data with the reported ones. The configuration is consistent with a synclinal transition state for pyrrolidine-based chiral organocatalysis. A suggested transition state model is shown in Figure 2. Hydrogen bond network among the thiourea moiety, tertiary ammonium, and nitro group would direct the nitrostyrene to attack the *si*-face of the enamine.

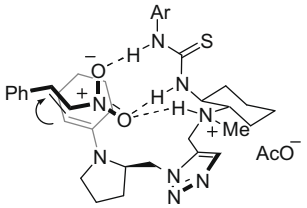

Figure 2. Proposed transition state for asymmetric Michael addition by trifunctional thiourea **13d**.

In conclusion, we have described the synthesis of several trifunctional thiourea catalysts bearing a 1,2,3-triazole tether in which one of the functional group is placed at a considerable distant position from the thiourea moiety. Regioisomeric catalysts having 1,5- and 1,4-disubstituted triazole were readily prepared by using ruthenium- and copper-catalyzed Huisgen cycloaddition, respectively. To the best of our knowledge, it is the first case for the preparation of asymmetric catalysts by Ru-catalyzed azide–alkyne click chemistry.[13] Moreover, we demonstrated the catalytic activity of synthesized thiourea-pyrrolidine-based catalysts in the enantioselective Michael addition. It was found that thiourea and pyrrolidine functions would synergistically activate substrates although they are placed at a sequentially remote position (7 atoms' tether length) to achieve acceleration of the reaction rate. Further application of synthetic catalysts and synthesis of a new class of trifunctional thioureas are currently under investigation and will be reported in due course.

Acknowledgments

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References and notes

1. Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005.
2. For recent reviews, see: (a) Bhadury, P. S.; Song, B.-A.; Yang, S.; Hu, D.-Y.; Xue, W. *Curr. Org. Synth.* **2009**, *6*, 380–399; (b) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117–1127; (c) Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465–5473; (d) Miyabe, H.; Takenomo, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785–795; (e) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393–406.
3. For representative examples of thiourea-based organocatalysis, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; (b) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643–1648; (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014; (d) Inokuma, T.; Takasu, K.; Sakaeda, T.; Takemoto, Y. *Org. Lett.* **2009**, *11*, 2425–2428.
4. Thiourea-pyrrolidine based organocatalysis: (a) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901–2904; (b) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2006**, *48*, 21–24; (c) Shen, Z.; Zhang, Y.; Jiao, C.; Li, B.; Ding, J.; Zhang, Y. *Chirality* **2007**, *19*, 307–312; (d) Carley, A. P.; Dixon, S.; Kilburn, J. D. *Synthesis* **2009**, 2509–2516.
5. Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686–6687.
6. Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613–628.
7. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
8. (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999; (b) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337–5339; (c) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Xhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930.

9. Zhang, Q.; Takacs, J. M. *Org. Lett.* **2008**, *10*, 545–548.
10. Spectral data for **13d**: white amorphous; $[\alpha]_D^{26}$ −0.41 (*c* 0.87, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 2H), δ 7.59 (s, 1H), 7.55 (s, 1H), 4.53 (dd, *J* = 13.2, 6.4 Hz, 1H), 4.35 (dd, *J* = 13.2, 5.6 Hz, 1H), δ 4.29 (m, 1H), 3.86 (br, 1H), 3.72–3.76 (m, 3H), 2.90–2.97 (m, 2H), 2.60 (br, 1H), 2.43–2.45 (m, 1H), 2.24 (s, 3H), 1.71–1.97 (m, 6H), 1.00–1.38 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.88, 141.38, 134.39, 134.38, 131.79 (q, *J* = 33.7 Hz), 123.15 (q, *J* = 275 Hz), 122.72, 117.34, 64.54, 57.47, 57.38, 54.70, 51.86, 46.11, 36.03, 32.85, 28.84, 24.97, 24.62, 24.47, 21.81; IR (neat) 3252, 2935, 2861, 1688, 1542, 1219 cm^{-1}; LRMS (FAB^+) 564 ($M+H^+$), 41; HRMS (FAB^+) calcd for $[C_{24}H_{32}F_6N_7S]^+$: 564.2344; Found: 564.2334.
11. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
12. (a) List, B.; Pojarliev, P.; Martin, H. J. *Org Lett.* **2001**, *3*, 2423–2425; (b) Enders, D.; Seki, A. *Synlett* **2002**, 26–28; (c) Beyancort, J. M.; Barbas, C. F., III *Org. Lett.* **2001**, *3*, 3737–3740; (d) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 2527–2530; (e) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559; (f) Cobb, A. J. A.; Longbottom, A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808–1809; (g) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369–1371; (h) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215; (i) Clarke, M. L.; Fuentes, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 930–933; (j) Chen, H.; Wang, Y.; Wei, S.; Sun, J. *Tetrahedron: Asymmetry* **2007**, *18*, 1308–1312; (k) Quintard, A.; Bournaud, C.; Alexakis, A. *Chem. Eur. J.* **2008**, *14*, 7504–7507; (l) Yakob, Z.; Shah, J.; Leistner, J.; Liebsher, J. *Synlett* **2008**, 2342–2344; (m) Xu, D.-Q.; Wang, L.-P.; Luo, S.-P.; Wang, Y.-F.; Zhang, S.; Xu, Z.-Y. *Eur. J. Org. Chem.* **2008**, 1049–1053; (n) Tan, B.; Zeng, X.; Lu, Y.; Chua, P. J.; Zhong, G. *Org. Lett.* **2009**, *11*, 1927–1930.
13. Syntheses of organocatalysts using Cu(I)-catalyzed click chemistry: (a) Luo, S.; Xu, H.; Mi, X.; Li, J.; Zheng, X.; Cheng, J.-P. *J. Org. Chem.* **2006**, *71*, 9244–9247; (b) Yan, Z.-Y.; Niu, Y.-N.; Wei, H.-L.; Wu, L.-Y.; Zhao, Y.-B.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2006**, *17*, 3288–3293.