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Threonine-derived Thioureas as Bifunctional Organocatalysts for Enantioselective Michael Addition

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ABSTRACT

A series of threonine-derived thioureas were developed through the facile modification of L-threonine chiral scaffold. The enantioselective efficiency were evaluated in the catalytic asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes, which afforded the chiral nitroalkylated naphthoquinone derivatives in high yields (up to 93%) and enantio-selectivities (up to 99% *ee*) under low catalyst loading (3 mol%).

Introduction

Hydrogen-bonding catalysis and a chiral counterion strategy have risen recently as a reliable synthetic methodology and much attention has been paid to the design of new organocatalysts.[1] Since Jacobsen successfully developed a chiral Schiff base-thiourea catalyzed asymmetric Strecker reaction, a large number of bifunctional tertiary amine-thioureas have emerged as efficient organocatalysts and applied in a variety of asymmetric transformations.[2] The essential to the great success of these thiourea-based catalysts is the functionality of the thiourea moiety as a hydrogen bond donor, which made it to be a general structural unit in the design of bifunctional catalysts. However, compared with thioureas conjugated with chiral cyclo-hexanediamine or Cinchona alkaloid, the success achieved by low-cost amino acids-derived thioureas was very limited so far. One of the important reasons is that the stereo-controlled ability of these thioureas was to a large extent limited by the kinds of amino acids available to be derived.

Recently, Lu's group introduced siloxy groups into L-threonine chiral scaffold to construct tert-phosphine bifunctional catalysts and succeseful used in asymmetric MBH reaction[3]. Encourgaed by the success of the above strategy, We assumed that the poor-tunability of amino acids-derived tertiary amine-thioureas could also be overcome. With our continuing interest in designing low-cost, fine-tunable and highly efficient organocatalysts for asymmetric transformations, here, a series of bifunctional tertiary amine-thioureas derived from L-threonine were elaborately designed (Figure 1). Besides retained tertiary amine and thiourea as necessary activated groups, L-threonine chiral scaffold which was modified through silicon etherification reaction was introducted into the new structure. We envisioned that not only designed catalyst candidates could provide dual activation through hydrogen bonding interactions in the catalytic cycle like bifunctional thioureas reported, but also the activities and stereoselectivities of them could be finely tuned by simply change of the substituent in the chiral scaffold derived from L-threonine. The Michael addition of 2-hydroxy-1,4-naphtho-quinones to nitroalkenes is particularly interesting because it produces chiral nitroalkylated compounds which are precursors of a variety of other functionalized bioactive compounds. This reaction has drawn much attentions and became an ideal model

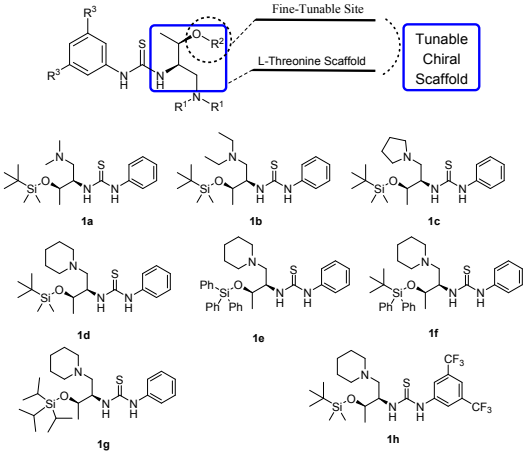


Figure 1. Structures of chiral bifunctional catalysts **1a~1h**.

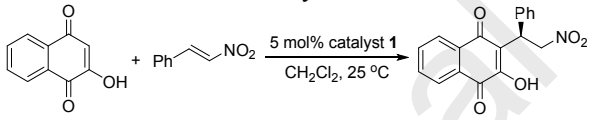
for evaluating many bifunctional catalysts.[4] To confirm our assumption, the bifunctional thioureas bearing a tunable threonine-scaffold were synthesized and their catalytic performance was evaluated in the asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes.

Results and Discussion

A series of chiral thiourea-based catalysts **1a-1h**(Figure 1) were synthesized from commercially available L-threonine via experimentally conventional protocols[3c,5-8] (see Supplementary data). The highly modular nature of chiral thioureas and facile introduction of siloxy groups facilitated the fine-tuning of their catalytic activities for asymmetric reactions.

The results of detailed evaluation of the catalysts **1a-1h** by the Michael addition of 2-hydroxy-1,4-naphthoquinone **2** to *β*-nitrostyrene **3a** were presented in Table 1. to investigate the catalytic effect of the tertiary amino group, catalysts **1a-1d** containing different alkyl group at R^1 site were initially prepared and evaluated (Table 1, entries 1-4). To our delight, cyclic and acyclic tertiary amines all gave the desired naphthoquinone derivative in moderate yields (65-75% yields) with high enantioselectivities (88-94% *ee*). In tested cases, cyclic piperidinyl group is the most promising substituent in tertiary amino structure unit (75% yields, 94% *ee*) (Table 1, entry 4). Then, we turned our attention to the R^2 site. Catalysts **1e-1g** were easily prepared by the introduction of additional three siloxy groups in the last synthetic step. When those catalysts were employed subsequently (Table 1, entries 5-7), highly enantio-selective Michael addition product was obtained (92-93% *ee*). It is noteworthy that the siloxy group has a significant impact on the yield of Michael addition product. Among the four siloxy derivatives, sterically small siloxy group seems to be favorable for chemical yield, and the catalyst **1d** containing the *tert*-butyldimethylsilyl (TBS) group gave the best results (75% yields, 94% *ee*) (Table 1, entry 4). Further synthesis and detection of catalyst with a strong electron-withdrawing group in tunable R^3 site were carried out (Table 1, entry 8). Although catalyst **1h** gave the product with high enantioselectivity as the same as catalyst **1d**, the remarkablely decreased yield was observed. Therefore, bifunctional thiourea **1d** was selected as the best catalyst for further optimization.

Table 1. Evaluation of the catalysts **1a-1h**.



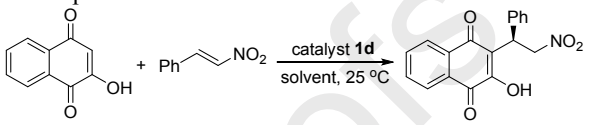
2 **3a** **4a**

Entry[a]	Catalyst	Yield [%][b]	*ee* [%][c,d]
1	**1a**	65	88
2	**1b**	67	90
3	**1c**	76	92
4	**1d**	75	94
5	**1e**	63	93
6	**1f**	52	92
7	**1g**	70	93
8	**1h**	65	94

[a] Unless noted otherwise, reactions were carried out with: 2-hydroxy-1,4-naphthoquinone **2** (0.2 mmol), *β*-nitrostyrene **3a** (0.24 mmol) and catalyst **1** (0.01 mmol) in CH_2Cl_2 (2 mL) at 25 °C for 24 h.
[b] Isolated yields after column chromatography purification.
[c] Determined by HPLC using a Daicel Chiralcel OJ-H column.
[d] The absolute configuration of the addition product(R-enantiomer) was assigned by comparison to the literature value of optical rotation in ref.10a.

The solvent employed in asymmetric transformations can have a dramatic influence on enantioselectivities and yields of product. Firstly, the common solvents (Table 2, entries 1-8) were examined in the **1d** catalyzed asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinones **2** to *β*-nitrostyrene **3a**. Obviously, high enantioselective Michael addition products (93-96% *ee*) were obtained in the moderate polar solvent (Table 2, entries 1-5), while strong polar solvent (Table 2, entries 6-8) gave more poor yields and enantioselectivities. The highest enantioselectivity (96% *ee*) was observed in toluene (Table 2, entry 4). Moreover, further improvement in enantioselectivity (97% *ee*) was achieved by appropriately increasing the amount of toluene (Table 2, entry 9). Adjusting the catalyst loading demonstrated that the high enantioselectivities were still maintained with a reduced catalyst loading from 5 to 2 mol% (Table 2, entry 10 and 11), and 3 mol% was chosen as the best catalyst loading because of no remarkable decrease in yields. When the reaction was performed at 0 °C (Table 2, entry 12), the Michael addition product with excellent enantioselectivity (>99% *ee*) was obtained, although a prolonged time was required (48 h).

Table 2. Optimization of the reaction conditions.



2 **3a** **4a**

Entry[a]	Solvent	Loading [mol%]	Time [h]	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	5	24	75	94
2	CH_2ClCH_2Cl	5	24	77	93
3	$CHCl_3$	5	24	79	93
4	$PhCH_3$	5	24	73	96
5	THF	5	24	69	95
6	EtOH	5	24	43	63
7	CH_3CN	5	24	65	76
8	DMF	5	24	25	23
9[d]	$PhCH_3$	5	24	71	97
10[d]	$PhCH_3$	3	24	67	97
11[d]	$PhCH_3$	2	36	55	97
12[d,e]	$PhCH_3$	3	48	72	>99

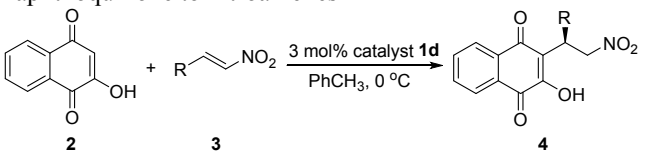
[a] Unless noted otherwise, reactions were carried out with: 2-hydroxy-1,4-naphthoquinone **2** (0.2 mmol), *β*-nitrostyrene **3a** (0.24 mmol) and catalyst **1d** (0.01 mmol) in solvent (2 mL) at 25 °C for 24 h.
[b] Isolated yields after column chromatography purification.
[c] Determined by HPLC using a Daicel Chiralcel OJ-H column.
[d] 4 ml of $PhCH_3$ was used.
[e] Reaction was carried out at 0 °C.

Further investigations into the scope and limitations of this asymmetric Michael addition was performed, and the results are summarized in Table 3. Various aromatic and aliphatic nitroalkenes were tested under the optimized catalytic conditions (Table 2, entry 12). Aromatic nitroalkenes bearing various substituents (CN, CF_3, F, Cl, Br, CH_3, OCH_3) at the *para* position on the phenyl ring reacted smoothly with 2-hydroxy-1,4-naphthoquinone to afford corresponding Michael addition products in moderate to good yields (71-91% yields) with high enantioselectivities (98- >99% *ee*) (Table 3, entries 2-8). When *ortho* or *meta*- substituted aromatic nitroalkenes (Table 3, entries 9-11) was used as an acceptor, desired products were obtained with very high enantioselectivities (99% *ee*), although a longer time was required to achieve moderate yields. Heteroaromatic nitroalkene (Table 3, entry 12) can also be applied in this Michael addition reaction, 96% ee was observed. In addition, aliphatic nitroalkenes were also suitable substrates (Table 3, entries 13-17). Linear and branched alkyl nitroalkenes all worked faster than aromatic nitroalkenes, and good yields (84-93% yields) and high *ee* values (97-99% *ee*) were attained. It is worth noting that compared to previous results, not only our catalyst loading can be reduced to lower amounts (3 mol%), but also aliphatic nitroalkenes (Table 3, entries13-17) provided the

corresponding Michael addition products in high yields and enantioselectivities (up to 98%).

Based on the experimental results described above, a plausible transition state was proposed in Figure 2. We envisioned that catalyst **1d** provide dual activation through hydrogen bonding interactions like similar bifunctional thiourea catalysts.[10] The 2-hydroxy-1,4-naphthoquinone is deprotonated by the basic nitrogen atom of the tertiary amine, while the nitroalkene is activited by the thiourea moiety through double hydrogen bonding between the NH groups and the nitro group. There are two type of transition states formed in this stage (as showed in Figure 2.), but TS-1 is favorable, The nucleophile attacks the fixed nitroalkene from the Si-face to afford the *R*-enantiomer as the major product.

Table 3. Scope of the Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes



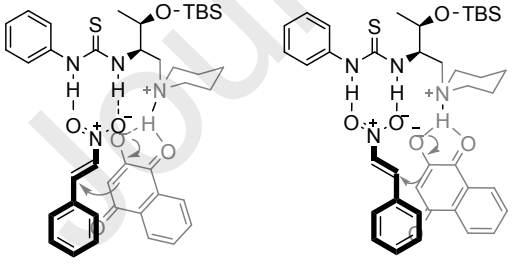
2 **3** **4**

Entry[a]	R (**4**)	Time [h]	Yield [%][b]	*ee* [%][c]
1	Ph (**4a**)	48	72	>99
2	4-CNC_6H_4 (**4b**)	72	71	>99
3	4-$CF_3C_6H_4$ (**4c**)	72	75	98
4	4-FC_6H_4 (**4d**)	72	75	98
5	4-ClC_6H_4 (**4e**)	72	78	98
6	4-BrC_6H_4 (**4f**)	72	80	98
7	4-$CH_3C_6H_4$ (**4g**)	48	86	98
8	4-$CH_3OC_6H_4$ (**4h**)	48	91	>99
9	2-BrC_6H_4 (**4i**)	96	56	>99
10	3-BrC_6H_4 (**4j**)	96	54	99
11	3-$CH_3C_6H_4$ (**4k**)	96	73	>99
12	2-Furyl (**4l**)	96	62	96
13	n-Propyl (**4m**)	24	93	99
14	*i*-Propyl (**4n**)	24	84	99
15	*i*-Butyl (**4o**)	24	89	97
16	Phenylethyl (**4p**)	24	88	98
17	Cyclohexyl (**4q**)	24	90	98

[a] Unless noted otherwise, reactions were carried out with: 2-hydroxy-1,4-naphthoquinone **2** (0.2 mmol), *β*-nitroalkenes **3** (0.24 mmol) and catalyst **1d** (0.006 mmol) in toluene (4 mL) at 0 °C.

[b] Isolated yields after column chromatography purification.

[c] Determined by HPLC using a Daicel Chiralcel OJ-H, AD-H or OD-H column.



TS-1 (favorable) TS-2 (unfacorable)

Figure 2. Proposed transition state.

Conclusions

In summary, chiral bifunctional thioureas **1a-1h** derived from threonine were designed, synthesized and verified as highly efficient organocatalysts in the asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes. The facile introduction of siloxy groups into the chiral scaffold makes these thioureas very flexible. The enantioselective efficiency were evaluated in the catalytic asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes, which afforded the chiral nitroalkylated naphthoquinone derivatives in high yields (up to 93%) and enantio-selectivities (up to 99% ee) . Because of the highly enantioselective efficiency and fine tunability of these bifunctional thioureas, further application in asymmetric organocatalysis has great potential, which is currently under investigation.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at

References and notes

[1] (a) Doyle, A. G.; Jacobsen, E. N. *Chem Rev*. 2007,107,5713–5743.
(b) Zhang, Z.; Schreiner, P. R. *Chem Soc Rev*. 2009,38,1187−1198.
(c) Busschaert, N.; Caltagirone, C.; Rossom, W. V.; Gale, P. A. *Chem Rev*. 2015,115,8038−8155.
(d) Connon, S. J. *Chem. - Eur. J*. 2006,12,5418−5427.
(e) Li H, Wang Y, Tang L, Deng L. *J Am Chem Soc*. 2004,126,9906-9907.
(f) Hu B, Deng L. *Angew Chemie Int Ed*. 2018,57,2233–2237.

[2] (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* 2006,45,1520-1543.
(b) Peterson, E. A.; Jacobsen, E. N. *Angew Chem In. Ed*. 2009,48, 6328−6331.
(c) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur J Org Chem*. 2014, 2014,2633−2646.
(d) Fang, X.; Wang, C.-J. *Chem Commun*. 2015,51,1185–1198.
(e) Siau, W.-Y.; Wang, J. *Catal Sci Technol*. 2011,1,1298−1310.
(f) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* 2013,11,7051−7071.
(g) Somanathan, R.; Chávez, D.; Servin, F. A.; Romero, J. A.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; Anaya de Parodi, C.; González, J. *Curr Org Chem*. 2012,16,2440−2461.
(h) Fang, X.; Wang, C. J. *Chem Commun*. 2015,51,1185−1197.
(i) Wang, Y.; Lu, H.; Xu, P.-F. *Acc Chem Res*. 2015,48,1832−1844.

[3] (a)Zhong F, Han X, Wang Y, Lu Y. *Angew Chemie Int Ed*. 2011,50, 7837–7841.
(c)Dou X, Han X, Lu Y. *Chem - A Eur J*. 2012,18,85–89.
(b) GX, Qu *J. Chem Commun*. 2012,48,5518–5520.

[4] For some catalytic asymmetry reaction of 2-hydroxy-1,4-naphthoquinone, see:
(a)Kim Y, Lee J, Jung J, Kim SG. *Tetrahedron Lett*. 2019,60,1625–1630.
(b)Zhou E, Liu B, Dong C. *Tetrahedron Asymmetry*. 2014,25,181–186.
(c)Jiménez EI, Vallejo Narváez WE, Román-Chavarría CA, Vazquez-Chavez J, Rocha-Rinza T, Hernández-Rodríguez M. *J Org Chem*. 2016,81,7419–7431.
(d)Zhang X, Chen YH, Tan B. *Tetrahedron Lett*. 2018,59,473–486.
(e)Jichu T, Inokuma T, Aihara K, Kohiki T, Nishida K, Shigenaga A, Yamada K ichi, Otaka A. *ChemCatChem*. 2018,10,3402–3405.
(f)Jiménez EI, Narváez WEV, Rocha-Rinza T, Hernández-Rodríguez M. *Catal Sci Technol*. 2017,7,4470–4477.
(g)Allingham MT, Bennett EL, Davies DH, Harper PM, Howard-Jones A, Mehdar YTH, Murphy PJ, Thomas DA, Caulkett PWR, Potter D, Lam CM, O'Donoghue AC. *Tetrahedron*. 2016,72,496–503.
(h)Kasaplar P, Rodríguez-Escrich C, Pericàs MA. *Org Lett*. 2013,15, 3498–3501.
(i)Kennedy CR, Lehnherr D, Rajapaksa NS, Ford DD, Park Y, Jacobsen EN. *J Am Chem Soc*. 2016,138,13525–13528.

[5] Kogen H, Kiho T, Nakayama M, Furukawa Y, Kinoshita T, Inukai M. *J Am Chem Soc*. 2000,122,10214–10215.

[6] L.-W. Xu, J. Luo, Y. Lu, *Chem Commun*. 2009,1807–1821

[7] L.-W. Xu, Y. Lu, *Org Biomol Chem*. 2008,6,2047–2053;
[8] E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem Rev*. 2007,107, 5759–5812.
[9] General Procedure for the Enantioselective Michael Addition Reaction: To a cooled solution (0 °C) of *β*-nitroalkenes **3** (0.24 mmol) and catalyst **1d** (0.006 mmol) in anhydrous toluene (4 mL) was added 2-hydroxy-1,4-naphthoquinone **2** (0.2 mmol). The reaction mixture was stirred at 0 °C for the requisite times as indicated in Table 3. Then the mixture was purified by silica gel column chromatography (CH_2Cl_2) to afford the desired products **4**. Compound **4a** was obtained according to the general procedure as yellow solid; reaction time 48 h; 46.5 mg (72%); m.p. 149-150 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OJ-H column (*n*-hexane : 2-propanol : CF_3COOH = 50 : 50 : 0.05, flow rate 1.0 mL/min, 254 nm). minor enantiomer t_r=14.7 min, major enantiomer t_r=44.0 min, >99% *ee*; $[\alpha]_D^{20}$: -36.1 (c 0.8, CH_3OCH_3); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (dd, J_1 = 13.8 Hz, J_2 = 7.5 Hz, 2H), 7.74 (dt, J_1 = 24.6 Hz, J_2 = 7.5 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.41-7.21 (m, 3H), 5.49 (dd, J_1 = 12.9 Hz, J_2 = 9.0 Hz, 1H), 5.42-5.27 (m, 1H), 5.15 (dd, J_1 = 12.9 Hz, J_2 = 6.6 Hz, 1H).
[10] (a) Yang W, Du DM. *Adv Synth Catal*. 2011, 353,1241–1246.
(b) Reddy BVS,Swain M, Reddy SM, Yadav JS. *RSC Adv*. 2013,3, 8756–8765.
(c) Hamza A, Schubert G, Soós T, Pápai I. *J Am Chem Soc*. 2006,128, 13151–13160.

Graphical Abstract

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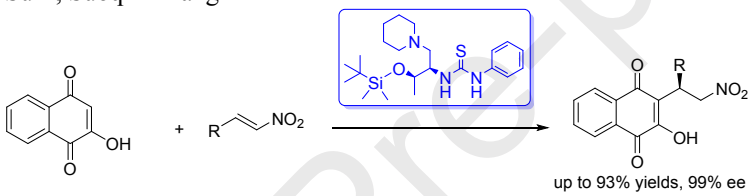

up to 93% yields, 99% ee

Highlights

1. A series of fine-tunable threonine-derived thioureas were developed as efficient organocatalysts.
2. A new approach to high-efficiency asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes.
3. The catalytic system can tolerate various substrates.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: