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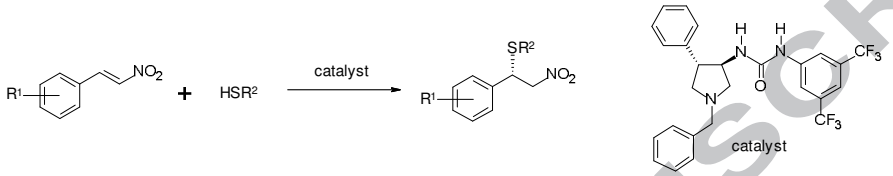

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Asymmetric Michael addition of thiols to β-nitrostyrenes using a novel phenylpyrrolidine-based urea catalyst

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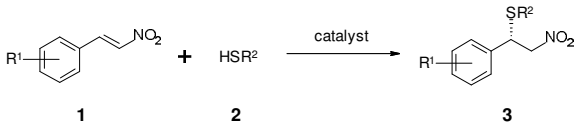
ABSTRACT

The catalyst 1-[(3*R*,4*S*)-1-benzyl-4-phenyl-pyrrolidin-3-yl]-3-[3,5-bis(trifluoromethyl)phenyl]-urea (**8**) designed base on 1-[(3*R*)-1-benzylpyrrolidin-3-yl]-3-[3,5-bis(trifluoromethyl)phenyl]-thiourea (**4**) and 1,3-bis[(3*R*,4*S*)-1-benzyl-4-phenylpyrrolidin-3-yl]urea (**7**) exhibited potent catalytic activity for the asymmetric Michael addition of thiols to β-nitrostyrenes. A mere 2 mol% of the catalyst afforded 2-nitro-1-phenylethylsulfides in high yields of up to 93% ee.

The treatment of sulfur sources with β-nitrostyrenes is a known methodology for the synthesis of 2-nitro-1-phenylethyl sulfides.[1] The derivatives of 2-nitro-1-phenylethyl sulfide are potential intermediate bioactive compounds, such as the dual antagonist of thromboxane A_2 and leukotriene D_4[2], as well as Sulconazole[3] which has a broad spectrum antifungal activity.

Asymmetric sulfa-Michael addition (SMA) has been developed in which several bifunctional organocatalysts play an important role.[4] Recently, SMA of thiols and nitroolefins has been reported by Connon[5] and Kowalczyk[6]. Connon's catalyst showed SMA between benzyl thiols and β-nitrostyrenes using a 10–20 mol% catalyst loading, with good yields of up to 96% ee, while Kowalczyk's catalyst **4** exhibited good yields with up to 87% ee (Scheme 1). Although these two works were impressive, there remains some potential for improving the reaction with regard to the loading amount, reaction yield, and enantioselectivity.

As such, we investigated the activity of a symmetric urea organocatalyst **7**; however, the results were not sufficient for the asymmetric Michael addition of thiols to β-nitrostyrenes because of a moderate enantioselectivity (~80% ee).[7] On the other hand, we obtained the structure-activity relationship of the catalyst, such as the ring size of amino moieties, substituents on the ring, and so on. The structures and results of catalyst **4–7** are shown in Table 1 and Figure 1. The catalytic activity was maintained, which resulted in a change of Kowalczyk's thio urea **4** to corresponding urea catalyst **5** (Entries 1–2). However, avoidance of the sulfur atom in urea may expand the substrate scope and decrease side reactions caused by the nucleophilicity of thio urea. The symmetric urea catalyst **6** exhibited a 47% ee (Entry 3). The organocatalyst **7**, which introduced a phenyl group into compound **6** at the *trans* position of urea on the pyrrolidine ring, increased the catalytic activity (Entry 4). From the viewpoint of synthesis, symmetrical urea can be prepared by a very simple method, however, asymmetric urea remains challenging. Therefore, we designed a urea catalyst **8** with a 3,5-bis(trifluoromethyl)phenyl urea group and a phenyl group on the *trans* side against the urea of the pyrrolidine ring.



Scheme 1. SMA of thiols to β-nitrostyrenes

The synthesis of catalyst **8** is shown in Scheme 2.[8] The transformation of (3*R*,4*S*)-1-benzyl-4-phenylpyrrolidine-3-carboxylic acid (**9**)[9a] was conducted via a Curtius rearrangement[9b] [3,5-bis(tri-fluoromethyl)aniline (**10**) (1.38 mL, 8.91 mmol), DPPA (0.42 mL, 1.95 mmol), DMF (2.5 mL), 100 °C, 5 h] to give catalyst **8** in a 40% yield. The structure of **8** was determined by X-ray crystal structure analysis with HBr salt, as shown in Figure 2.[10] The results indicated that the stereochemistry between the phenyl group and the urea nitrogen on the pyrrolidine ring

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was in a *trans* configuration. The absolute configuration of carboxylic acid **9** is reflected from that of optically active styrene oxide. This makes possible to prepare the catalyst with different absolute configurations.

The activity of catalyst **8** was evaluated for the asymmetric Michael addition of 4-*tert*-butylbenzyl thiol (**2a**) to β-nitrostyrene (**1a**) using our general procedure.[11] The results are shown in Table 1. Based on Connon's report, the absolute configuration was determined by high-performance liquid chromatography (HPLC) analysis.[5] Treatment of catalyst **8** in a standard condition, based on our previous results, showed an 88% isolated yield and the enantioselectivity of (*S*)-**3b** was 93% ee (Entry 6). In contrast, treatment of catalyst **7** resulted in a 78% ee (Entry 5).

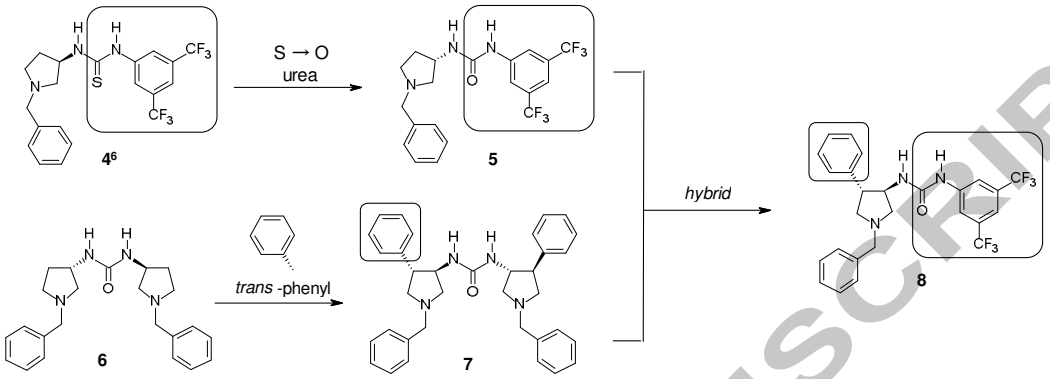
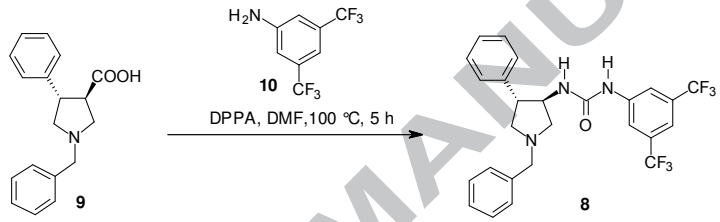


Figure 1. Design of organocatalyst **8**.



Scheme 2. Synthesis of catalyst **8**.

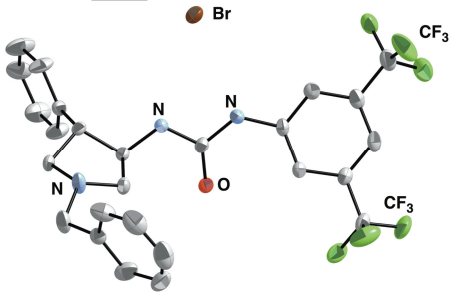
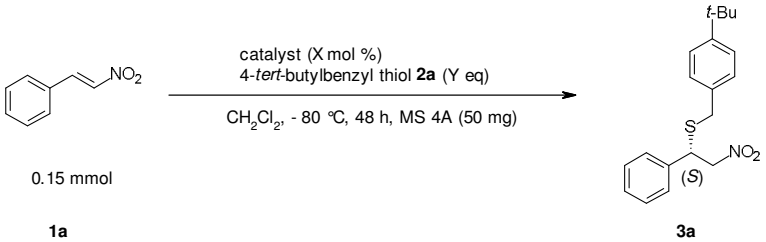


Figure 2. ORTEP view of **8** HBr salt at 50% probability.

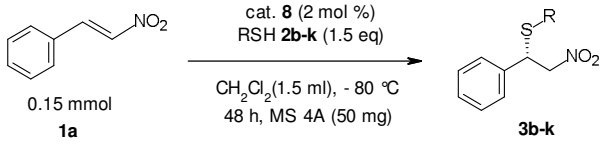
Table 1
Asymmetric addition of thiol to β-nitrostyrene



Entry	Catalyst (X mol %)	**2a** (Y equiv.)	Yield (%)[a]	Ee (%)[b]
1[c]	**4**, 2.5 mol %	1.05	[76]	[87 (*S*)]
2	**5**, 2.5 mol %	1.05	72	84 (*R*)
3	**6**, 2.5 mol %	1.05	80	47 (*R*)
4	**7**, 2.5 mol %	1.05	80	80 (*S*)
5	**7**, 2.0 mol %	1.5	88	78 (*S*)
6	**8**, 2.0 mol %	1.5	88	93 (*S*)

[a] Isolated yield.
[b] Determined by chiral-HPLC analysis.
[c] Kowalczyk's paper.

Table 2
Asymmentric addition of various thiols to β-nitrostyrene



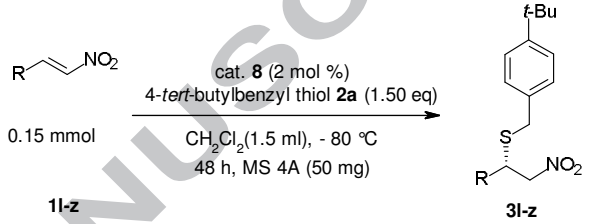
Entry	R	Product	Yield (%)[a]	Ee (%)[b]
1	Ph (**2b**)	**3b**	94	6
2	$PhCH_2$ (**2c**)	**3c**	89	89
3	$PhCH_2CH_2$ (**2d**)	**3d**	100	35
4	$PhCH_2CH_2CH_2$ (**2e**)	**3e**	91	29
5	cyclohexyl (**2f**)	**3f**	82	4
6	*t*-Bu (**2g**)	**3g**	11	racemi
7	4-$MeOC_6H_4CH_2$ (**2h**)	**3h**	89	88
8	4-$MeO_2CC_6H_4CH_2$ (**2i**)	**3i**	95	56
9	4-$ClC_6H_4CH_2$ (**2j**)	**3j**	92	66
10	2-$ClC_6H_4CH_2$ (**2k**)	**3k**	100	90

[a] Isolated yield.
[b] Determined by chiral-HPLC analysis.

We tried several thiols **2b–2e** with β-nitrostyrene **1a** (Table 2). The reaction of compounds **1b–1e** afforded the corresponding products **31–3e** in good yields (Entries 1–4). The thiophenol derivative **3b** showed little enantioselectivity (Entry 1). The benzyl thiol **2c** gave compound **3c** in 89% yield with 89% ee (Entry 2). The phenethyl derivative **3d** showed 35% ee and quantitative yield (Entry 3). The 3-phenylpropan thiol **2e** gave compound **3e** in 91% yield with 29% ee. Depending on the methylene chain length (CH_{2n}, n: 0 – 3), enantioselectivities had been changed. The cyclohexyl derivative **3f** afforded a good isolated yield (82%) but only a 4% ee (Entry 5). The *tert*-butyl thiol gave a lower yield of **3g** due to the slower conversion rate at low reaction temperature[13], and **3g** did not exhibit any enantioselectivity (Entry 6). The primary and secondary thiols gave Michael adducts in good yields; however, the reaction of tertiary thiol was less favorable. The benzyl thiol tended to induce enantioselectivity among the thiols. Then the benzyl thiols were screened. The thiols **2h–2k** afforded the corresponding products **3h–3k** in good yields (Entries 7–12). The 4-methoxybenzyl derivative **3h** gave high enantioselectivity of 88% ee (Entry 7). The compound **3i**, having a 4-methoxy-carbonyl group on the 4-position of the benzene ring, resulted in a smaller enantioselectivity of 56% ee (Entry 8). The Cl atom on the 4-position and 2-position of benzyl thiol gave **3j** (66% ee) and **3k** (90% ee), respectively (Entries 9–10). Compound **3a** showed the highest ee.

Next we evaluated the Michael addition between 4-*tert*-butylbenzyl thiol (**2a**) and several β-nitroorefins **1l–z** (Table 3).[12] The reaction of compounds **1l–1s** afforded the corresponding products **3l–3s** in good yields (Entries 1–8). Compound **3l** (2-Me), **3m** (3-Me), and **3n** (4-Me) showed 76% ee, 85% ee, and 91% ee, respectively (Entries 1–3). Compound **3o** (4-Cl) showed 89% ee (Entry 4), while the electron-donating 4-MeO derivative **3p** maintained an 83% ee (Entry 5). On the other hand, the electron-withdrawing 4-nitro derivative **3q** exhibited a low 66% ee (Entry 6). 3-Br derivative **3r** showed 89% ee (Entry 7). The 3-hydroxymethyl derivative **3s** presented an inadequate enantioselectivity of 48% ee. Enantioselectivity can be considered to be dependent on the hydrogen bond between the catalyst and the substrate. The 3-hydroxymethyl benzene of **3s** alone may be confused with the benzyl thiol **2a** in the hydrogen bonding system that expresses enantioselectivity. 1-Naphthyl derivative **3t** decreased enantioselectivity to 69% ee, while 2-naphthyl derivative **3u** maintained an 86% ee. The 2-furyl compound **3v**, 2-thienyl compound **3w** and 3-pyridinyl compound **3x**, which had hetero-cycles instead of the phenyl group, showed 91% ee, 92% ee and 61% ee, respectively (Entries 11–13). The 1-methyl-3-indolyl compound **3y** and phenetyl compound **3z** having linkers between nitroolefin and benzene ring decreased enantioselectivity to 31% ee and 56% ee, respectively (Entries 14–15). These results indicate possibilities of widely application to not only nitrostyrenes but also nitroolefins.

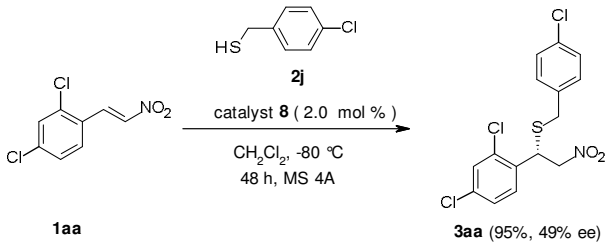
Table 3
Asymmentric addition of thiol to various nitroolefins



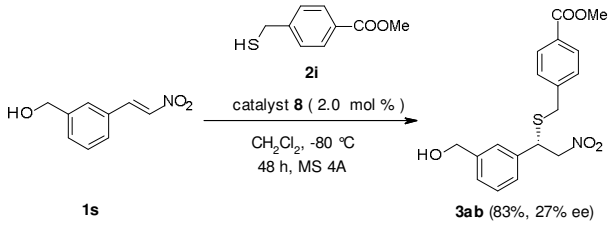
Entry	R	Product	Yield (%)[a]	Ee (%)[b]
1	2-MeC_6H_4 (**1l**)	**3l**	100	76
2	3-MeC_6H_4 (**1m**)	**3m**	100	85
3	4-MeC_6H_4 (**1n**)	**3n**	99	91
4	4-ClC_6H_4 (**1o**)	**3o**	93	89
5	4-$MeOC_6H_4$ (**1p**)	**3p**	99	83
6[c]	4-$NO_2C_6H_4$ (**1q**)	**3q**	94	66
7	3-BrC_6H_4 (**1r**)	**3r**	99	89
8[d]	3-$HOCH_2C_6H_4$ (**1s**)	**3s**	87	48
9	1-naphthyl (**1t**)	**3t**	98	69
10	2-naphthyl (**1u**)	**3u**	95	86
11	2-furyl (**1v**)	**3v**	85	91
12	2-thienyl (**1w**)	**3w**	98	92
13[c]	3-pyridinyl (**1x**)	**3x**	99	61
14	1-methyl-3-indolyl (**1y**)	**3y**	60	31
15	phenethyl (**1z**)	**3z**	83	56

[a] Isolated yield.
[b] Determined by chiral-HPLC analysis.
[c] 5.5 ml of CH_2Cl_2 were used.
[d] 2.5 ml of CH_2Cl_2 were used.

In the case of an intermediate sulconazol which is an antifungal agent,[3,6] 4-chlorobenzyl thiol (**2j**) and 2,4-dichloro-1-(2-nitrovinyl)benzene (**1aa**) were treated with SMA condition to give corresponding product, 4-chlorobenzyl[1-(2,4-dichloro-phenyl)-2-nitroethyl] sulfide (**3aa**), in 95% yield with 49% ee (Scheme 3). Finally, we evaluated the asymmetric Michael addition between β-nitrostyrene **1s** and benzyl thiol **2i** (Scheme 4). We obtained the intermediate of the dual antagonist of thromboxane A_2 and leukotriene D_4, (*S*)-Methyl 4-{[(3-hydroxy-methylphenyl)-2-nitro-ethyl]thiomethyl}benzoate (**3ab**), with 83% yield and 27% ee. We could enrich ee of **3ab** which was treated as racemate.[1a]



Scheme 3. Synthesis of **3aa**



Scheme 4. Synthesis of **3ab**

In summary, we rationally designed a new organocatalyst **8** for SMA between thiols and β-nitrostyrenes. In comparison to symmetric urea **5**, catalyst **8** showed a higher enantioselectivity despite only one pyrrolidine unit. This result was very effective with regard to furthering pyrrolidine catalyst design and synthesis. For the common target compound **3a**, a mere 2 mol% of the catalyst afforded 2-nitro-1-phenylethylsulfides in high yields with up to 93% ee. This enantioselectivity was more than competitive with the 10 mol% loading of Connon's catalyst. In addition, catalyst **8** showed the same or slightly better catalytic activity than that of Kowalczyk's catalyst **4** in several cases. Thus, we determined that urea **8** was effective for use in SMA, and that benzyl thiols were particularly appropriate for the reaction.

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8. Synthesis of catalyst **8**[9]: The mixture of (3*R*,4*S*)-1-benzyl-4-phenylpyrrolidine-3-carboxylic acid (**9**) (0.50 g, 1.78 mmol), DPPA (0.42 mL, 1.95 mmol), 3,5-bis(trifluoromethyl)aniline (**10**) (1.38 mL, 8.91 mmol), and DMF 2.5 mL was heated to 100°C. After stirring for 5 h, the mixture was cooled to r.t., then added with 5M NaOHaq 1.07 mL and water 10 mL. Organic layer (lower) was separated. Water layer was extracted with EtOAc 2 mL. Organic layers were collected then diluted with water 15 mL and EtOAc 15 mL then organic layer was separated. The solvents were concentrated under reduced pressure. The residue was purified by column chromaotgraphy (*n*-heptane/EtOAc = 3/1 → 1/1) to afford 1-[(3*R*,4*S*)-1-benzyl-4-phenylpyrrolidin-3-yl]-3-[3,5-bis(trifluoro-methyl)phenyl]urea (**8**) 361 mg (0711 mmol, y. 40%) as a pale yellow foam.
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10. **8** HBr was crystallized from MeOH/H_2O. Crystal system = orthorhombic, a = 5.8181(4) Å, b = 16.7744(11) Å, c = 26.5596(18) Å, V = 2592.1(3) Å^3, space group = $P2_12_12_1$, Z = 4, μ = 1.658 cm^{-1}, T = 133 K, $R[F^2 > 2\sigma(F^2)]$ = 0.0400, wR_2 = 0.1233, GOF = 0.871, Refl/param. = 5838/334. Complete crystallo- graphic data for compound **8** HBr have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 1022570. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 0044 1223 336 033, via www.ccdc.cam.ac.uk/data_request/cif.
11. General procedure: To MS 4A (50 mg) heated and dried under reduced pressure for 10 min in a two-necked round bottom flask (30 mL) were added β-nitrostyrene (**1a**) (22.4 mg, 0.15 mmol), catalyst **8** (0.003 mmol), and CH_2Cl_2 (1 mL) at room temperature. After stirring for 20 min, the mixture was cooled to −80 °C. To the mixture was added the solution of 4-*tert*-butylbenzyl thiol (**2a**) (40.6 mg, 0.225 mmol) in CH_2Cl_2 (0.5 mL) during 10 min at −80 °C. After stirring for 48 h, the mixture was filtered and the solution was separated on TLC (*n*-hexane/EtOAc = 24/1) to give (4-*tert*-butylbenzyl)(2-nitro-1-phenylethyl)sulfide (**3a**) 42 mg [88%, 93%ee, $[\alpha]^{20}_D$+ 177 (c 0.428, CH_2Cl_2)] as a oil.
12. Synthesis of β-nitrostyrenes (a) Jakubec, P.; Cockfield, D. M.; Hynes, P. S.; Cleator, E.; Dixon. D. J. *Tetrahedron: Asymmetry* **2011**, *22*, 1147-1155. (b) Trost, B. M.; Muller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438-2439. (c) Mahmood, S. Y.; Lallemand, M.-C.; Sader-Bakaouni, L.; Charton, O.; Vérité, P.; François, H. D. *Tetrahedron*, **2004**, *60*, 5105-5110. (d) Atokinson, D.; Meredith, P. *Synlett* **2003**, *12,* 1853–1855. (e) Liu, J.-T.; Yao, C.-F. *Tetrahedron Lett.* **2001**, *42,* 6147–6150. (f) Kuster, G. J. T.; Steeghs, R. H. J.; Scheeren, H. W. *Eur. J. Org. Chem.* **2001**, *3*, 553-560. (g) Canoira, L., Rodriguez, J. G.; Subirats, J. B.; Escario, J.-A., Jimenez, I.; Martinez-Fernandez A. R. *Eur. J. Med. Chem.* **1989**, *24*, 39-42. (h) Worrall, D. E. *Org. Synth.* **1929**, *9*, 66–68.
13. Racemic standards were prepared at room temperature.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at