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PLANAR CHIRAL [2.2]PARACYCLOPHANE-BASED BIS(THIOUREA)-CATALYZED HIGHLY DIASTEREO- AND ENANTIOSELECTIVE MICHAEL ADDITION REACTION OF NITROETHANE TO NITROSTYRENES

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‡This paper is dedicated to Professor Dr. Yasuyuki Kita on celebration of his 77th birthday.

Abstract – To demonstrate the utility of [2.2]paracyclophane as a chiral organocatalyst backbone, we evaluated a planar chiral pseudo-*ortho*-[2.2]paracyclophane-based bis(thiourea) catalyst in the Michael addition reaction of nitroethane to nitrostyrenes. The catalyst produced the desired 1,3-dinitro compounds in high yields and high diastereo- and enantioselectivities.

The thiourea functionality serves as a double hydrogen-bonding donor, and catalyzes a variety of organic transformations under mild conditions.[1] Most of chiral thiourea catalysts have been developed as a bifunctional catalyst linked with a basic functionality, such as an amine or phosphine. The bis(thiourea) catalysts shown in Figure 1 have also proven to be effective for diverse asymmetric reactions, which include not only the reactions promoted by a thiourea molecule alone, such as the Diels-Alder reactions[2] and Friedel-Crafts reactions[3,4] but also the reactions with the need of an external base, such as the Morita-Baylis-Hillman (MBH) reaction,[5] Henry reaction,[6] and kinetic resolution of amines.[7,8] The chiral scaffolds allowing the dual activation of the substrate and reactant are mainly based on the *trans*-1,2-diaminocyclohexane or 2,2'-diamino-1,1'-binaphthalene framework.[9,10]

[2.2]Paracyclophane (PCP) is recognized as a useful planar chiral scaffold for ligands used in transition metal catalysts.[11,12] A variety of asymmetric reactions based on catalysts with planar chiral PCP-based ligands, combined with the appropriate central chirality, have already been reported. However, there is little information available about the development of PCP-based organocatalysts,[13] especially acid

catalysts.[14] In this context, we have developed the PCP-based bis(thiourea) catalyst (R_p)-**1**, derived from pseudo-*ortho*-diamino-PCP (Figure 1). The planar chiral bis(thiourea) (R_p)-**1** exhibits a high reactivity and good enantioselectivity in the Henry reaction of nitroalkanes with various aldehydes although the diastereoselectivity of the products is low (Scheme 1, eq. 1).[15] We now report an extension of the application of the catalyst (R_p)-**1** to the Michael addition reaction of nitroalkane to β-nitrostyrenes (eq. 2). Based on the recognition of the nitro group with the thiourea functionality, a high reactivity and selectivities in the reaction have been expected for bis(thiourea) (R_p)-**1**. The reaction product-derived compounds, such as 1,3-diamines, are important key synthetic intermediates for biologically-active compounds.[16] Although several chiral transition metal catalysts[17] and acid-base-hybrid organocatalysts[18] achieving highly enantioselective reactions have already been reported, lowering the reaction temperature is usually needed, and the *syn/anti* selectivities are not necessarily high. This type of Michael reaction catalyzed by chiral bis(thiourea) molecules have not yet been reported.

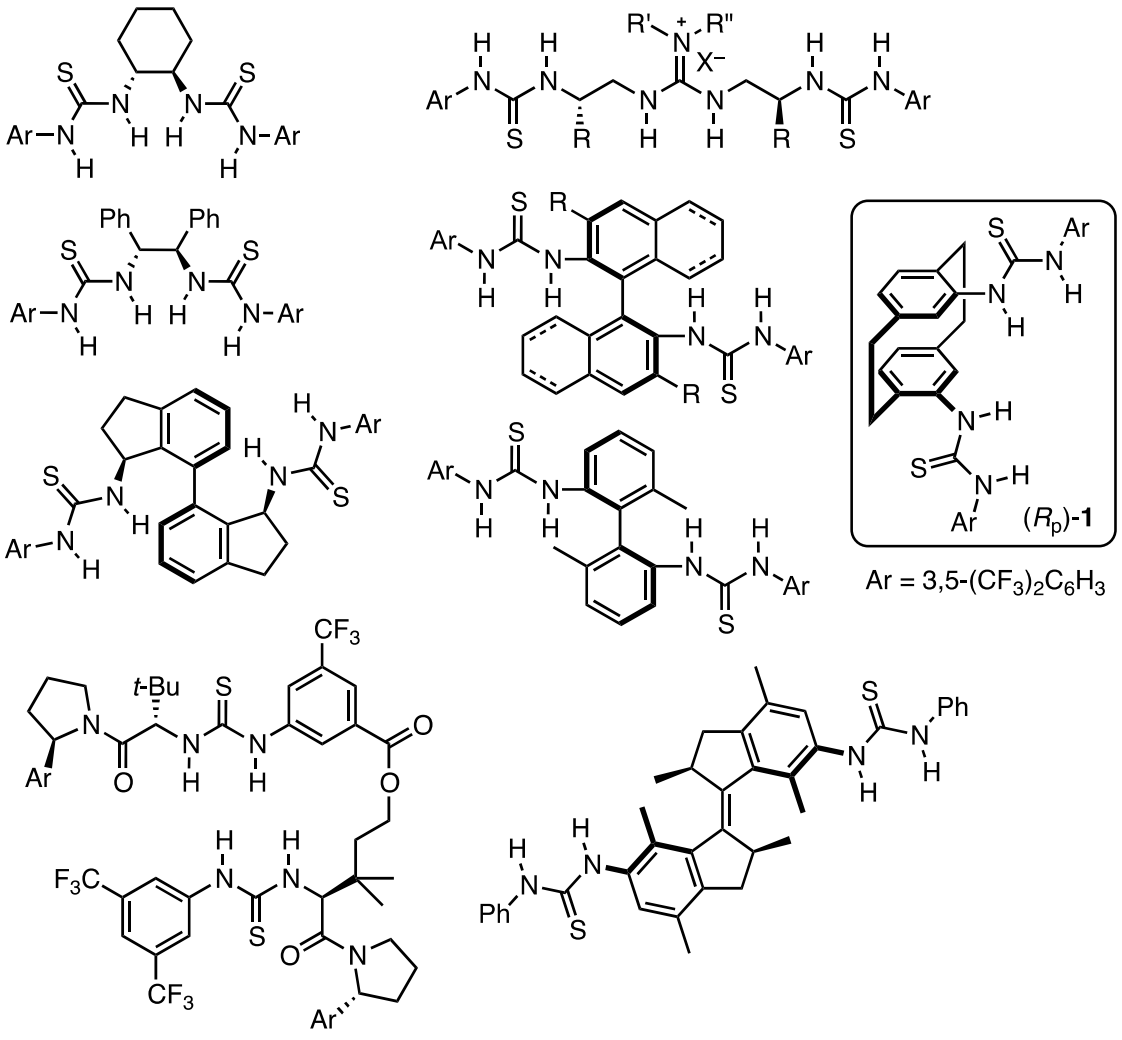
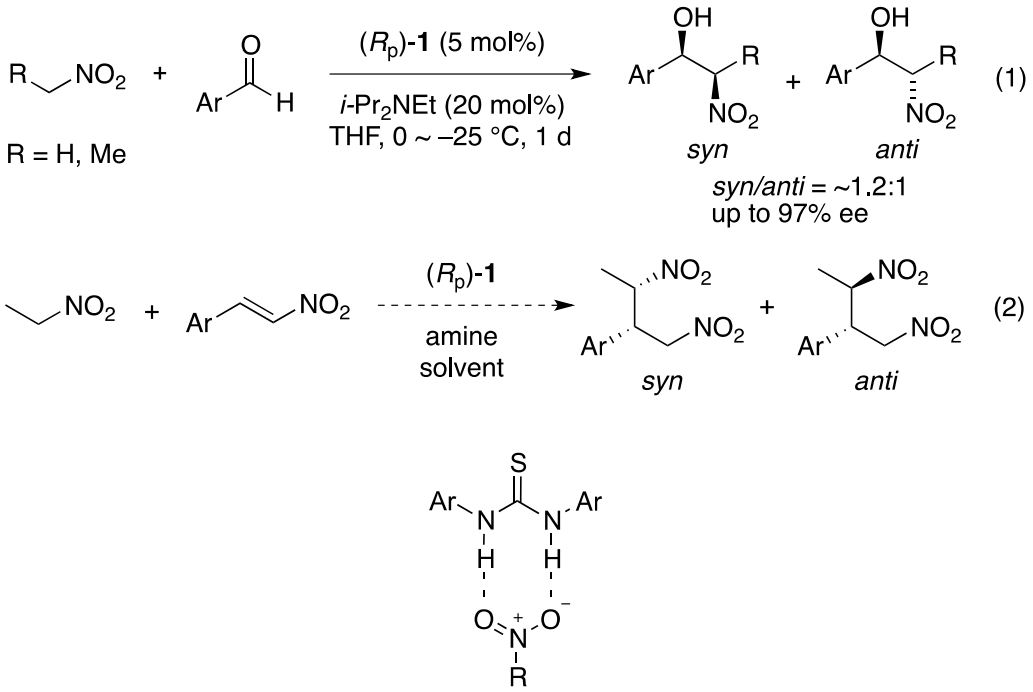


Figure 1. Chiral bis(thiourea) catalysts



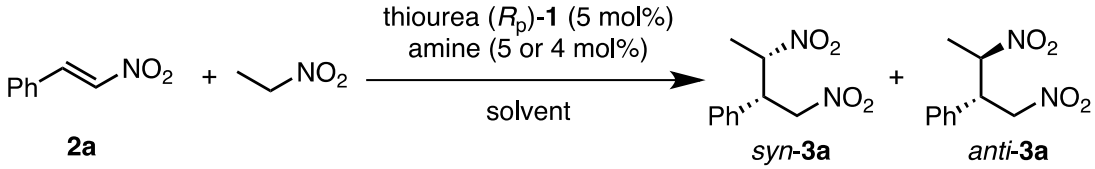
Scheme 1. PCP-Based bis(thiourea) catalyzed reactions

Our initial investigations involved screening of the solvent for the reaction of nitroethane and nitrostyrene using 5 mol% bis(thiourea) (R_p)-**1** and 5 or 4 mol% triethylamine at room temperature. Among the solvents evaluated, acetonitrile was most effective in terms of the reaction rate (reaction time: 4 h, >99% yield), *syn/anti* selectivity and the enantioselectivity of the *syn* product (93:7, 88% ee) (Table 1, entry 5). Nitroethane itself also showed high diastereo- and enantioselectivities but a low conversion yield (entry 7). A racemic product was obtained using DMF having a higher dielectric constant and Lewis basicity (entry 6). The use of less polar and Lewis basic toluene and dichloromethane decreased both the diastereo- and enantioselectivities (entries 1 and 2). The ethereal solvents, such as diethyl ether and THF, which is the most suitable solvent for the Henry reaction with bis(thiourea) (R_p)-**1**, were not as appropriate solvents as acetonitrile (entries 3 and 4).

The effects of base were next investigated. The amount of the added base had a significant influence on the reactivity and selectivity. The reaction with 10 mol% triethylamine was completed within 2.5 h, but decreased the diastereo- and enantioselectivities (entry 8). The use of 2.5 mol% triethylamine afforded the desired product in a lower conversion yield but with a 96:4 *syn/anti* selectivity and 91% ee for the *syn* product (entry 9). Diisopropylethylamine (5 mol%) showed a similar product yield and selectivities to triethylamine, while other amines, such as DABCO, DBU, and imidazole, gave unsatisfactory results in terms of their selectivities or conversion yields (entries 10–13). Reduction of the loading amount of the catalyst to 2 mol% based on enlarging the reaction scale didn't affect the product yield and enantioselectivity, but led to a prolonged reaction time and a slight decrease in the diastereoselectivity

(entry 14). Epimerization of the product was confirmed along with a slight reduction of the optical purity of the *syn*-product in the presence of bis(thiourea) (5 mol%) and amine (5 mol%) at room temperature for 24 h (Scheme 2). Finally, the use of 5 mol% triethylamine in acetonitrile at 0 °C was determined as the optimized conditions (entry 15).

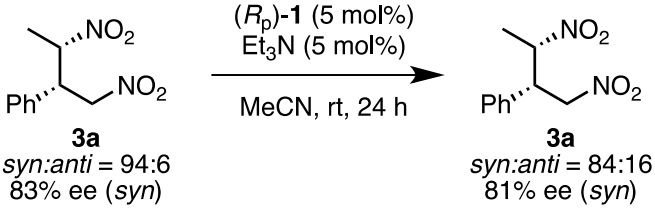
Table 1. Optimization of reaction conditions[a]



2a *syn*-**3a** *anti*-**3a**

Entry	Amine	Solvent	Temp.	Time (h)	Yield (%)[b]	*syn*:*anti* [c]	Ee of *syn* (%)[c]
1	Et_3N	toluene	rt	23	91	68:32	65
2	Et_3N	CH_2Cl_2	rt	3.5	99	88:12	79
3	Et_3N	Et_2O	rt	4	>99	87:13	80
4	Et_3N	THF	rt	168	99	87:13	74
5	Et_3N	MeCN	rt	4	>99	93:7	88
6	Et_3N	DMF	rt	3.5	82	84:16	1
7	Et_3N	–	rt	43	60[d]	94:6	87
8	Et_3N[e]	MeCN	rt	2.5	89	89:11	81
9	Et_3N[f]	MeCN	rt	24	40[d]	96:4	91
10	*i*-Pr_2NEt	MeCN	rt	6	>99	94:6	89
11	DABCO	MeCN	rt	3	>99	61:39	83
12	DBU	MeCN	rt	2	97	75:25	6
13	imidazole	MeCN	rt	48	12[d]	92:8	–
14[g]	Et_3N[h]	MeCN	rt	96	90	91:9	89
15	Et_3N	MeCN	0 °C	22	>99	96:4	91
16	Et_3N	MeCN	–20 °C	24	96	97:3	90

[a] Reaction conditions: **2a** (0.056 mmol), nitroethane (1.4 mmol), (R_p)-**1** (5 mol%), triethylamine (5 or 4 mol%) in solvent (0.1 mL) under N_2. [b] Isolated yields of *syn/anti* mixture. [c] Determined by HPLC. [d] Conversion yields. [e] Triethylamine (10 mol%) was used. [f] Triethylamine (2.5 mol%) was used. [g] Nitrostyrene (0.2 mmol) and (R_p)-**1** (2 mol%) were used. [h] Triethylamine (1.6 mol%) was used.



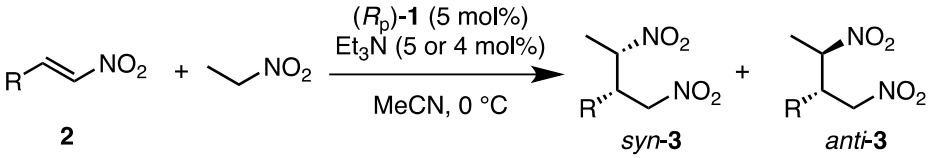
3a
syn:anti = 94:6
83% ee (*syn*)

3a
syn:anti = 84:16
81% ee (*syn*)

Scheme 2. Epimerization of **3a**

We next explored the substrate generality with respect to the nitrostyrenes. For all the nitrostyrenes examined, the reactions under the optimized conditions afforded the 1,3-dinitro compounds in good to excellent yields (67–>99%) with a high *syn/anti* selectivity (87:13–96:4) and enantioselectivity (79–92% ee). The electron-donating group-substituted nitrostyrenes afforded higher diastereo- and enantioselectivities than the electron-withdrawing group-substituted ones (Table 2, entries 2–5 vs. entries 6–11). The position of the substituent didn't affect the product yield and selectivities. The naphthyl and heteroaryl styrenes could also be successfully employed to give the desired product in good yields and selectivities (entries 12–14).

Table 2. Substrate scope[a]



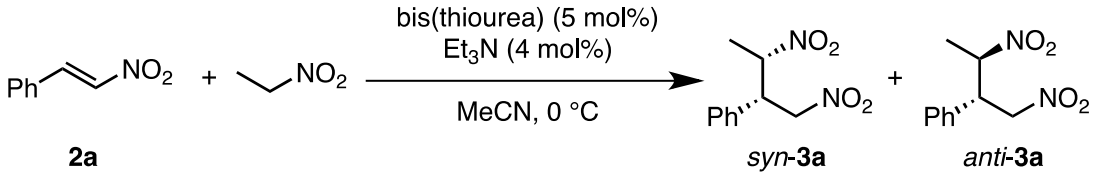
2 *syn*-**3** *anti*-**3**

Entry	**2**	Nitroalkene (R)	Time (h)	Yield (%)[b]	*syn*:*anti* [c]	Ee of *syn* (%)[c]
1	**2a**	Ph	22	>99	96:4	91
2	**2b**	2-$MeOC_6H_4$	40	>99	94:6	92
3	**2c**	3-$MeOC_6H_4$	42	>99	93:7	87
4[d]	**2d**	4-$MeOC_6H_4$	48	85	92:8	87
5	**2e**	4-MeC_6H_4	7	67	92:8	91
6	**2f**	2-ClC_6H_4	12	>99	94:6	84
7[d]	**2g**	3-ClC_6H_4	2	98	90:10	81
8[d]	**2h**	4-ClC_6H_4	6	>99	89:11	83
9	**2i**	2-BrC_6H_4	11	>99	93:7	82
10[d]	**2j**	3-BrC_6H_4	4	94	92:8	80
11[d]	**2k**	4-BrC_6H_4	3	94	89:11	86
12[d]	**2l**	2-Naphthyl	3	96	91:9	89
13	**2m**	2-Furyl	70	78	87:13	87
14[d]	**2n**	2-Thienyl	6	84	87:13	79

[a] Reaction conditions: **2** (0.056 mmol), nitroethane (1.4 mmol), (R_p)-**1** (5 mol%), triethylamine (5 or 4 mol%) in solvent (0.1 mL) under N_2. [b] Isolated yields of *syn/anti* mixture. [c] Determined by HPLC. [d] (R_p)-**1** (10 mol%) and triethylamine (10 mol%) were used.

Effects of the chiral scaffold in the bis(thiourea) catalyst were investigated. The use of neither *trans*-1,2-diaminocyclohexane-based (1*R*,2*R*)-**4** nor 2,2'-diamino-1,1'-binaphthalene-based (R_a)-**5** afforded the 1,3-dinitro compounds with satisfactory diastereo- and enantioselectivities, suggesting that the planar chiral cyclophane backbone is superior to the cyclohexyl and binaphthyl backbones in the chiral induction for this Michael reaction (Table 3).

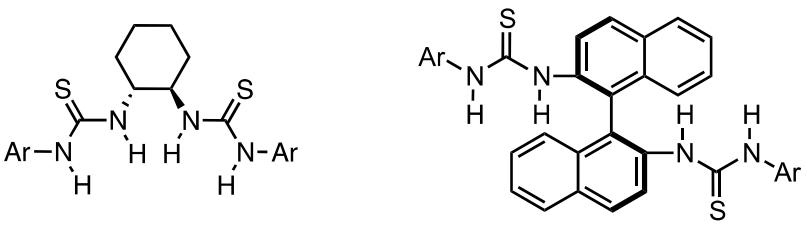
Table 3. Effects of chiral backbone[a]



2a *syn*-**3a** *anti*-**3a**

Entry	Bis(thiourea)	Time (h)	Yield (%)[b]	*syn*:*anti* [c]	Ee of *syn* (%)[c]
1	(R_p)-**1**	22	>99	96:4	91
2	(1*R*,2*R*)-**4**	48	62	84:16	22
3	(R_a)-**5**	24	86	85:15	33

[a] Reaction conditions: **2a** (0.056 mmol), nitroethane (1.4 mmol), (R_p)-**1** (5 mol%), triethylamine (4 mol%) in solvent (0.1 mL) under N_2. [b] Isolated yields of *syn/anti* mixture. [c] Determined by HPLC.



(1*R*,2*R*)-**4** Ar = 3,5-$(CF_3)_2C_6H_3$ (R_a)-**5**

The absolute configuration of the *syn*-products **3** in the reaction using (R_p)-**1** was determined to be (2*S*,3*S*) based on comparison of the HPLC data with those of the literature.[17,18] The transition state model, proposed at this stage to account for the observed stereochemistry, are shown in Figure 2. Assuming that each nitro group of the nitronate and the nitrostyrene is fixed and activated by dual hydrogen bonding with each thiourea functionality on the catalyst, the nitronate would be attacked on the *Si* face of the nitrostyrene affording (2*S*,3*S*)-**3**.

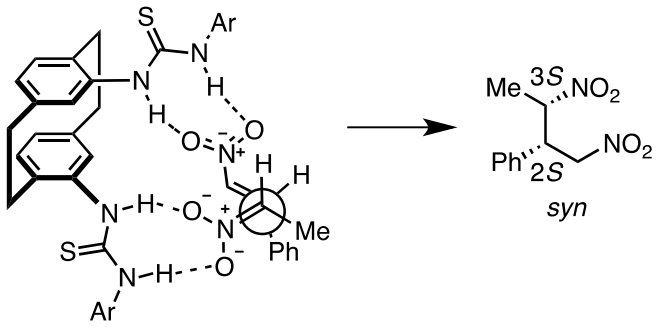


Figure 2. Proposed transition state model for diastereo- and enantioselectivities

In summary, we found that the planar chiral PCP-based bis(thiourea) catalyst (R_p)-**1** efficiently catalyzed the Michael addition reaction of nitroethane to nitrostyrenes, other than the Henry reaction, to produce optically-active 1,3-dinitro compounds. The catalyst works well in the reaction with a variety of nitrostyrenes, showing high diastereo- and enantioselectivities even at 0 °C. Efforts toward the improvement of the enantioselectivity including further modification of the catalyst structure and further studies of the application of the catalysts (R_p)-**1** in other asymmetric reactions are currently underway.

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SUPPORTING INFORMATION

Supplementary (typical procedure for Michael reaction, HPLC chromatograms, ^{1}H and ^{13}C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26833/103/2

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