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Planar chiral [2.2]paracyclophane-based bis(thiourea) catalyst: application to asymmetric Henry reaction†

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A bis(thiourea) organocatalyst with a planar chiral [2.2]paracyclophane backbone has been synthesized and applied to the Henry reaction. The obtained high reactivity and enantioselectivity from the reaction of aromatic aldehydes with nitroalkanes suggested the significant potential of [2.2]paracyclophane to serve as the backbone of the organocatalyst.

Optically active bis(thiourea) hydrogen-bond-donating catalysts have proven to be effective for diverse asymmetric reactions,[1–6] such as the Morita–Baylis–Hillman (MBH) reaction,[2] Mannich-type reaction,[3] kinetic resolution of amines,[4] and Diels–Alder reaction.[5] However, the chiral backbone has been mainly limited to the centrally chiral *trans*-1,2-diaminocyclohexane or axially chiral 1,1′-binaphthyl-2,2′-diamine, thus the development of new scaffolds to achieve other types of transformations with excellent enantioselectivities is highly desirable (Fig. 1).[7]

[2.2]Paracyclophane have attracted considerable attention as a new type of planar chiral backbone[8] for a mono- or bidentate ligand since [2.2]PHANEPHOS,[9] the pseudo-*ortho*-bis(diphenylphosphino)[2.2]paracyclophane ligand, realized the highly enantioselective hydrogenation of olefins or ketones catalyzed by a rhodium or ruthenium complex. On the other hand, [2.2]paracyclophane-based Brønsted acid organocatalysts have been relatively unexplored and the results reported so far suggest that it is not easy for the cyclophane compounds to promote any organocatalytic reaction in a highly enantioselective manner.[10] During our ongoing studies on the planar chiral cyclophane-based bifunctional organocatalyst, we recently addressed this issue by combining an acid functionality with a nucleophilic phosphine, which efficiently catalyzed the enantioselective aza-Morita–Baylis–Hillman reaction.[11] We now report that the [2.2]paracyclophane framework is suitable as a backbone for the bis(thiourea) catalyst, which realizes the highly enantioselective Henry reaction.

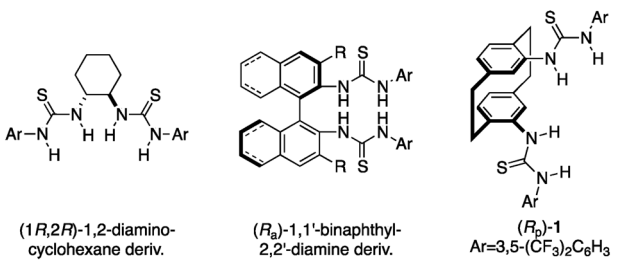

Fig. 1 Bis(thiourea) derivatives.

The pseudo-*ortho*-substituted pattern of the [2.2]paracyclophane was selected as the target because we believe that it would construct a wider and more efficient chiral pocket than the pseudo-geminal- or *ortho*-substituted ones.[11] Pseudo-*ortho*-diamino[2.2]paracyclophane **4**, which was selected as the synthetic intermediate for the target bis(thiourea) **1**, has been reported to be prepared in the racemic form by the Buchwald–Hartwig amination of (±)-dibromocyclophane.[12] However, it was synthesized from the readily available optically pure bromo[2.2]paracyclophanyl triflate **2**.[13] Thus, the palladium-catalyzed diamination of (R_p)-**2** using *N*-*tert*-butyl carbamate as the ammonia equivalent and JohnPhos as the ligand,[14] and subsequent exposure to trifluoroacetic acid afforded the diamine (R_p)-**4** in an acceptable yield. Finally, treatment of the amine with 3,5-bis(trifluoromethyl)phenyl isothiocyanate produced the desired bis(thiourea) (R_p)-**1** (Scheme 1).

The crystal suitable for an X-ray diffraction study was obtained for *rac*-**1** from a THF–hexane solution. The solid structure was found to have a s-*cis*, *trans* conformation for each thiourea moiety and included three THF molecules, one of which was simultaneously bound to each thiourea hydrogen atom, indicating one of the possible activation scenarios of the substrate or reagent in the reaction pathway if this thiourea catalyzes any reaction (Fig. 2).[15]

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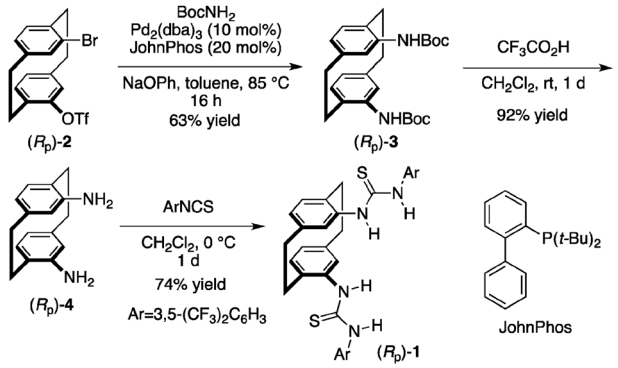


Scheme 1 Preparation of bis(thiourea) (R_p)-**1**.

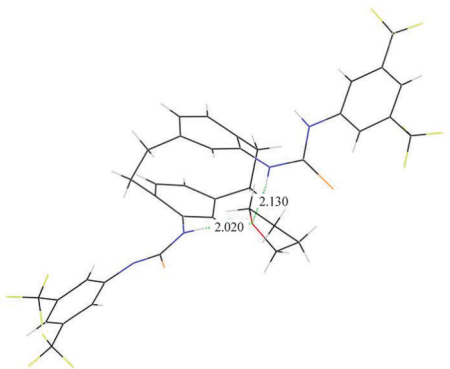
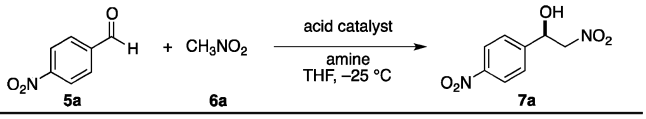


Fig. 2 X-ray crystal structure of *rac*-**1**-THF. Hydrogen-bond distances are given in Å (hydrogen atoms except NHs and other THF molecules were omitted for clarity).

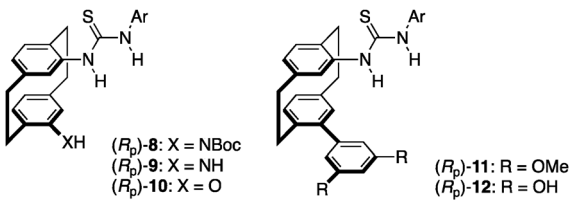
With the cyclophanyl thiourea catalysts in hand, we turned our attention to their application in the organocatalytic Henry reaction.[16] Our initial experiment was carried out using *p*-nitrobenzaldehyde **5a** and nitromethane **6a** in THF at −25 °C under the influence of 10 mol% of (R_p)-**1** and 20 mol% of diisopropylethylamine. We were delighted to find that the reaction proceeded smoothly to produce the desired adduct (*R*)-**7a** in 89% yield with 94% ee (Table 1, entry 1). The reduction of the catalyst loading to 5/10 mol% {(R_p)-**1**/amine} gave similar results (entry 2). The bis(thiourea)/amine ratio affected the enantioselectivity of the product and the best result (97% ee) was obtained using a ratio of 5/20 (entries 3 and 4). The thiourea catalyst could be recovered in *ca.* 65% by column chromatography on silica gel from the reaction mixture, and the recovered catalyst worked well without any loss of its reactivity and enantioselectivity up to at least the third reuse (entry 5). Raising the reaction temperature to 0 °C or the reduction of the catalyst loading to 2/8 mol% {(R_p)-**1**/amine} led to a decrease in the enantioselectivity, but maintained the level of >90% (entries 6 and 7). The use of triethylamine or DABCO instead of diisopropylethylamine and dichloromethane or toluene instead of THF did not improve the enantioselectivity (entries 8–11). The change of one of the two thioureas to a *tert*-butyl carbamoyl group or amino group[17] decreased the enantioselectivity (entries 12 and 13). The use of hydroxy-thiourea (R_p)-**10**[17] gave results similar to that of amino-thiourea (R_p)-**9** (entries 13 and 14). The phenyl group-inserted hydroxy-thiourea (R_p)-**12**[13] and the methyl-protected

Table 1 Enantioselective Henry reaction of **5a** and **6a**



Entry	Acid (mol%)	Amine (mol%)	Time (h)	Yield of **7a**[a] (%)	ee[b] (%)
1	(R_p)-**1** (10)	i-Pr$_2$NEt (20)	4	89	94
2	(R_p)-**1** (5)	i-Pr$_2$NEt (10)	4	84	95
3	(R_p)-**1** (5)	i-Pr$_2$NEt (5)	4	80	91
4	(R_p)-**1** (5)	i-Pr$_2$NEt (20)	4	84	97
5[c]	(R_p)-**1** (5)	i-Pr$_2$NEt (20)	4	86	96
6[d]	(R_p)-**1** (5)	i-Pr$_2$NEt (20)	1	82	92
7	(R_p)-**1** (2)	i-Pr$_2$NEt (8)	24	77	91
8	(R_p)-**1** (5)	Et$_3$N (20)	2	82	94
9	(R_p)-**1** (5)	DABCO (20)	10	72	91
10[e]	(R_p)-**1** (5)	i-Pr$_2$NEt (20)	1.5	87	90
11[f]	(R_p)-**1** (5)	i-Pr$_2$NEt (20)	1.5	84	63
12	(R_p)-**8** (5)	i-Pr$_2$NEt (20)	3	75	44
13	(R_p)-**9** (5)	i-Pr$_2$NEt (20)	3	81	24
14	(R_p)-**10** (5)	i-Pr$_2$NEt (20)	3	78	30
15	(R_p)-**11** (5)	i-Pr$_2$NEt (20)	9	66	0
16	(R_p)-**12** (5)	i-Pr$_2$NEt (20)	3	68	19

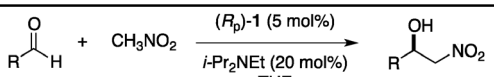
[a] Isolated yield. [b] Determined by HPLC analysis using Daicel Chiralcel OD-H. [c] Result of the thiourea's 3rd reuse. [d] Performed at 0 °C. [e] Performed in CH_2Cl_2. [f] Performed in toluene.



(R_p)-**11**[17] further reduced the enantioselectivity, the latter having a lower reactivity and no enantiodiscrimination (entries 15 and 16). These results suggested the importance of the second thiourea functionality, which has a proper steric hindrance and hydrogen bond donor activity.

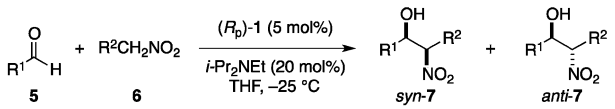
The substrate scope of the (R_p)-**1**-catalyzed Henry reaction was examined next. Arylaldehydes with an electron-deficient group at the *para* position could be smoothly transformed into the corresponding nitroalcohols in good yields and high enantiomeric excesses (Table 2, entries 1 and 2). Benzaldehyde or the

Table 2 Enantioselective Henry reaction of **5** and **6a** catalyzed by (R_p)-**1**



Entry	Aldehyde **5** (R)	(R_p)-**1** (mol%)	Temp. (°C)	Time (h)	Product **7**[a] (yield, %)	ee[b] (%)
1	**5a** (*p*-NO$_2$C$_6$H$_4$)	5	−25	4	**7a** (84)	97
2	**5b** (*p*-ClC$_6$H$_4$)	5	−25	48	**7b** (80)	95
3	**5c** (C$_6$H$_5$)	5	0	24	**7c** (57)[c]	90
4	**5d** (*p*-MeOC$_6$H$_4$)	10	0	12	**7d** (70)[c]	86
5	**5e** (*m*-NO$_2$C$_6$H$_4$)	5	−25	3	**7e** (91)	96
6	**5f** (*o*-NO$_2$C$_6$H$_4$)	5	−25	1	**7f** (91)	94
7	**5g** (3-Pyridyl)	10	−40	5	**7g** (73)	91
8	**5h** (1-Naphthyl)	10	0	12	**7h** (80)	91
9	**5i** (PhCH$_2$CH$_2$)	10	−25	24	**7i** (72)	68

[a] Isolated yield. [b] Determined by HPLC analysis using a chiral column. [c] Reaction was quenched before complete conversion of the starting material.



Aldehyde **5** (R^1)	Nitroalkane **6** (R^2)	Time (h)	Product	Yield of **7**	Dr (*syn*:*anti*)	% Ee (*syn*/*anti*)
5a (*p*-$NO_2C_6H_4$)	**6b** (CH_3)	7	**7j**	79%	43:57	89/93
5a (*p*-$NO_2C_6H_4$)	**6c** (C_2H_5)	24	**7k**	83%	56:44	86/91
5b (*p*-ClC_6H_4)	**6b** (CH_3)	48	**7l**	85%	39:61	89/91

Scheme 2 Enantioselective Henry reaction of **5** with **6b,c** catalyzed by (R_p)-**1**.

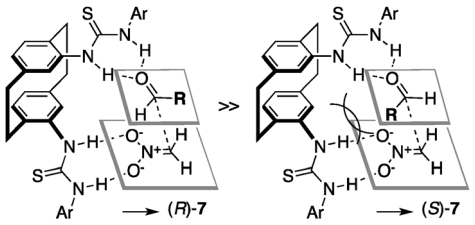


Fig. 3 Plausible transition state model.

electron-donating arylaldehyde required a prolonged reaction time and higher reaction temperature, and led to a slight decrease in the enantioselectivity due to the retro-Henry reaction (entries 3 and 4).[18] The position of the aryl-substituent had a minor effect on the enantioselectivities (entries 1, 5 and 6). The desired products from 3-pyridyl- and 1-naphthyl-aldehyde were obtained in good yields and high enantioselectivities through a slight modification of the reaction conditions (entries 7 and 8). Thus, bis(thiourea) (R_p)-**1** proved to work very well for a variety of arylaldehydes. An aliphatic aldehyde produced the corresponding nitroalcohol smoothly, as expected, but its ee was not high enough compared to those derived from arylaldehydes (entry 9).

Diastereoselective reactions were examined using nitroethane or nitropropane under several conditions, and it was found that both *syn*- and *anti*-products were obtained in high enantiomeric excesses although a higher diastereomer ratio was not achieved (Scheme 2).

Although it is too soon to propose the stereochemical pathway at this stage, the preferential formation of (*R*)-**7** might be explained by the transition state model inspired by the dual activation mode, which has been proposed by Nagasawa and co-workers for the MBH reaction using bis(thiourea), derived from diaminocyclohexane (Fig. 3).[7] Thus, the left one in Fig. 3 is less crowded and should lead to the adduct (*R*)-**7**.

In conclusion, we designed and synthesized a planar chiral bis(thiourea) catalyst based on the pseudo-*ortho*-substituted [2.2]paracyclophane backbone and found that its asymmetric environment realized a highly enantioselective Henry reaction. Further studies regarding the details of the reaction mechanism as well as the application of planar chiral bis(thiourea) derivatives in other asymmetric organocatalytic reactions are currently in progress.

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18 Time-course studies on the reaction of **5c** with **6a** in the presence of (R_p)-**1** (5 mol%) and diisopropylethylamine (20 mol%) in THF at 0 °C showed that the ee of the product gradually decreased (6 h: 94% ee, 12 h: 92% ee, 24 h: 90% ee).