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PAPER

Readily available hydrogen bond catalysts for the asymmetric transfer hydrogenation of nitroolefins†

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This paper focuses on readily accessible thiourea hydrogen bond catalysts derived from amino acids, whose steric and electronic features are modulated by their degree of substitution at the carbinol carbon center. These catalysts were applied in the asymmetric transfer hydrogenation of nitroolefins furnishing the chiral products in up to 99% yield and 86% enantiomeric excess. The proposed catalyst's mode of action is supported by mechanistic investigations.

Introduction

The hydrogenation of nitroolefins and nitro acrylates yields chiral nitro compounds, thus offering an efficient access to chiral β-amines and β^2-amino acid derivatives. Chiral amines are extensively used as chiral building blocks, as resolving agents or as chiral auxiliaries.[1] Amino acid derivatives play an important role in the generation of artificial peptide structures. This multifaceted application of amines makes the synthesis of enantiopure nitrogen-containing compounds an attractive field of research. A biomimetic access to enantiopure nitro-compounds by transfer hydrogenation of nitroolefins[2] and nitroacrylates[3] with Hantzsch's esters[4,5] was first described by List *et al.* The applied monofunctional cyclohexyl-diamine-derived thiourea catalysts[6] furnished the hydrogenated products in excellent yields and enantioselectivities. Apart from those Jacobsen-type catalysts, amino alcohol related thiourea derivatives[7] have been successfully employed in the Morita–Baylis–Hilmann reaction,[8] in the conjugate addition,[9,10] in the Diels–Alder reaction[11] and in the Friedel–Crafts–alkylation of indole with nitroolefins.[12] In the latter report Ricci *et al.* discussed the interaction of a highly polarized indole-NH with an alcohol group as being essential for activity and enantioselectivity.[12]

Our report introduces readily available amino-alcohol-derived thiourea structures as new catalysts for the asymmetric hydrogen bond mediated transfer hydrogenation of nitroolefins. Our investigations show that the dihydropyridine-NH-bond (Hantzsch's ester) significantly contributes to the efficiency and enantioselectivity of the asymmetric hydrogen transfer promoted by hydroxy substituted thiourea derivatives.

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† Electronic supplementary information (ESI) available: detailed experimental procedures, analytical data and HPLC traces can be obtained from the author or from the web. See DOI: 10.1039/c1ob05059a

Results and Discussion

The bifunctional[13] thiourea structures[14] were obtained from the reaction of commercially available and readily accessible amino alcohols with 3,5-(trifluormethylphenyl)thioisocyanate (Fig. 1, see ESI† for synthetic procedures and full characterization). The synthesized bifunctional thiourea derivatives (Fig. 1) differ in the degree of substitution at the carbinol carbon atom (**1a–1p**) and can thus be divided into three classes: structures bearing a tertiary, secondary or primary alcohol functionality. This feature allows studying the catalyst's performance depending on the degree of substitution at the carbinol functionality. The results of the hydrogen bond mediated asymmetric transfer hydrogenation of (*E*)-2-phenyl-1-nitro-propene (**2a**) with *tert*-butyl-Hantzsch's ester (**3**) are summarized in Table 1.

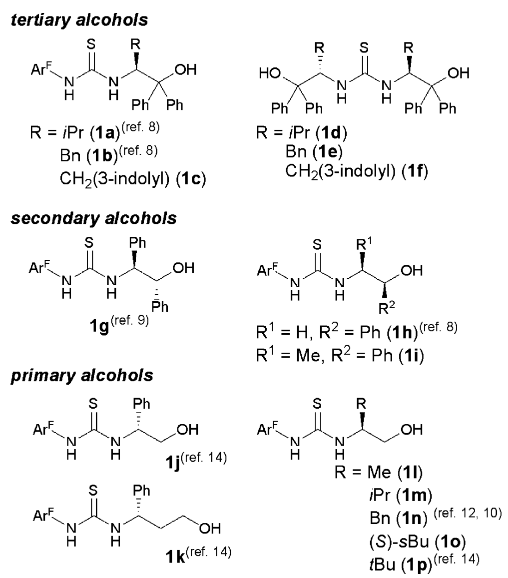
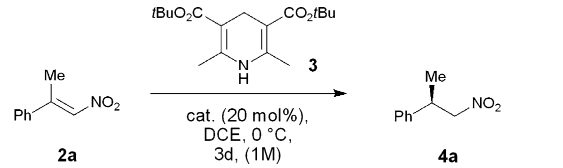


Fig. 1 Bifunctional thiourea catalysts derived from amino alcohols (Ar^F = 3,5-$(CF_3)_2$–C_6H_3).

Table 1 Asymmetric transfer hydrogenation of **2**



Entry	Catalyst	Yield (%)[a]	ee (%)[b]
1[c]	—	5	n.d.
2	**1a**	81	<5 (*S*)[d]
3	**1b**	72	13 (*S*)
4	**1c**	26	<5 (*R*)
5	**1d**	46	11 (*R*)
6	**1e**	39	<5 (*S*)
7	**1f**	31	16 (*R*)
8	**1g**	70	20 (*R*)
9	**1h**	90	40 (*S*)
10	**1i**	88	62 (*R*)
11	**1j**	99	61 (*S*)
12	**1k**	78	50 (*S*)
13	**1l**	99	61 (*R*)
14	**1m**	91	67 (*R*)
15	**1n**	99	60 (*R*)
16	**1o**	94	67 (*R*)
17	**1p**	99	70 (*R*)
18	*epi*-**1p**	99	65 (*S*)

[a] Yields were determined by GC with dodecane as the internal standard. [b] The enantiomeric excess was determined after purification on silica gel by HPLC with chiral stationary phase. [c] Reaction was performed at 40 °C in toluene; n.d. not determined. [d] The absolute configuration was determined by comparison with literature values (see ESI†).

Generally, the reaction is catalyzed by hydroxy-functionalized thiourea derivatives. Catalysts bearing tertiary alcohol groups furnished the nitro alkane **4a** in good yields (entries 2 and 3), while the tryptophan-derived catalyst (**1c**, entry 4) was not sufficiently active. The C_2-symmetric catalysts **1d–1f** (entries 5–7) were generally less active than the corresponding unsymmetrical thiourea derivatives. Although the catalysts **1a** and **1b** displayed good activity, the enantioselectivity achieved was low (<20% ee). Catalysts featuring a secondary alcohol function were more active and furnished **4a** in 70–90% yield (entries 8–10). Diverging activities and enantioselectivities were observed for **1g** and **1i** (entries 8 and 10, 70% yield, 20% ee and 88% yield, 62% ee) resulting from the relative configuration of the 1,2-amino alcohol fragment. This may be rationalized by assuming that different conformers in **1g** and **1i** are present in solution. The conformations of ephedrine- and 1,2-diphenyl-2-amino ethanol derivatives have been studied in solid state[15] and in solution by NMR.[16] In most cases the *gauche* conformation, featuring an internal hydrogen bond, has been identified by coupling-constant analysis of the vicinal protons as the most abundant conformer. However, the catalyst systems **1g–i** proved too dynamic on the NMR timescale for coupling-constant analysis. The 2-amino-2-phenyl ethanol substructure in catalyst **1j** is isomeric to structure **1h**. The catalyst **1j** features a primary hydroxy functionality and furnished the hydrogenation product **4a** in high yield (entry 11, 99% yield). The enantioselectivity is improved to 61% ee compared to catalyst **1h** (entry 9). This indicates that the transfer of stereo information (from the catalyst to the product) is more efficient from the chiral vicinity of the thiourea moiety than from the asymmetric carbinol functionality (entries 9–11). The ethylene spacer group in the catalyst's structure proved to be optimal for transfer hydrogenation. The 2-amino-2-phenyl propanol derived catalyst **1k** provided the product in 78% yield and 50% ee (entry 12). For this reason we investigated the efficiency of the thiourea derivatives depending on the bulkiness of the alkyl chain at the stereogenic carbon center (entries 13–17). Surprisingly, the smallest alkyl group, such as a methyl group (**1l**), already generated a highly efficient catalyst (entry 13, 99% yield and 61% ee). Moving along in the series of *i*Pr (**1m**), Bn (**1n**), *s*Bu (**1o**) and *t*Bu (**1p**) (entry 14–17) the enantioselectivity of the catalyzed process gradually improved to 70% ee while the excellent activity of the catalyst was preserved (91–99%). When the reaction was prefromed in diethylether **4a** was obtained with 77% ee but with unsatisfactory yield (55% see ESI† for further optimization studies).[17] To demonstrate that both enantiomers of the saturated product **4a** are accessible by this methodology, we conducted the reaction with the catalyst's enantiomer *epi*-**1p**. The hydrogenation of **2a** furnished the *S*-configured product in quantitative yield with 65% enantiomeric excess (entry 18).

We then turned our interest to the substrate scope for the thiourea-catalyzed transfer hydrogenation of unsaturated nitro compounds using our best performing catalyst **1p** (Table 2). All substrates were converted to the saturated nitro compounds in good to excellent yields (84–99%). However, the enantioselectivity of these transformations differed significantly depending on the substitution pattern. Methyl-aryl-substituted nitroolefins were obtained with an enantiomeric excess of 50–70% (entries 1–6). Electron withdrawing as well as electron donatin groups on the aryl ring are tolerated and the products were furnished with 50–67% ee. Higher enantioselectivities up to 87% ee were observed for nitro alkenes bearing bulkier substituents (entry 8, *t*Bu). Additionally, the thiourea **1p** showed excellent activity in the reduction of nitro acrylates (Table 3). The products **6a–6c** were formed in excellent yield. Surprisingly, the methyl (**6a**), ethyl (**6b**) and *i*propyl (**6c**) esters were obtained with almost the same enantiomeric excess (54–60% ee) revealing an unique opportunity to synthesize a wide variety of ester derivatives.

In order to comprehend the varied performance of the synthesized catalysts a hydrogen-bonded structure can be conceived. The formation of a ternary complex incorporating the thiourea derivative (**1p**), the nitroolefin (**4a**) and the reducing agent **3** can serve as a rationalization for the observed activities and enantioselectivities. Literature precedent supports the assumption that hydroxyl groups are beneficial for organocatalytic transformations where polarized N–H bonds are involved.[2c,11,12] The formation of a N–H ··· O hydrogen bond between a heterocycle and the catalyst has already been proposed and investigated for the Friedel–Crafts alkylation of indole.[12] We decided to study the role of the hydroxy group of our catalyst in the asymmetric transfer hydrogenation by selective suppression of important substrate-catalyst interactions. For this purpose we identified two significant interactions apart from the nitro-thiourea-interaction: 1) hydrogen-bonding between the nitro- and the hydroxy group (N═O ··· H–O); 2) hydrogen-bonding between the Hantzsch's ester and the hydroxy-group (N–H ··· O) (Scheme 1).

1) To suppress the simultaneous binding of the nitro-compound to the thiourea and the hydroxy group the silylated thiourea **7** was synthesized. In this structure, the postulated coordination of the

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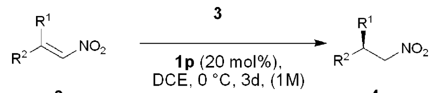
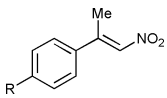
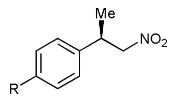
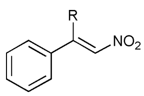
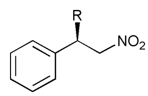
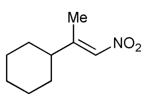
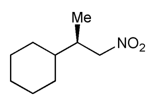
Table 2 Substrate scope for the catalyzed transfer hydrogenation of nitroolefins

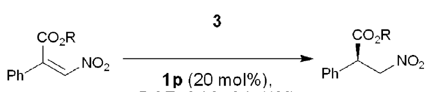


2 → 4

Entry	Nitroolefin		Product	Yield (%)[a]	ee (%)[b]
					
1	R = H	(**2a**)	**4a**	99	70
2	R = Me	(**2b**)	**4b**	99	50
3	R = OMe	(**2c**)	**4c**	99	62
4	R = Cl	(**2d**)	**4d**	97	67
5	R = F	(**2e**)	**4e**	95	63
6	R = CN	(**2f**)	**4f**	88	56
					
7	R = Et	(**2g**)	**4g**	95	68
8	R = *t*Bu	(**2h**)	**4h**	76	87
9		(**2i**)	 (**4i**)	84[c]	40

[a] After purification by column chromatography. [b] The enantiomeric excess was determined by HPLC with chiral stationary phase. [c] The yield was determined by GC with dodecane as the internal standard.

Table 3 Asymmetric reduction of nitroacrylates



5 → 6

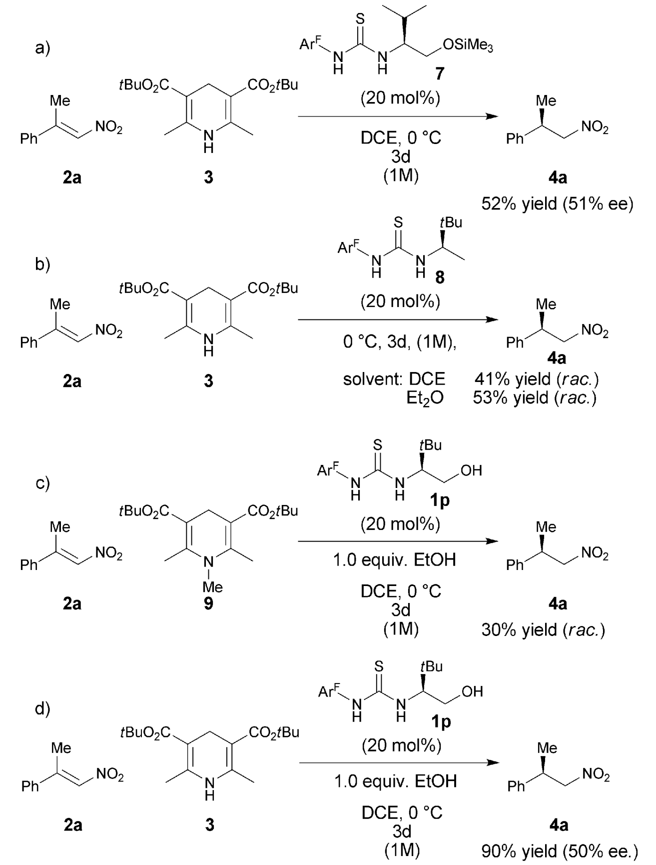
Entry	Nitroacrylate	Product	Yield (%)[a]	ee (%)[b]
1	R = Me (**5a**)	**6a**	95	60
2	R = Et (**5b**)	**6b**	99	58
3	R = *i*Pr (**5c**)	**6c**	93	54

[a] after purification by column chromatograpy; [b] the enantiomeric excess was determined by HPLC with chiral stationary phase.

nitro-compound by both the thiourea- and the hydroxy-group is not possible, while the interaction of the Hantzsch's ester (**3**) to the Lewis-basic oxygen atom is still feasible.[18] The application of **7** in the transfer hydrogenation of **2a** furnished the product **4a** in lower yield and in slightly diminished enantioselectivity (52% yield, 51% ee; Scheme 1a). This may be explained by the lack additional hydrogen bonds between the hydroxy- and nitro-functionality. Additionally, the free hydroxy group in **1p** might facilitate the proton transfer to the formed nitronate species from the conjugate hydride attack to the nitroolefin. To probe the interaction of the nitro group with the unmasked hydroxy group in **1p** we conducted ^{1}H NMR experiments. However, the addition of 0.5, 1.0, 5.0 and 10 equiv. of nitroolefin **2a** to a 0.2 M solution of catalyst **1p** did not result in significant changes in the ^{1}H NMR-spectrum (see ESI†).

2) The significance of the Lewis-basic oxygen atom in the proposed N–H···O-interaction was demonstrated by two experiments: by the complete removal of the hydroxy functionality and by masking the NH-group of the Hantzsch's ester (**3** → **9**) with a methyl group (Scheme 1b and 1c). The defunctionalized thiourea-derivative **8** afforded the saturated nitro-compound **4a** as racemic material in DCE and Et_2O (Scheme 1b). Consequently, the complete removal of the Lewis-basic oxygen atom from the catalysts structure generated an unselective catalyst. This underlines the importance of the hydroxy-functionality tethered to the catalyst for an enantioselective reaction. Use of the protected Hantzsch's ester **9**[19] together with our best catalyst **1p** and one equivalent of ethanol as a proton source[20] also furnished the product **4a** as racemic material (Scheme 1c, 30% yield). The control experiment using **3** and one equiv. of ethanol as proton source supplied **4a** in 90% yield with significant enantioenrichment (Scheme 1d, 50% ee). Hence, the constructive interaction between the catalyst and the Hantzsch's ester is essential for the enantioselective hydrogen transfer. This conclusion is supported by the fact, that racemic **4a** was obtained when DMSO was applied as cosolvent (DMSO/DCE, 1 : 1; see ESI†) under best reaction conditions. Concluding this experimental data set, a ternary complex consisting of the catalyst (**1p**), the nitroolefin (**2a**) and the Hantzsch's ester (**3**) as transient species according to Fig. 2 seems instructive.

The catalyst is able to coordinate the nitroolefin in two different ways: one in which the hydroxy group is located on the *Re*-face of the nitroolefin (Fig. 2 left) and one in which the hydroxy group is



Scheme 1 Mechanistic investigations for the enantioselective transfer hydrogenation catalyzed by **1p**.

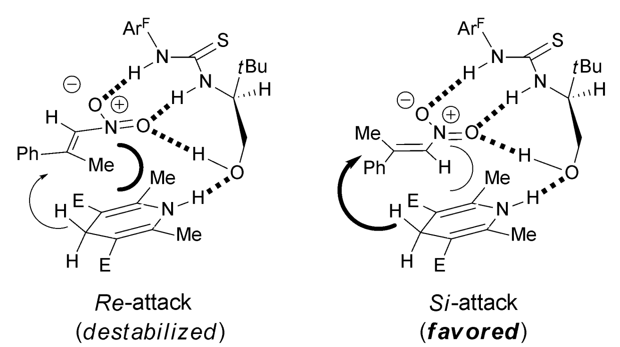


Fig. 2 Postulated ternary substrate-catalyst complex leading to the stereoselective hydride transfer.

located on the *Si*-face (Fig. 2 right). This results in the selective delivery of the hydride to the enantiotopic faces, hence determining the stereoselectivity of the reduction.[21] The coordination of the nitroolefin for the *Re*-face attack is less stabilized by encountering steric clashes between the methyl group and the catalyst (Fig. 1 left). On the contrary, the coordination of the nitroolefin for the *Si*-face attack is favored because now the vinylic hydrogen atom in **2a** is oriented towards the catalyst's backbone resulting in lower steric interactions. This model supports our experimental observations of high selectivity with bulky substrates, together with the observed stereochemical outcome of the product. Nitroolefin **2h** (*t*Bu-Ph) should coordinate with its *Si*-face pointing towards the Hantzsch's ester (**3**) to avoid steric interactions of the *t*Bu-group with the catalyst's side chain, resulting in the hydride delivery to the *Si*-face with 76% yield and 87% enantiomeric excess.

Conclusions

We have disclosed an efficient synthesis and derivatization of chiral bifunctional thiourea catalysts for the asymmetric transfer hydrogenation of nitroolefins. The configurational features of **1i** and **1g** led us to the development of highly active and enantioselective catalyst structures, *e.g.* **1p**. This catalyst displayed a rather wide substrate scope and furnished the products in excellent yields (up to 99%) and moderate to good enantioselectivities (up to 87% ee). The mode of action of the catalyst was probed by selective suppression of three distinct substrate-catalyst interactions. These mechanistic investigations suggest a transient, ternary substrate-catalyst-structure for the described enantioselective transfer hydrogenation of nitroolefins.

Experimental section

N-((*S*)-(2-amino-3,3-dimethylbutanol))-*N′*-(3,5-bis-(trifluoromethyl)phenyl)thiourea (1p)

To a solution of (*S*)-*tert*-leucinol (800 mg, 6.83 mmol, 1.0 equiv.) in dry CH_2Cl_2 (7.0 mL) was added 3,5-bis(trifluoromethyl)phenylisothiocyanate (1.37 mL, 7.51 mmol, 1.10 equiv.). After stirring at 40 °C for 3 h, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 80/20 v/v). The compound was obtained as a white foamy solid (2.49 g, 6.40 mmol, 94%). m.p. 56 °C (capillary); R_f (cyclohexane/ethyl acetate, 80 : 20) = 0.34; $[\alpha]_D^{20}$ −75.6 (*c* 0.5 in chloroform); δ_H (400 MHz, acetone-d$_6$) 9.50 (br s, 1H, OH), 8.38 (s, 2H, HAr), 7.67 (s, 1H, HAr), 7.58 (d, *J* = 7.4 Hz, 1H, NH), 4.64–4.55 (m, 1H, CH), 3.94–3.83 (m, 2H, CH_2, NH), 3.81–3.73 (m, 1H, CH_2), 1.04 (s, 9H, CH_3); δ_C (100 MHz, acetone-d$_6$) 184.0 (C=S), 144.1 (CAr), 132.9 (q, *J* = 33.0 Hz, 2C, CCF_3), 125.4 (q, *J* = 271.9 Hz, 2C, CF_3), 123.9 (2C, CHAr), 118.1 (CHAr), 64.8 (CH), 62.9 (CH_2), 36.4 (C), 28.6 (3C, CH_3) ppm; δ_F (376 MHz, $CDCl_3$) −63.10 (m, 6F, CF_3); IR (Platinum ATR) ν_{max}/cm^{-1} 3265 (vw), 2965 (vw), 1532 (w), 1471 (vw), 1379 (w), 1342 (vw), 1273 (m), 1169 (w), 1124 (m), 1042 (w), 996 (vw), 972 (vw), 885 (w), 847 (vw), 700 (w), 680 (w), 571 (vw), 401 (vw); MS (FAB), *m*/*z* 389.1 ([M + H]$^+$, 100%), 370.1 (20%), 355.1 (10%), 289.1 ([$C_9H_7F_6N_2S$]$^+$, 15%); HRFABMS calcd for $C_{15}H_{19}F_6N_2OS$: 389.1119, found 389.1122 [M + H]$^+$; elemental analysis: Found: N 6.97, C 45.97, H 4.51. $C_{15}H_{18}F_6N_2OS$ requires N 7.21, C 46.39, H 4.67.

Procedure for the asymmetric transfer hydrogenation of nitroolefins and nitroacrylates

A solution of the respective nitroolefin or nitro acrylate (0.3 mmol) in dichloroethane (0.3 mL) was cooled to 0 °C. Subsequently catalyst **1p** (0.06 mmol) and *t*Bu-Hantzsch's ester **3** (0.36 mmol) were added successively as a solid. The reaction was stirred at 0 °C for 3 d. The mixture was diluted with pentane/Et_2O (99 : 1 v/v, 0.7 mL) and subjected to column chromatography (SiO_2, pentane/Et_2O 99 : 1–98 : 2 v/v for nitroalkanes and 95/5 v/v for esters).

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(*R*)-2-(4-Methylphenyl)-1-nitropropane (4a)

δ_H (250 MHz, $CDCl_3$) 7.45–7.23 (m, 5H, HAr), 4.63–4.46 (m, 2H, CH_2NO_2), 3.75–3.59 (m, 1H, CH), 1.42 (d, J = 7.0 Hz, 3H, CH_3); δ_C (125 MHz, $CDCl_3$) 140.8 (C), 129.0 (2C, CHAr), 127.6 (CHAr), 126.9 (2C, CHAr), 81.9 (CH_2), 38.6 (CH), 18.7 (CH_3).

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