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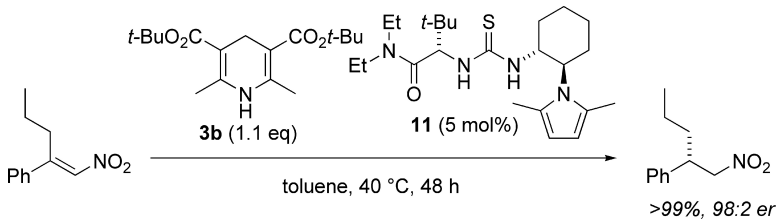

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Organocatalytic Asymmetric Transfer Hydrogenation of Nitroolefins

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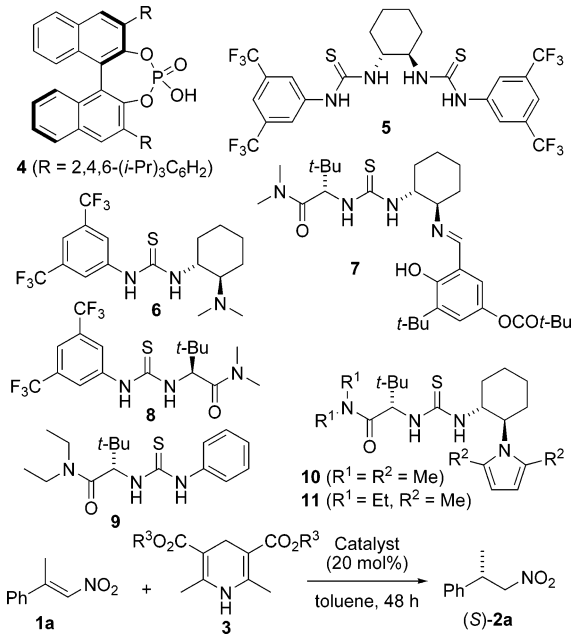
Catalytic enantioselective conjugate reductions of β,β-disubstituted nitroolefins are useful for the synthesis of chiral β-branched nitroalkanes.[1] The approach is particularly attractive because nitroolefins are relatively easy to synthesize either by condensing ketones with nitroalkanes or via nitration of olefins. Furthermore, the resulting nitroalkanes are valuable intermediates, such as for further reduction to chiral amines. So far, only one biocatalytic and one transition-metal-catalyzed variant have been realized. Carreira et al. developed an elegant chiral copper complex-catalyzed version using a silane as stoichiometric reductant,[2] and Ohto et al. used fermenting bakers' yeast in the presence of glucose.[3] Recently, Hantzsch esters have been introduced to asymmetric catalysis as convenient reagent for a number of transfer hydrogenations.[4] We have now explored their utility in conjugate reductions of nitroolefins. Here we report the preliminary results of this investigation culminating in a highly enantioselective, organocatalytic transfer hydrogenation of β,β-disubstituted nitroolefins using a Jacobsen-type thiourea catalyst.

Because acetic acid is a known catalyst of Hantzsch ester mediated conjugate reductions of nitroolefins,[5] and because chiral urea derivatives have recently been used to activate nitroolefins for conjugate additions,[6] we reasoned that chiral Brønsted acids[4g,i,7] and hydrogen-bonding catalysts would be particularly promising for the development of an organocatalytic transfer hydrogenation of nitroolefins. As a model reaction, we investigated the transfer hydrogenation of (*E*)-1-nitro-2-phenyl-1-propene (**1a**) with commercially available Hantzsch esters **3** (Table 1). Chiral binol-derived phosphoric acid catalyst **4**, which we have recently used in a number of reactions[4d,f,h,j,8] proved to be an active catalyst for this reaction but gave the desired product with poor enantioselectivity (entry 1). More promising results were obtained using hydrogen-bonding or general acid-type thiourea catalysts. Bisthiourea catalyst **5** gave nitroalkane **2a** with moderate conversion and 40:60 er (entry 2).[9] Takemoto catalyst **6** proved to be essentially inactive for the reaction, even at elevated temperature (entry 3).[6a,b] We also investigated thiourea derivatives **7**−**11**, identical or similar to those pioneered by Jacobsen and co-workers (entries 4−10).[10] In particular, catalysts **7** and **10** turned out to be active and highly enantioselective catalysts (entries 4−6 and 9). Further structural fine-tuning of thiourea **10** (see Supporting Information) led to catalyst **11**, which proved optimal in terms of reactivity and enantioselectivity (entry 10). Running the reaction at slightly elevated temperature (40 °C) improved the reaction rate presumably by increasing the solubility of the Hantzsch ester (entries 4 and 5). After optimizing solvent, substrate concentration, Hantzsch ester structure, and catalyst loading, the following protocol was subsequently used: Treating nitroolefins **1** (1.3 M) with commercially available Hantzsch ester **3b** (1.1 equiv) in the presence of thiourea catalyst **11** (5 mol %) at 40 °C in toluene for 24−48 h gave the saturated β,β-disubstituted nitroalkane **2** in high yields and enantioselectivities (Table 2).

Table 1. Catalyst Development[a]



entry	catalyst	Hantzsch ester[b]	*T* (°C)	conv. (%)	er
1	**4**	**3a**	rt	85	45:55
2	**5**	**3a**	rt	55	40:60
3	**6**	**3a**	40	6	48:52
4	**7**	**3a**	rt	10	95:5
5	**7**	**3a**	40	85	93:7
6	**7**	**3b**	40	94	97:3
7	**8**	**3a**	40	47	81:19
8	**9**	**3b**	40	66	83:17
9	**10**	**3b**	40	94	97:3
10	**11**	**3b**	40	95	98:2

[a] For additionally studied catalysts, see Supporting Information. [b] **3a**: R^3 = Et, **3b**: R^3 = *t*-Bu.

The reaction has a broad substrate scope and gives products with high yields and enantioselectivities with a number of β-alkyl-substituted nitrostyrenes (entries 1−3). Various substituents at the phenyl ring and other aromatic groups are tolerated (entries 4−10). Aliphatic nitroalkenes are equally suitable. *tert*-Butyl-substituted nitroolefin **1k** gave the corresponding product in good yield and excellent enantioselectivity (entry 11). Aliphatic nitroolefin **1l** is also reduced in high yields (entries 12 and 13). Remarkably, the enantioselectivity is strongly dependent on the olefin geometry. We partially separated the two olefin diastereomers by HPLC and found that (*E*)-**1l** gave nitroalkane **2l** with significant enantioselectivity (entry 12). A sample enriched in the (*Z*)-isomer gave the opposite enantiomer but in much lower selectivity (entry 13). The absolute configuration of compound **2c** was determined by measuring its known optical rotation.[2]

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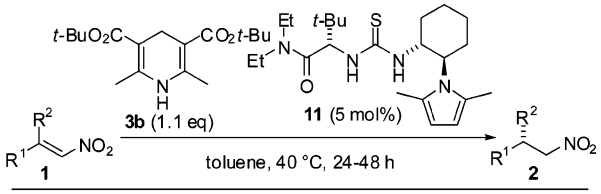
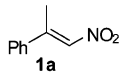
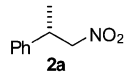
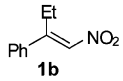
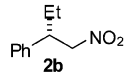
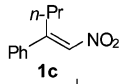
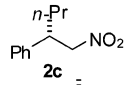
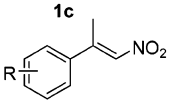
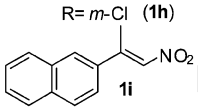
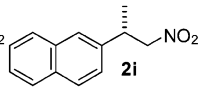
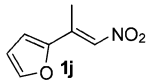
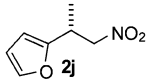
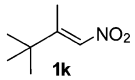
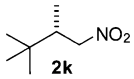
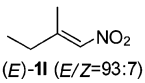
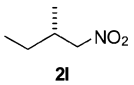
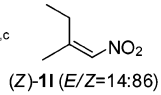
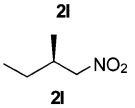
Table 2. Preliminary Scope of the Transfer Hydrogenation



entry	nitroolefin[a]	product	yield [%]	er
(1)	 **1a**	 **2a**	97	97:3
(2)	 **1b**	 **2b**	94	97:3
(3)	 **1c**	 **2c**	>99	98:2
(4)	 R= *p*-Me (**1d**)	**2d**	99	97:3
(5)[b]	R= *p*-CN (**1e**)	**2e**	99	95:5
(6)	R= *p*-F (**1f**)	**2f**	97	95:5
(7)	R= *p*-Cl (**1g**)	**2g**	99	97:3
(8)	R= *m*-Cl (**1h**)	**2h**	97	95:5
(9)[b]	 **1i**	 **2i**	>99	96:4
(10)[b]	 **1j**	 **2j**	84	96:4
(11)[b]	 **1k**	 **2k**	82	96:4
(12)[b,c]	 (*E*)-**1l** (*E*/*Z*=93:7)	 **2l**	97	82:18
(13)[b,c]	 (*Z*)-**1l** (*E*/*Z*=14:86)	 **2l**	95	44:56

[a] *E*/*Z* > 98:2. [b] With 10 mol % of catalyst **11**. [c] Yield and er of volatile product **2l** determined by GC.

We speculate the reaction to proceed via a hydrogen-bonding interaction of the nitro group with the thiourea moiety of the catalyst. It will be interesting to elucidate the details of the mechanism of this reaction and similar transformations in future studies.

We conclude that enantioselective hydrogen-bonding general acid type catalysis is useful for Hantzsch ester mediated conjugate reductions of nitroolefins. Our organocatalytic variant complements previously developed transition metal and biocatalyzed versions. The utility of readily available and inexpensive Hantzsch esters in asymmetric catalysis is further expanded. Successfully employed substrates currently include α,β-unsaturated aldehydes and ketones, ketimines and aldimines, α-keto esters, and now nitroolefins. The modest atom economy of such reactions may be counterbalanced by the practical and convenient use of bench-stable, crystalline Hantzsch esters. Further developments in our laboratories will be reported in due course.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and HPLC and GC traces (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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