Enantioselective hydroxylation of nitroalkenes: an organocatalytic approach†

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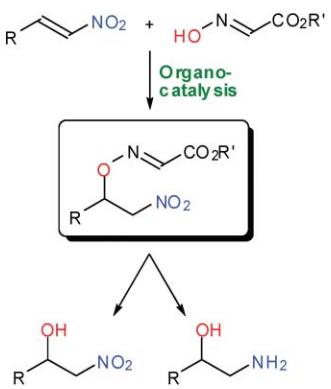
An easy hydroxylation of aliphatic nitroalkenes in high yields and enantioselectivities is catalysed by bifunctional thiourea-cinchona alkaloids giving access to optically active nitroalcohols and aminoalcohols as final products.

During the recent rise in the development of organocatalytic methodologies,[1] the asymmetric 1,4-conjugate additions have emerged as efficient and environmentally-friendly processes for the synthesis of chiral organic compounds.[2] Traditionally, two activation methods have been employed: (i) a covalent method, which often consists of the formation of an iminium ion from an unsaturated carbonyl compound and a chiral amine, or (ii) a non-covalent activation method in which *e.g.* the cinchona-alkaloids represent a cornerstone in the functionalisation of nitroalkenes.[3] Optically active nitro compounds are *e.g.* versatile intermediates in life-science and numerous transformations allow further reactions with the nitro group.[4]

The enantioselective addition of *O*-nucleophiles to nitroalkenes has to the best of our knowledge not yet been performed in an organocatalytic manner.[5] Considering the general importance of compounds originating from the β-hydroxylation of nitroalkenes, it is of great interest to develop methods for the asymmetric version (Scheme 1).

Recently, the first enantioselective organocatalysed β-hydroxylation of α,β-unsaturated aldehydes was reported employing secondary amine catalysts and benzaldehyde oxime as the oxygen source.[6] Intrigued by the ability to add oximes to unsaturated carbonyl compounds, we envisioned that oximes might be used as an oxygen donor for the addition to nitroalkenes.



Scheme 1 Organocatalytic asymmetric β-hydroxylation of aliphatic mitroalkenes and formation of nitro- or aminoalcohols.

The products obtained from the oxime addition to nitroalkenes would present a powerful alternative to the Henry reaction.[7] The enantioselective organocatalytic versions of the Henry reaction have mainly been successful for the addition of nitroalkanes to aromatic aldehydes and lower enantioselectivities are generally observed for aliphatic nitroalkenes.[8]

Here we wish to present the first enantioselective organocatalytic β-hydroxylation of functionalised aliphatic nitroalkenes using bifunctional thiourea-cinchona alkaloid catalysts,[9] and thereby, giving easy access to optically active aliphatic nitro- or aminoalcohols (Fig. 1).

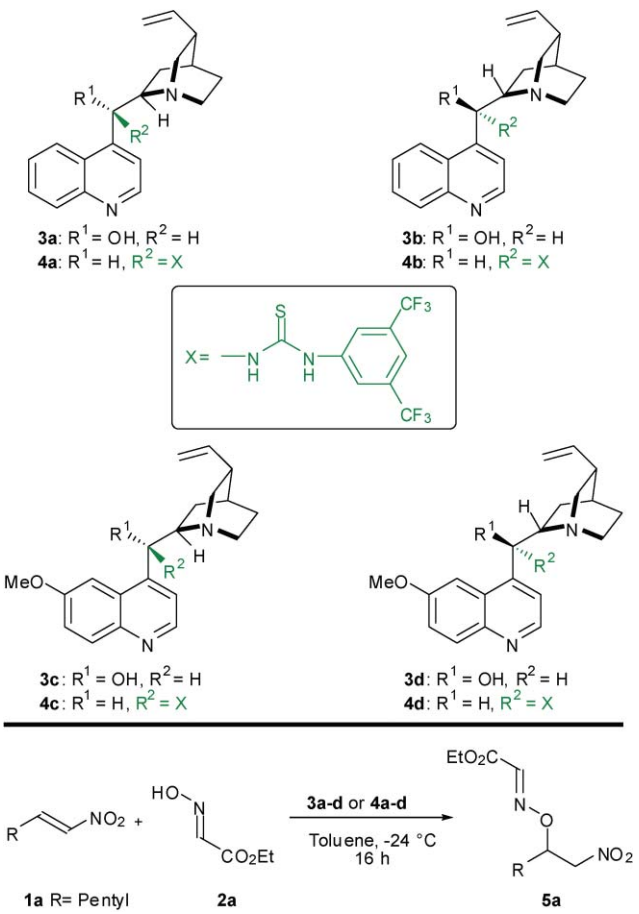


Fig. 1 Screening of cinchona and thiourea-cinchona catalysts for the enantioselective hydroxylation of nitroalkenes.

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Initially, several different cinchona alkaloids, such as cinchonine **3a**, cinchonidine **3b**, quinidine **3c**, and quinine **3d** were tested in the reaction of (*E*)-1-nitrohept-1-ene **1a** with different oximes, such as ethyl glyoxylate oxime **2a**, (*E*)-benzaldehyde oxime **2b** and acetone oxime **2c** in toluene. The oximes **2b,c** did not react with **1a**, while the reaction with **2a** proceeded to full conversion; however, the enantioselectivity for the reaction was poor (5–10% ee). Performing the reaction at −24 °C led to a lower conversion (73–82%, Table 1, entries 1–4), but only a minor increase in the enantioselectivity was observed.

Table 1 Screening of various cinchona catalysts **3a–d** and **4a–d** for the addition of ethyl glyoxylate oxime **2a** to nitroalkene **1a**[a]

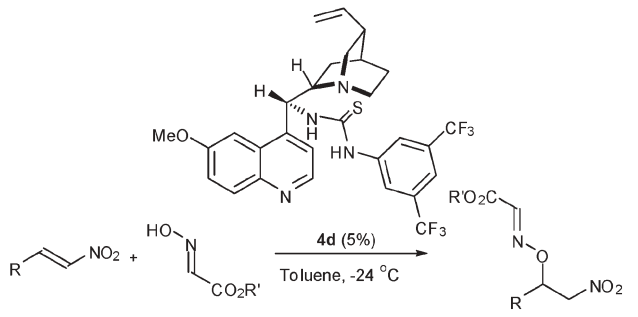
Entry	Cat. – (%)	[**1**]	Conv.[b] (%)	ee[c] (%)
1	**3a** – (10)	1.0	73	40 (+)
2	**3b** – (10)	1.0	77	27 (−)
3	**3c** – (10)	1.0	76	9 (+)
4	**3d** – (10)	1.0	82	15 (−)
5	**4a** – (10)	1.0	>95	82 (−)
6	**4a** – (5)	0.25	>95	87 (−)
7	**4b** – (5)	0.25	>95	91 (+)
8	**4c** – (5)	0.25	>95	81 (−)
9	**4d** – (5)	0.25	>95	91 (+)

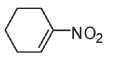
[a] Performed at −24 °C with **1a** (0.125 mmol), **2a** (0.375 mmol), and **3** or **4** in toluene. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC.

Due to the low stereoselectivity of the cinchona alkaloids, we also tested the thiourea-cinchona alkaloids **4a–d** as catalysts for the addition of **2a** to nitroalkene **1a**. These catalysts have the potential of activation of both the oxime by hydrogen bonding to the basic quinuclidine nitrogen atom and by Lewis-acid activation of the nitroalkene by the thiourea moiety. In this study, four different thiourea-cinchona alkoloids **4a–d**, derived from cinchonine, cinchonidine, quinidine and quinine, respectively, have been used. To our delight, catalyst **4a** (10 mol%) catalysed the addition of oxime **2a** to the nitroalkene **1a** at −24 °C in toluene to full conversion within 16 h with good enantioselectivity (82% ee, Table 1, entry 5). A decrease of the concentration led to an increase of the enantioselectivity to 87% ee and the catalyst loading could be lowered to 5 mol% without loss of enantioselectivity (entry 6). A further increase in the enantioselectivity was observed when employing catalyst **4b** and **4d** (91% ee, entries 7, 9).

With the optimised conditions, we investigated the scope of the reaction for the addition of **2a,d** to different nitroalkenes, which yielded the oxime addition products **5a–j** in high yields and enantioselectivities.[10] The results in Table 2 show that nitroalkenes, having a simple alkyl chain, all yielded the corresponding optically active oxime addition products in high yields (up to 83%) and high enantioselectivities (up to 91% ee) regardless of the oxygen source (entries 1–5). The enantioselective β-hydroxylation also proceeded for substrates having a phenyl ring in the alkyl chain to give product **5f** in good yield and enantioselectivity (entry 6). Several functional groups were tolerated in the side chain of the nitroalkene such as a non-conjugated double bond, an ester functionality, or a thioether which all gave the optically active products with high yields and stereoselectivities (entries 7–9). The hydroxylated cyclohexyl derivative **5e** is of special interest, since the corresponding aminoalcohol has shown very promising adrenergic mimicking effect.[11] The disubstituted nitroalkene,

Table 2 Scope of the organocatalytic addition of oximes **2a,d** to nitroalkenes **1**[a]



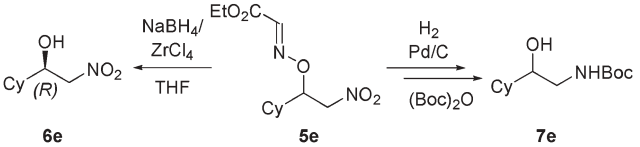
Entry	R	R′	Yield[b] (%)	ee (dr)[c] (%)
1	Pentyl	Et (**2a**)	**5a** – 79	91
2	Pentyl	*t*-Bu (**2d**)	**5b** – 83	90
3	Methyl	Et	**5c** – 63	90
4[d]	*t*-Butyl	Et	**5d** – 69	90
5	Cyclohexyl	Et	**5e** – 82	90
6	$Ph(CH_2)_2$	Et	**5f** – 68	89
7	Hex-3-enyl	Et	**5g** – 79	93
8	$CH_3OCO(CH_2)_4$	Et	**5h** – 68	89
9	$CH_3S(CH_2)_2$	Et	**5i** – 82	89
10[e]		Et	**5j** – 73	48 (20 : 1)

[a] Performed with **1** (0.25 mmol), **2** (0.5 mmol), **4d** (0.0125 mmol) in toluene (1 mL). [b] Purified by flash chromatography on Iatrobeads. [c] Determined by chiral HPLC. [d] **4d** (0.025 mmol), toluene (0.125 mL). [e] **4d** (0.050 mmol), toluene (0.125 mL).

1-nitrocyclohex-1-ene, reacted slower than the monosubstituted nitroalkenes and the reaction had to be performed at higher concentration (2 M) with an increased catalyst loading (20 mol%). The catalytic system led to product **5j** in high diastereoselectivity (dr 20 : 1); however, the enantioselectivity was only moderate (48% ee) (entry 10). Styrenes proved to be prone to retro-Michael addition and the products eluded isolation even on neutral Iatrobeads.

The cleavage of the O–N bond in the oxime moiety has been demonstrated to be possible under hydrogenation conditions at atmospheric pressure.[6] However, for the nitro products obtained in the present reactions, hydrogenation should lead to partial reduction of the nitro group. Increasing the pressure to 15 bar allowed full reduction to the biologically active amino alcohol **7e** (Scheme 2), which was isolated as the corresponding carbamate.

Selective cleavage of the O–N bond in the in the optically active products was also acheived using $ZrCl_4$ and $NaBH_4$. This methodology gave access to the optically active nitroalcohol **6e**, from which the absolute configuration was determined to be (*R*), based on a comparison of the optical rotation with the literature value.[12]



Scheme 2 Transformations of β-hydroxylated nitroalkenes.

In conclusion, we have presented the first catalytic highly stereoselective conjugate hydroxylation of nitroalkenes using oximes as easily accessible oxygen sources and bifunctional thiurea-cinchona organocatalysts. The products obtained give access to both optically active nitro- and aminoalcohols.

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10 The products proved to be unstable to normal flash chromatography on silica-gel, and were therefore isolated on neutral Iatrobeads and always kept neat.

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