*Cinchona Alkaloids*

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# Asymmetric Organocatalytic Henry Reaction**

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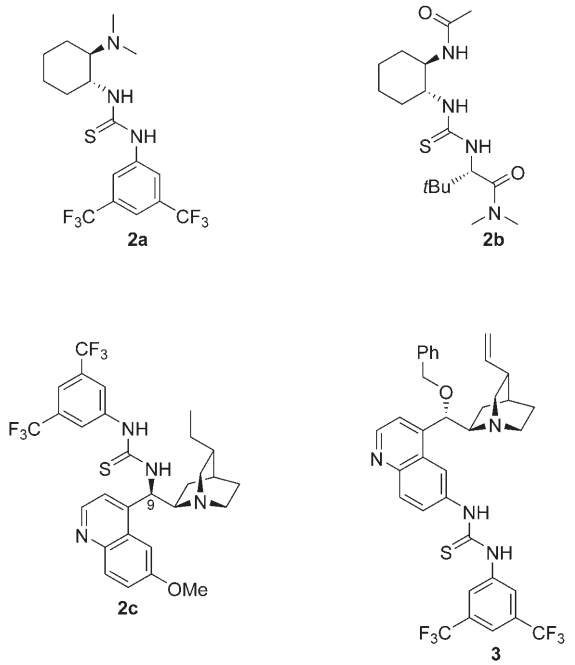
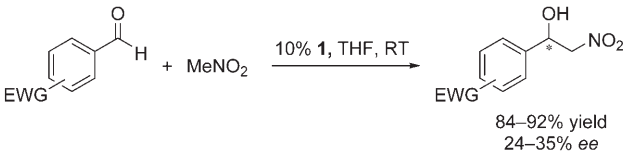
*Dedicated to Professor Goffredo Rosini on the occasion of his 65th birthday*

The reaction between a carbonyl compound and a nitroalkane, known as the Henry (or nitroaldol) reaction, is a powerful synthetic tool for the construction of complex molecules.[1] In recent years, several efficient catalytic enantioselective methods to perform this reaction have been described.[2] Typically, an aldehyde[3–7] (or an activated ketone)[8,9] is treated with a nitroalkane (mainly nitromethane or nitroethane) in the presence of a chiral metal complex and other additives, such as tertiary amines or molecular sieves, to obtain nitroalcohols with good to excellent optical purities. In the last decade, asymmetric organocatalysis has proven to be a robust and valid alternative to traditional metal-based catalysis for a number of reactions.[10] High enantiomeric excesses have been achieved in the reaction between nitroalkanes and imines (aza-Henry reaction) using chiral, enantiopure organic catalysts. Remarkable results were obtained in particular by Takemoto and co-workers[11] and Yoon and Jacobsen,[12] who employed thioureas **2a** and **2b**, respectively. To date, the use of metal-free catalysts in the parent nitroaldol reaction has never resulted in enantioselectivities exceeding 54% *ee*.[13]

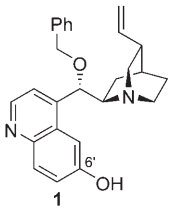
We recently reported the use of *Cinchona* derivatives as asymmetric catalysts for the reaction between activated aromatic aldehydes and nitromethane (Scheme 1).[14] The scope and enantioselectivities were modest, but we proved that a hydrogen-bond donor at the C6′ position of an appropriate *Cinchona* derivative is required to induce preferential formation of one enantiomer. Because the phenol moiety and the basic quinuclidine nitrogen atom can be in reasonable proximity in solution, the enantioselectivity could arise from a double activation of both the nucleophile and electrophile.[15] We envisaged that replacement of the phenol moiety with a better hydrogen-bond donor could result in a more powerful and more enantioselective catalyst.[16] Triggered by a recent report by Soos and co-workers on the introduction of an activated thiourea at the C9 position of the *Cinchona* scaffold **2c**,[17] we decided to functionalize **1** with the same moiety (Scheme 2). Catalyst **3**, a bench-stable crystalline solid, was synthesized on a multigram scale by a reliable and high-yielding sequence (see Supporting Information).




***Scheme 2.*** Thiourea catalysts. **2a**: Takemoto and co-workers[11]; **2b**: Yoon and Jacobsen[12]; **2c**: Soos and co-workers.[17]




***Scheme 1.*** Reaction between activated aromatic aldehydes and nitromethane. EWG = electron-withdrawing group.




Our initial experiments were performed using benzaldehyde (**4a**) as a model substrate with 10 equivalents of nitromethane and 20% of **3** (Table 1). We were delighted to observe that reaction of **4a** in dimethylformamide (DMF) at room temperature afforded the corresponding nitroalcohol **5a** after 6 h in 67% *ee* (Table 1, entry 4). The use of solvents other than DMF or THF mostly led to products with surprisingly low optical purity. Reaction in methanol afforded **5a** in a noteworthy 49% *ee*, whereas reaction in nitromethane, dichloromethane, and toluene essentially gave the racemic product. These results were somewhat puzzling because methanol is generally considered a poor solvent in

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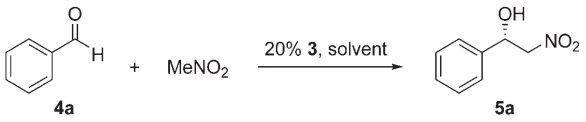
***Table 1:*** Optimization of the reaction conditions.[a]

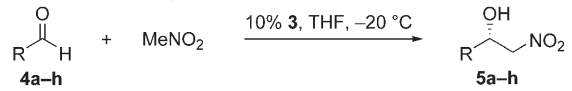



**4a** **5a**

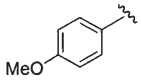
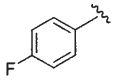
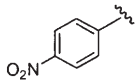
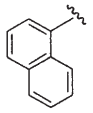
| Entry | Solvent | $T$ [°C] | $t$ [h] | Conversion [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | THF | 25 | 6 | 90 | 62 |
| 2 | $CH_2Cl_2$ | 25 | 6 | 97 | 6 |
| 3 | MeCN | 25 | 6 | 99 | 42 |
| 4 | DMF | 25 | 6 | 96 | 67 |
| 5 | $MeNO_2$[d] | 25 | 6 | 92 | 7 |
| 6 | MeOH | 25 | 6 | 91 | 49 |
| 7 | $Et_2O$ | 25 | 6 | 99 | 30 |
| 8 | toluene | 25 | 6 | 83 | 5 |
| 9 | DMF | −20 | 48 | 90 | 82 |
| 10 | THF | −20 | 48 | 99 | 89 |

[a] Reactions were carried out with **4a** (0.1 mmol), $MeNO_2$ (1.0 mmol), and **3** (0.02 mmol) in 100 μL of solvent. [b] Determined by $^1$H NMR spectroscopic analysis. [c] Determined by HPLC analysis using a Chiralcel OD-H column. [d] $MeNO_2$ (100 μL) was used as the solvent/reactant.

***Table 2:*** Substrate scope.[a]

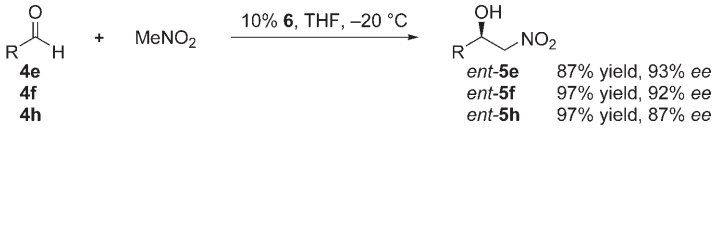


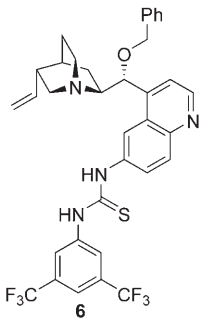

**4a–h** **5a–h**

| Entry | Substrate | R | $t$ [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **4a** |  | 48 | 90 | 92 |
| 2 | **4b** |  | 96 | 97 | 91 |
| 3 | **4c** |  | 168 | 94 | 89 |
| 4 | **4d** |  | 24 | 99 | 85 |
| 5 | **4e** |  | 4 | 91 | 86 |
| 6 | **4f** |  | 48 | 99 | 92 |
| 7 | **4g** |  | 24 | 91 | 86 |
| 8 | **4h** |  | 24 | 95 | 91 |

[a] Reactions were carried out with **4** (1.0 mmol), $MeNO_2$ (10.0 mmol), and **3** (0.1 mmol) in 1.0 mL of solvent at −20°C. [b] Yield of isolated product. [c] Determined by HPLC analysis using a Chiralcel OD-H column. Boc = *tert*-butoxycarbonyl.

hydrogen-bond-controlled organocatalysis. On the other hand, Wittkopp and Schreiner demonstrated that a similar thiourea can retain its catalytic activity in protic solvents.[18] Lowering the temperature provided synthetically useful levels of asymmetric induction at a still reasonable reaction rate (Table 1, entry 10). Further optimization revealed that these reactions could be carried out on a 1-mmol scale with only 10% catalyst: under these conditions **5a** was obtained after 48 h in 90% yield of isolated product and with 92% *ee*. Unfortunately, these conditions did not prove suitable for the reaction of aliphatic aldehydes: cyclohexanecarboxaldehyde and isobutyraldehyde were not completely converted into the corresponding nitroalcohols after 1 week and the enantiomeric excess of the products was disappointingly low (<20% *ee*). Nevertheless, a variety of aromatic aldehydes could be transformed into nitroalcohols **5b–h** in consistently high yields and enantiomeric excess (Table 2). Unactivated aromatic aldehydes required long reaction times but the reactions were clean, and we did not observe dehydration to the corresponding nitroalkenes (Table 2, entries 2 and 3). Not surprisingly, activated aldehydes typically furnished the nitroaldol product in one day or less (Table 2, entries 4 and 5). The protocol proved to be also compatible with heterocyclic aldehydes (Table 2, entries 7 and 8). Quinine-derived catalyst **6** (the pseudo enantiomer of **3**) gave access to nitroalcohols with the opposite configuration and comparable enantiomeric excess, as shown by three examples in Scheme 3.

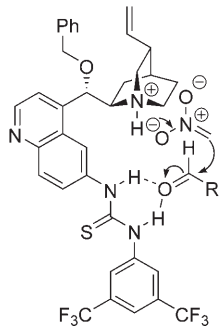



***Scheme 3.*** The use of quinine-derived catalyst **6** (the pseudo-enantiomer of **3**) to prepare nitroalcohols with the opposite configuration.

Although the reasons for the observed enantioselectivity are still not clear, we believe that the aldehyde is activated by the thiourea moiety through double hydrogen bonding,[16] while the nitromethane is activated by the basic quinuclidine nitrogen atom (Scheme 4). Besides providing control over the stereochemical outcome of the reaction, this behavior may also serve to increase the reactivity (catalyst **3** yields faster conversion than **1** under the same conditions). We also believe that the observed solvent dependency of the enantioselectivity may be because of the high conformational freedom of



***Scheme 4.*** Proposed mode of action of catalyst **3**.

**3**,[19] because our results cannot be rationalized on the basis of the polarity of the reaction medium.

In conclusion, we have developed a new organocatalyst capable of promoting the direct enantioselective nitroaldol reaction of aromatic and heteroaromatic aldehydes with nitromethane in high yields and enantiomeric excess. To the best of our knowledge, this is the first example of a highly enantioselective organocatalytic Henry reaction of aromatic aldehydes.[20] Although not general, we believe that our protocol constitutes an important step forward in this field. A study aimed at the understanding of the mechanism and the reasons for the observed enantioselectivity is currently underway. We envision that this will allow us to design new catalysts and widen the scope of this transformation.

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**Keywords:** alkaloids · asymmetric catalysis · Henry reaction · hydrogen bonds · organocatalysis

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