Asymmetric Catalysis

# Highly Enantioselective Thiourea-Catalyzed Nitro-Mannich Reactions**

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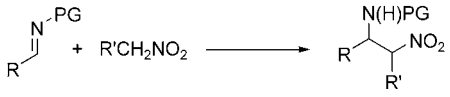
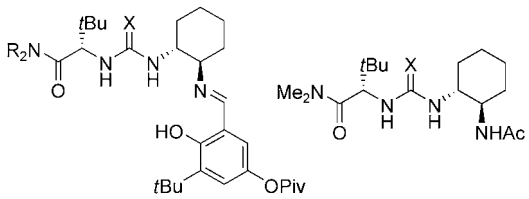
The addition of a nitroalkane across the C=N bond of an imine [Eq. (1), PG = protecting group], known as the nitro-




(1)

Mannich (or aza-Henry) reaction, is a carbon–carbon bond-forming process that can result in the generation of two contiguous nitrogen-bearing stereogenic centers. This reaction allows straightforward entry to a variety of nitrogen-containing chiral building blocks such as vicinal diamines by reduction of the nitro group [1,2] and α-amino carbonyl compounds by means of the Nef reaction.[3] As a result, considerable effort has been directed toward the development of catalytic asymmetric versions of the nitro-Mannich reaction over the past several years. Shibasaki et al. have described the enantioselective addition of nitroalkanes to *N*-phosphinoyl imines using chiral ytterbium[4] and aluminum[5] catalysts, while Jørgensen et al. have reported asymmetric copper-catalyzed additions to α-iminoesters.[6] Beyond these metal-catalyzed variants, two reports of enantioselective organocatalytic nitro-Mannich reactions have appeared recently. Takemoto et al. have reported a bifunctional thiourea catalyst that induces moderate enantioselectivity in the addition of nitromethane to a variety of aromatic *N*-phosphinoyl imines,[7] and Johnston et al. have developed a chiral bisamidine triflate salt that effects the diastereoselective addition of nitroethane to a range of electron-deficient *N*-Boc imines.[8]

Our laboratory has identified a family of chiral urea and thiourea catalysts (e.g. **1a** and **1b**, Figure 1) that catalyze a variety of enantioselective reactions with imines, including




**1a** X = O, $NR_2$ = NHBn
**1b** X = S, $NR_2$ = $NMe_2$
**2a** X = O
**2b** X = S

***Figure 1.*** Urea and thiourea catalysts. Piv = pivaloyl.

hydrocyanation,[9] Mannich,[10] hydrophosphonylation,[11] and acyl-Pictet–Spengler[12] reactions. Intrigued by the possibility that these compounds might constitute an emerging class of "privileged"[13] enantioselective catalysts, we investigated their activity in the asymmetric nitro-Mannich reaction. Herein, we report the discovery that the new thiourea catalyst **2b** efficiently promotes the diastereoselective nitro-Mannich reaction of nitroalkanes with *N*-Boc imines with high levels of enantioselectivity.

Our initial exploratory efforts directed toward thiourea-catalyzed asymmetric nitro-Mannich reactions involved screening of catalysts **1a** and **1b**, which had been developed and optimized in the context of Strecker-type reactions.[9] Surprisingly, while the first-generation Strecker urea catalyst **1a** afforded promising activity in the model reaction of nitroethane with benzaldehyde-derived *N*-Boc imine **3a** [Eq. (2)] (20% conversion, 2.1:1 *syn*:*anti*, 50% *ee*; Table 1, entry 1), the improved thiourea Strecker catalyst **1b**[9b] failed to accelerate this transformation (entry 2). Systematic variation of catalyst structure revealed that the simplified acetamide catalyst **2a** provided excellent enantio- and diastereoselectivity at 0°C, although the poor solubility of the catalyst in ether resulted in poor activity (entry 3, 34% conversion, 7.5:1 *syn*:*anti*, 92% *ee*). On the other hand, catalyst **2a** displayed improved solubility in toluene, and the reaction proceeded to completion within 24 h with similar enantio- and diastereoselectivity (entry 4, >95% conversion, 8.4:1 *syn*:*anti*, 91% *ee*). However, the reaction under these conditions proved to be poorly reproducible and quite sensitive to the purity of the starting imine; high *ee* values were largely limited to the benzaldehyde-derived imine **3a**. After a screen of additives, it was discovered that the addition of powdered 4-Å molecular sieves improved the reproducibility of the process and provided a more diastereoselective

***Table 1:*** Optimization of reaction conditions [Eq. (2), Ar = Ph].

| Entry | Cat. | Solv. | Base (equiv) | Mol. sieves (4 Å) | *T* [°C] | *t* [h] | Conv. [%] | d.r. (*syn*:*anti*) | *ee* [%] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | ether | $Et_3N$ (0.2) | – | 23 | 4 | 20 | 2.1:1 | 50 |
| 2 | **1b** | ether | $Et_3N$ (0.2) | – | 23 | 4 | 0 | – | – |
| 3 | **2a** | ether | $Et_3N$ (1) | – | 0 | 18 | 34 | 7.5:1 | 92 |
| 4 | **2a** | toluene | $Et_3N$ (1) | – | 0 | 24 | >95 | 8.4:1 | 91 |
| 5 | **2a** | toluene | $Et_3N$ (1) | + | 0 | 24 | >95 | 10:1 | 92 |
| 6 | **2a** | toluene | $iPr_2NEt$ (1) | + | 0 | 24 | 36 | 11:1 | 91 |
| 7 | **2b** | toluene | $iPr_2NEt$ (1) | + | 0 | 18 | >95 | 15:1 | 92 |

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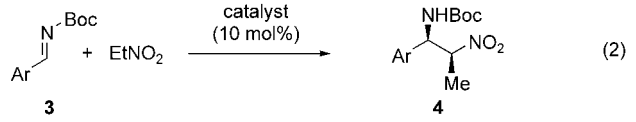
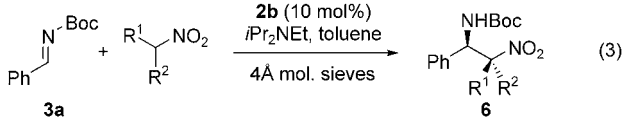
reaction (entry 5, 10:1 *syn*:*anti*). Variation of the tertiary amine base then led to the observation that the diastereoselectivity of the process could be improved further by the use of Hünig's base, albeit at the expense of reactivity (entry 6, 36% conversion, 11:1 *syn*:*anti*). Finally, a second screen of catalyst structures revealed that thiourea catalyst **2b** was significantly more reactive in the presence of molecular sieves than its urea analogue, allowing complete conversion to nitro-Mannich adduct **4** in 92% *ee* and 15:1 d.r. after 18 h (entry 7).[14]




(2)

Results obtained in the addition of nitroethane to a variety of *N*-Boc imines are summarized in Table 2. High enantioselectivities were obtained with a series substituted benzaldimine derivatives bearing both electron-donating and electron-withdrawing substitutents (entries 1–7, 92–96% *ee*).[15] These substrates also afforded good *syn* diastereoselectivity (7–16:1 *syn*:*anti*) in all cases examined, with the exception of *ortho*-chloro-substituted imine **3d** (entry 4, 2:1 *syn*:*anti*). This substrate proved to be less reactive than its *meta* and *para* isomers, and required slightly more forcing conditions for complete conversion (5 equiv nitroethane, 2 equiv Hünig's base). Aromatic heterocyclic *N*-imines (entries 8–9, 6–7:1 *syn*:*anti*, 93–97% *ee*) and 2-naphthaldehyde-derived imine **3j** (entry 10, 5:1 *syn*:*anti*, 97% *ee*) underwent reaction with excellent enantioselectivity and provided products with synthetically useful levels of diastereoselectivity.

As revealed in Table 3, useful results were obtained in nitro-Mannich reactions with a variety of nitroalkanes.[16] 1-Nitropropane underwent smooth reaction with *N*-Boc benzaldimine **3a** to provide adduct **6a** in 7:1 d.r. and 92% *ee* (entry 1: [Eq. (3)]). Nitromethane proved to be considerably less reactive and required longer reaction times (40 h) for complete conversion, but the adduct was obtained in 92% *ee* (entry 2). Reaction with the more sterically challenging 2-nitropropane did not proceed at all under the standard conditions, but when triethylamine was used as the tertiary base additive the desired product **5c** was obtained in 87% yield and 92% *ee* (entry 3). Finally, reaction of β-silyloxy nitroalkane **5** afforded the protected amino alcohol **6d** in 4:1 d.r. and 95% *ee* (entry 4). No desilylation or elimination of the silyloxy group was observed under the mild conditions of this catalytic process.




(3)

***Table 3:*** Enantioselective nitro-Mannich reactions with representative nitroalkanes [Eq. (3)].[a]

| Entry | Nitroalkane | Adduct | $R^1$ | $R^2$ | Yield [%][b] | d.r. (*syn*:*anti*)[c] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | 1-nitropropane | **6a** | Et | H | 99 | 7:1 | 95 |
| 2 | nitromethane | **6b** | H | H | 87 | – | 92 |
| 3[d] | 2-nitropropane | **6c** | Me | Me | 87 | – | 92 |
| 4[e] | $TBSOCH_2CH_2NO_2$ (**5**) | **6d** | $TBSOCH_2$ | H | 85 | 4:1 | 95 |

[a] Unless otherwise noted, reactions were carried out with 1 equiv **3a** (0.25 mmol), 5 equiv nitroalkane, 10 mol% **2b**, 2 equiv DIPEA, and powdered 4-Å molecular sieves (150 mg) in toluene (1 mL) at 4°C. [b] Yield of product isolated after silica gel chromatography. [c] Determined by HPLC by using commercial chiral columns; see Supporting Information. [d] Reaction performed by using 2 equiv triethylamine. [e] Reaction performed by using 2.5 equiv **5** and 1 equiv DIPEA; TBS = *tert*-butyldimethylsilyl.

***Table 2:*** Enantioselective catalytic addition of nitroethane to representative *N*-Boc imines [Eq. (2)].[a]

| Entry | Ar | Adduct | Yield [%][b] | d.r. (*syn*:*anti*)[c] | *syn ee* [%][c] |
|---|---|---|---|---|---|
| 1 | Ph (**3a**) | **4a** | 96 | 15:1 | 92 |
| 2 | *p*-$ClC_6H_4$ (**3b**) | **4b** | 98 | 7:1 | 95 |
| 3 | *m*-$ClC_6H_4$ (**3c**) | **4c** | 85 | 7:1 | 96 |
| 4[d] | *o*-$ClC_6H_4$ (**3d**) | **4d** | 99 | 2:1 | 93 |
| 5 | *p*-$MeC_6H_4$ (**3e**) | **4e** | 90 | 12:1 | 96 |
| 6 | *m*-$MeC_6H_4$ (**3e**) | **4f** | 99 | 9:1 | 95 |
| 7 | *p*-$(MeO)C_6H_4$ (**3g**) | **4g** | 95 | 16:1 | 96 |
| 8[d] | 3-pyridyl (**3h**) | **4h** | 79 | 7:1 | 97 |
| 9 | 2-furyl (**3i**) | **4i** | 95 | 6:1 | 93 |
| 10[d] | 2-naphthyl (**3j**) | **4j** | 91 | 5:1 | 97 |

[a] Unless noted otherwise, reactions were carried out with 1 equiv *N*-Boc imine (0.25 mmol), 2.5 equiv nitroethane, 10 mol% **2b**, 1 equiv diisopropylethylamine (DIPEA), and powdered 4-Å molecular sieves (150 mg) in 1 mL toluene at 4°C. [b] Yield of product isolated after silica gel chromatography. [c] Determined by HPLC using commercial chiral columns; see Supporting Information. [d] Reaction performed by using 5 equiv nitroethane and 2 equiv DIPEA.

In summary, the new thiourea catalyst **2b** was found to promote the stereoselective addition of a range of nitroalkanes to aromatic *N*-Boc imines. This new procedure represents an advance in the asymmetric nitro-Mannich reaction with regard to both enantioselectivity and substrate scope. A number of different mechanistic scenarios may be considered for this catalytic transformation. The sense of imine enantioface selectivity is the same as that observed in previously reported thiourea-catalyzed Strecker, Mannich, and hydrophosphonylation reactions, suggesting a common mechanism of imine activation. However, thiourea derivatives are also known to bind to and modulate the reactivity of nitronate anions;[17] therefore the role of **2b** in this transformation could be activation of the nitroalkane component[18] or dual activation of both reaction partners.[19] Further investigations into the mechanism and scope of this reaction are underway and will be reported in due course.

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**Keywords:** amines · asymmetric catalysis · diastereoselectivity · enantioselectivity · Mannich reaction

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[14] The role of powdered 4-Å molecular sieves in this process has not yet been established. Use of other desiccants, including 3-Å and 5-Å molecular sieves, had a detrimental effect on rate and enantioselectivity. This raises the intriguing possibility that the 4-Å sieves may play a more direct role in the reaction mechanism.
[15] Only aromatic imines were investigated because, as yet, no useful method exists for the synthesis of aliphatic *N*-Boc imine derivatives.
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[19] For a recent example of dual-activation catalysis, see: G. M. Sammis, H. Danjo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 9928 – 9929.

  