CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201002415

Asymmetric Organocatalytic Formal Aza-Michael Addition of Ammonia to Nitroalkenes

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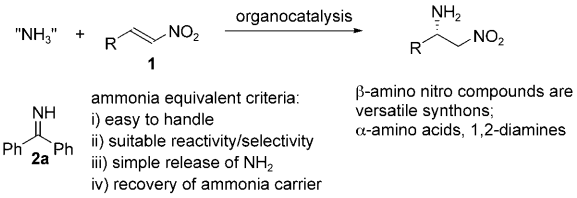
Stereogenic centers containing C–N bonds are found in many important biomolecules, such as amino acids[1] and glycosamines.[2] Moreover, the activity of numerous pharmaceuticals depends on the absolute configuration of one or more nitrogen-containing stereogenic centers.[3] Therefore, the development of efficient stereoselective catalytic C–N bond forming reactions is of significant interest in organic chemistry. Giving access to valuable compounds and structural complexity, the catalytic enantioselective conjugate addition of nitrogen-based nucleophiles to Michael acceptors[4] using organocatalysts[5] has attracted considerable attention in recent years.

In particular, the addition of ammonia equivalents[6] to nitroalkenes gives rise to the synthetically interesting β-amino-nitro functionality (Scheme 1), which, due to the unique chemistry of the nitro group,[7] can be transformed to a variety of attractive compounds such as α-amino acids[8] and 1,2-diamines.[9] Traditionally, the organocatalytic formation of β-amino nitro compounds is afforded by the nitro-Mannich (aza-Henry) reaction,[10] while the aza-Michael addition to nitroalkenes has only received limited attention. The first asymmetric organocatalytic aza-Michael addition to nitroalkenes was demonstrated in 2006 by Wang et al.,[11] employing aromatic heterocyclic benzotriazoles as nitrogen-centred nucleophiles; however, the synthetic applicability of the products are limited. Surprisingly, only two other examples of organocatalytic amination of nitroalkenes, giving access to enantioenriched primary amines, have been reported. In 2007, it was demonstrated that TMS-protected azide can be employed as a masked ammonia equivalent in a high yielding asymmetric base catalysed addition to aliphatic nitroalkenes;[6i] however, the enantioselectivity obtained was low to moderate. Recently, Ooi et al.[6g] reported the aza-Michael addition of 2,4-dimethoxyaniline to nitroalkenes in excellent yields and enantioselectivities by Brønsted-acid catalysis using chiral arylaminophosphonium barfates. A minor drawback is that 2.5 equivalents of CAN (cerium ammonium nitrate) were required for deprotection to afford the primary amine. The smallest nitrogen-based nucleophile, ammonia, is conceptually the optimal nucleophile, concerning atom economy,[12] but its volatile nature, high reactivity and toxicity makes it difficult to work with in catalytic systems. However, in the palladium-catalyzed Buchwald–Hartwig coupling[13] the challenge of synthesizing anilines was solved by applying imines as ammonia equivalents. The resulting *N*-aryl imines are conveniently protected anilines, which are deprotected by simple acidic work up.



Scheme 1. Concept for organocatalytic formal aza-Michael addition of ammonia to nitroalkenes.

Inspired by the palladium-catalyzed amination protocol, we envisioned that employing benzophenone imine **2a**, as an ammonia equivalent to react with nitroalkenes **1** under organocatalytic conditions would allow us to formally produce optically active β-amino nitro compounds (Scheme 1). Previous studies have shown that chiral thiourea-based catalysts are prime specimens for conducting the activation of nitroalkenes towards nucleophilic attack in a highly enantioselective manner.[14] Despite the abundance of numerous thiourea catalyzed 1,4-additions, the enantioselective thiourea catalyzed aza-Michael addition to nitroalkenes has to the best of our knowledge not been reported. Hence, we per-

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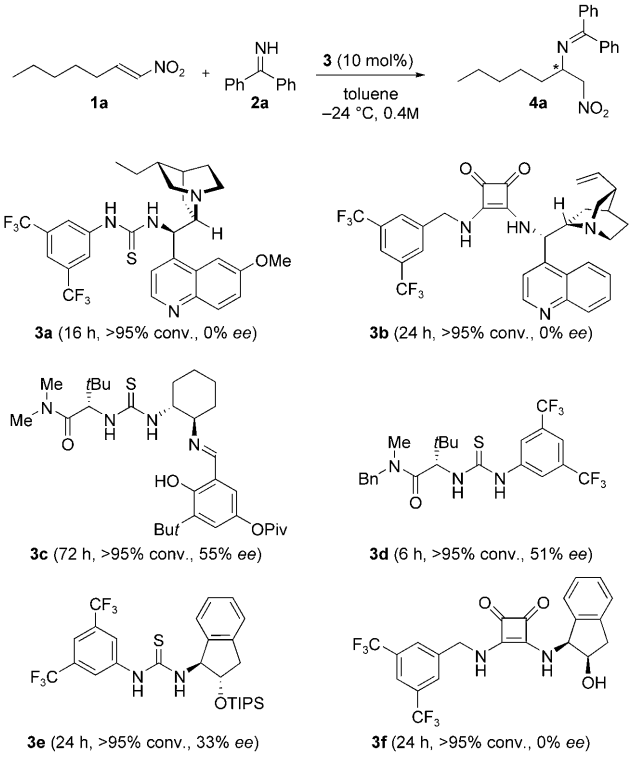
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002415.

formed our initial screening using different chiral hydrogen-bond donating catalysts.[15]

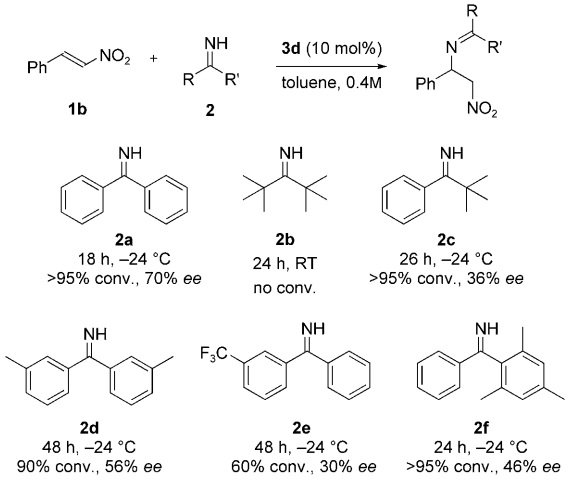
We first examined the reaction between (*E*)-1-nitrohept-1-ene **1a** and benzophenone imine **2a** catalyzed by different chiral thioureas and squaramides, as the model system (see Supporting Information) and Scheme 2 shows some selected



Scheme 2. Selected results from catalyst screening.

screening results. We were pleased to find that the thiourea modified quinidine **3a** efficiently catalyzed the reaction in toluene but, unfortunately, no enantioenrichment of product **4a** was found. The hydrogen-bonding donor squaramide modified cinchonidine **3b** was also investigated, affording **4a** as a racemate. Catalysts **3a** and **3b** are both bifunctional catalysts containing a Brønsted basic quinuclidine moiety, which might be responsible for the lacking selectivity due to non-stereoselective activation of **1a**. The Jacobsen-type thiourea catalysts **3c** and **3d**, gave **4a** in moderate enantioselectivity and with full conversion (Scheme 2). The results for **3c** and **3d** showed that the latter catalyst is more active compared to **3c**, as a significant shorter reaction time was required for **3d**. In catalyst **3d**, one nitrogen atom of the thiourea is attached to an electron-deficient 3,5-bis(trifluoromethyl)-aryl substituent which provides stronger hydrogen-bond donating ability.[16] Additionally, we applied thiourea **3e** which contained the 3,5-bis(trifluoromethyl)-aryl functionality; however, lower enantioselectivity was observed (33% *ee*, *ent*-**4a**). Finally, the chiral squaramide **3f** was tested but this catalyst showed no stereoselection. The preliminary catalyst screening suggested that **3d**[17] was a promising catalyst for the reaction.

With the optimal catalyst in hand, nitrostyrene **1b** was tested as the aromatic model substrate for the reaction with benzophenone imine **2a**. The application of **1b** gave a significant increase in enantioselectivity and provided **4b** in up to 70% *ee* (Scheme 3).



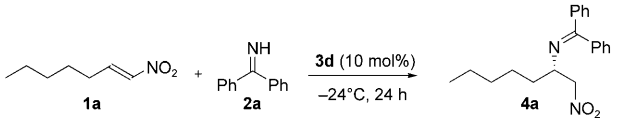
Scheme 3. Screening for optimal ammonia equivalent structure.

In the next stage, the optimal structure of the ammonia equivalent was investigated (Scheme 3). We envisioned that bulkier substituents than the two phenyls in **2a** would enable the catalyst to enhance the face discrimination in the addition to the nitroalkene. Unfortunately, 2,2,4,4-tetramethylpentan-3-one imine (**2b**) was unreactive under the given conditions. Replacing one phenyl group with a *tert*-butyl group (**2c**) revealed a more reactive imine, but disappointingly, an enantioselectivity of only 36% *ee* was observed. Another strategy was to introduce steric bulk by placing substituents on the phenyl rings. Imine **2d** bearing one *meta*-methyl on both aryl groups needed prolonged reaction time (48 h) with an enantioselectivity of 56% *ee*. Replacing a phenyl group with a mesityl group afforded a reasonable reactive imine (**2f**); however, lower enantioselectivity (46% *ee*) was observed. Finally, placing an electron-withdrawing trifluoromethyl in one of the *meta* positions also had a negative effect on both reaction time (48 h) and enantioselectivity (30% *ee*). These investigations of the nucleophile revealed that our attempts to optimize the structure resulted in prolonged reaction times and lower enantioselectivities. We therefore concluded that the benzophenone imine **2a** was the best ammonia source. Fortunately, the optimal nucleophile **2a** and catalyst **3d** are both commercially available compounds, which make this ready-to-use amination methodology very attractive, and enhance the synthetic applicability.

Having found the optimal nucleophile and catalyst, we initiated optimizing the reaction conditions for the aliphatic nitroalkene **1a**. First, we screened various solvents (Table 1,

entries 1–9). Generally, full conversion was obtained in all solvents studied; however, the enantioselectivity of **4a** is significantly dependent on the polarity of the solvent (0–69% *ee*). Especially, saturated hydrocarbons proved to be promising solvents, with *n*-heptane as slightly superior (Table 1, entry 8). By reducing the catalyst loading to 5 mol%, prolonged reaction time and decreased enantioselectivity of **4a** were observed (Table 1, entry 10). Secondly, we investigated the effect of dilution (Table 1, entry 11). We were pleased to observe that the enantioselectivity of **4a** was enhanced to 81% *ee*, at a concentration of only 0.05 M. It should be mentioned that lowering the temperature prolonged the reaction time significantly, while affording no additional enantioselectivity. Furthermore, at room temperature the enantioselectivity decreases dramatically. Finally, it should be noted that all experiments were performed in non-dried solvents and under ambient conditions. We have also investigated the effect of adding 10 mol% water to the reaction mixture in the presence of 4 Å molecular sieves (Table 1, entries 12 and 13). The addition of water had no effect on the results, whereas, the presence of 4 Å molecular sieves provided 30% *ee* of the opposite enantiomer of **4a**. This suggests that water might have a crucial role on the stereochemical outcome of the reaction (see Scheme 5).

Table 1. Optimisation of reaction conditions.[a]

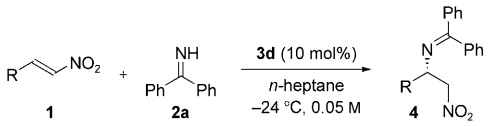


Entry	Solvent	*c* [M]	Conv. [%]	*ee* [%][b]
1	toluene	0.4	>95	51
2	*m*-xylene	0.4	>95	62
3	CH_2Cl_2	0.4	>95	7
4	MeCN	0.4	>95	0
5	THF	0.4	>95	2
6	*n*-hexane	0.4	>95	68
7	*n*-pentane	0.4	>95	64
8	*n*-heptane	0.4	>95	69
9[c]	*c*-hexane	0.4	>95	62
10[d]	*n*-heptane	0.4	90	63
11	***n*-heptane**	**0.05**	**>95**	**81**
12[e]	*n*-heptane	0.05	>95	81
13[f]	*n*-heptane	0.05	>95	−30

[a] All reactions performed using **1** (0.20 mmol), **2** (0.10 mmol) and **3** (0.01 mmol) at −24 °C until full conversion was observed by TLC. Values in bold indicate optimal conditions. [b] Determined by chiral stationary-phase HPLC. [c] Reaction temperature: 5 °C. [d] Catalyst loading reduced to 5 mol%, reaction time 48 h. [e] 10 mol% water was added. [f] Reaction conducted in presence of 4 Å molecular sieves, under N_2 atmosphere.

To present the scope of this aza-Michael reaction, a representative set of alkyl and aryl substituted nitroalkenes **1** was reacted with benzophenone imine **2a** under the optimal reaction conditions. For nitroalkenes having linear, branched and non-conjugated unsaturated substituents (Table 2, entries 1 and 3–5), the products, **4a** and **4c–e**, were obtained in high to excellent yields (85–95%), and high enantioselectivities (78–89% *ee*). Aromatic nitroalkenes bearing both electron-withdrawing and -donating substituents (Table 2, entries 2 and 6–9) also afforded the products, **4b** and **4f–i**, in high yields (79–88%), and high enantioselectivities (81–92% *ee*).

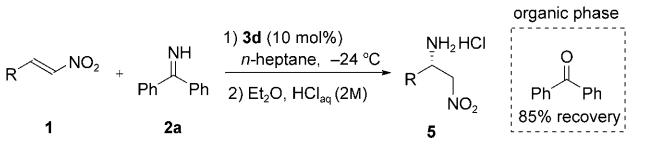
Table 2. Scope of the reaction.



Entry	**1**, R	**4**, Product	Yield [%][b]	*ee* [%][c]
1	*n*-pentyl **1a**	**4a**	95	81
2	Ph **1b**	**4b**	80	83 (*S*)
3	Cy **1c**	**4c**	85	81 (*S*)
4	*t*Bu **1d**	**4d**	89	89
5	(*Z*)-3-hexenyl **1e**	**4e**	89	78[d]
6	*p*-Br-Ph **1f**	**4f**	79	81
7	*p*-F-Ph **1g**	**4g**	80	87 (*S*)
8	*p*-OMe-Ph **1h**	**4h**	85	83 (*S*)
9	*o*-Cl-Ph **1i**	**4i**	88	92

[a] All reactions performed on a 0.10 mmol scale (0.05 M in heptane) using **1** (0.20 mmol), **2** (0.10 mmol) and **3** (0.01 mmol) at −24 °C. [b] Isolated by FC. [c] Determined by chiral stationary-phase HPLC. [d] Determined from the *N*-Boc-protected product, as the enantiomers of **4e** could not be separated by HPLC.

To demonstrate that the reaction is a formal addition of ammonia, we have developed a one-pot asymmetric aza-Michael addition–acidic hydrolysis protocol. Thus, upon completion of the addition step, 2 M HCl (aq) and Et_2O were added to the reaction mixture. Isolating the aqueous phase, and subsequent removal of water as azeotrope with toluene, furnished the hydrochloride salt of the primary β-amino nitro compounds **5** (Scheme 4). Both aliphatic and aromatic



5a: R = Cy; 62% yield, 80% *ee*
5b: R = (*Z*)-3-hexenyl; 72% yield, 78% *ee*
5c: R = Ph; 80% yield, 82% *ee*
5d: R = *p*-F-Ph; 70% yield, 84% *ee*
5e: R = *p*-OMe-Ph; 60% yield, 78% *ee*

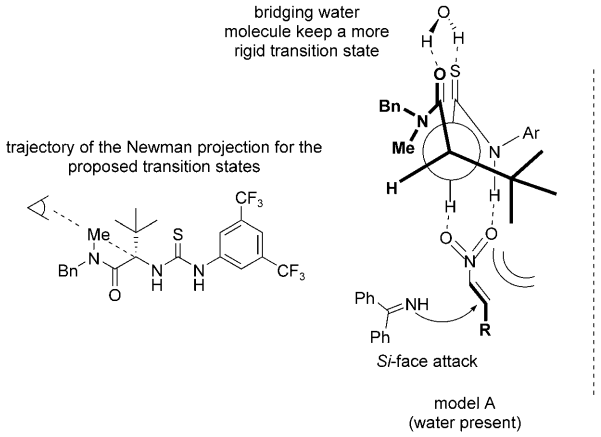
Scheme 4. One-pot aza-Michael addition and acidic hydrolysis protocol.

substituents were tolerated (**5a–5e**), giving good yields (60–80%, 2 steps) and enantioselectivities (78–84% *ee*) consistent with the results obtained for the addition products **4**. Remarkably, while no further purification of hydrochloride salts **5** were required, benzophenone was recovered in 85% yield from the organic phase. Benzophenone imine **2a** is industrially produced in a patented process by condensation of benzophenone and ammonia,[18] therefore protecting

group recovering and recycling, would minimize the environmental impact of waste production in the present methodology.

The absolute configurations of product **4b**,**c** and **4g**,**h** were assigned to be *S* by chemical correlation with the corresponding described *N*-Boc-protected amines.[11b] The remaining configurations of adducts **4** and salts **5** are assumed by analogy.

Extensive mechanistic studies of the role of this class of chiral thiourea catalysts using kinetic and computational work have previously been performed.[19] These investigations include, for example, the activation of nitroalkenes by the thiourea moiety and the stereochemical outcome of the nucleophilic approach to the activated substrate. Based on these models and the role of water on the stereochemical outcome of the present reaction, two working models are suggested in Scheme 5. Model **A** accounts for the presence



Scheme 5. Proposal activation models.

of water in the reaction affording the product with *S* configuration. The water molecule is proposed to bridge the thiourea sulphur and amide oxygen atoms,[20] placing the *tert*-butyl group in such a way that the *Re* face of the nitroalkene is shielded, allowing only *Si*-face attack of benzophenone imine **2a**. Model **B** accounts for the obtained *R* configuration (in low enantiomeric excess, Table 1, entry 13) in the absence of water. In this model, the *tert*-butyl group is shielding the other face of the nitroalkene, giving the observed *Re*-face approach of **2a**. This is proposed to be due to the lack of the bridging water molecule, which allows for more rotational freedom, lowering the enantioselectivity under these reaction conditions.

In summary, we have developed the formal addition of ammonia to nitroalkenes by an enantioselective thiourea catalyzed aza-Michael addition of benzophenone imine. The scope for the reaction is demonstrated for a number of aliphatic and aromatic nitroalkenes for the synthesis of protected optically active β-amino nitro compounds in high yields and enantioselectivities. Operational simple one-pot deprotection, with recovery of benzophenone demonstrates that benzophenone imine is an appropriate ammonia equivalent to apply in combination with mild organocatalytic activations.

Acknowledgements

This work was made possible by grants from Carlsberg Foundation and OChemSchool. D.M. thanks the Ministerio de Ciencia e Innovación of Spain for a postdoctoral fellowship.

Keywords: alkenes · Michael addition · nitroalkenes · organocatalysis

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Received: August 20, 2010
Published online: October 29, 2010

