Asymmetric Michael Addition of Nitrobenzyl Pyridines to Enals via Iminium Catalysis

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Abstract: The asymmetric Michael addition of nitrobenzyl pyridines to α,β-unsaturated aldehydes is described. This unprecedented transformation highlights the possibility of extending the nucleophile scope of iminium catalysis to include diaryl compounds in which the reactive methylene centre is not activated by classical electron-withdrawing groups. Indeed, combining the electronic effects of a *p*-nitro- or *o*-nitro-substituted aromatic and of a pyridine system fulfils the requirements for nucleophile activation. The synthetic utility of the method has been demonstrated via rapid access to enantioenriched tetrahydro-1-benzazepines.

Key words: asymmetric catalysis, secondary amine, Michael addition, organocatalysis, pyridine

Asymmetric aminocatalysis[1] is today recognised as an established synthetic tool for asymmetrically functionalising carbonyl compounds. In particular, iminium catalysis using chiral secondary amine catalysts is a reliable way of directly introducing a nucleophilic component at the β position of α,β-unsaturated aldehydes.[2] This activation mode has found successful application in many enantioselective conjugate additions of carbon nucleophiles, a fundamental and often employed chemical transformation for stereoselectively forming a new carbon–carbon bond. Two principle classes of carbon nucleophile are suitable substrates for the iminium-catalysed Michael addition to α,β-unsaturated aldehydes: π-electron-rich nucleophiles, which undergo Friedel–Crafts-type alkylation,[3] and pro-nucleophilic species bearing an activated methylene group[4–8] (Figure 1).

A rationalisation of the acidity-reactivity profiles of the employed C–H acid substrates points to a functional pK_a barrier for nucleophilic activation that lies between the pK_a values of 16 and 17.[4,6,8] Generally, addressing this criterion requires the presence of two geminal electron-withdrawing groups, such as 1,3-dicarbonyl compounds.[4] For a few specific compounds, the presence of a single well-tailored electron-withdrawing functional group is enough to lower the pK_a value of the active methylene moiety to the desired functional level. Nitroalkanes,[5] trifluoroethyl thioesters,[6] benzofuranone,[7] and nitrophenylacetonitrile,[8] which can form enolate-like anions,[10] have been successfully used in the asymmetric Michael addition to enals under iminium catalysis.

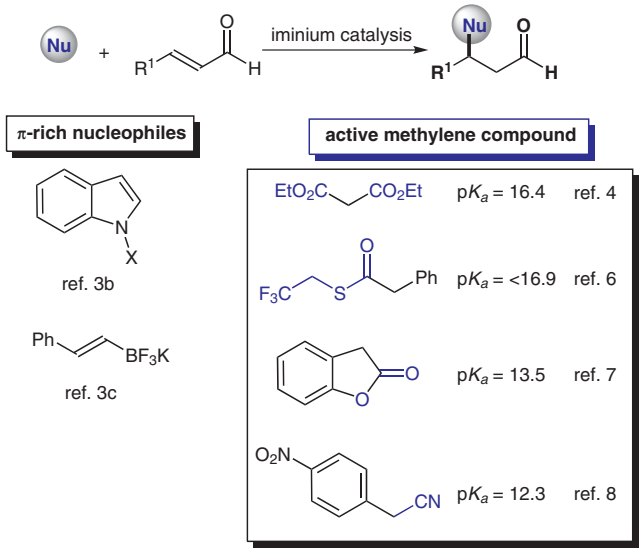
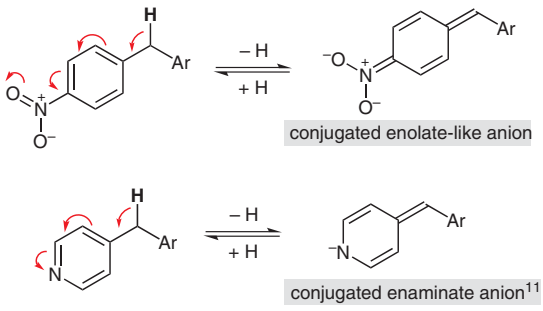


Figure 1 Michael addition to enals under iminium catalysis: the nucleophile scope. Activation of the methylene compounds generally requires at least one, and generally two, electron-withdrawing functional groups. The pK_a values refer to DMSO; see ref 9.

Here, we show that iminium catalysis of enals can be extended to include diaryl compounds that do not contain classical activating electron-withdrawing groups (generally a carbonyl moiety) directly bound to the nucleophilic methylene centre. Specifically, we found that the combination of electron-deficient aryl and heteroaryl groups strongly increases the acidity of the benzylic protons, fulfilling the requirements for nucleophile activation. In-



Scheme 1 Nucleophile activation by the *p*-nitrophenyl and pyridyl groups: stabilisation of the negative charge by conjugation and inductive effects

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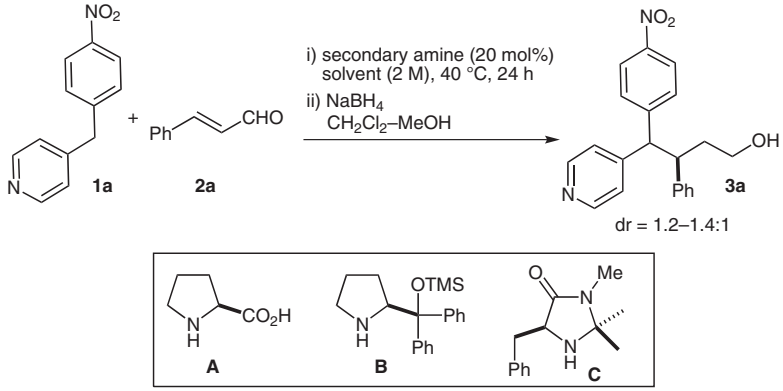
deed, nitrobenzyl pyridine derivatives **1** proved to be suitable prochiral nucleophiles that effectively underwent a highly stereoselective Michael addition to a range of α,β-unsaturated aldehydes under the iminium activation of chiral secondary amines.

We reasoned that the delocalising ability of a *p*-nitro-substituted aromatic ring and of a pyridine system may be synergistically combined to produce a strong acidifying effect on the methylene moiety (Scheme 1).[10,11] On these grounds, we decided to explore the reactivity profile of 4-(4-nitrobenzyl)pyridine (**1a**) within the context of an iminium-catalysed Michael addition pathway.

To assess the feasibility of such an aminocatalytic strategy, we focused on using some of the most widely employed chiral secondary amines to catalyse the addition of **1a** to cinnamaldehyde (**2a**) in toluene as the solvent (Table 1). While the use of both proline (**A**) and the hydrochloride salt of the imidazolidinone **C** resulted in a sluggish Michael addition process, the catalyst **B**[12] proved an effective iminium catalyst (entries 1–6).

The efficiency of the catalytic system was greatly increased upon addition of a basic co-catalyst. Extensive optimisations along this line identified DABCO (0.5 equiv) as the more suited additive for designing an effi-

Table 1 Optimisation Studies[a]



Entry	Catalyst	Additive (equiv)[b]	Solvent	Conversion (%)[c]	ee (%)[d]
1	**A**	none	toluene	12	–
2	**B**	none	neat	18	–
3	**B**	Et_3N (1)	neat	79	58:56
4	**B**	Et_3N (1)	toluene	47	80:78
5	**C**·HCl	Et_3N (1)	toluene	15	–
6	**B**	DABCO (1)	toluene	63	80:86
7	**B**	DABCO (0.5)	toluene	75	78:81
8	**B**	DABCO (0.25)	toluene	23	–
9	**B**	DMAP (0.5)	toluene	65	63:70
10	**B**	DABCO (0.5)	MeCN	83	47:47
11	**B**	DABCO (0.5)	dioxane	65	77:79
12	**B**	DABCO (0.5)	THF	76	79:83
13[e]	**B**	DABCO (0.5)	THF	78	94:94
14[e,f]	**B**	DABCO (0.5)	THF	71	92:92
15[e,f]	**B**	DABCO (0.5)	THF–H_2O (9:1)	90	92:92

[a] The reactions were carried out on a 0.1-mmol scale with **2a** (2 equiv) and [**1a**]$_0$ = 2 M in different solvents. All the reactions afforded a poor diastereomeric distribution (ranging from 1.4:1 to 1.2:1).
[b] DABCO: 1,4-diazabicyclo[2.2.2]octane; DMAP: 4-dimethylaminopyridine.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by HPLC analysis, on chiral stationary phases, of the purified alcohol **3a**, obtained by in situ $NaBH_4$ reduction of the corresponding aldehyde. The two distinct ee values refer to the enantiomeric excess of both the diastereoisomers.
[e] Reaction was carried out at r.t.
[f] The amount of catalyst **B** used was 10 mol%.

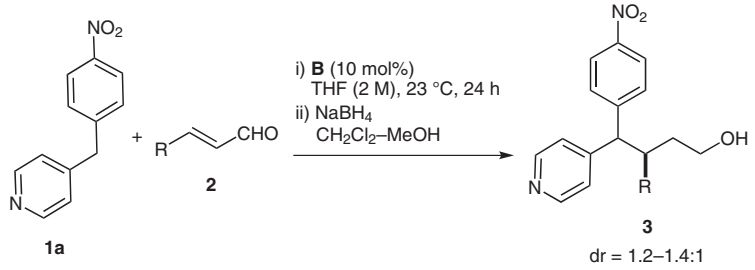
cient transformation (entries 6–9). Interestingly, increasing the amount of DABCO to one equivalent had negligible influence on the conversion (entries 6 and 7), whereas the use of 0.25 equivalent resulted in a dramatic reduction of the reaction rate (entries 7 and 8).

A survey of the reaction media (entries 10–12) revealed that both dioxane and THF were suitable solvents for the Michael addition. THF was selected for further investigation since it engenders a higher catalytic activity. Significantly, this allowed the reaction to be carried out at room temperature, a key parameter for obtaining a much higher stereoselectivity (94% ee on both the diastereoisomers; entries 12 and 13). Additionally, it was possible to reduce the catalyst loading of amine **B** to 10 mol% without compromising the chemical and the enantiomeric purity (entry 14). Aqueous THF, a solvent system selected in the Merck laboratories for the upscaling of a **B**-catalysed conjugate addition of a carbon nucleophile to enals,[13] gave also in the present case slightly better yield while keeping high level of enantiocontrol (entry 15).

We next performed a series of experiments to determine the scope of the aldehydic component in this asymmetric Michael addition protocol, using 10 mol% of catalyst **B**. THF was selected as the reaction medium, since the reaction did not always perform with uniform efficiency when the THF–water combination was used (entries 3, 5 and 7, Table 2).[14]

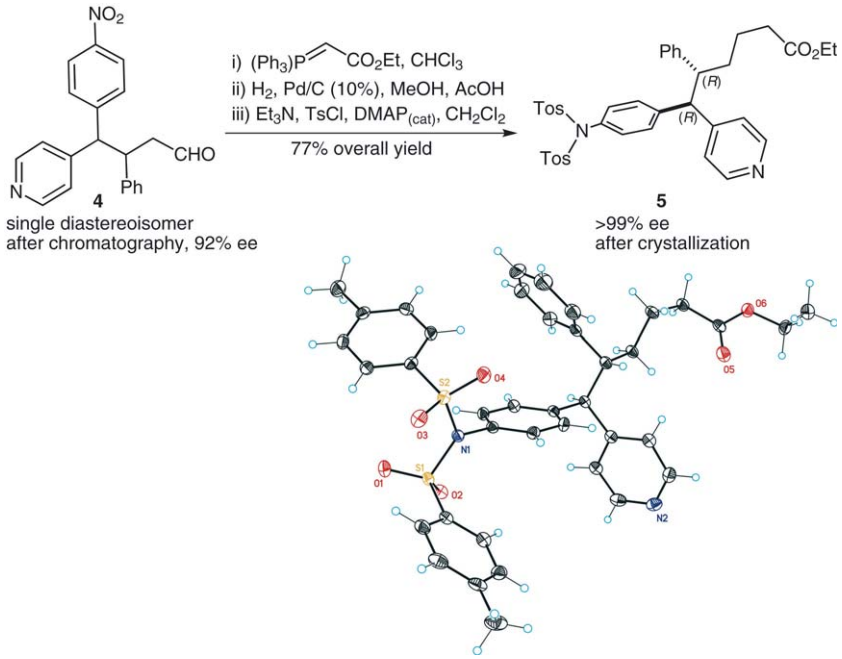
As highlighted in Table 2, the method proved successful for a wide range of enal β-substituents, including differently substituted aryl groups as well as heteroaryl and alkenyl moieties. The desired products **3** were isolated in high to excellent enantiomeric excess (ee values ranging from 75% to 94%) and good yield.[15] The system main-

Table 2 Secondary Amine Catalysed Asymmetric Conjugate Addition of 4-(4-Nitrobenzyl)pyridine (**1a**) to Enals[a]



Entry	R	3	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph	**3a**	24	66 (32:34)	92:92
2[d]	Ph	**3a**	48	57 (27:30)	95:96
3[e]	Ph	**3a**	24	80 (37:43)	92:92
4	4-$MeOC_6H_4$	**3b**	48	58 (24:34)	84:88
5[e]	4-$MeOC_6H_4$	**3b**	48	60 (21:39)	82:84
6[f]	4-$O_2NC_6H_4$	**3c**	24	85 (39:46)	92:92
7[e]	4-$O_2NC_6H_4$	**3c**	96	no reaction	–
8[g]	4-ClC_6H_4	**3d**	24	75 (34:41)	92:93
9	2-BrC_6H_4	**3e**	24	62 (30:32)	96:98
10	4-$F_3CC_6H_4$	**3f**	24	65 (32:33)	92:94
11	4-MeC_6H_4	**3g**	24	66 (33:33)	88:88
12	2-furyl	**3h**	24	82 (39:43)	88:87
13	$CH_2(CH=CH)Me$	**3i**	48	30 (14:16)	80:80

[a] The reactions were carried out at r.t. on a 0.1-mmol scale, using **2** (2 equiv) and $[\mathbf{1a}]_0$ = 2 M in THF, without any precautions for excluding moisture. All the reactions afforded a poor diastereomeric distribution (ranging from 1.4:1 to 1.2:1).
[b] The total yield is reported; the values between brackets refer to the yield of the isolated diastereomerically pure compounds **3**, which could be easily separated by chromatography (see supplementary information for details).
[c] Determined by HPLC analysis on chiral stationary phases. The two distinct ee values refer to the enantiomeric excess of the two diastereoisomers.
[d] Reaction was carried out on a 2.0-mmol scale using 15 mol% of **B**.
[e] THF–H_2O (9:1) mixture was used as the reaction medium.
[f] $[\mathbf{1a}]_0$ = 1 M in THF.
[g] Reaction was carried out at 40 °C.



Scheme 2 X-ray structure of the derivative **5**[18]

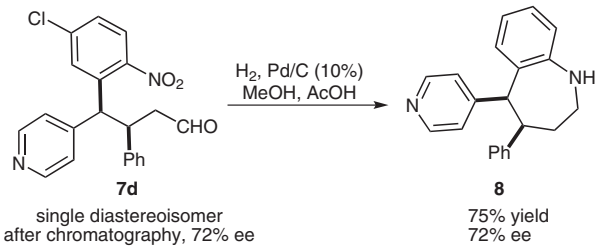
tained its efficiency also when applied on a synthetically useful scale (2.0 mmol), leading to the formation of the adduct **3** with comparable yield and slightly higher enantiopurity (entry 2). Although the conjugate addition proceeds with poor control over the relative configuration,[16] the synthetic utility of the process is increased by the possibility of easy isolation, by simple chromatography, of the two diastereoisomers for all of the adducts **3**.[17]

To determine the stereochemical outcome of the reaction, the diastereomerically pure aldehyde **4** was readily transformed into **5** by an olefination–reduction sequence followed by a ditosylation of the free amino moiety. Crystals of the derivative **5** were suitable for X-ray analysis, which unambiguously established the absolute configuration of the product (Scheme 2).[18]

Finally, we studied the possibility of using different diaryl compounds as the nucleophilic component of the Michael reaction. The results reported in Table 3 illustrate how both the *p*-nitro-substituted aromatic and the pyridine system are essential for obtaining nucleophile activation. Indeed, when the individual acidifying effects are not combined, the pK_a of the benzylic protons is not in a useful range (entries 1–4).

Significantly, different pyridine isomers were well tolerated and the 2-pyridyl analogue reacted well under the established reaction conditions (entries 5 and 6). On the other hand, the less-pronounced acidifying effect of the 2-nitro aryl moiety was directly reflected in a total loss of reactivity (entry 8). However, by fine-tuning the electronic nature of the aryl group, such as including a further electron-withdrawing chlorine atom, it was possible to regenerate the required conditions for nucleophile activation (entry 9).

Developing new methods for the easy incorporation of heteroaromatic groups[19a] in complex molecules is of fundamental importance in small-molecule drug discovery.[19b] Therefore, this new organocatalytic methodology could find application for the generation of potential medicinal agents. To highlight this possibility, an easy and stereoselective synthesis of the highly functionalised 1-benzazepine derivative **8** from the Michael adduct **7d** was accomplished (Scheme 3).[20]

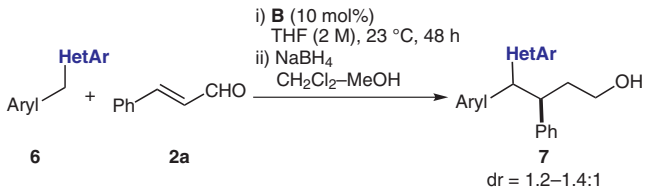


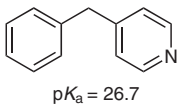
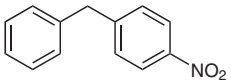
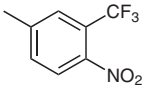
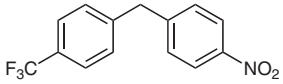
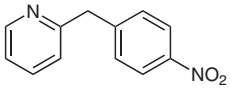
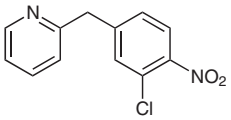
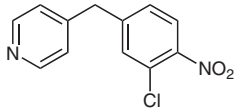
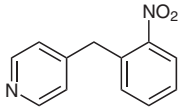
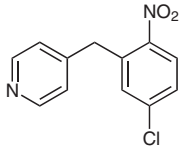
Scheme 3 Direct synthesis of substituted 2,3,4,5-tetrahydro-1-benzazepines

In summary, we have demonstrated that diaryl compounds are suitable nucleophilic partners for the iminium-catalysed Michael addition chemistry.[21] In view of the wide application of heteroaromatics in drug discovery and the good tolerance for a series of diverse functional groups demonstrated by the presented organocatalytic reaction, we believe that this novel approach may be useful to the chemical community.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 3 Nucleophile Scope: Activation Effects of the Aryl and Pyridyl Moieties[a]



Entry	6	7	Yield (%)[b]	ee (%)[c]
1	 pK_a = 26.7		no reaction	–
2			<5% conv.	–
3			no reaction	–
4			<5% conv.	–
5		**7a**	60 (26:34)	84:90
6		**7b**	84 (39:45)	85:90
7		**7c**	80 (39:41)	82:83
8			no reaction	
9[d]		**7d**	90 (41:49)	n.d./72

[a] The reactions were carried out at r.t. on a 0.1-mmol scale, using **2a** (2 equiv) and $[\mathbf{6}]_0$ = 2 M in THF. See ref. 9 for information about pK_a values.
[b] Total yield of the isolated products; the values between brackets refer to the yield of the diastereomerically pure compounds **7**, which could easily be isolated by chromatography (see supplementary information for details).
[c] Determined by HPLC analysis on chiral stationary phases. The two distinct ee values refer to the enantiomeric excess of the two diastereoisomers.
[d] The reaction was carried out at 40 °C with 20 mol% of catalyst **B**. n.d.: not determined; it was not possible to measure the ee of one of the diastereoisomers of **7d**.

Acknowledgment

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(13) For the industrial scale asymmetric synthesis of Telcagepant, see: Xu, F.; Zacuto, M.; Yoshikawa, N.; Desmond, R.; Hoerrner, S.; Itoh, T.; Journet, M.; Humphrey, G. R.; Cowden, C.; Strotman, N.; Devine, P. *J. Org. Chem.* **2010**, *75*, 7829.
(14) The lack of consistency in the conversion when using THF–H_2O as the solvent system is probably a consequence of the

poor solubility of some among the unsaturated aldehydes **2** in this reaction media.

(15) The presence of an alkyl substituent at the β-position of the enal is not tolerated under the reaction condition: i.e., crotonaldehyde remained unreactive.

(16) The observed modest diastereocontrol is not surprising: the privileged secondary amine catalysts, such as **B**, generally infer high enantioselectivity but with poor diastereocontrol when promoting the conjugate addition of prochiral carbon nucleophiles to α,β-unsaturated aldehydes; see, for example, ref. 6.

(17) Both the diastereomerically pure aldehydes and the corresponding alcohols are stable, with no epimerisation events observed after storing in the fridge for several weeks. The $NaBH_4$ reduction is requested since the alcohols **3** allow for a far easier HPLC analysis than the aldehyde precursors.

(18) Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, accession number CCDC 802673(**5**), and are available free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(19) (a) Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 8082; and references therein. (b) Pitt, W. R.; Parry, D. M.; Perry, B. G.; Groom, C. R. *J. Med. Chem.* **2009**, *52*, 2952.

(20) Benzazepines are the core structure of numerous biologically active compounds. More specifically, the tetrahydro-1-benzazepine scaffold can be found in a series of approved drugs such as Tolvaptan, Benazepril, Mozavaptan and Zilpaterol among others.

(21) **Experimental Procedure of the 2.0-mmol Scale Reaction (Table 2, entry 2)**: In an ordinary vial equipped with a magnetic stir bar, catalyst **B** (0.3 mmol, 97.5 mg, 15 mol%) and cinnamaldehyde (**2a**; 4 mmol, 503 μL) were dissolved in THF (1 mL). After 10 min stirring at r.t., 4-(4-nitrobenzyl)-pyridine (**1a**; 2.0 mmol, 427 mg) and DABCO (1 mmol, 112.2 mg, 0.5 equiv) were added. The vial was capped and the resulting mixture was stirred at r.t. After 48 h, the reaction mixture was cooled to 0 °C, diluted with MeOH (10 mL) and then a suspension of $NaBH_4$ (132.3 mg, 3.5 mmol) in MeOH (10 mL) was added dropwise. The resulting mixture was stirred for 30 min at 0 °C and then was quenched with H_2O (30 mL). The product was extracted with CH_2Cl_2 (3 × 30 mL) and the organics were dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the crude products were purified by flash chromatography on silica gel (CH_2Cl_2 → CH_2Cl_2–MeOH, 95:5). Both of the diastereoisomers of compound **3a** were easily isolated due to the appreciable difference in the R_f. First diastereoisomer: 187 mg (27% yield); 95% ee; R_f 0.28 (CH_2Cl_2–MeOH, 95:5); second diastereoisomer: 206 mg (31% yield); 96% ee; R_f 0.15 (CH_2Cl_2–MeOH, 95:5). See Supporting Information for full experimental details and product characterisation.