Organocatalytic enantioselective aza-Michael reaction of nitrogen heterocycles and α,β-unsaturated aldehydes†

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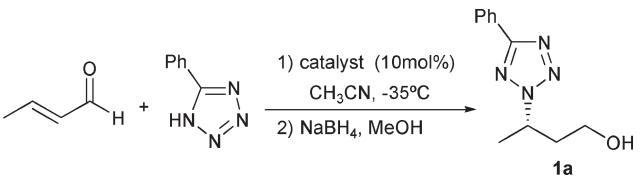
The asymmetric organocatalytic aza-Michael reaction of several nitrogen heterocycles and α,β-unsaturated aldehydes has been studied in detail; under the optimised conditions, the conjugate addition products have been obtained in high to excellent enantioselectivities.

In recent years, there has been increased research interest in asymmetric organocatalysis, as a result both of the novelty of the concept, and the high efficiencies and selectivities attained by many organocatalytic transformations.[1] As a remarkable additional feature, organocatalysis does not involve the use of toxic metals, which makes this methodology even more interesting from an environmental point of view. Given the operational and economical advantages associated with organocatalysis, many research groups worldwide have engaged in the development of novel organocatalytic procedures for performing transformations that are typically undertaken using transition metal catalysis. In this context, proline and other chiral secondary amines have been shown to be extremely useful catalysts in many C–C and C–heteroatom bond forming reactions, the formation of an intermediate enamine or iminium species being a common feature in all of these cases.

However, while a variety of asymmetric organocatalysts have been explored for the conjugate addition of different nucleophiles to electron deficient olefins,[1] the organocatalytic asymmetric aza-Michael reaction has remained significantly less developed.[2] In fact, as far as we know, a very small number of examples of organocatalytic asymmetric aza-Michael reactions have appeared to date in the literature,[3–5] most of them published during the last year, and only a few of them involving secondary amine catalysis.[4,5] The main reason for this is associated with the additional chemoselectivity issues that have to be controlled in this particular transformation. This is due to the fact that both the catalyst and the nucleophile are secondary amine species, and the role that these two reagents play in the reaction must be absolutely established. Therefore, the chiral secondary amine chosen as the catalyst must not undergo a conjugate addition reaction, which would lead to catalyst consumption, and the amine reagent selected as nucleophile must not participate in iminium ion formation, which would lead to the generation of an achiral intermediate and therefore to the formation of a racemic product.

With all of these precedents in mind, we decided to explore the ability of certain nitrogen heterocycles to act as nucleophiles for the organocatalytic asymmetric conjugate addition to α,β-unsaturated aldehydes.[6] We wish to present, herein, our recent results in this effort, which has also opened up a way for the preparation of highly enantiomerically enriched *N*-substituted heteroaromatic derivatives. Potential applications include, for example, the preparation of novel non-natural nucleosides, a class of compounds with a broad range of important biological applications.[7]

We began our study using the model reaction between 5-phenyltetrazole and crotonaldehyde in acetonitrile at −35 °C (Scheme 1, Table 1).[8] However, we found that the β-tetrazolyl aldehyde adduct was configurationally unstable, observing that it quickly racemized upon standing at RT. For this reason, we decided to carry out the *in situ* reduction of the aza-Michael adduct in order to obtain the corresponding primary alcohol,



Scheme 1

Table 1 Optimisation reaction conditions for the organocatalytic asymmetric aza-Michael reaction of crotonaldehyde and 5-phenyltetrazole[a]

Entry	Catalyst	Solvent	*T*/°C	Time/h	Yield (%)[b]	ee (%)[c]
1	**2**	CH_3CN	−35	48	65	60
2	**3**	CH_3CN	−35	48	15	nd[d]
3	**4**	CH_3CN	−35	48	67	15
4	**5**	CH_3CN	−35	48	30	47
6	**2**	Toluene	−35	48	80	29
5	**2**	$CHCl_3$	−35	48	75	5
7	**2**	THF	−35	48	46	3
8	**2**	DMF	−35	48	32	41
9	**2**	CH_3CH_2CN	−35	48	62	60
10	**2**	CH_3CH_2CN	−78	120	48	70
11	**2**·TFA	CH_3CH_2CN	−78	48	70	78
12	**2**·TFA	CH_3CH_2CN	−88	120	78	84

[a] All reactions were carried out on a 1.00 mmol scale with 1–5 equiv. of 5-phenyltetrazole and 1 equiv. of the aldehyde, in the presence of 10 mol% of the catalyst, at the indicated temperature in 3 mL of solvent. [b] Yield of pure isolated product. [c] Determined by chiral HPLC analysis of the corresponding acetate esters (see ESI). [d] nd = not determined.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterisation of all new compounds, copies of their ^1H and ^{13}C NMR spectra, and chiral HPLC chromatograms. See DOI: 10.1039/b700831g

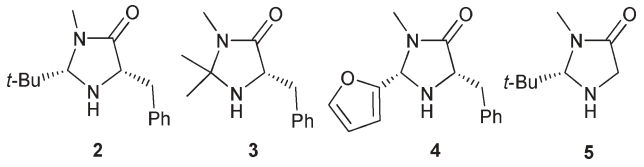


Fig. 1 Chiral imidazolidinone catalysts tested.

which was isolated after flash column chromatography purification. We interpreted this configurational lability in terms of the reversibility of the aza-Michael reaction. This reversibility might also be responsible for the very low enantioselectivities observed in all the reactions performed at RT.[8]

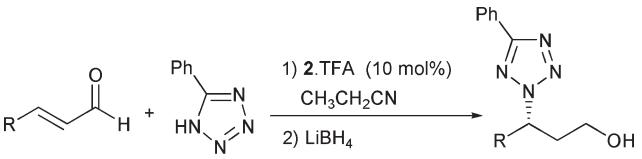
We carried out a series of experiments directed towards identifying the best amine catalyst, and therefore we performed a preliminary screening of several commercially available chiral secondary amines with different electronic and steric features. Of all the catalysts tested, we generally obtained better results when chiral imidazolidinones (Fig. 1) were employed,[9] with the best result being found with catalyst **2**. In this case, the aza-Michael adduct **1a** was isolated in 65% yield and with a promising 60% ee (Table 1, entry 1). It has to be pointed out that the reaction also proceeded with complete regioselectivity, affording exclusively the N2-alkyl-substituted tetrazole derivative **1a**.[10] Other imidazolidinones, such as **3**, **4** and **5**, gave poorer results (Table 1, entries 2–5).

Continuing with our study, we directed our efforts to improve the enantioselectivity of the reaction, starting first with the optimisation of the reaction solvent. From all the conditions tested (Table 1, entries 6–8), we found that, although the yield could be significantly improved by using less polar solvents, such as toluene or chloroform, the enantioselectivity dropped dramatically compared to the reaction in which acetonitrile was used. We also evaluated the use of other nitrile solvents, such as propionitrile, but almost identical results were obtained in this case (Table 1, entry 9). This solvent allowed us to perform the reaction at lower temperatures, showing that the enantioselectivity could be improved by working at −78 °C, although a considerably longer reaction time was required in order to reach to an acceptable yield (Table 1, entry 10).[11] Finally, we found that the addition of 10 mol% TFA as a co-catalyst resulted in a remarkable reaction rate acceleration, together with a slight improvement in the enantioselectivity (Table 1, entry 11). We could reach an 85% ee of the final adduct by running the reaction at even lower temperatures (Table 1, entry 12).

Having established an optimal protocol for the reaction, we proceeded next to examine the scope and limitations of the method with regard to the α,β-unsaturated aldehyde substrate (Table 2). We therefore performed the reaction using a variety of aldehydes. In all cases, the reaction was carried out at both −78 and −88 °C. As can be seen in Table 2, the reaction proceeded well with most of the aldehydes employed, furnishing good to excellent levels of enantioinduction in all cases, although better enantioselectivities were obtained at the lower temperature. Concerning to the yield of the reaction, we observed that increasing the length of the alkyl chain of the aldehyde or lowering the temperature resulted in the need for longer reaction times in order to reach synthetically useful yields.

Determination of the absolute configuration of the newly generated stereogenic centre was performed by chemical correlation as follows: The aza-Michael reaction of (*E*)-2-pentenal with 5-phenyltetrazole, under the conditions very recently reported by Jorgensen,[5b] furnished levorotatory (*R*)-3-(5-phenyltetrazolyl)-pentan-1-ol (*ent*-**1b**) ($[\alpha]_D^{20} = -13.6$ (c = 1.0, CH_2Cl_2)), while adduct **1b**, obtained by us using catalyst **2**, gave the dextrorotatory isomer ($[\alpha]_D^{20} = +15.5$ (c = 1.0, CH_2Cl_2)).

Table 2 Scope of the reaction[a]

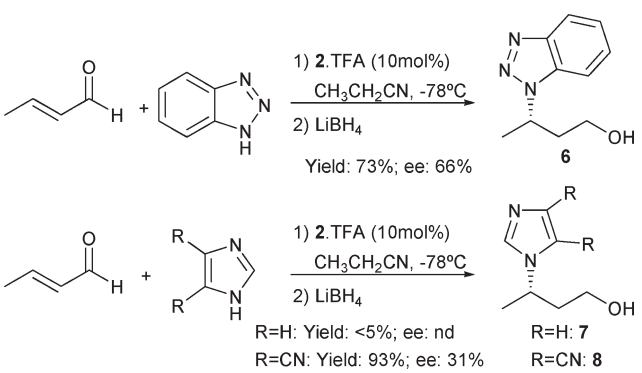


Entry	R	Product	T = −78 °C Yield (%)[b]	T = −78 °C ee (%)[c]	T = −88 °C Yield (%)[b]	T = −88 °C ee (%)[c]
1	Me	**1a**	70	78	78	84
2	Et	**1b**	67	86	67	98
3	*n*-Pr	**1c**	76	74	87	91
4	*i*-Pr	**1d**	60	82	97	99
5	*n*-Bu	**1e**	62	71	79	87
6	n-C_5H_{11}	**1f**	68	75	88	85
7	(*Z*)-EtCH=CH(CH_2)$_2$	**1g**	59	72	70	76

[a] All reactions were carried out on a 1.00 mmol scale with 5 equiv. of 5-phenyltetrazole and 1 equiv. of the aldehyde, in the presence of 10 mol% of the catalyst at the indicated temperature in 3 mL of solvent. [b] Yield of pure isolated product. [c] Determined by chiral HPLC analysis of the corresponding acetate esters (see ESI).

Finally, in this preliminary survey, we also decided to check whether this methodology was applicable to other *N*-heterocycles (Scheme 2). In this context, the reaction of crotonaldehyde with benzotriazole, followed by reduction, furnished adduct **6** as a single regioisomer, and in moderate yield and enantioselectivity. Imidazole afforded very low yields but 4,5-dicyanoimidazole underwent a clean reaction, furnishing the addition product **8** in 93% yield and 31% ee. We also surveyed the use of purine as a nucleophile but, although the formation of the conjugate addition product was observed during the reaction, it was seen to be unstable under the reducing conditions and therefore we were not able to evaluate the enantioselectivity of the reaction in this particular case.

In conclusion, we have described the organocatalytic aza-Michael reaction of nitrogen heterocycles to α,β-unsaturated



Scheme 2

aldehydes, which has led to the synthesis of a wide range of chiral non-racemic *N*-alkyl-substituted heterocycles. The methodology presented herein has a broad scope, furnishing the conjugate adducts in moderate to good yields and with good to excellent enantioselectivities. Further research on its application to the synthesis of pharmaceutically useful compounds is in progress.

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Notes and references

1 For some recent reviews on asymmetric organocatalysis, see: (*a*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (*b*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*c*) Special issue on organocatalysis: *Acc. Chem. Res.*, 2004, **37**, 487. See also: (*d*) A. Berkessel and H. Groger, in *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, Germany, 2005.

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4 (*a*) Y. K. Chen, M. Yoshida and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 9328. One example of an amine-catalyzed aziridination of α,β-unsaturated aldehydes *via* a stepwise aza-Michael reaction, followed by intramolecular nucleophilic substitution, has also been reported: (*b*) J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios and A. Cordova, *Angew. Chem., Int. Ed.*, 2007, **46**, 778.

5 After this manuscript was submitted, Córdova and co-workers reported the organocatalytic asymmetric aza-Michael reaction of *N*-carbamoylhydroxylamines to α,β-unsaturated aldehydes and the group of Jørgensen reported the enantioselective conjugate addition of nitrogen heterocycles to the same kind of aldehydes, both using diarylprolinol silyl ethers as catalysts: (*a*) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao and A. Córdova, *Chem. Commun.*, 2007, 849; (*b*) P. Dinér, N. Nielsen, M. Marigo and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 1983.

6 It is well known that nitrogen heterocycles, such as triazoles, tetrazoles, purines and imidazoles, amongst others, undergo conjugate addition to α,β-unsaturated carbonyl compounds under transition metal catalysis. See, for example: M. Gandelman and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2005, **44**, 2393.

7 M. G. M. Purwanto and K. Weisz, *Curr. Org. Chem.*, 2003, **7**, 427 and references therein.

8 A first screening of several amine catalysts indicated that, although the reaction proceeded efficiently at RT, leading to the formation of the aza-Michael adduct in yields ranging from 20 to 95%, very low enantioselectivities (<5% ee) were obtained in all cases.

9 Other representative examples: L-proline (12% ee), L-proline methyl ester (16% ee), L-prolinol (12% ee), L-prolinol *tert*-butyldimethylsilyl ether (6% ee), (*S*)-2-(diphenylmethyl)pyrrolidine (0% ee).

10 The electronic effect of tetrazole C-aryl substituents in promoting nucleophilic reactions preferably at N2 is known: G. Shaw, H. Wamhoff and R. N. Butler, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky, C. W. Rees and K. T. Potts, Pergamon, Oxford, vol. **5**, 1984, ch. 4.13.

11 When working at low temperatures, the reduction step was carried out using the more reactive $LiBH_4$ reagent.