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Organocatalytic asymmetric aza-Michael reaction: enantioselective addition of *O*-benzylhydroxylamine to chalcones

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Abstract—A novel organocatalytic approach for aza-Michael reaction of chalcones using commercial and non-expensive *O*-benzylhydroxylamine and a readily available organocatalyst is provided. The use of this simple protocol results in β-keto hydroxylamines in up to 60% ee, thus extending the generality of the catalytic enantioselective aza-Michael reaction.

The Michael addition of aza-nucleophiles is one of the most convenient procedures for the generation of stereogenic carbon–nitrogen bonds.[1] This approach provides an attractive route to optically active β-amino carbonyl scaffolds which are important building blocks in organic synthesis and common structures found in biologically active compounds,[2] and as a result this area has received much attention by organic chemists. However, most methods are based on stoichiometric procedures and the few available catalytic protocols mainly rely on the use of metal-based chiral Lewis acids.[1b–3] The corresponding organocatalytic version of this reaction is also relatively unexplored, enlightening its intrinsic challenge as most of the organocatalysts commonly used are based on secondary amines, thus resembling the nucleophiles used in the aza-Michael reaction. Only in 2006 the MacMillan's group disclosed the first organocatalyzed aza-Michael reaction using *N*-silyloxycarbamates as nucleophiles in the addition to α,β-unsaturated aldehydes, which allowed the performance of the well-established iminium catalysis avoiding any competition from the nucleophile.[4a] Shortly after, several other contributions appeared dealing with the use of N-heterocycles,[4b,c] hydrazones,[4d] and amino benzaldehydes as nucleophiles.[4e]

The 1,4-addition of hydroxylamine derivatives has recently raised much attention since the resulting products are useful intermediates for the preparation of aziridines,[5] β-amino acids[2] and isoxazolidinones.[6] Following our previous work[7] in organocatalytic asymmetric reactions, we decided to undertake a study in order to further extend the area of organocatalytic aza-Michael reactions. We speculated that the use of chalcones as electrophiles in the addition of O-substituted hydroxylamines would be feasible since the structural features of the chalcones favor the 1,4-addition over the corresponding 1,2-addition. Although several catalytic highly enantioselective 1,4-addition protocols available based on the use of hydroxylamines[3] were known, only during the course of our investigations the first example of an enantioselective addition of hydroxylamines to tailor-made enoates promoted (and in two cases catalyzed) by an organic molecule, specifically a bifunctional thiourea, appeared in the literature.[8] This prompted us to disclose herein our results on the development of the organocatalytic asymmetric aza-Michael addition of hydroxylamines to chalcones.

Thus, a study was initiated on the organocatalyzed (**1a**–**e**) addition of the commercially available *O*-benzylhydroxylamine to chalcone (**2a**) (Table 1). Performing the reactions using 0.1 mmol of chalcone **2a** and 0.12 mmol of *O*-benzylhydroxylamine in the presence of 20 mol % catalysts **1a**–**e** highlighted the key role played by the thiourea group present in the organocatalysts, since using quinine **1a** lacking the thiourea moiety resulted in poor activity (less than 15% conversion). In

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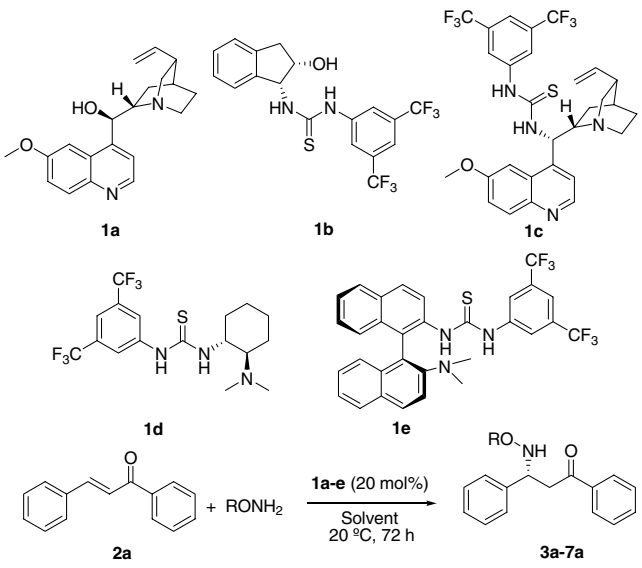
Table 1. Initial screening of reaction conditions[a]



Entry	R	Product	Catalyst	Solvent	Conv.[b] (%)	ee[c] (%)
1	Bn	**3a**	**1a**	Toluene	14	—
2	Bn	**3a**	**1b**	Toluene	62	19
3	Bn	**3a**	**1c**	Toluene	73	55
4	Bn	**3a**	**1d**	Toluene	48	28
5	Bn	**3a**	**1e**	Toluene	45	25
6	Bn	**3a**	**1c**	Xylenes	70	48
7	Bn	**3a**	**1c**	THF	50	48
8	Bn	**3a**	**1c**	EtOH	>95	0
9	Bn	**3a**	**1c**	Toluene/MeOH	>95	15
10	Me	**4a**	**1c**	Toluene	53	35
11	Et	**5a**	**1c**	Toluene	45	44
12	TBS	**6a**	**1c**	Toluene	<15	—
13	Allyl	**7a**	**1c**	Toluene	60	45
14	Bn	**3a**	**1c**	Toluene	>95[d]	56

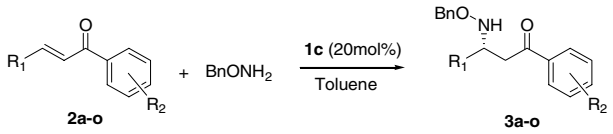
[a] The reactions were carried out at 20 °C using 0.1 mmol chalcone, 0.12 mmol *O*-hydroxylamine and 0.02 mmol catalyst in 0.5 mL of solvent (0.2 M).
[b] Conversions were determined by ^{1}H NMR.
[c] The enantiomeric excess was determined by chiral HPLC. Absolute configuration was determined by comparison of the literature data, see Ref. 3a.
[d] The reaction was performed using 0.1 mL solvent (1.0 M).

contrast, catalysts **1b**–**e** afforded moderate to good conversions of the starting chalcone **2a** (entries 2–5). With catalyst **1b,** having a hydroxyl group besides the thiourea moiety, good conversions of **2a** were achieved but the reaction proceeded with low enantioselectivity (entry 2, 19% ee). Catalyst **1c**[9] was more effective resulting in 73% conversion and leading to product **3a** with a 55% ee (entry 3). Other thiourea-based organocatalysts bearing a tertiary amino group, such as **1d**,**e**, were tested as well but were found to be somewhat inferior with respect to **1c**.[10]

Further screening of solvents and O-substituted hydroxylamines revealed that the combined use of toluene as a solvent and *O*-benzylhydroxylamine as an aminating agent was the optimal choice. The use of solvents other than toluene or of *O*-methyl, ethyl, allyl or TBS-hydroxylamine led to products with lower optical purity (entries 6–13). Most interestingly, nearly complete conversions could be obtained, without decreasing the enantioselectivity, by using more concentrated reaction solutions (entry 14).

We then proceeded to investigate the scope of this reaction using substituted chalcones as substrates in the organocatalytic aza-Michael addition of *O*-benzylhydroxylamine.[11,12] As shown in Table 2, several substituted chalcones (**2a**–**o**) were tested, with both electron withdrawing and electron donating groups in the phenyl ring at C-4. The corresponding aminated products (**3a**–**o**) were obtained in acceptable to good yields within 2–days at 20 °C, and with enantiomeric excesses varying within a narrow range, suggesting that electronic and steric features have a marginal effect on these processes. However, some trends could be noticed. The presence of electron donating substituents, such as *p*-OMe (entry 2, 58% ee), *p*-Me (entry 4, 56% ee), *m*-Me (entry 9, 56% ee), *o*-Me (entry 5, 56% ee), resulted in slightly higher enantiomeric excess as compared to the effect displayed by electron withdrawing groups, such as *p*-Cl (entry 3, 50% ee) or *o*-Cl (entry 6, 50% ee), or *m*-NO_2 (entry 7, 40% ee). Unfortunately, the use of substrates with *t*-butyl and *n*-butyl aliphatic side chains resulted in a lowering of the enantioselectivity (entries 11 and 12). Using chalcones substituted in the benzoyl ring

Table 2. Asymmetric organocatalytic aza-Michael addition of chalcones[a]



Entry	2	R_1	R_2	3	T (°C)	t (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	H	H	**3**[a]	20	48	84	56
2	**2b**	*p*-OMe–C_6H_4	H	**3b**	20	48	72	58
3	**2c**	*p*-Cl–C_6H_4	H	**3c**	20	48	72	50
4	**2d**	*p*-Me–C_6H_4	H	**3d**	20	45	76	56
5	**2e**	*o*-Me–C_6H_4	H	**3e**	20	46	80	56
6	**2f**	*o*-Cl–C_6H4_4	H	**3f**	20	50	77	50
7	**2g**	*m*-NO_2–C_6H_4	H	**3g**	20	63	80	40
8	**2h**	*m*-Me–C_6H_4	H	**3h**	20	63	66	56
9	**2i**	2-Furyl	H	**3i**	20	64	73	51
10	**2j**	1-Naphtyl	H	**3j**	20	64	94	52
11	**2k**	*t*-Bu	H	**3k**	20	61	71	45
12	**2l**	*n*-Bu	H	**3l**	20	64	45	30
13	**2m**	H	*p*-OMe	**3m**	20	64	78	56
14	**2n**	H	*p*-NO_2	**3n**	20	64	82	27
15	**2o**	H	*o*-Me	**3o**	20	64	77	38
16	**2a**	H	H	**3a**	4	64	76[d]	60
17	**2b**	*p*-OMe–C_6H_4	H	**3b**	4	93	35[d]	60
18	**2e**	*o*-Me–C_6H_4	H	**3e**	4	93	44[d]	52
19	**2h**	*m*-Me–C_6H_4	H	**3h**	4	93	61[d]	59
20	**2m**	H	*p*-OMe	**3m**	4	93	56[d]	50

[a] The reactions were carried out at 20 °C using 0.1 mmol chalcone, 0.12 mmol *O*-hydroxylamine and 0.02 mmol catalyst in 0.1 mL of solvent.
[b] Isolated yields.
[c] The enantiomeric excess was determined by chiral HPLC.
[d] Reactions were carried out at 4°C.

indicated a more pronounced effect of the substituents, and again, the use of electron rich aromatic moieties led to higher ees (compare entries 13–15). Finally, an enantioselectivity/temperature profile performed for some substrates documented that a small increase of the enantioselectivities, maintaining acceptable yields of the products, was available by running the reactions at 4 °C using prolonged reaction times (entries 16–20).

A proposal for the role of catalyst **1c** in the aza-Michael reaction is shown in Figure 1. As the initial screening of catalysts showed the importance of the thiourea hydrogen donating group, we believe that the chalcone is activated by hydrogen bonding from the catalysts.[13] One possible explanation for the fact that catalyst **1c** is somewhat more efficient than other thioureas can be ascribed to the presence of the quiniclidinic nitrogen in the catalyst. It could play an important role as could orient and position the nucleophile via H-bond, contributing to the conformational rigidification in the reaction intermediate and subsequent formation of the desired product with substantial enantioselectivity. Most likely, the amine of the nucleophile can be a part of a proton relay/shuttle system similar to that proposed by Yamabe.[14] These observations suggest that, in order to obtain highly enantioenriched products it would be desirable to develop catalytic systems where both the substrate and the nucleophile are coordinated to the catalyst in the enantiodetermining step and in close proximity within the catalyst chiral environment.

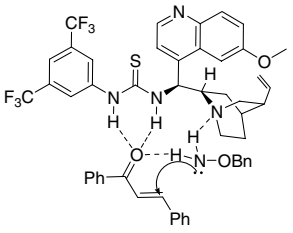


Figure 1. A proposal for the role of the catalyst in the aza-Michael addition.

In conclusion, we have developed an organocatalytic, asymmetric aza-Michael addition employing hydroxylamines. The use of this simple protocol results in β-keto hydroxylamines in up to 60% ee, thus broadening the generality of catalytic enantioselective aza-Michael additions. Further efforts in this area are currently being made in our laboratory.

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10. Using the dihydro derivative of **1b** as catalyst resulted in similar conversion but slightly lower enantioselectivity (50% ee).
11. *Typical procedure*: To a solution of chalcone **2b** (0.1 mmol) and catalyst **1c** (0.02 mmol) in toluene (100 μl) was added *O*-benzylhydroxylamine (0.12 mmol, 14.7 μl). The reaction was stirred at 20 °C for 48 h, after which the β-keto amine **3b** was obtained as a colorless oil in 72% yield through direct purification of the reaction mixture by column chromatography on silica gel (ethyl acetate/*n*-hexane 1:15). Chiral HPLC analysis (Chiralpak AD-H, 80:20 *n*-hexane/*i*-PrOH 0.75 mL/min, $\lambda = 254$ nm) indicated 58% ee, t_R(minor) = 18.0 min, t_R(major) = 19.0 min. $[\alpha]_D^{20}$ +12.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 3.19 (dd, $J = 5.5$, 17.1 Hz, 1H) 3.43 (dd, $J = 7.7$, 17.1 Hz, 1H), 3.72 (s, 3H), 4.46 (d, $J = 11.8$ Hz, 1H), 4.50 (d, $J = 11.8$ Hz, 1H), 4.59 (dd, $J = 5.5$, 7.7 Hz, 1H), 6.02 (br s, 1H), 6.77–6.83 (m, 2H) 7.10–7.52 (m, 10H), 7.80–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 43.0, 55.5, 60.8, 76.8, 114.0, 127.9, 128.3, 128.5, 128.7, 128.8, 129.1, 133.1, 133.4, 137.1, 137.9, 159.3, 198.6; HRMS calcd for $C_{23}H_{23}NO_3$ *m*/*z*: 361.1678 found, 361.1682.
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