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A general, highly enantioselective Michael addition of nitroalkanes to α,β-unsaturated enones catalyzed by 9-amino(9-deoxy)-*epi*-quinine: a remarkable additive effect

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ABSTRACT

A particularly general protocol for the organocatalytic asymmetric Michael addition of nitroalkanes to α,β-unsaturated enones is reported. The Michael reaction proceeded smoothly and provided the desired adducts in moderate to excellent yields (55–99%) and good to excellent enantioselectivities (65–99% ee). The addition of readily available achiral base significantly enhanced the reactivity without compromising the enantioselectivity.

1. Introduction

Chiral primary amines are effective covalent-based activators of sterically hindered carbonyl compounds,[1] and overcome the intrinsic limitations of chiral secondary amine catalysis,[2] which is restricted to the functionalization of unhindered aldehyde compounds. They enrich the aminocatalytic activation modes and provide new opportunities for developing challenging and non-conventional transformations in carbonyl compound chemistry. Among all reported primary aminocatalysts, cinchona-derived primary amines[1e,f] constantly infer high levels of stereocontrol in the case of various iminium ion,[3] vinylogous iminium ion,[4] enamine,[5] dienamine,[6] and trienamine[7] activation modes, thus providing a reliable catalytic platform for functionalization of hindered carbonyl compounds at their α,[5] β,[3] γ[6] and even δ[4] positions. Although cinchona-based primary amines have been successfully applied to a range of highly enantioselective conjugate additions,[3a,b,8] quite poor reactivity was observed in the case of Michael addition of nitroalkane to α,β-unsaturated enone.[9] Although good conversion was later achieved under high-pressure condition, the utility and easy scale-up of this transformation were therefore limited to a certain extent.

The development of efficient chiral catalyst is crucial to a successful catalytic asymmetric course. However, not every chemist is fortunate enough to always obtain satisfactory catalyst from routine design and synthesis. Furthermore, even the superior catalyst is presumably obtained after long-term optimization and design in most cases. On the other hand, it is indicated that the addition of suitable achiral additive will lead to impressive improvement of reactivity and even enantioselectivity in some cases,[10] when comparing with the use of organocatalyst alone.[11] This economical approach is beneficial in avoiding tedious chemical synthesis and will allow highly efficient construction of libraries of catalyst system via simply changing the additives of choice. Considering the outstanding catalytic performance of cinchona-derived primary amines, the combination of easily accessible additive with them is clearly worthy exploring.[3a] The positive influence exerted by additive will efficiently avoid large screening of catalysts during the course of optimization of reaction conditions, therefore researchers can concentrate on exploring novel reactivity patterns and expanding the synthetic potential of aminocatalysis.

Based on our continuous interest in asymmetric conjugate addition reactions,[12] herein we present a highly enantioselective Michael reaction of nitroalkanes to α,β-unsaturated enones[9,13] in

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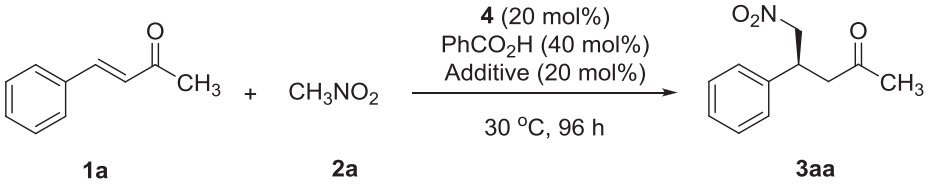
the presence of 9-amino(9-deoxy)-*epi*-quinine. Remarkably, the addition of appropriate additives greatly enhanced the reactivity of this asymmetric process. As a result, this asymmetric Michael reaction proceeded smoothly under ambient pressure with high levels of enantioselectivity.

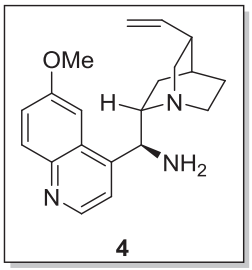
2. Result and discussion

Considering the poor reactivity of Michael addition of nitromethane to cyclic α,β-unsaturated enones exhibited in the previous report,[9] we initially performed the model reaction in neat nitromethane. In agreement with the early study,[9] the Michael addition of nitromethane to cinnamone afforded sluggish conversion again (Table 1, entry 1). Less than half of desired adduct **3a** was obtained even after 96 h, albeit with excellent enantioselectivity. It was documented that a twofold excess of acid with respect to the aminocatalyst was generally essential for the iminium ion-promoted transformations of unsaturated carbonyl compounds, because condensation with carbonyl group could be considerably accelerated under acidic conditions.[1f] As a consequence, the more basic tertiary amine of the quinuclidine core was preferentially protonated, thereby losing ability to deprotonate nitromethane. Having realized that the low conversion might be caused by protonation of the basic bridge-head nitrogen atom, we assumed that introducing extra base might improve reactivity.[3a] Indeed, the model reaction was remarkably accelerated by a range of tertiary amines with minimal loss of enantioselectivity (entries 2–5). Triethylamine (TEA) and *N*-methylmorpholine (NMM) significantly improved the isolated yields from early 48% to later 91% and 96%, respectively (entries 2 and 3). However, relatively lower rate was observed in the presence of Hunig's base (DIPEA, *N*,*N*-diisopropylethylamine) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (entries 4 and 5). Especially for DABCO, prolonged reaction time (144 h) was required to achieve acceptable yield. Encouraged by the reactivity enhancement afforded by these tertiary amines, we successively evaluated the effect of easily accessible secondary amines. Piperidine and the hindered base, 2,2,6,6-tetramethylpiperidine (TMP), both enabled the model transformation to complete within due time and afforded the desired adducts with 95% ee (entries 6 and 7). On the other hand, tetrahydropyrrole led to a significant activity improvement (24 h, 92% yield) at the cost of pronounced enantioselectivity erosion, presumably owing to the intensive background reaction (entry 8). Apparently, the observed catalytic reactivity was closely correlated with the basicity of additive. In accordance with DABCO, the strongly basic additives, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and tetramethylguanidine (TMG), both generated adduct **3aa** in somewhat poorer yields (entries 5, 9 and 10). Meanwhile, proton-sponge (1,8-bis(dimethylamino)naphthalene) could also efficiently accelerate this asymmetric process and generated the adduct **3aa** almost

Table 1
Additive evaluation in the Michael addition of nitromethane **2a** to cinnamone **1a**[a]



1a **2a** **3aa**



4

Entry	Additive	Yield (%)[b]	ee (%)[c]
1	/	48	97
2	TEA	91	94
3	NMM	96	96
4	DIPEA	86	96
5[d]	DABCO	78	96
6	Piperidine	97	95
7	TMP	93	95
8[e]	Tetrahydropyrrole	92	49
9	DBU	80	90
10	TMG	68	94
11	Proton-sponge	96	97
12	K_2CO_3	87	95
13	$KHCO_3$	58	96
14	KOAc	67	96
15	Na_2CO_3	63	94
16	NaOH	NR	/

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **1a**, 20 mol % **4**, 40 mol % benzoic acid and 20 mol % additive in 1 mL of nitromethane at 30 °C for 96 h. NR=no reaction.
[b] Isolated yield after flash chromatography on silica gel.
[c] Determined by HPLC on chiral AS-H column.
[d] The reaction time was 144 h.
[e] The transformation completed after 24 h.

without compromise of enantiopurity (entry 11 vs entry 1). In addition to the organic base, the inorganic base could also serve as effective additive, albeit relatively less reactivity improvement was detected (entries 12–15). Notably, the involvement of NaOH totally suppressed this transformation (entry 16).

Once indentifying proton-sponge as the optimal additive, we turned our attention to investigate the effect of acid cocatalyst. A variety of substituted aromatic acids proved to be efficient cocatalysts (Table 2, entries 2–5). The model reaction proceeded smoothly in the presence of these substituted acids and afforded the desired adduct in 82–93% yields, however, slightly poorer enantiomeric excesses were afforded in contrast with benzoic acid (entries 2–5 vs entry 1). Further study revealed that aliphatic acid displayed diminished catalytic activity in comparison with aromatic acids (entry 6 vs entries 1–5). Notably, the model reaction almost didn't occur in the presence of commonly-used strong acids, including trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (TsOH) and trifluoromethanesulfonic acid (TfOH) (entries 7–9). The reactivity and enantioselectivity slightly decreased when benzoic acid and **4** was combined in a 1:1 ratio (entry 10). Moreover, the reactivity was also relatively sensitive to the loading of additive. Diminished catalytic efficiency was observed when 10 mol % of proton-sponge was utilized, however, only negligible reactivity improvement was achieved in the presence of 40 mol % of proton-sponge (entries 11 and 12). Furthermore, the yield of **3aa** decreased to 80% when the amount of aminocatalyst **4** was reduced to 10 mol % (entry 13). To our delight, elevating reaction temperature exerted beneficial effect on catalytic activity. Nearly quantitative desired adduct was formed almost without loss of enantioselectivity at 40 °C after 48 h (entry 14). After careful investigation, the optimal reaction conditions were therefore found to be a combination of cinchona-derived primary amine **4** (20 mol %), benzoic acid (40 mol %) and proton-sponge (20 mol %) as additive at 40 °C.

Table 2
Optimization of reaction conditions for Michael addition of nitromethane **2a** to cinnamone **1a**[a]

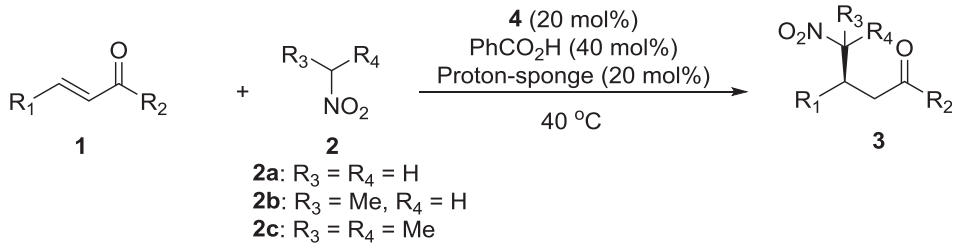
Entry	Additive	Yield (%)[b]	ee (%)[c]
1	BA	96	97
2	PNBA	91	96
3	ONBA	82	96
4	SA	86	94
5	OFBA	93	97
6	HOAc	70	95
7	TFA	NR	/
8	TsOH	NR	/
9	TfOH	NR	/
10[d]	BA	93	96
11[e]	BA	80	96
12[f]	BA	98	96
13[g]	BA	80	96
14[h]	BA	99	96

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **1a**, 20 mol % **4**, 40 mol % benzoic acid and 20 mol % proton-sponge in 1 mL of nitromethane at 30 °C for 96 h. BA=benzoic acid, PNBA=*p*-nitrobenzoic acid, ONBA=*o*-nitrobenzoic acid, SA=salicylic acid, OFBA=*o*-fluorobenzoic acid.
[b] Isolated yield after flash chromatography on silica gel.
[c] Determined by HPLC on chiral AS-H column.
[d] With 20 mol % benzoic acid.
[e] With 10 mol % proton-sponge.
[f] With 40 mol % proton-sponge.
[g] The reaction was performed with 10 mol % **4**, 20 mol % benzoic acid and 20 mol % proton-sponge.
[h] The reaction was conducted at 40 °C for 48 h.

With the optimal reaction conditions in hand, we subsequently examined a range of α,β-unsaturated enones and nitroalkanes to explore the generality of this novel catalytic system. As illustrated in Table 3, cinnamone derivatives **1b**–**h** possessing various substituents on the aromatic rings worked properly and furnished the desired adducts **3ab**–**ah** in high yields with excellent enantioselectivities (Table 3, entries 2–8). This asymmetric process was independent of the electronic character of substituted group. Both electron-deficient cinnamones **1b**–**e** and electron-rich analogues **1f**–**h** undertook complete transformations and displayed high degree of enantioselectivities (entries 2–5 vs entries 6–8). At the same time, the steric hindrance imposed by the substituents located on the aromatic rings exerted limited influence on the reactivity and stereocontrol. The *ortho*-substituted electrophiles **1e** and **1g** were fully converted into target products within 48 h (entries 5 and 7). Compounds **1i** and **1j**, both possessing a bulky naphthyl group on the terminal site of double bond, were also suitable acceptors and afforded the desired adducts with 93% and 99% ee, respectively (entries 9 and 10). The heteroaromatic acceptors **1k** and **1l** were all well tolerated, however, prolonged reaction time was required probably owing to the electron-rich property of furanyl and thiophenyl groups (entries 11 and 12). In addition, aliphatic enones **1m** and **1n** were competent acceptors and afforded the corresponding adducts **3am** and **3an** with high optical purities (entries 13 and 14). In line with previous research,[13i–k] these substrates exhibited relatively poorer reactivity and 144 h was necessary for their complete conversions. After a careful investigation of substituted groups at the end of double bond, we next evaluated the effect of substituent at the α′-site of enones (entries 15–16). In general, relatively poorer reactivity was observed for these compounds in comparison with cinnamones bearing a methyl group adjacent to the carbonyl group (entries 15 and 16 vs entry 1).[13j,k] Even after 168 h, less than 80% isolated yields were attained in the case of ethyl-substituted **1o** and isopropyl-substituted **1p** (entries 15 and 16). The bulky alkyl group beside the carbonyl group might retard formation of iminium ion with primary aminocatalyst **4**, thereby leading to poor reactivity. To our delight, cyclic enones, such as 2-cyclohexene-1-one and 2-cyclopenten-1-one, were all highly active acceptors (entries 17 and 18). Reactions of **1q** and **1r** went to completion within 24 h and provided the desired adducts with good levels of enantioselectivity (96% ee for **1aq**, 81% ee for **1ar**). Gratifyingly, trace double Michael addition products were detected for these two cyclic acceptors and the desired mono-addition adducts were isolated in 98% and 92% yields, respectively. As mentioned by previous approach, double addition was found to be prone to occur in the case of cyclic enones.[13l] Besides nitromethane, nitroethane and 2-nitropropane were favorably applicable to this asymmetric process (entries 19 and 20). When nitroethane reacted with cinnamone **1a**, excellent enantioselectivities were obtained for both diastereoisomers, but the diastereomeric ratio was close to 1:1, presumably due to facile epimerization of the adduct in the presence of proton-sponge. More importantly, this Michael addition also occurred efficiently when the amount of donor was reduced. The model reaction completed within 96 h in the case of nine equivalent of nitromethane and afforded the desired adduct **3aa** in satisfactory yield and excellent enantiomeric excess (entry 21).

To our delight, our organocatalytic protocol was also effective with chalcones, a class of challenging substrates for iminium ion activation.[3b,12a] As demonstrated in Table 4, the Michael reactions of chalcone **5a** and its analogues **5b**–**i** proceeded smoothly, generating the desired adducts **6a**–**i** with good to excellent enantioselectivities (65–97% ee) (Table 4, entries 1–9). Owning to the steric hindrance imposed by the aromatic ring adjacent to the carbonyl group, chalcone and its analogues displayed relatively lower reactivity in comparison with cinnamones. Nevertheless, good conversions could be achieved when reaction time was prolonged to 168 h. Gratifyingly, both electron-neutral **5a**, electron-rich **5b**–**c**, **5f** and electron-poor chalcones **5d**, **5g** delivered the corresponding adducts in good yields and with satisfactory

Table 3
Substrate scope of Michael addition of nitroalkanes to cinnamones and its analogues[a]



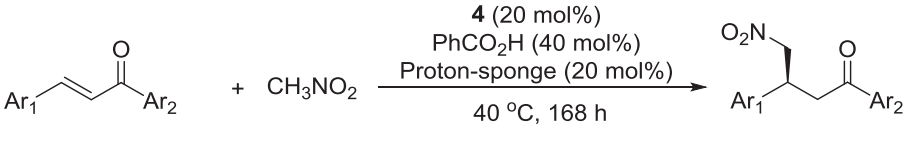
Entry	R_1	R_2	1	3	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph	Me	**1a**	**3aa**	48	99	96
2	*p*-FC_6H_4	Me	**1b**	**3ab**	48	92	95
3	*p*-ClC_6H_4	Me	**1c**	**3ac**	48	93	98
4	*m*-ClC_6H_4	Me	**1d**	**3ad**	48	98	98
5	*o*-ClC_6H_4	Me	**1e**	**3ae**	48	96	95
6	*p*-MeC_6H_4	Me	**1f**	**3af**	48	95	97
7	*o*-MeC_6H_4	Me	**1g**	**3ag**	48	98	95
8	*p*-$MeOC_6H_4$	Me	**1h**	**3ah**	48	91	98
9	1-Naphthyl	Me	**1i**	**3ai**	48	97	93
10	2-Naphthyl	Me	**1j**	**3aj**	48	99	99
11	2-Furanyl	Me	**1k**	**3ak**	96	75	96
12	2-Thiophenyl	Me	**1l**	**3al**	96	78	95
13	Me	Me	**1m**	**3am**	144	99	92
14	*n*-Bu	Me	**1n**	**3an**	144	95	95
15	Ph	Et	**1o**	**3ao**	168	75	97
16[d]	Ph	*i*-Pr	**1p**	**3ap**	168	61	95
17	$-C_3H_6-$		**1q**	**3aq**	24	98	96
18	$-C_2H_4-$		**1r**	**3ar**	8	92	81
19[e]	Ph	Me	**1a**	**3ba**	36	93[f](47+46)	98(96)
20[g]	Ph	Me	**1a**	**3ca**	24	99	95
21[h]	Ph	Me	**1a**	**3aa**	96	92	97

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **1**, 20 mol % **4**, 40 mol % benzoic acid and 20 mol % proton-sponge in 1 mL of nitromethane at 40 °C.
[b] Isolated yield after flash chromatography on silica gel.
[c] Determined by HPLC on chiral column.
[d] With 40 mol % proton-sponge.
[e] With 1 mL of nitroethane as the donor.
[f] Total yield for both diastereoisomers. The diastereomeric ratio (*syn*/*anti*) was 1:1, and the ee value of the *anti*-diastereoisomer was shown in parentheses.
[g] With 1 mL of 2-nitropropane as the donor.
[h] The reaction was performed with 0.2 mmol of **1**, 1.8 mmol of nitromethane, 20 mol % **4**, 40 mol % benzoic acid and 20 mol % proton-sponge in 0.5 mL of tetrahydrofuran at 40 °C.

enantiomeric excesses (entries 1–4, 6 and 7). Notably, **6g** was the crucial intermediate of the therapeutically useful GABA (γ-amino-butyric acid) receptor agonist, baclofen, and our approach allowed its synthesis with significantly high enantioselectivity (entry 7).[14]

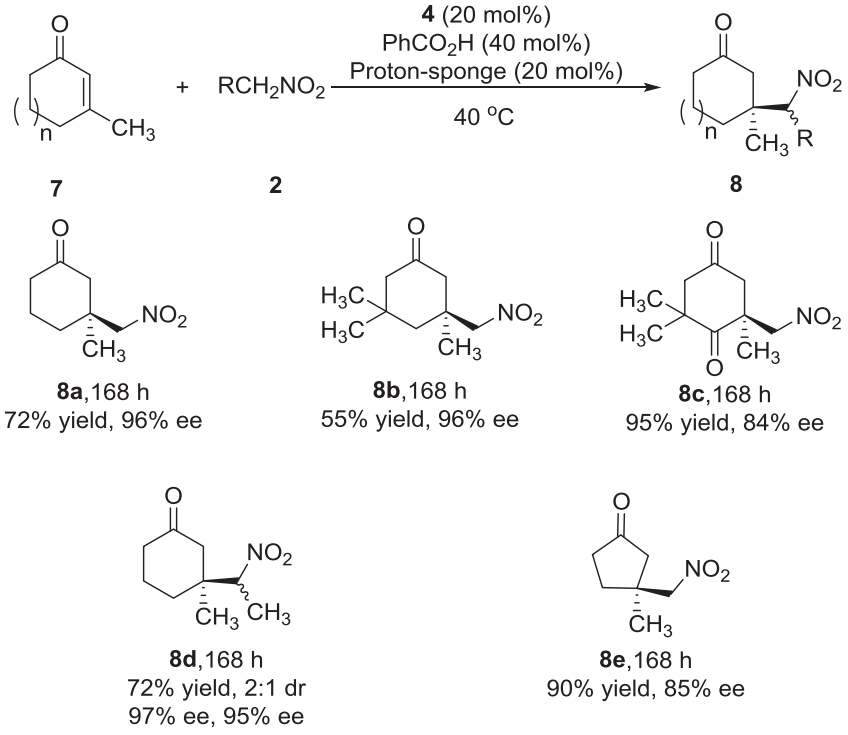
Fortunately, the heteroaromatic chalcones **5e** and **5h**–**i**, which had been rarely reported before, underwent clean reactions and gave rise to the desired products in moderate to good yields and good to excellent enantioselectivities (entries 5, 8 and 9).

Table 4
Substrate scope of Michael addition of nitromethane to chalcones[a]



Entry	Ar_1	Ar_2	5	6	Yield (%)[b]	ee (%)[c]
1	Ph	Ph	**5a**	**6a**	87	95
2	Ph	*p*-MeC_6H_4	**5b**	**6b**	85	97
3	Ph	*p*-$MeOC_6H_4$	**5c**	**6c**	82	97
4	Ph	*p*-FC_6H_4	**5d**	**6d**	85	92
5[d]	Ph	2-Thiophenyl	**5e**	**6e**	60	65
6	*p*-$MeOC_6H_4$	Ph	**5f**	**6f**	78	92
7	*p*-ClC_6H_4	Ph	**5g**	**6g**	82	92
8	2-thiophenyl	Ph	**5h**	**6h**	76	95
9[d]	2-furanyl	Ph	**5i**	**6i**	67	93

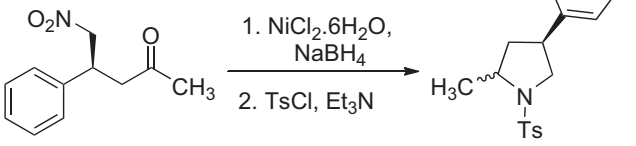
[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **5**, 20 mol % **4**, 40 mol % benzoic acid and 20 mol % proton-sponge in 1 mL of nitromethane at 40 °C.
[b] Isolated yield after flash chromatography on silica gel.
[c] Determined by HPLC on chiral column.
[d] With 40 mol % proton-sponge.



Scheme 1. Michael addition of nitromethane to β,β-disubstituted enones.

Finally, this catalytic system was also compatible with a variety of sterically congested β,β-disubstituted enones **7** (Scheme 1). As a result, a range of adducts **8a**–**e** containing an all-carbon quaternary carbon center were efficiently created in highly enantioselective manner. This approach proceeded with exclusive regioselectivity in the case of 2,6,6-trimethylcyclohexene-1,4-dione (see product **8c**). This observation revealed that the primary amino catalyst **4** preferred to activate the less sterically hindered carbonyl group. Notably, this catalytic conjugate addition allowed the direct and stereocontrolled creation of adjacent carbon-substituted quaternary and tertiary stereocenters. For instance, the Michael addition of nitroethane to 3-methylcyclohex-2-enone generated highly congested **8d** in acceptable yield. Additionally, excellent enantioselectivities were observed for both diastereoisomers. Furthermore, five-membered cyclic enone was also suitable acceptor for this conversion (see product **8e**).

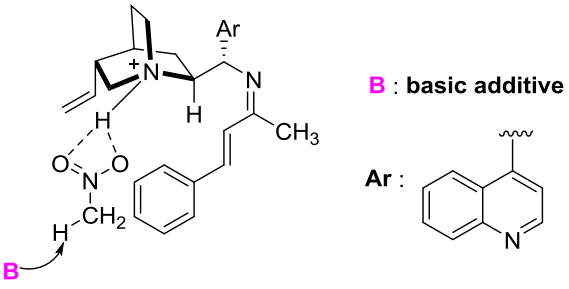
The optically active adduct obtained via this new methodology was valuable starting material for the preparation of chiral pyrrolidine (Eq. 1). Upon treatment of **3aa** with $NaBH_4/NiCl_2\cdot 6H_2O$, reduction of nitro group and the following reductive cyclization proceeded smoothly. After subsequent N-protection, the 2,4-disubstituted pyrrolidine **9** was efficiently constructed in overall 73% yield without compromise of enantiopurity. This three-step synthesis was conveniently conducted in one-pot without isolation of reaction intermediate. Remarkably, the resulting 4-phenylpyrrolidine was the central structural motif of kainic acid analogues, which could be employed as dual NK-1 antagonists and selective serotonin reuptake inhibitors.[15]



(1)

The absolute configuration of Michael adduct **8** was determined to be *S* by comparison of HPLC traces and optical rotation value with those of literatures reported.[13j–l] The other adducts were similarly assigned on the basis of the assumed similar reaction pathway.

A plausible transition state model was depicted in Scheme 2. The primary amine motif of 9-amino(9-deoxy)-*epi*-quinine **4** was engaged in iminium formation with the carbonyl group of benzalacetone **1a**. Subsequently, nitromethane was activated via hydrogen-bonding interaction with the protonated tertiary amine moiety of aminocatalyst **4**, thereby leading to feasible deprotonation of nitromethane by basic additive. As a result, the corresponding Michael addition proceeded smoothly. In this context, the relatively poorer reactivity of strongly basic additive (Table 1, entries 5, 9, 10 and 16) might be caused by inefficient iminium



Scheme 2. Postulated transition state model for the Michael addition.

formation. As postulated by Melchiorre, the protonated tertiary amine moiety of aminocatalyst **4** played a crucial role during the course of iminium formation.[1f] The strongly basic additives could competitively combine with acidic cocatalyst, thereby retarding the iminium formation. On the other hand, the sluggish conversion of strongly acidic cocatalysts (Table 2, entries 7–9) might result from the consumption of basic additive. Once the basic additive was protonated by the strongly acidic cocatalyst, it should lose ability to deprotonate nitromethane. All these observations suggested that the combination of aminocatalyst **4** with proper acid and base was crucial for achieving high reactivity. Nevertheless, the real catalytic mechanism still awaits further investigation.

3. Conclusion

In conclusion, we have established a highly efficient protocol for the enantioselective Michael addition of nitroalkanes to α,β-unsaturated enones in moderate to high yields (55–99%) with good to excellent enantiomeric excesses (65–99% ee). The reaction allows utilization of a quite wide range of enones with a considerable degree of structural variations, including cinnamones as well as its analogues, various chalcones, sterically hindered β,β-disubstituted enones and cyclic enones. Notably, the heteroaromatic chalcones could also afford the desired adducts with moderate to excellent enantioselectivity. Remarkably, an appropriate basic additive efficiently improves reactivity of this transformation without compromise of enantiocontrol. Compared with Gong's[13i] and Ye's[13l] well-designed primary aminocatalysts, the primary amine employed in our approach can be obtained via a straightforward one-step conversion from naturally occurring cinchona alkaloid, thereby avoiding the tedious synthetic procedure. This approach further expands applicable scope of cinchona-based primary aminocatalyst, providing an efficient optimization fashion for primary aminocatalysis.

Acknowledgements

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.07.008.

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