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Double Michael addition of nitromethane to divinyl ketones: A remarkably positive effect of additive

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ABSTRACT

An efficient double Michael addition of nitromethane to divinyl ketones was established in good to high yields (75–99%). A wide range of cyclohexanones were obtained with excellent diastereocontrol (up to >20:1 dr) and enantioinduction (91–99% ee) in a one-pot fashion. The involvement of basic additive significantly enhanced the reactivity of this cascade sequence.

1. Introduction

Cyclohexanones and their derivates constitute crucial skeletal components common in enormous natural products and pharmaceutical molecules.[1] Among all established synthetic strategies, double Michael additions of dual nucleophiles to divinyl ketones construct the corresponding frameworks in a single operation via utilizing simple precursors, thus successfully addressing efficiency and economic concerns.[2] In particular, the organocatalytic double Michael addition allows facile access to a variety of functionalized cyclohexanones possessing multiple stereogenic centers in a highly stereocontrolled fashion.[3] In these domino processes,[4] however, the often-used double nucleophiles are mainly restricted to malononitrile,[3b] oxindole[3d] and pyrazolone.[3f] On the other hand, nitromethane is revealed as a challenging nucleophile. The corresponding double conjugate addition failed to proceed properly in the presence of 9-amino-9-deoxyepiquinine[3b] and cinchona alkaloid.[3e] Moreover, even the strong inorganic base, $CsOH \cdot H_2O$, couldn't effectively promote this domino sequence as well.[2c] Although Wang group successfully realized the corresponding dual Michael addition mediated by the combination of a bifunctional thiourea and a strong inorganic base, this transformation actually proceeded via a stepwise manner.[3c] When the initial intermolecular Michael addition completed in the presence of bifunctional thiourea, the intermediate had to be isolated and purified. Subsequently, the following intramolecular Michael addition was promoted by a strong base, KOH. Although the desired adducts were later obtained with satisfactory enantiocontrol via this two-step process, the synthetic efficiency was simultaneously decreased. Moreover, the utility and easy scale-up of this transformation were therefore limited to a certain extent.

Indeed, nitroalkane displayed relatively poorer reactivity in the Michael additions of α,β-unsaturated enones in comparison with other widely-used nucleophiles.[5] In most cases, largely excessive nitroalkane, even neat nitroalkane, was essential to achieve synthetically useful conversion.[6] The poor reactivity was presumably exemplified by the double Michael addition of dienone. During the cause of double conjugate addition, a bulky multi-substituted nitroalkane was firstly formed, which might retard further Michael addition owing to steric hindrance.[6b,7] Recently, our group found that addition of appropriate base could efficiently improve catalytic activity of cinchona alkaloid-based primary amine.[8] In this context, various nitroalkanes, including disubstituted one, smoothly coupled with a variety of α,β-unsaturated enones, even

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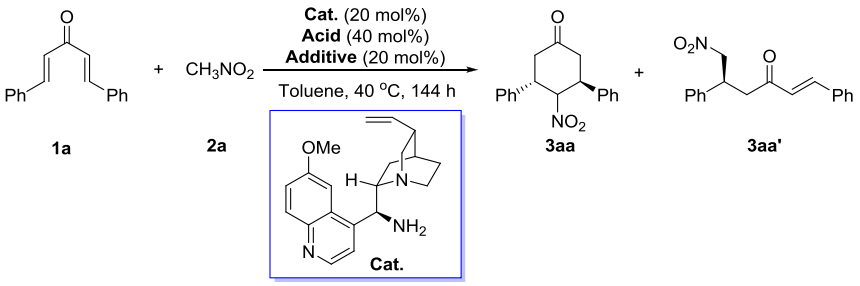
β,β-disubstituted enones, in satisfactory yields. Inspired by this observation, herein we would like to extend this efficient strategy to double Michael addition of nitromethane to divinyl ketones.[9]

2. Result and discussion

In accordance with Yan's observation,[3b] the double Michael addition of nitromethane to divinyl ketone **1a** didn't occur in the presence of 9-amino(9-deoxy)-*epi*-quinine and trifluoroacetic acid (TFA) (Table 1, entry 1). Inspired by our previous finding,[5a] 20 mol% of basic additive, 1,8-bis(dimethylamino)naphthalene (Proton-sponge), was subsequently added. To our disappointment, mono-addition product **3aa′** was formed as the only adduct (entry 2).[3c,10] Fortunately, the formation of desired cyclohexanone **3aa** was achieved when benzoic acid (BA) was utilized as co-catalyst (entry 3). This led to a dramatic improvement of reaction efficiency and allowed exclusive access to the expected dual addition product. In agreement with previous reports, *anti*-diastereomer was predominantly obtained with excellent enantioselectivity (99% ee).[11] Encouraged by this finding, we further examined the effect of other acidic co-catalysts. The adduct **3aa** was generated with high degrees of enantiomeric excesses in the presence of substituted aromatic acids, whereas slightly poorer reactivities were observed in comparison with benzoic acid (entries 4–7 *vs* entry 3). Further study indicated that aliphatic acid and sulfonic acid exhibited poorer catalytic activities in contrast with aromatic acids (entries 8–10). Remarkably, the commonly-used strong acid, trifluoromethanesulfonic acid (TfOH) only afforded trace mono-addition product (entry 10). Furthermore, we turned our attention to the catalytic efficiency of basic additives.[12] The model reaction worked well in the presence of various readily available organic bases, albeit slightly diminished reactivities and enantioselectivities were observed in comparison with Proton-sponge (entries 11–18 *vs* entry 3). Notably, the inorganic base, K_2CO_3, also proved to be effective for this cascade reaction; however, diminished isolated yield was afforded within due time (entry 19). Apparently, the observed catalytic reactivity was closely correlated with the basicity of additive. Similar with sluggish activity of tetramethylguanidine (TMG) (entry 18), the model reaction was totally suppressed in the case of the strong inorganic base, NaOH (entry 20).

Having identified benzoic acid and Proton-sponge as the optimal combination, further optimization study was based on this catalytic system. The titled double Michael addition was quite

Table 1
Evaluation of acid and additive.[a]



Entry	Acid	Additive	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%)[d]
1	TFA		NR		
2	TFA	Proton-sponge	34[e]	/	95[f]
3	BA	Proton-sponge	89	>20:1	99
4	ONBA	Proton-sponge	75	>20:1	97
5	PNBA	Proton-sponge	79	>20:1	99
6	OFBA	Proton-sponge	74	>20:1	99
7	SA	Proton-sponge	80	>20:1	99
8	HOAc	Proton-sponge	37	>20:1	98
9	TsOH	Proton-sponge	42	>20:1	98
10	TfOH	Proton-sponge	<5[e]	/	85[f]
11	BA	Tetrahydropyrrole	56	>20:1	99
12	BA	TMP	86	>20:1	98
13	BA	TEA	87	>20:1	98
14	BA	DABCO	69	>20:1	97
15	BA	DIPEA	64	>20:1	98
16	BA	DMAP	68	>20:1	98
17	BA	DBU	77	>20:1	99
18	BA	TMG	53	>20:1	98
19	BA	K_2CO_3	71	>20:1	98
20	BA	NaOH	NR		

[a] Unless otherwise noted, the reaction was performed with 0.2 mmol of **1a**, 20 mol% of catalyst, 20 mol% of base, 40 mol% of acid and 10 mmol of nitromethane in 0.5 mL of toluene at 40 °C for 144 h. ONBA = *o*-nitrobenzoic acid, PNBA = *p*-nitrobenzoic acid, OFBA = *o*-fluorobenzoic acid, SA = salicylic acid, HOAc = acetic acid, TsOH = *p*-toluenesulfonic acid, TMP = 2,2,6,6-tetramethylpiperidine, TEA = triethylamine, DABCO = 1,4-diazabicyclo[2.2.2]octane, DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, DBU = 8-diazabicyclo[5.4.0]undec-7-ene.
[b] Isolated yield of **3aa**.
[c] Diastereomeric ratio of **3aa** determined by ^{1}H NMR analysis of the crude mixture.
[d] Enantiomeric excess of **3aa**, determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H).
[e] Yield of **3aa′**.
[f] Enantiomeric excess of **3aa′**.

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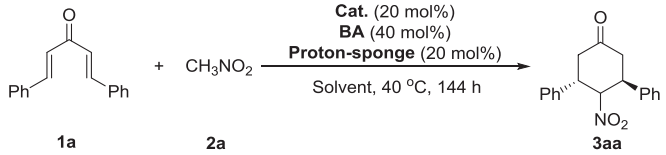
Table 2
Optimization of reaction conditions.[a]

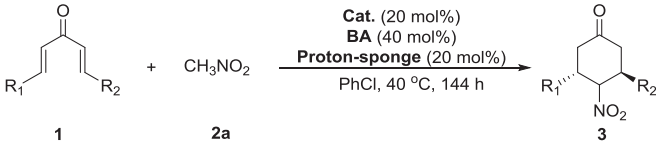


1a 2a 3aa

Entry	2a	Solvent	Yield (%)[b]	ee (%)[c]
1	50 equiv	toluene	89	99
2	30 equiv	toluene	80	99
3	60 equiv	toluene	82	98
4	50 equiv	$PhCF_3$	92	98
5	50 equiv	PhCl	93	99
6	50 equiv	DCE	86	98
7	50 equiv	$CHCl_3$	93	98
8	50 equiv	THF	73	98
9	50 equiv	EtOH	89	89

[a] Unless otherwise noted, the reaction was performed with 0.2 mmol of **1a**, 20 mol% of catalyst, 20 mol% of base, 40 mol% of acid and nitromethane in 0.5 mL of solvent at 40 °C for 144 h. In all cases, only *anti*-diastereomer was detected.
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H).

Table 3
Substrate scope of double Michael addition of nitromethane to dienones.[a]



1 2a 3

Entry	R_1/R_2	3	Yield (%)[b]	dr[c]	ee (%)[d]
1	Ph (**1a**)	**3aa**	93 (95)[e]	>20:1	99 (96)[e]
2	*p*-FC_6H_4 (**1b**)	**3ab**	98	>20:1	99
3	*o*-ClC_6H_4 (**1c**)	**3ac**	95	>20:1	99
4	*m*-ClC_6H_4 (**1d**)	**3ad**	86	>20:1	98
5	*p*-ClC_6H_4 (**1e**)	**3ae**	85	>20:1	98
6	2,4-Cl_2–C_6H_3 (**1f**)	**3af**	94	>20:1	91
7	*p*-BrC_6H_4 (**1g**)	**3ag**	44 (75)[f]	>20:1	99 (93)[f]
8	*p*-$CF_3C_6H_4$ (**1h**)	**3ah**	86	>20:1	97
9	*o*-MeC_6H_4 (**1i**)	**3ai**	99	>20:1	98
10	*p*-MeC_6H_4 (**1j**)	**3aj**	94	>20:1	99
11	*p*-$MeOC_6H_4$ (**1k**)	**3ak**	93	>20:1	98
12	1-naphthyl (**1l**)	**3al**	88	>20:1	98
13	2-thiophenyl (**1m**)	**3am**	86	>20:1	97
14	2-furanyl (**1n**)	**3an**	88	>20:1	98
15	PhCH=CH (**1o**)	**3ao**	83	>20:1	98
16	isopropyl (**1p**)	**3ap**	NR		
17	*p*-ClC_6H_4/Ph(**1q**)	**3aq**	80	1:1	99/98
18	Ph/*p*-$MeOC_6H_4$ (**1r**)	**3ar**	76	1:1	98/98
19	Ph/*p*-MeC_6H_4 (**1s**)	**3as**	93	1:1	99/98

[a] Unless otherwise noted, the reaction was performed with 0.2 mmol of **1a**, 20 mol% of catalyst, 20 mol% of base, 40 mol% of acid and 10 mmol nitromethane in 0.5 mL of chlorobenzene at 40 °C for 144 h.
[b] Yield of the isolated diastereomeric mixture.
[c] Determined by ^1H NMR analysis of the crude mixture.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] Performed at 80 °C for 72 h.
[f] Performed at 80 °C for 144 h.

sensitive to the amount of nitromethane. Reducing the amount to 30 equiv led to a decrease of yield (Table 2, entry 2). Moreover, increasing the amount to 60 equiv failed to improve the isolated yield within due time (entry 3). Subsequent solvent screening revealed that aromatic solvents were favorable for this transformation (entries 4 and 5). Chlorobenzene emerged as the solvent of choice due to its high enantioselectivity and reactivity. Other chloride-containing solvents were also appropriate, albeit furnished adduct **3aa** with slightly lower optical purities (entries 6 and 7). The reactivity dropped to a certain extent in the more polar ether (entry 8), while an erosion of enantiopurity was observed in protic solvent (entry 9).

With the optimal reaction conditions in hand, we successively examined a variety of divinyl ketones to establish the general utility of this catalytic transformation. As described in Table 3, the dual Michael additions of a range of electron-deficient divinyl ketones proceeded smoothly in chlorobenzene, exclusively providing the desired products **3ab-3ah** as *anti*-diastereomers in highly optically enriched forms (Table 3, entries 2–8). Relatively poorer reactivity was observed in the case of *para*-bromide substituted dienone **1g** due to its extremely poor solubility in chlorobenzene (entry 7). Gratifyingly, significant reactivity enhancement was achieved when this reaction was carried out at 80 °C, accompanied by slight compromise of enantiopurity.[5c,13] Electron-rich dienones **1i-1k** also underwent clean conversions and delivered the enantioenriched adducts **3ai-3ak** in satisfactory yields (entries 9–11). All these results clearly demonstrated that this double Michael addition was independent of electron nature of acceptors. Moreover, the steric hindrance imposed by substituent on the aromatic ring exerted limited influence on this domino sequence. The *ortho*-substituted compounds **1c** and **1i** fully converted into the desired cyclohexanones with high degrees of enantioselectivities and diastereoselectivities (entries 3 and 9). Moreover, **1l**, possessing a bulky naphthyl group on the end of double bond, was well tolerated to furnish **3al** in 88% yield and 98% ee (entry 12). Meanwhile, heteroaryl dienones were competent acceptors for this catalytic system (entries 13 and 14). Vinyl-substituted acceptor **1o** reacted properly with nitromethane and gave the desired cyclic product as a single diastereomer with high levels of optical purity (98% ee) (entry 15). Except aromatic acceptor, the aliphatic acceptor **1p** was also treated with nitromethane. In accordance with early studies, this aliphatic acceptor was completely inert under the standard conditions (entry 16).[3a-f] Similar with precedent finding, unsatisfactory diastereoselectivities were obtained for unsymmetric dienones **1q**-**1s** (entries 17–19).[3b,3c,3f] The poor diastereocontrol was presumably caused by facile deprotonation of cyclohexanones **3q-3s** on the 4-positions, which were adjacent to strongly electron-withdrawing nitro groups. To our delight, both diastereomers could be accessed with equally excellent enantioselectivities. In contrast, only one diastereomer was obtained with satisfactory optical purity in the case of Wang's approach, and another diastereomer was generated with moderate enantiomeric excess (64% ee) with regard to **3aq**.[3c] Notably, higher reactivity could be achieved with a marginal erosion of enantioselectivity when the model reaction was performed at elevated temperature (entry 1). Generally speaking, this one-pot procedure allowed access to the annulation products in higher isolated yields and superior enantioselectivities when compared with previously presented stepwise process.[3c]

Moreover, more sterically demanding donor, nitroethane, was exposed to dienone under the optimal conditions as well. However, only trace annulation product was detected. Instead, the adduct **3ba** incorporating two equiv nitroethane was attained as a 3:1 mixture of separable diastereomers (eq (1)).

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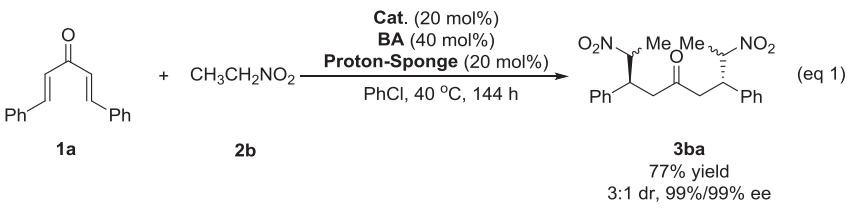


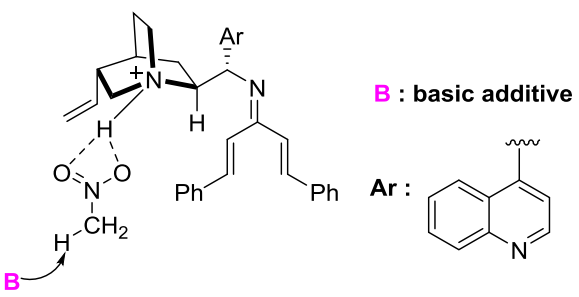
(1)

The absolute configuration of Michael adduct **3af** was determined to be (3*S*, 5*S*) by comparison of HPLC traces and optical rotation value with that of literature reported.[3c] The other adducts were similarly assigned on the basis of the assumed similar reaction pathway.[10,14]

This double Michael addition might proceed via successive iminium activation.[3b,3d] As depicted in Scheme 1, the primary amine motif of 9-amino(9-deoxy)-*epi*-quinine was engaged in iminium formation with the carbonyl group of dienone **1a**. Subsequently, nitromethane was activated via hydrogen-bonding interaction with the protonated tertiary amine moiety of aminocatalyst, thereby leading to feasible deprotonation of nitromethane by basic additive.[15] The additive and co-catalyst screening procedure discussed above afforded some reasonable hints for this reaction pathway. The titled domino sequence proceeded slowly in the presence of strong acid (Table 1, entries 2, 9 and 10) and strongly basic additive (Table 1, entries 18 and 20). The poor reactivity of strong acid might be caused by consumption of basic additive. Once the basic additive was protonated by strong acid, it lost ability to deprotonate nitromethane. On the other hand, the relatively sluggish conversion of strongly basic additive might result from inefficient iminium formation. It was demonstrated that the protonated tertiary amine moiety of aminocatalyst played a crucial role during the course of iminium formation.[16] The strongly basic additives could competitively combine with acidic co-catalyst, thereby retarding the iminium formation.

3. Conclusion

In conclusion, we have successfully developed a highly efficient approach to construct 4-nitrocyclohexanones in a one-pot manner. The involvement of basic additive dramatically improves the reactivity of double Michael additions of nitromethane to divinyl ketones, affording a broad range of annulation adducts in a highly stereoselective fashion. This observation definitely indentifies the crucial role of additive in the primary aminocatalysis. Further extension of the present protocol is well underway in our laboratory, and the results will be reported in due course.



Scheme 1. Postulated transition state model for double Michael addition.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.03.018.

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