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

Yongqi Yao [a], Yingying Liu [a], Ling Ye [b], Feng Chen [a], Xinying Li [a], Zhigang Zhao [a], Xuefeng Li [a,*]

[a] College of Chemistry and Environment Protection Engineering, Southwest University for Nationalities, Chengdu 610041, China
[b] Faculty of Geosciences and Environmental Engineering, Southwest Jiaotong University, Chengdu 610031, China

ARTICLE INFO

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.

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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·H$_2$O, 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

* Corresponding author.
   E-mail address: lixuefeng@swun.edu.cn (X. Li).

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 enantio-selectivities 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]
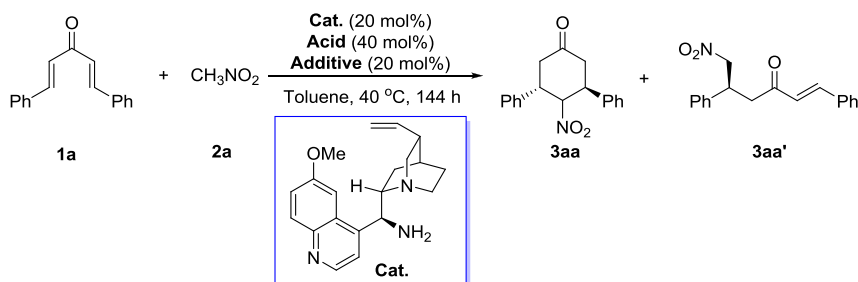
Entry	Acid	Additive	Yield (%)[b]	dr (*anti/syn*)[c]	ee (%)[d]
1	TFA		NR		
2	TFA	Proton-sponge	34[e]	/	95[f]
3	BA	Proton-sponge	89	>20:1	99
4	ONBA	Proton-sponge	75	>20:1	97
5	PNBA	Proton-sponge	79	>20:1	99
6	OFBA	Proton-sponge	74	>20:1	99
7	SA	Proton-sponge	80	>20:1	99
8	HOAc	Proton-sponge	37	>20:1	98
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 ^1H 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**′.