



 Cite this: *RSC Adv.*, 2021, 11, 203

 Received 23rd October 2020  
 Accepted 3rd December 2020

DOI: 10.1039/d0ra09041g

rsc.li/rsc-advances

# Simple primary $\beta$ -amino alcohols as organocatalysts for the asymmetric Michael addition of $\beta$ -keto esters to nitroalkenes†

 Zubeda Begum,<sup>a</sup> Haruka Sannabe,<sup>a</sup> Chigusa Seki,<sup>a</sup> Yuko Okuyama,<sup>b</sup> Eunsang Kwon,<sup>c</sup> Koji Uwai,<sup>a</sup> Michio Tokiwa,<sup>d</sup> Suguru Tokiwa,<sup>d</sup> Mitsuhiro Takeshita<sup>d</sup> and Hiroto Nakano \*<sup>a</sup>

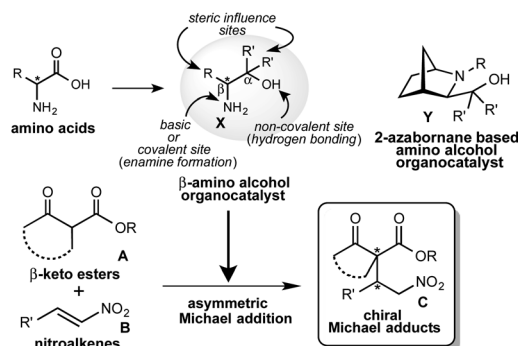
Simple primary  $\beta$ -amino alcohols act as an efficient organocatalysts in the asymmetric Michael addition of  $\beta$ -keto esters with nitroalkenes affording highly pure chiral Michael adducts. Also, both enantiomers of the adducts were obtained, depending on the specific catalyst used and reaction temperature.

## 1. Introduction

From the last decade, the development of new optically active multifunctional organocatalysts and their use in asymmetric synthesis as independent chiral sources have drawn considerable interest in the scientific community.<sup>1</sup> A lot of excellent covalent and non-covalent organocatalysts have been developed for use in a wide range of asymmetric reactions.<sup>2</sup> However, it is always a challenging task to design and synthesize a new class of multifunctional organocatalysts and to explore them as self-determining and eco-friendly catalysts in asymmetric synthesis. In recent years, we are continuously exploring the multifunctional  $\beta$ -amino alcohol organocatalysts **X** (Scheme 1),<sup>3</sup> that are easily derived from commercially available amino acids in one or two steps and are less sensitive to air, show low toxicity and are eco-friendly. This amino alcohol **X** contains an amino group acting as a basic or covalent enamine formation site, a non-covalent hydroxyl group acting as a hydrogen bonding site in a single molecule and also the substituents at  $\alpha$ - and  $\beta$ -positions, which might also be effective in controlling the enantioselective reaction course (Scheme 1). In our previous study, this catalyst has worked as an efficient organocatalyst in 1,3-dipolar cycloaddition,<sup>4</sup> Diels–Alder reactions<sup>5</sup> and aldol reactions.<sup>6</sup> Asymmetric Michael addition is recognized as a versatile and powerful key carbon–carbon bond and also a powerful tool for constructing carbon–heteroatom bond providing an effective

route for the synthesis of chiral compounds which act as precursor for a range of biologically and pharmaceutically important compounds. Furthermore, this addition is also useful for the construction of chiral building blocks containing quaternary carbon stereocenters, which act as a key synthetic intermediates for the complex compounds and synthetic drug candidates.<sup>7</sup> Consequently, several efforts have been made in recent years to develop an efficient organocatalyst for this reaction.<sup>8</sup> Our group has reported that the cage type 2-azanorbornane-based amino alcohols **Y** act as an efficient organocatalyst in this addition.<sup>10</sup> However, this catalyst **Y** has a complex structure and requires a multistep route for the synthesis, although efficient catalytic activity is observed. Based on these backgrounds, we have planned to try the asymmetric Michael addition of  $\beta$ -keto esters **A** with nitroalkenes **B** using more simplified  $\beta$ -amino alcohol organocatalyst **X** (Scheme 1).

In this paper, we describe an efficient catalytic activity displayed by  $\beta$ -amino alcohol organocatalyst catalyst **X** in the Michael addition of **A** with **B** to afford chiral Michael adducts **C** at satisfactory chemical yields and stereoselectivities (up to



Scheme 1 Asymmetric Michael addition of  $\beta$ -keto esters with nitroalkenes.

<sup>a</sup>Division of Sustainable and Environmental Engineering, Graduate School of Engineering, Muroran Institute of Technology, 27-1 Mizumoto-cho, Muroran 050-8585. E-mail: catanaka@mmm.muroran-it.ac.jp

<sup>b</sup>Tohoku Medical and Pharmaceutical University, 4-4-1 Komatsushima, Aoba-Ku, Sendai 981-8558, Japan

<sup>c</sup>Research and Analytical Center for Giant Molecules, Graduate School of Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-Ku, Sendai 980-8578, Japan

<sup>d</sup>Tokiwakai Group, 62 Numajiri Tsuduri-Chou Uchigo, Iwaki 973-8053, Japan

† Electronic supplementary information (ESI) available: Experimental details and HPLC data. See DOI: 10.1039/d0ra09041g



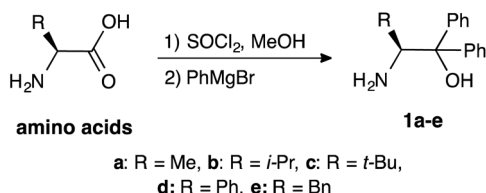
80%, up to dr = 99 : 1, up to 99% ee). In addition, an interesting property was observed that both enantiomers of the adducts were obtained depending on used specific catalyst and a reaction temperature with excellent stereoselectivities (up to 99 : 1, up to 99% ee).

## 2. Results and discussion

### 2.1. Preparation and screening of catalysts

$\beta$ -Amino alcohol organocatalysts **1a–e** with different substituents at the  $\alpha$ - and  $\beta$ -position were prepared from the corresponding amino acids (Scheme 2). The reaction of amino acids with thionyl chloride in methanol, followed by Grignard reaction of the obtained methyl esters afforded the desired **1a–e**.<sup>5a</sup>

In order to investigate the asymmetric catalytic activity of the obtained amino alcohols **1a–e**, model reaction was carried out using methyl-2-oxocyclopentanecarboxylate **2a** and nitrostyrene **3a** in toluene at 0 °C and –30 °C for 48 h (Table 1) respectively. All catalysts showed a catalytic activity in this reaction (entries 1–5). When the reaction was carried out at 0 °C using catalyst **1a** with methyl group at  $\beta$ -position, the desired Michael adduct [2*S*,3*R*]-**4** was obtained with moderate chemical yield,



Scheme 2 Preparations of  $\beta$ -amino alcohols **1a–e**.

diastereoselectivity and low enantioselectivity (62%, dr = 83 : 17, 45% ee) (entry 1). Similar reaction using catalyst **1b** with isopropyl group did not show a much change in the chemical yield and diastereoselectivity, but enantioselectivity was quite increased (64%, dr = 88 : 12, 56% ee) (entry 2). Interestingly, the use of catalyst **1c** with bulky *tert*-butyl group afforded the enantiomer adduct [2*S*,3*R*]-**4'** of **4** in moderate chemical yield, diastereoselectivity and good enantioselectivity (68%, dr = 91 : 9, 88% ee) (entry 3). In addition, catalyst **1d** with more sterically influential phenyl group provided adduct **4** with moderate chemical yield, good diastereoselectivity and low enantioselectivity (65%, dr = 83 : 17, 11% ee) (entry 4). Furthermore, catalyst **1e** with benzyl group also did not show satisfactory enantioselectivity, although chemical yield and diastereoselectivity were moderate (55%, dr = 86 : 14, 10% ee) (entry 5). On the other hand, the decrease of temperature to –30 °C substantially improved diastereoselectivity and enantioselectivities (entries 1–5). Catalyst **1a** afforded adduct **4** with good chemical yield, excellent diastereoselectivity and enantioselectivity (75%, dr = 99 : 1, 99% ee) (entry 1). Catalyst **1b** also afforded **4** with good chemical yield and in excellent diastereoselectivity and enantioselectivity (70%, dr = 96 : 4, 98% ee) (entry 2). Interestingly, the enantiomer adduct **4'** of **4** was obtained at 0 °C using **1b**, but the decrease to –30 °C afforded **4**, although the reason is not clear. Similarly, the use of catalyst **1c** gave **4'** in good chemical yield and diastereoselectivity with excellent enantioselectivity (80%, dr = 98 : 2, 99% ee) (entry 3). The use of bulky catalyst **1d** significantly increased the enantioselectivity with good chemical yield and diastereoselectivity (65%, dr = 96 : 4, 98% ee) (entry 4). Bulkier catalyst **1e** brought about the increase of enantioselectivity to afford **4'**, but satisfactory chemical yield and stereoselectivities were not obtained

Table 1 Asymmetric Michael addition of  $\beta$ -keto ester **2a** with nitrostyrene **3a** using amino alcohol organocatalysts **1a–e**

Entry	Catalyst <b>1a–e</b>	Adduct <b>4,4'</b>		Yield <sup>a</sup> (%)		dr <sup>b</sup> <b>4 : 4''</b>		ee <sup>c</sup> (%)	
		0 °C	–30 °C	0 °C	–30 °C	0 °C	–30 °C	0 °C	–30 °C
1	<b>a</b>	<b>4</b>	<b>4</b>	62	75	83 : 17	99 : 1	45	99
2	<b>b</b>	<b>4'</b>	<b>4</b>	64	70	88 : 12	96 : 4	56	98
3	<b>c</b>	<b>4'</b>	<b>4'</b>	68	80	91 : 9	98 : 2	88	99
4	<b>d</b>	<b>4</b>	<b>4</b>	65	65	83 : 17	96 : 4	11	98
5	<b>e</b>	<b>4</b>	<b>4'</b>	55	50	86 : 14	85 : 15	10	60

<sup>a</sup> Isolated yields. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>c</sup> Determined by HPLC using Daicel Chiralcel OD-H column.



(50%, dr = 85 : 15, 60% ee) (entry 5). However, similarly to the adduct from catalyst **1b**, the use of catalyst **1e** also afforded the enantiomer adduct **4'** of **4**, although the reason is not clear. Each catalyst showed satisfactory asymmetric catalytic activity at  $-30\text{ }^{\circ}\text{C}$ . It might be for a reason that the conformation of the transition state of this Michael addition reaction using catalyst **1a** with substrates **2a**, **3a** was fixed at the decrease of reaction temperature at  $-30\text{ }^{\circ}\text{C}$  affording high enantioselectivity, although the reason is not clear. Especially, catalyst **1a** with methyl group and **1c** with bulky *tert*-butyl group at  $\beta$ -position showed better catalytic activity than others. The determination of absolute configuration and stereoselectivity of **4**, **4'** were confirmed on comparison with previous data.<sup>10</sup>

To further improve the results, we evaluated the effect of solvents, molar ratio of catalyst or substrates, and reaction time using the simplest superior catalyst **1a** (Table 2). Initially, solvent effect was examined (entries 1–9). The reaction of **2a** (2 eq.) with **3a** (1 eq.) using 10 mol% of catalyst **1a** was performed at  $-30\text{ }^{\circ}\text{C}$  for 48 h in polar solvents ( $\text{CH}_3\text{CN}$ , DMSO and MeOH), respectively (entries 1–3). However, catalyst **1a** did not show satisfactory catalytic activity in those solvents ( $\text{CH}_3\text{CN}$ : 26%, dr = 88 : 19, 38% ee) (DMSO: 40%, dr = 75 : 25, 9% ee) (MeOH: 45%, dr = 83 : 17, 9% ee) (entries 1–3). In addition, non-polar hexane also did not work as better solvent for this reaction (hexane, 40%, dr = 90 : 10, 46% ee) (entry 4). On the other hand, catalyst **1a** showed enough catalytic activity in ether solvents ( $\text{Et}_2\text{O}$ , *i*-Pr<sub>2</sub>O) ( $\text{Et}_2\text{O}$ : 60%, dr = 95 : 5, 98% ee) (*i*-Pr<sub>2</sub>O: 73%, dr = 98 : 2, 98% ee) (entries 5 and 6). However, cyclic etherate THF did not work as a good solvent (28%, dr = 85 : 5, 20% ee) (entry 7). Furthermore, halogenated  $\text{CH}_2\text{Cl}_2$  also was not effective

solvent (45%, dr = 83 : 17, 64% ee) (entry 8). From these results, toluene was observed to be the best solvent for this reaction using **1a** (76%, dr = 99 : 1, 99% ee) (entry 9). Next, the molar ratio of catalyst **1a** was examined in this reaction (entries 10–12). The reaction was carried out using 20 mol%, 5 mol% and 2.5 mol% of **1a** at  $-30\text{ }^{\circ}\text{C}$  in toluene, respectively. The use of 20 mol% of **1a** afforded almost same results (75%, dr = 97 : 3, 98% ee) as that of 10 mol% of **1a** (entry 10). The reaction using 5 mol% of **1a** brought about the significant decrease of chemical yield, but the diastereoselectivity and enantioselectivity were kept a high level of value (45%, dr = 95 : 5, 94% ee) (entry 11). However, the use of 2.5 mol% of **1a** brought about decrease in chemical yield and enantioselectivity except for diastereoselectivity (36%, dr = 93 : 7, 50% ee) (entry 12). From the above results, it was revealed that the optimum amount of **1a** was 10 mol%. The ratio of substrate amounts of **2a** and **3a** (**2a** : **3a** = 1 : 1 and **2a** : **3a** = 1 : 2) were examined in the presence of **1a** (10 mol%) (entries 13 and 14). However, these ratios brought about a decrease of chemical yield and enantioselectivity, except for diastereoselectivity (38%, dr = 93 : 7, 52% ee) (56%, dr = 94 : 6, 90% ee) (entries 13 and 14). Furthermore, the effect of reaction times (24 h and 72 h) also did not afford better results, as the yields and stereoselectivities (42%, dr = 95 : 5, 88% ee) (60%, dr = 84 : 16, 95% ee) (entries 15 and 16) were observed to be inferior compared to 48 h. Based on the above results, it was revealed that 10 mol% of catalyst **1a**, 2 eq. of **2a**, 1 eq. of **3a**, toluene as a solvent, 48 h of reaction time and  $-30\text{ }^{\circ}\text{C}$  temperature are the optimum condition to obtain the Michael adduct [2*R*,3*S*]-**4** with good chemical yield, excellent diastereoselectivity and enantioselectivity. Next, we examined

Table 2 Optimal condition examination in asymmetric Michael addition of  $\beta$ -keto esters **2a** with nitrostyrene **3a** using amino alcohol organocatalyst **1a**

Entry	Catalyst <b>1a</b> (mol%)	<b>2a</b> (eq.)	<b>3a</b> (eq.)	Solvent	Time (h)	Yield <sup>a</sup> (%)	dr <sup>b</sup> <b>4</b> : <b>4''</b>	ee <sup>c</sup> (%)
1	10	2.0	1.0	$\text{CH}_3\text{CN}$	48	26	88 : 19	38
2	10	2.0	1.0	DMSO	48	40	75 : 25	9
3	10	2.0	1.0	MeOH	48	45	83 : 17	9
4	10	2.0	1.0	Hexane	48	40	90 : 10	46
5	10	2.0	1.0	$\text{Et}_2\text{O}$	48	60	95 : 5	98
6	10	2.0	1.0	<i>i</i> -Pr <sub>2</sub> O	48	73	98 : 2	98
7	10	2.0	1.0	THF	48	28	85 : 15	20
8	10	2.0	1.0	$\text{CH}_2\text{Cl}_2$	48	45	83 : 17	64
9	10	2.0	1.0	<b>Toluene</b>	48	76	99 : 1	99
10	20	2.0	1.0	Toluene	48	75	97 : 3	98
11	5	2.0	1.0	Toluene	48	45	95 : 5	94
12	2.5	2.0	1.0	Toluene	48	36	93 : 7	50
13	10	1.0	1.0	<b>Toluene</b>	48	38	93 : 7	52
14	10	1.0	2.0	<b>Toluene</b>	48	56	94 : 6	90
15	10	2.0	1.0	Toluene	24	42	95 : 5	88
16	10	2.0	1.0	Toluene	72	60	84 : 16	95

<sup>a</sup> Isolated yields. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>c</sup> Determined by HPLC using Daicel Chiralcel OD-H column.



the effect of substituents on amino organocatalysts **5a–e**<sup>9</sup> in this addition of **2a** with **3a** (Scheme 3, Table 3). The reaction of **2a** (2 eq.) with **3a** (1 eq.) was carried out in toluene at  $-30\text{ }^{\circ}\text{C}$  for 48 h (Table 3). Catalyst **5a**<sup>9a</sup> with no substitution at the  $\alpha$ -position only showed low catalytic activity (40%, dr = 60 : 40, 31%) and afforded enantiomer adduct **4'** of **4** (entry 1). Furthermore, when **5b**<sup>9b</sup> in which the hydroxyl group was masked by TMS group was used, the chemical yield and, stereoselectivities were significantly less than the result that afforded by **1a** with free hydroxyl group (45%, dr = 77 : 23, racemate) (entry 2). We also carried out the reaction using **5c**<sup>9c</sup> with no substitution for the hydroxyl group at  $\beta$ -position, but this catalyst did not show satisfactory catalytic activity (48%, dr = 66 : 34, 20%) (entry 3). From these results, the hydroxyl group at the  $\alpha$ -position on catalyst **1a** may need to promote this reaction with enough enantioselectivity. The reactions using catalysts **5d**<sup>9d</sup>, **5e**<sup>9e</sup> with secondary and tertiary amino groups at the  $\alpha$ -position were expected to be more basic than **1a** with primary amino group were examined (entries 4 and 5). However, only racemate adduct **4** was obtained with good chemical yield and moderate diastereoselectivity (**5d**: 75%, dr = 68 : 32, racemate) (**5e**: 70%, dr = 55 : 45, racemate). In the reactions using catalysts **5a–e**, no better result was obtained than the result using catalyst **1a**. Based on the above results, the utility of  $\beta$ -amino alcohol having a primary amino group at the  $\beta$ -position acting as a base and hydrobonding site, phenyl group at the  $\alpha$ -position performing as stereocontrolling site and a hydroxy group forming hydrogen bonds with the substrates was revealed in order to achieve satisfactory chemical yield and stereoselectivities.

## 2.2. Substrate scope

Under the optimized reaction condition using catalyst **1a**, the generality of **1a** was examined in the asymmetric Michael addition of various  $\beta$ -keto esters with nitroolefins (Schemes 4 and 5). First the reactions of **2a** with **6a–i** were carried out in toluene at  $-30\text{ }^{\circ}\text{C}$  for 48 h (Scheme 4) respectively. As summarized in Scheme 4, the desired Michael adducts **7–15** were obtained at moderate to good chemical yields and stereoselectivities. The reaction of  $\beta$ -keto ester **2a** with *p*-halogenated nitrostyrenes **6a–d** proceeded with good chemical yield and diastereoselectivities with moderate to good enantioselectivities to afford **7–10** (**7**, 86%, dr = 94 : 6, 72% ee) (**8**, 88%, dr = 98 : 2, 74% ee) (**9**, 86%, dr = 98 : 2, 69% ee) (**10**, 51%, dr = 78 : 22, 49% ee). Although the reaction using *p*-methylated



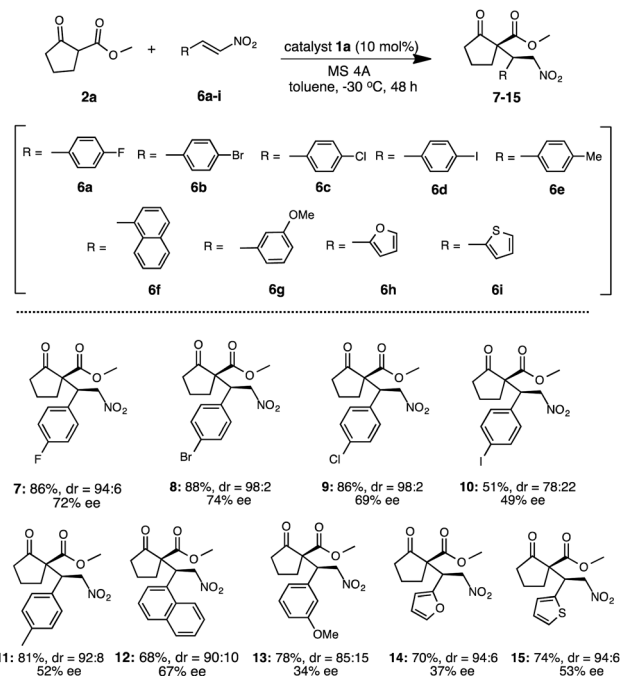
Scheme 3 Substituted amino alcohol organocatalysts **5a–e**.

Table 3 Optimal condition examination in asymmetric Michael addition of  $\beta$ -keto ester **2a** with nitrostyrene **3a** using amino alcohol organo catalysts **5a–e**

Entry	Catalyst <b>5a–e</b>	Adduct <b>4, 4'</b>	Yield <sup>a</sup> (%)	dr <sup>b</sup> <b>4 : 4''</b>	ee <sup>c</sup> (%)
1	<b>a</b>	<b>4'</b>	40	60 : 40	31
2	<b>b</b>	<b>4</b>	45	77 : 23	racemic
3	<b>c</b>	<b>4</b>	48	66 : 34	20
4	<b>d</b>	<b>4</b>	75	68 : 32	racemic
5	<b>e</b>	<b>4</b>	70	55 : 45	racemic

<sup>a</sup> Isolated yields. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>c</sup> Determined by HPLC using Daicel Chiralcel OD-H column.

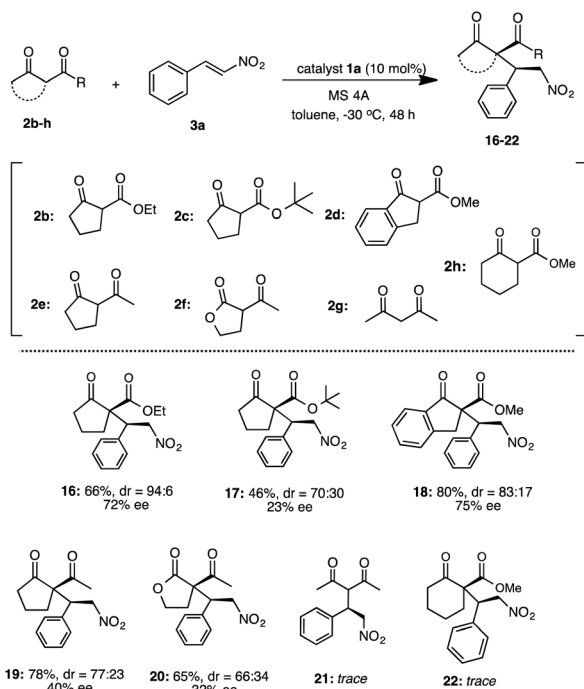
nitrostyrene **6e** also afforded the corresponding adduct **11**, the enantioselectivity was slightly decreased (**11**: 81%, dr = 92 : 8, 52% ee). Furthermore, the use of 1-naphthyl nitroolefin **6f** also afforded **12** at good chemical yield, moderate diastereoselectivity and enantioselectivity (**12**: 68%, dr = 90 : 10, 67% ee). Similarly, 3-methoxynitrostyrene **6g** also yielded **13** at good chemical yield and diastereoselectivity, but with low enantioselectivities (**13**: 78%, dr = 85 : 15, 34% ee). Moreover, the reaction using heterocyclic 2-(2-furyl)-2-nitroethylene **6h** was carried out and the corresponding **14** was obtained in good chemical yield and diastereoselectivity with low enantioselectivity (**14**: 70%, dr = 94 : 6, 37% ee). Similarly, the use of



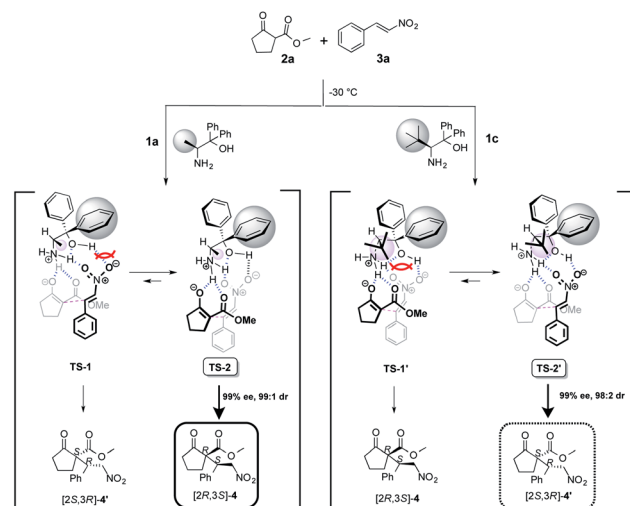
Scheme 4 Asymmetric Michael addition of **2a** with **6a–i**.





Scheme 5 Asymmetric Michael addition of **2b–h** with **3a**.

heterocyclic 2-[(*E*)-2-nitrovinyl]thiophene **6i** also afforded **15** at good chemical yield and diastereoselectivity, but with moderate enantioselectivity (**15**: 74%, dr = 94 : 6, 53% ee). In addition, we also examined the reaction of various  $\beta$ -keto esters **2b–d** or  $\beta$ -diketones **2e–g** with nitrostyrene **3a** (Scheme 5). The reactions of  $\beta$ -keto esters **2b–d** with **3a** respectively, afforded the corresponding Michael adducts **16–18** with moderate to good chemical yields and moderate stereoselectivities. The reaction using cyclopentanone ethyl ester **2b** afforded **16** with moderate chemical and good stereoselectivities (**16**: 66%, dr = 94 : 6, 72% ee). Moreover, the use of bulky cyclopentanone *tert*-butyl ester **2c** afforded **17**, but the reaction brought about the decrease of chemical yield and stereoselectivities (**17**: 46%, dr = 70 : 30, 23% ee).<sup>11b</sup> On the other hand, the reaction using indanone ester **2d** proceeded to afford **18** at good chemical yield and stereoselectivities (**18**: 80%, dr = 83 : 17, 75% ee).<sup>11c</sup> Although, the reaction using diketones such as 2-acetyl cyclopentanone **2e** or 2-acetyl butyrolactone **2f** with **3a**, respectively, also afforded the corresponding **19**, **20** the enantioselectivities were low to moderate (**19**: 78%, dr = 77 : 23, 40% ee)<sup>11a</sup> (**20**: 65%, dr = 66 : 34, 32% ee).<sup>11c</sup> On the other hand, the use of acyclic diketone **2g** and gave only a trace of **21**. Reaction using six membered ring diketo ester **2h** was also tried, however the reaction did not proceed. The reaction using a large amount of substrate (**3a**: 1.0 g, **2a**: 1.9 g) was examined to demonstrate the practical utility in the best reaction condition. As a result, the Michael adduct **4** was obtained with 60% chemical yield with good stereoselectivities (dr = 91 : 9, 86% ee) at 40 h reaction time, although a slight decrease of ee was observed. From this result, it is expected that this Michael addition reaction using simple primary  $\beta$ -amino alcohol organocatalyst may be useful for practical aspect.



Scheme 6 Plausible reaction course for Asymmetric Michael addition.

### 2.3. Reaction mechanism

The uses of catalyst **1a** with methyl group at  $\alpha$ -position afforded the Michael adduct **4a** and of **1c** with *tert*-butyl group at  $\alpha$ -position afforded enantiomer adduct **4'** of **4** with excellent in the reaction of methyl 2-oxocyclopentanecarboxylate **2a** and nitrostyrene **3a** at -30 °C, respectively (Table 1). Stereoselectivities (**1a**: dr = 99 : 1, 99% ee, **1c**: dr = 98 : 2, 99% ee) Based on the observed excellent stereoselectivities, we proposed the plausible mechanism *via* a transition state (TS) model to rationalize the stereochemical of Michael addition as shown in Scheme 6. In the mentioned TS, both catalysts **1a** and **1c**, respectively, act as a base and abstracts a proton on **2a** to generate an enolate and then the species is fixed with the ammonium site of catalyst part by hydrogen bonding. In addition, substrate **3a** is also fixed with ammonium and hydroxyl group sites on catalyst part by hydrogen bonding. After the fixing of catalyst and substrates, the reaction using catalyst **1a** with less bulky methyl group might be assumed to proceed through **TS-2** that does not have the steric interaction between phenyl group at  $\alpha$ -position on catalyst part and **3a** than that of **TS-1**, to afford **[2*S*,3*R*]-4** with excellent stereoselectivities.

On the other hand, the reaction using **1c** with bulky *tert*-butyl group might be assumed to proceed through **TS-2'** that does not have the large steric interaction of bulky *tert*-butyl group on catalyst part and enolate species than that of **TS-1'**. It may be for a reason that the steric interaction between the bulky *tert*-butyl group at  $\beta$ -position on catalyst species and enolate species is prioritized in contrast with the steric interaction between phenyl group at  $\alpha$ -position on catalyst species and nitrostyrene **3a**, to afford **[2*S*,3*R*]-4'** as a major adduct with high stereoselectivity.

## 3. Conclusion

We have developed simple primary  $\beta$ -amino alcohols, which act as an efficient organocatalysts in the asymmetric Michael addition of  $\beta$ -keto esters with nitroalkenes, affording highly pure chiral Michael adducts. In particular, simplest  $\beta$ -amino



alcohols **1a** with methyl group at  $\alpha$ -position showed the best catalytic activity and the corresponding Michael adducts having a quaternary chiral carbon center with good to excellent chemical yields (up to 80%), diastereoselectivities (up to 99 : 1) and enantioselectivities (up to 99% ee). Furthermore, we have found that the both enantiomers of Michael adducts **4**, **4'** are separately made by using specific  $\beta$ -amino alcohol organo-catalysts such as catalysts **1a** with methyl group and **1c** with *tert*-butyl group at  $\beta$ -position, respectively. And also, interestingly, when  $\beta$ -amino alcohols **1b** or **1e** were used in this reaction, both enantiomers of Michael adducts ([2*R*,3*S*]-**4** and [2*S*,3*R*]-**4'**) were separately made, depending on the reaction temperature.

## 4. Experimental

### 4.1. General information

All reagents and dry solvents were purchased from commercial vendors and used directly without further purification. All reactions were placed in dried sample vials inserted with magnetic beads. Thin-Layer Chromatography (TLC) was performed on Merck silica gel 60 F254 plates and the analytes were identified under UV light. Flash column chromatography was performed using silica gel pore size 60 N (40–100  $\mu$ m). Infrared (IR) spectra were measured with a JASCO FT/IR-4100 spectrophotometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data were recorded using a JEOL JNM-ECA500 instrument with tetramethylsilane as the internal standard. HPLC data were collected using the TOSOH instrument equipped with (UV-8020, DP-8020, and SD-8022) detectors using Daicel CHIRALCEL OD-H column. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. MS were taken on a JEOL-JMS-700 V spectrometers.

### 4.2. General procedure for catalytic asymmetric Michael addition of $\beta$ -keto esters, ketones **2a,2b–g** with nitrostyrenes **3a,6a–h** using catalyst **1a**

To a solution of catalyst **1a** (10 mol%) in dry toluene (2 mL) with molecular sieves 4A was added  $\beta$ -keto esters, ketones **2a,2b–g** (0.4 mmol) at RT under inert atmosphere and the solution was stirred at same temperature. After 1 h, the reaction was cooled to  $-30\text{ }^\circ\text{C}$  and the respective nitrostyrene **3a,6a–i** (0.2 mmol) was added. The reaction was allowed to stir at  $-30\text{ }^\circ\text{C}$  for 48 h. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (*n*-hexane/AcOEt = 10/1) to give the corresponding chiral Michael adduct. The compounds are the known compounds and the structures were identified by spectral data which were in good agreement with those reported.<sup>10,11</sup>

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- 1 (a) A. Lattanzi, *Org. Lett.*, 2005, 7, 2579; (b) Y. Chi and S. H. Gellman, *Org. Lett.*, 2005, 7, 4253; (c) R. M. De

- Figueiredo and M. Christmann, *Eur. J. Org. Chem.*, 2007, 16, 2575; (d) D. W. C. MacMillan, *Nature*, 2008, 455, 304; (e) S. Bertelsen and K. A. Jorgensen, *Chem. Soc. Rev.*, 2009, 38, 2178; (f) E. MarquesLopez, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.*, 2010, 27, 1138; (g) A. Moyano and R. Rios, *Chem. Rev.*, 2011, 111, 4703; (h) P. Kasaplar, C. R. Escrich and M. A. Pericas, *Org. Lett.*, 2013, 15, 3498; (i) H. X. He and D. M. Du, *RSC Adv.*, 2013, 3, 16349; (j) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, 114, 2390; (k) X. Fang and C. J. Wang, *Chem. Commun.*, 2015, 51, 1185; (l) J. Chen, S. Meng, L. Wang, H. Tang and Y. Huang, *Chem. Sci.*, 2015, 6, 4184; (m) L. Xu, J. Huang, Y. Liu, Y. Wang, B. Xu, K. Ding, Y. Ding, Q. Xu, L. Yu and Y. Fan, *RSC Adv.*, 2015, 5, 42178; (n) T. Sekikawa, T. Kitaguchi, H. Kitaura, T. Minami and Y. Hatanaka, *Org. Lett.*, 2016, 18, 646; (o) U. Varal, M. Durmaz and A. Sirit, *Org. Chem. Front.*, 2016, 3, 730; (p) J. Kaur, P. Chauhan and S. S. Chimni, *Org. Biomol. Chem.*, 2016, 14, 7832; (q) H. Zhang, M. Han, T. Chen, L. Xu and L. Yu, *RSC Adv.*, 2017, 7, 48214; (r) Y. Zheng, A. Wu, Y. Ke, H. Cao and L. Yu, *Chin. Chem. Lett.*, 2019, 30, 937; (s) S. H. Xiang and B. Tan, *Advances in asymmetric organocatalysis over the last 10 years*, *Nat. Commun.*, 2020, 11, 3786.
- 2 (a) C. Bolm and J. A. Gladysz, *Chem. Rev.*, 2003, 103, 2761; (b) A. H. Cherney, N. T. Kadunce and S. E. Reisman, *Chem. Rev.*, 2005, 115, 9587; (c) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH Weinheim, Germany, 2007; (d) T. Mallat, E. Orglmeister and A. Baiker, *Chem. Rev.*, 2007, 107, 4863; (e) S. Kobayashi, Y. Mori, J. S. Fossey and M. M. Salte, *Chem. Rev.*, 2011, 111, 2626; (f) J. Gascon, A. Corma, F. Kapteijn and F. X. L. Xamena, *ACS Catal.*, 2014, 4, 361; (g) D. F. Chen, Z. Y. Han, X. L. Zhou and L. Z. Gong, *Acc. Chem. Res.*, 2014, 47, 2365; (h) G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev.*, 2015, 115, 9922.
- 3 (a) J. Kumagai, Y. Kohari, C. Seki, K. Uwai and Y. Okuyama, *Heterocycles*, 2014, 90, 1124; (b) U. V. S. Reddy, M. Chennapuram, C. Seki, E. Kwon, Y. Okuyama and H. Nakano, *Eur. J. Org. Chem.*, 2016, 24, 4124; (c) H. Nakano, I. A. Owolabi, M. Chennapuram, Y. Okuyama, E. Kwon, C. Seki, M. Tokiwa and M. Takeshita, *Heterocycles*, 2018, 97, 647.
- 4 (a) T. Otsuki, J. Kumagai, Y. Kohari, Y. Okuyama, E. Kwon, C. Seki, K. Uwai, Y. Mawatari, N. Kobayashi, T. Iwasa, M. Tokiwa, M. Takeshita, A. Maeda, A. Hashimoto, K. Turuga and H. Nakano, *Eur. J. Org. Chem.*, 2015, 33, 7292; (b) H. Cui, P. V. Chouthaiwale, F. Yin and F. Tanaka, *Asian J. Org. Chem.*, 2016, 5, 153.
- 5 (a) Y. Kohari, Y. Okuyama, E. Kwon, T. Furuyama, N. Kobayashi, T. Otuki, J. Kumagai, C. Seki, K. Uwai, G. Dai, T. Iwasa and H. Nakano, *J. Org. Chem.*, 2014, 79, 9500; (b) J. Kumagai, T. Otsuki, U. V. S. Reddy, Y. Kohari, C. Seki, K. Uwai, Y. Okuyama, E. Kwon, M. Tokiwa, M. Takeshita and H. Nakano, *Tetrahedron: Asymmetry*, 2015, 26, 1423; (c) T. Takahashi, U. V. S. Reddy, Y. Kohari, C. Seki, T. Furuyama, N. Kobayashi, Y. Okuyama, E. Kwon,



- K. Uwai, M. Tokiwa, M. Takeshita and H. Nakano, *Tetrahedron Lett.*, 2016, **57**, 5771; (d) U. V. S. Reddy, M. Chennapuram, C. Seki, E. Kwon, Y. Okuyama and H. Nakano, *Eur. J. Org. Chem.*, 2016, **24**, 4124.
- 6 U. V. S. Reddy, M. Chennapuram, K. Seki, C. Seki, B. Anusha, E. Kwon, Y. Okuyama, K. Uwai, M. Tokiwa, M. Takeshita and H. Nakano, *Eur. J. Org. Chem.*, 2017, **26**, 3874.
- 7 (a) J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, **35**, 4481; (b) R. Manzano, J. M. Andres, M. D. Muruzabal and R. Pedrosa, *Adv. Synth. Catal.*, 2010, **352**, 3364; (c) B. D. Mather, K. Vishwanathan, K. M. Miller and T. E. Long, *Prog. Polym. Sci.*, 2006, **31**, 487; (d) J. Luo, L. W. Xu, R. A. S. Hay and Y. Lu, *Org. Lett.*, 2009, **11**, 437; (e) H. Guo, F. Xing, G. F. Du, K. W. Huang, B. Dai and L. He, *J. Org. Chem.*, 2015, **80**, 12606; (f) Y. Zhou, Z. L. Xia, Q. Gu and S. L. You, *Org. Lett.*, 2017, **19**, 762; (g) C. F. Nising and S. Brase, *Chem. Soc. Rev.*, 2008, **37**, 1218; (h) M. S. Rosello, J. L. Acena, A. S. Fuentes and C. D. Pozo, *Chem. Soc. Rev.*, 2014, **43**, 7430.
- 8 (a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119; (b) Z. H. Zhang, X. Q. Dong, D. Chen and C. J. Wang, *Chem.–Eur. J.*, 2008, **14**, 8780; (c) A. M. Flock, A. Krebs and C. Bolm, *Synlett*, 2010, **8**, 1219; (d) K. Murai, S. Fukushima, S. Hayasi, Y. Takahara and H. Fujioka, *Org. Lett.*, 2010, **12**, 964; (e) T. Nemoto, K. Obuchi, S. Tamura, T. Fukuyama and Y. Hamada, *Tetrahedron Lett.*, 2011, **52**, 987; (f) A. Lattanzi, C. D. Fusco, A. Russo, A. Poater and L. Cavallo, *Chem. Commun.*, 2012, **48**, 1650; (g) D. F. Chen, P. Y. Wu and L. Z. Gong, *Org. Lett.*, 2013, **15**, 3958; (h) P. Vinayagam, M. Vishwanath and V. Kesavan, *Tetrahedron: Asymmetry*, 2014, **25**, 568; (i) M. Bera, T. K. Ghosh, B. Akhuli and P. Ghosh, *J. Mol. Catal. A: Chem.*, 2015, **408**, 287; (j) M. S. Ullah and S. Itsuno, *Chem. Lett.*, 2018, **47**, 1220; (k) C. S. Afrin and S. Itsuno, *J. Catal.*, 2019, **377**, 543; (l) M. A. Abdelkawy, E. A. Aly, M. A. El-Badawi and S. Itsuno, *Catal. Commun.*, 2020, **146**, 106132.
- 9 (a) C. Tianhao and H. Yanwei, *Zhongguo Yiyao Gongye Zazhi*, 2001, **32**, 322; (b) Y. Sakuta, Y. Kohari, N. D. M. R. Hutabarat, K. Uwai, E. Kwon, Y. Okuyama, C. Seki, H. Matsuyama, N. Takano, M. Tokiwa, M. Takeshita and H. Nakano, *Heterocycles*, 2012, **86**, 1379; (c) D. O. Hagan and M. Tavasli, *Tetrahedron: Asymmetry*, 1983, **10**, 1189; (d) A. Tadatoshi, H. Motoo, Y. Yukio, S. Gohfu, European Patent organisation, EP 75868 A2 1983-04-06, 1983; (e) M. Gacek and K. Undheim, *Acta Chem. Scand., Ser. B*, 1975, **29**, 206.
- 10 (a) R. Togashi, M. Chennapuram, C. Seki, Y. Okuyama, E. Kwon, K. Uwai, M. Tokiwa, M. Takeshita and H. Nakano, *Eur. J. Org. Chem.*, 2019, **24**, 3882; (b) D. Ganesan, M. Chennapuram, Z. Begum, C. Seki, Y. Okuyama, E. Kwon, K. Uwai, M. Tokiwa, S. Tokiwa, M. Takeshita and H. Nakano, *Heterocycles*, 2019, **98**, 1536.
- 11 (a) C. J. Wang, Z. H. Zhang, X. Q. Dong and X. J. Wu, *Chem. Commun.*, 2008, 1431; (b) P. Chauhan and S. S. Chimni, *Asian J. Org. Chem.*, 2012, **1**, 138; (c) N. Horitsugi, K. Kojima, K. Yasui, Y. Sohtome and K. Nagasawa, *Asian J. Org. Chem.*, 2014, **3**, 445.

