

## The carbamate esters as organocatalysts in asymmetric Michael addition reactions in aqueous media: when pyrrolidine backbone surpasses 1,2-diaminocyclohexane

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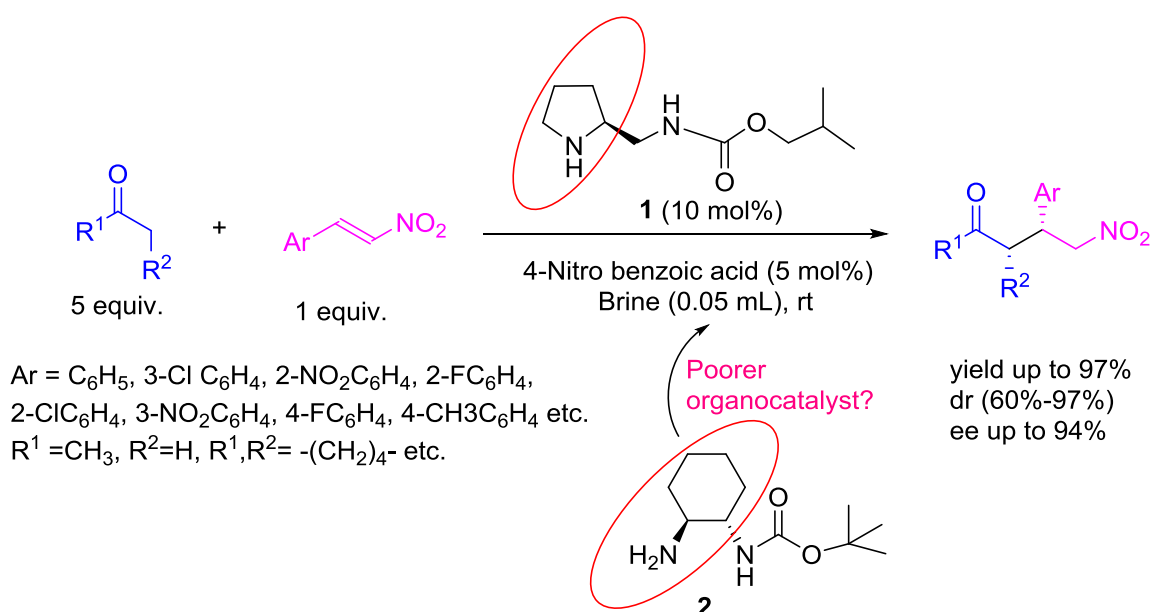
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### Abstract

A pyrrolidine ring containing carbamate ester, pyrrolidine-2-ylmethyl-carbamic acid isobutyl ester has been synthesized. The newly developed pyrrolidine ring containing carbamate ester surpassed 1,2-diaminocyclohexane derived carbamate ester in asymmetric Michael addition reactions in aqueous media providing Michael products with yields (up to 97%), *syn* diastereoselectivities (up to 97%) and enantioselectivities (up to 94%).



**Keywords:** Asymmetric organocatalysis, Michael reaction, pyrrolidine-based carbamate ester, aqueous media

## Introduction

Asymmetric C-C bond-forming reactions provide a plethora of opportunities towards the synthesis of diverse chiral compounds of significant applications in wide array of fields.<sup>1-3</sup> It is to note that catalytic asymmetric Michael addition reaction or 1,4-conjugate addition reaction is one of the most important and versatile C-C bond forming reaction apart from aldol reactions, Diels-Alder reactions, Mannich reactions etc.<sup>4-9</sup> Multiple stereogenic centers can be generated in a single step process by this conjugate addition reaction.

Chiral metal complex catalysis and biocatalysis have been the main focus of research in the Michael addition reactions along with other classical C-C bond-forming transformations until the beginning of 21<sup>st</sup> century.<sup>10-21</sup> Barbas group and MacMillan group independently initiated a new asymmetric catalysis which was judiciously termed as 'organocatalysis' by MacMillan. The aforesaid groups exploited the organocatalysis in asymmetric intermolecular aldol reactions and asymmetric Diels-Alder reactions respectively.<sup>19-20</sup> In addition to these reports, Hanessian and group unveiled the first asymmetric organocatalytic intermolecular Michael addition reaction in organic media.<sup>21</sup> Since then, there have been several reports on asymmetric organocatalytic Michael addition reactions and other classical C-C bond-forming reactions in organic media.

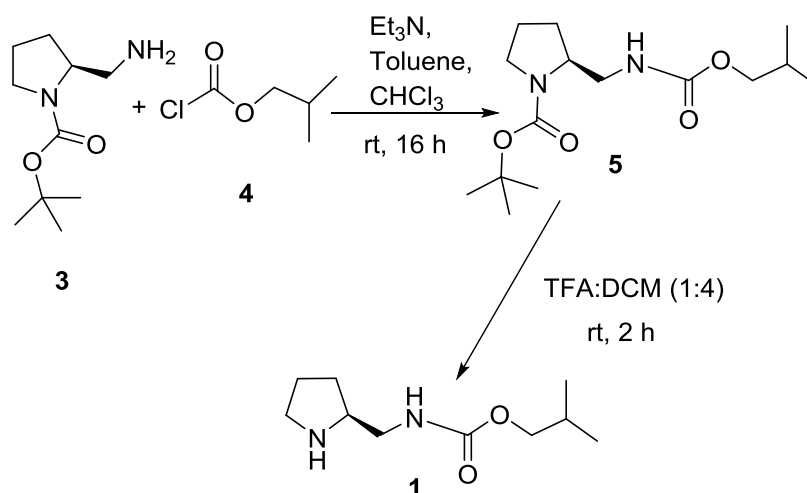
Organocatalysis employing aqueous conditions is a very common practice.<sup>22-26</sup> However, surprisingly very few reports were found for asymmetric organocatalytic Michael reactions in aqueous media.<sup>27-51</sup> Use of water as solvent may be beneficial with multiple advantages in the 1, 4-conjugate addition reactions. It was evident that water not only accelerated the reaction rates but also it could enhance the stereoselectivity.<sup>52</sup> Various derivatives of proline showed significant catalytic activity as organocatalyst in asymmetric Michael addition reactions in aqueous and semi-aqueous media, and remarkably high enantioselective Michael products were resulted under this condition.<sup>53-54</sup>

Even though there have been many proline derived organocatalysts but a proline-based carbamate type organocatalyst is not known in the literature. However, Chincilla and group developed a 1, 2-diamino cyclohexane-based carbamate ester **2** for its application in Michael addition reaction between arylketones and acetone to nitroalkenes in organic media.<sup>55</sup> The said catalyst **2** unfortunately provided very poor yield (53%) and enantioselectivity (60% ee) for the Michael reaction between acetophenone and  $\beta$ -nitrostyrene in water media. Even in the hazardous organic solvent such as chloroform, the catalyst **2** afforded highest 93% enantioselectivity. Moreover, 1, 2-diamino cyclohexane-based carbamate ester **2** catalyzed  $\alpha,\alpha$ -disubstituted aldehydes and maleimides as Michael donor and acceptor respectively to furnish products with only 32% ee in water media.<sup>56</sup> Notably, in presence of the same catalyst **2** for similar substrates, the enantioselectivity of Michael products reached to 94% in deep eutectic solvent.<sup>57</sup> All these results indicate that the 1,2-diaminocyclohexane backbone in the carbamate type structure is somehow incapable of imparting good level of stereoselectivity in pure water media.

We then argued whether a pyrrolidine ring containing carbamate ester could be a better choice? Perhaps a pyrrolidine moiety in the carbamate type organocatalyst could be arguably an interesting choice for Michael reactions in aqueous media. In this context, a carbamate type organocatalyst, pyrrolidine-2-ylmethyl-carbamic acid isobutyl ester **1** has been synthesized starting from inexpensive and commercially available reagents such as isobutyl chloroformate **4** and 2-aminomethylpyrrolidine-1-carboxylic acid *tert*-butyl ester **3**. Herein, we report the detailed study of a proline-derived carbamate ester organocatalyst **1** in Michael addition reactions in eco-friendly solvent like brine without any organic co-solvent.

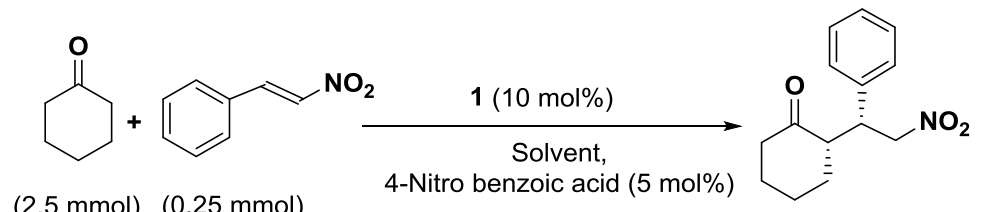
## Results and Discussion

Carbamate ester **1** has been synthesized from commercially available N-Boc protected 2-amino methylpyrrolidine **3** and isobutyl chloroformate **4** following a very simple reaction sequence stated in Scheme 1. Initially, the N-Boc protected 2-amino methylpyrrolidine **3** was coupled with commercially available isobutyl chloroformate **4** to obtain the N-Boc protected compound **5**, which upon trifluoro acetic acid treatment provided the desired catalyst **1** with 95% yield.



**Scheme 1.** Preparation of the catalyst **1**.

The newly synthesized pyrrolidine carbamate ester **1** was then employed as catalyst in asymmetric Michael addition reaction of cyclohexanone to  $\beta$ -nitro styrene separately in aqueous and organic media to observe the catalytic activity of that organocatalysts. Frequently used organic solvents like toluene, chloroform, dichloromethane furnished the Michael adducts with only 46-54% ee (entry 1-3, Table 1). These results indicate that catalyst **1** is inferior to catalyst **2** in organic media. Apart from the organic solvents, we were very curious to observe any positive effect of water as sole reaction medium when the catalyst is **1**. Indeed, the organocatalyst **1** afforded the Michael product with an increased diastereoselectivity (91% de) and enantioselectivity (80% ee) in pure water media (entry 4, Table 1). A similar experiment was also performed in 0.05 ml of brine for the same Michael reaction. Interestingly, the catalyst **1** was found to be more efficient in brine media with an improved stereoselectivity (91% de, 86% ee) (entry 7, Table 1). Furthermore, it was also observed that the same Michael reaction resulted inferior yield (90%) and stereoselectivity in neat condition (88% de, 82% ee) (entry 5, Table 1). Thus, the synchronization of brine as solvent with organocatalyst **1** in providing the optimum result has been observed in this particular reaction. To further optimize the reaction condition, the additive quantity was then varied in brine. A higher additive loading (10 mol%) was found to be detrimental to both diastereoselectivity (90% de) and enantioselectivity (81% ee) in brine media (entry 6, Table 1).

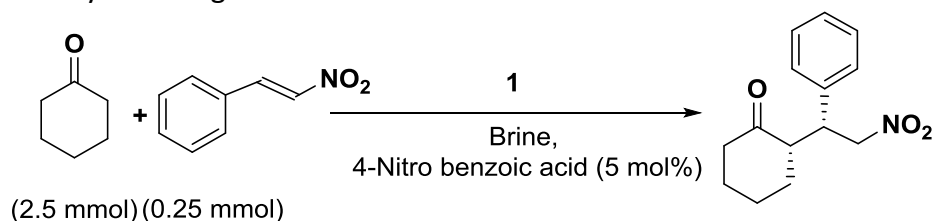
**Table 1.** Screening of solvents and additive loading


Entry	Solvent	yield <sup>a</sup>	%de <sup>b</sup>	%ee <sup>c</sup>
1	Toluene	91	76	46
2	CH <sub>2</sub> Cl <sub>2</sub>	97	79	48
3	CHCl <sub>3</sub>	81	82	54
4	H <sub>2</sub> O	93	91	80
5	-	90	88	82
6 <sup>d</sup>	Brine	93	90	81
<b>7</b>	<b>Brine</b>	<b>93</b>	<b>91</b>	<b>86</b>

<sup>a</sup> Yield after purification by column chromatography. <sup>b</sup> Diastereomer ratios (*anti/syn*) were determined by <sup>1</sup>H NMR spectrum of the crude product mixture. <sup>c</sup> Enantiomeric excess were determined by the chiral HPLC study of the *syn* isomer. <sup>d</sup> 10 mol% additive was used.

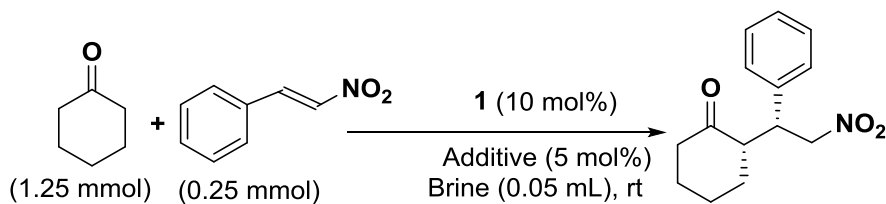
Once brine was found to be the best solvent, we next checked the volume of brine for the optimization of yield and stereoselectivity in the present asymmetric Michael addition reaction. Different results were obtained by altering the volume of brine. As we have already observed when the brine volume was taken 0.05 ml with 10 mol% of catalyst **1**, 93% yield and 86% ee of Michael product was obtained (entry 7, Table 1). Increasing or decreasing the brine volume otherwise affected both the yields and stereoselectivities (entry 1 & 2, Table 2). Subsequently, interesting results were obtained during the optimization studies with different catalyst loading. It was noticed that the 10 mol% catalyst loading afforded best yield as well as stereoselectivity in the Michael reaction (entry 7, Table 1). A lower catalyst loading (5 mol%) furnished only 80% ee (entry 3, Table 2), while a higher loading (20 mol%) increased the chemical yield to 98%, however, the enantioselectivity was only 68% for the Michael product (entry 4, Table 2). Next, we examined different ratio of nitrostyrene and cyclohexanone to see their effect. Very interestingly, an improved enantioselectivity (94% ee) was obtained when 5 equiv. of cyclohexanone was taken with respect to nitrostyrene in brine medium (entry 5, Table 2). Further lower (1:3) ketone/nitrostyrene ratio furnished only 59% ee in brine media (entry 6, Table 2).

Acid additive often can significantly influence the outcome of both yield and enantioselectivity in organocatalyzed asymmetric Michael addition reaction.<sup>58</sup> In order to see such influence, we examined various acid additives such as trifluoroacetic acid, benzoic acid, adipic acid, citric acid etc. apart from 4-nitrobenzoic acid in the Michael reaction in brine media. After the sincere additive screening, it was found that all the acid additives afforded inferior enantioselectivity compared to 4-nitro benzoic acid (Table 3). The same Michael reaction without any acid additive also furnished a lower enantioselectivity (79%) (entry 2, Table 3). Notably, the aromatic acid additives with medium acidity showed better chemical reactivity providing higher yield of the Michael products compared to strong aliphatic acid additives (Table 3). At this moment no concrete explanation is available with us, even though it may be assumed that in the presence of strong acid additive, the catalyst **1** is probably getting deactivated during the reaction.

**Table 2** Screening of catalyst loading and volume of brine

Entry	Catalyst (mol%)	Brine(mL)	Yield (%) <sup>a</sup>	de (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	10	0.1	20	99	82
2	10	0.01	51	73	81
3	5	0.05	27	77	80
4	20	0.05	98	86	68
<b>5<sup>d</sup></b>	<b>10</b>	<b>0.05</b>	<b>92</b>	<b>94</b>	<b>94</b>
6 <sup>e</sup>	10	0.05	85	93	59

<sup>a</sup> Yield after purification by column chromatography. <sup>b</sup> Diastereomer ratios (*anti/syn*) were determined by <sup>1</sup>H NMR spectrum of the crude product mixture. <sup>c</sup> Enantiomeric excess were determined by the chiral HPLC study of the *syn* isomer. <sup>d</sup> Cyclohexanone (1.25 mmol),  $\beta$ -nitro styrene (0.25 mmol) were used. <sup>e</sup> Cyclohexanone (0.75 mmol),  $\beta$ -nitro styrene (0.25 mmol) were used.

**Table 3** Screening of acid additives

Entry	Additive (pK <sub>a</sub> )	Yield (%) <sup>a</sup>	de (%) <sup>b</sup>	ee (%) <sup>c</sup>
<b>1</b>	<b>4-Nitro benzoic acid (3.41)</b>	<b>92</b>	<b>94</b>	<b>94</b>
2	-	95	95	79
3	3,5-Dinitro benzoic acid (2.77)	93	91	66
4	<i>p</i> -Anisic acid (4.47)	85	94	70
5	Benzoic acid (4.2)	99	94	73
6	Stearic acid (10.15)	96	95	67
7	Abietic acid (4.64)	93	94	75
8	Adipic acid (4.43)	90	95	63
9	Citric acid (3.14)	33	89	64
10	L-(+)-Tartaric acid (2.89)	27	90	64
11	Trifluoro acetic acid (0.23)	10	82	69
12	<i>p</i> -Toluene Sulphonic acid (-2.8)	27	91	74
13	Picric acid (0.38)	27	85	75

<sup>a</sup> Yield after purification by column chromatography. <sup>b</sup> Diastereomer ratios (*anti/syn*) were determined by <sup>1</sup>H NMR spectrum of the crude product mixture. <sup>c</sup> Enantiomeric excess were determined by the chiral HPLC study of the *syn* isomer.

After getting the optimized reaction condition, we then examined the substrate scope. Studies with various electron donating and electron withdrawing group substituted nitroolefins and ketones were performed to check the catalytic activity of our synthesized organocatalyst **1** (Table 4). Except acetone as Michael donor, most of the substrates furnished good diastereo- and enantioselectivity in presence of the newly developed carbamate organocatalyst **1** in brine. The cyclohexanone as Michael donor and  $\beta$ -nitrostyrene as Michael acceptor were found to be best substrates in terms of chemical yield as well as stereoselectivity in presence of organocatalyst **1** in brine (entry 1, Table 4). Nitro group substitution at meta position of the phenyl ring also afforded similar results (entry 10, Table 4). Fluoro- and chloro- substitution furnished little lower but similar enantioselectivities (entry 2, 5, 6, 7, 9, Table 4). In general, cyclohexanone was found to be better compared to cyclopentanone and acetone as Michael donor. All the Michael reactions were found to complete between 3-6 days in brine in presence of this pyrrolidine ring containing carbamate organocatalyst **1**.

**Table 4.** Enantioselective Michael addition reaction of ketones to nitroolefins

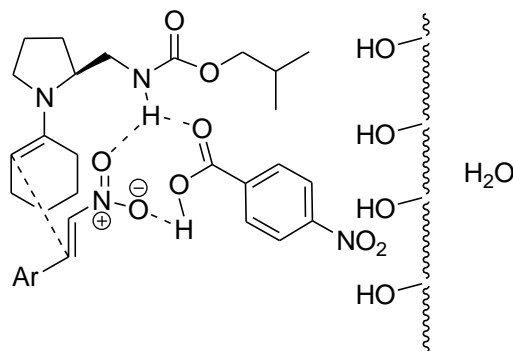
$$\text{R}^1\text{-C(=O)-CH}_2\text{-R}^2 + \text{Ar-CH=CH-NO}_2 \xrightarrow[\text{4-Nitro benzoic acid (5 mol\%), Brine (0.05 mL), rt}]{\text{1 (10 mol\%)}} \text{R}^1\text{-C(=O)-CH(Ar)-CH(R}^2\text{)-CH}_2\text{-NO}_2$$

(1.25 mmol)      (0.25 mmol)

Entry	Product	Time <sup>d</sup>	Yield (%) <sup>a</sup>	de (%) <sup>b</sup>	ee (%) <sup>c</sup>
<b>1</b>	<b>Ar = C<sub>6</sub>H<sub>5</sub> (6)</b>	<b>3</b>	<b>92</b>	<b>94</b>	<b>94</b>
2	Ar = 3-Cl C <sub>6</sub> H <sub>4</sub> ( <b>7</b> )	5	97	80	85
3	Ar = 2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ( <b>8</b> )	6	90	90	85
4	Ar = 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>9</b> )	4	96	90	83
5	Ar = 3-F C <sub>6</sub> H <sub>4</sub> ( <b>10</b> )	4	95	82	86
6	Ar = 2-FC <sub>6</sub> H <sub>4</sub> ( <b>11</b> )	3	85	97	74
7	Ar = 2-Cl C <sub>6</sub> H <sub>4</sub> ( <b>12</b> )	5	88	95	87
8	Ar = 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>13</b> )	4	83	95	87
9	Ar = 4-F C <sub>6</sub> H <sub>4</sub> ( <b>14</b> )	4	92	93	87
10	Ar = 3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ( <b>15</b> )	5	95	72	93
11	R <sup>1</sup> , R <sup>2</sup> = (CH <sub>2</sub> ) <sub>3</sub> ( <b>16</b> )	4	91	60	72
12	R <sup>1</sup> = CH <sub>3</sub> , R <sup>2</sup> = H, ( <b>17</b> )	4	93	--	33

<sup>a</sup> Yields were determined by the column chromatography. <sup>b</sup> Diastereomer ratios (*anti/syn*) were determined by <sup>1</sup>H NMR spectrum of the crude product mixture. <sup>c</sup> Enantiomeric excess were determined by the chiral HPLC study of the *syn* isomer. <sup>d</sup> Days of reaction.

A plausible transition state has been depicted for the Michael reaction in brine media in Figure 1. The figure 1 shows how water and acid additive may stabilize the proposed transition state through hydrogen bonding. The isobutyl moiety in the catalyst structure may shield the upper face of the double bond of nitrostyrenes favouring downface attack that results the desired stereochemical outcome in the reaction.



**Figure 1.** Proposed transition state in presence of catalyst **1**.

## Conclusions

In summary, we have successfully synthesized a new carbamate organocatalysts **1** following a simple two step reaction protocol starting from commercially available reagents with good overall yield and utilized the catalyst **1** in the asymmetric Michael addition reaction in brine media. The organocatalyst **1** is the first proline-based carbamate organocatalyst which has been tested in asymmetric Michael addition reaction in an aqueous environment. Various substrates with different electronic nature furnished Michael products with moderate to good enantioselectivity. Some of the very strong acid additives were found to deactivate the carbamate organocatalyst **1** in brine affording poor reaction yield. However, aromatic acid additives, especially 4-nitrobenzoic acid positively impacted Michael reactions in presence of the organocatalyst **1**. The cheap starting materials and easy synthesis of the organocatalyst **1** may influence widening of its applications to other C-C bond-forming reactions in aqueous media.

## Experimental Section

**General.** All reagents and starting materials were obtained from commercial sources and used as received. Routine monitoring of reaction was performed by TLC, using precoated silica gel TLC plates obtained by E-Merck. All the column chromatographic separations were done by using silica gel (60-120 mesh). Petroleum ether used was of boiling range 60-80 °C. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on 400 MHz Bruker spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal standard. Infrared (IR) spectroscopy was recorded on a FT-IR spectrometer (Shimadzu). Analytical high performance liquid chromatography (HPLC) was carried out on Agilent instrument using Chiralpak AD-H (4.6mm×250mm) column at 25 °C temperature, optical rotations were measured on a B+S ADP-410 digital polarimeter at λ=589 nm.

### General experimental procedure

**Procedure for preparation of compound 5.** Isobutyl chloroformate **4** (0.13 ml, 1 mmol) was added to compound **3** (200 mg, 1 mmol) in toluene (2 ml) at room temperature. Triethyl amine (0.14 ml, 1 mmol) in chloroform (2 ml) was added to the reaction mixture. The flask was then sealed with CaCl<sub>2</sub> guard tube and left stirring for 16 hours at room temperature. Organic layer was then evaporated under vacuum and the product

was purified by column chromatography. A colourless semi-solid **5** was obtained. Yield= 259 mg (80%).  $[\alpha]_D^{20} = -30$  (c 1.0,  $\text{CHCl}_3$ ); IR (film,  $\text{cm}^{-1}$ ): 3346, 2962, 2876, 1721, 1661, 1528;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.904 (6H, d,  $J=6.4$  Hz), 1.455 (9H, s), 1.713-1.976 (5H, m), 3.221-3.436 (4H, m), 3.799-3.930 (3H, m), 5.873 (1H, s);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) 19.17, 23.23, 23.99, 28.14, 28.57, 29.31, 44.81, 44.07, 44.09, 56.98, 71.07, 79.87, 156, 157.42; HRMS ( $m/z$ ): calcd for  $\text{C}_{15}\text{H}_{28}\text{N}_2\text{O}_4$  [ $\text{M}+\text{Na}$ ]: 323.1947; found: 323.1952.

**Procedure for preparation of compound 1.** The BOC protected colourless semi-solid **5** (323 mg, 1 mmol) was dissolved in a mixture of TFA (1 ml) and DCM (4 ml) and stirred for two hours at room temperature. Then the mixture was basified with concentrated ammonia solution. The organic layer was separated and the aqueous phase was extracted two times by dichloromethane. The combined organic layer was then dried over sodium sulphate and evaporated under vacuum to give a yellowish semi-solid **1**. Yield= 191 mg (95%).  $[\alpha]_D^{20} = -20$  (c 1.0,  $\text{CHCl}_3$ ); IR (film,  $\text{cm}^{-1}$ ): 3400, 2962, 2875, 2375, 1717, 1571;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.91 (6H, d,  $J=6.8$  Hz), 1.44-1.91 (6H, m), 2.98-3.31 (4H, m), 3.81 (3H, m), 5.50 (1H, s);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) 19.16, 22.81, 25.68, 28.13, 29.81, 44.77, 58.45, 71.19, 157.38; TOF MS  $\text{ES}^+$  ( $m/z$ ): calcd for  $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_2$  [ $\text{M}+$ ]: 201.1500; found: 201.1300.

**General Procedure for asymmetric Michael addition reaction.** To a stirred solution of catalyst **1** in brine, additive was added followed by ketone at room temperature. After 15 minutes of stirring, nitrostyrene was added and the reaction mixture was stirred vigorously at room temperature for 3-6 days and monitored by TLC. The Michael product was then purified by column chromatography using hexane/ethylacetate.

**(S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (6).** NMR data matched with the previously reported one.<sup>59</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (90:10), Flow rate = 0.5 ml/min;  $\lambda = 254$  nm;  $t_R(\text{minor}) = 22.5$  min,  $t_R(\text{major}) = 27.7$  min.

**(S)-2-((R)-1-(3-Chlorophenyl)-2-nitroethyl)cyclohexanone (7).** NMR data matched with the previously reported one.<sup>60</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (90:10), Flow rate = 0.5 ml/min;  $\lambda = 254$  nm;  $t_R(\text{minor}) = 22.597$  min,  $t_R(\text{major}) = 24.454$  min.

**(S)-2-((R)-2-Nitro-1-(2-nitrophenyl)ethyl)cyclohexanone (8).** NMR data matched with the previously reported one.<sup>59</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (85:15), Flow rate = 0.5 ml/min;  $\lambda = 254$  nm;  $t_R(\text{minor}) = 16.863$  min,  $t_R(\text{major}) = 27.665$  min.

**(S)-2-((R)-2-Nitro-1-*p*-tolylethyl)cyclohexanone (9).** NMR data matched with the previously reported one.<sup>61</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (96:4), Flow rate = 0.5 ml/min;  $\lambda = 254$  nm;  $t_R(\text{minor}) = 30.049$  min,  $t_R(\text{major}) = 39.336$  min.

**(S)-2-((R)-1-(3-Fluorophenyl)-2-nitroethyl)cyclohexanone (10).** NMR data matched with the previously reported one.<sup>59</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (90:10), Flow rate = 0.5 ml/min;  $\lambda = 254$  nm;  $t_R(\text{minor}) = 22.884$  min,  $t_R(\text{major}) = 25.720$  min.

**(S)-2-((R)-1-(2-Fluorophenyl)-2-nitroethyl)cyclohexanone (11).** NMR data matched with the previously reported one.<sup>62</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (90:10), Flow rate = 0.5 ml/min;  $\lambda = 254$  nm;  $t_R(\text{minor}) = 20.263$  min,  $t_R(\text{major}) = 23.941$  min.

**(S)-2-((R)-1-(2-Chlorophenyl)-2-nitroethyl)cyclohexanone (12).** NMR data matched with the previously reported one.<sup>59</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (95:5), Flow rate = 0.5 ml/min;  $\lambda = 254$  nm;  $t_R(\text{minor}) = 30.121$  min,  $t_R(\text{major}) = 52.219$  min.

**(S)-2-((R)-2-Nitro-1-(4-(trifluoromethyl)phenyl)ethyl)cyclohexanone (13).** NMR data matched with the previously reported one.<sup>61</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (90:10), Flow rate = 0.5 ml/min;  $\lambda = 254$  nm;  $t_R(\text{minor}) = 22.326$  min,  $t_R(\text{major}) = 43.176$  min.



**(S)-2-((R)-1-(4-Fluorophenyl)-2-nitroethyl)cyclohexanone (14).** NMR data matched with the previously reported one.<sup>59</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (90:10), Flow rate = 0.5 ml/min;  $\lambda$  = 254 nm;  $t_R$ (minor) = 27.298 min,  $t_R$ (major) = 36.514 min.

**(S)-2-((R)-2-Nitro-1-(3-nitrophenyl)ethyl)cyclohexanone (15).** NMR data matched with the previously reported one.<sup>63</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (90:10), Flow rate = 1 ml/min;  $\lambda$  = 254 nm;  $t_R$ (minor) = 21.653 min,  $t_R$ (major) = 26.482 min.

**(S)-2-((R)-2-Nitro-1-phenylethyl)cyclopentanone (16).** NMR data matched with the previously reported one.<sup>59</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (95:5), Flow rate = 1 ml/min;  $\lambda$  = 254 nm;  $t_R$ (minor) = 16.882 min,  $t_R$ (major) = 23.388 min.

**(R)-5-Nitro-4-phenylpentan-2-one (17)**

NMR data matched with the previously reported one.<sup>59</sup> The ee value was determined by the AD-H chiral column. Mobile phase = *n*-Hexane : IPA (90:10), Flow rate = 0.4 ml/min;  $\lambda$  = 254 nm;  $t_R$ (minor) = 27.625 min,  $t_R$ (major) = 29.624 min.

## Acknowledgements

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## Supplementary Material

Copies of <sup>1</sup>H, <sup>13</sup>C NMR spectra, HRMS for compounds **1** and **5**. Chiral HPLC chromatograms of all the compounds **6-17**.

## References

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