

# Asymmetric Michael addition of glycine imines via quaternary ammonium ion catalysis

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**Abstract**—The asymmetric Michael addition of glycine imine esters to simple  $\alpha,\beta$ -unsaturated ketones via PTC is investigated. It is found that by employing 1 mol % of a chiral quaternary ammonium salt, derived from  $\alpha$ -methylnaphthylamine in conjunction with  $\text{Cs}_2\text{CO}_3$ , high enantioselectivities can be obtained in conjugate additions involving simple alkylvinylketones. © 2005 Elsevier Ltd. All rights reserved.

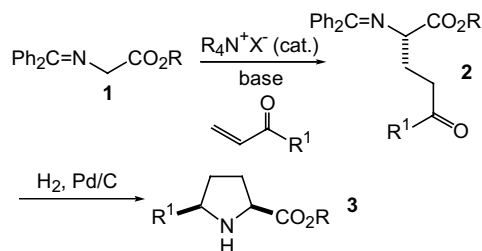
The quaternary ammonium salt catalysed Michael addition of benzophenone glycine imines **1** to  $\alpha,\beta$ -unsaturated ketones offers rapid access to a range of useful amino acid derivatives such as **2** and **3** (Scheme 1).<sup>2</sup> However, to date there have been relatively few highly enantioselective versions of this process reported.<sup>3–7</sup> Given the wide range of chiral quaternary ammonium salts that have now been found to promote the corresponding alkylation reactions between imines **1** and alkyl halides,<sup>8</sup> we considered that it should be possible to expand the scope of this chemistry and in this letter we outline some of our preliminary studies in this area.

We recently demonstrated that the  $\alpha$ -methylnaphthylamine derived quaternary ammonium salt **4**<sup>8a</sup> is a highly effective catalyst for the alkylation of imine **5** (Fig. 1).<sup>9</sup> Unfortunately initial attempts to employ this catalyst

in the asymmetric conjugate addition of imine **5** to methyl vinyl ketone (MVK) gave disappointing results.

For example, alkylation of imine **5** with benzyl bromide using 1 mol % of **4** in an aqueous KOH/toluene mixture gave the (*S*)-enantiomer of imine **6** in near quantitative yield and with high enantioselectivity. The corresponding reaction of **5** with MVK also gave the desired product **7**<sup>10</sup> in near quantitative yield, but in this case the enantioselectivity was substantially lower (Scheme 2).

In order to gain more insight into the factors influencing the enantioselectivity of this latter process we performed the reaction under a wide range of conditions. Some typical results from this study are shown in Table 1. As can be seen, successful reaction could be achieved using 1 mol % **4** under both liquid–liquid (entries 1–5) and solid–liquid (entries 6–16) phase-transfer catalysis (PTC) conditions. The nature of the base had a significant



Scheme 1.

**Keywords:** Phase-transfer catalysis; Michael addition; Amino acids.

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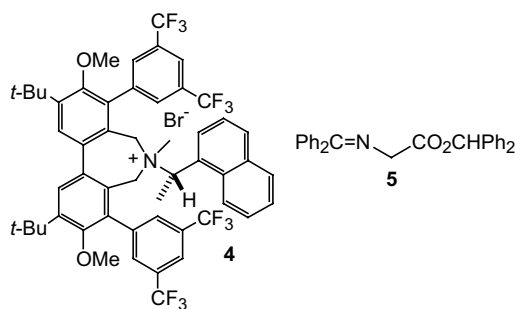
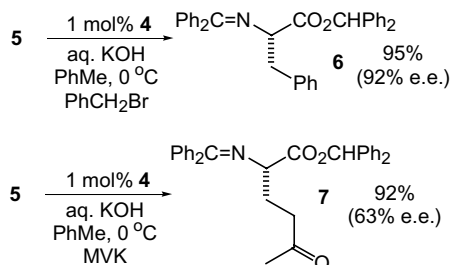


Figure 1.



Scheme 2.

Table 1.

$5 \xrightarrow[\text{MVK, 2-18 h, base (10 eq)}]{1 \text{ mol\% } 4} 7$				
Entry	Solvent	Base	Temperature (°C)	ee <sup>a</sup> (%)
1	PhMe	9 M aq KOH	0	63
2	PhMe	9 M aq KOH	−30	64
3	CH <sub>2</sub> Cl <sub>2</sub>	9 M aq KOH	−30	6
4	THF	9 M aq KOH	−30	11
5	Et <sub>2</sub> O	9 M aq KOH	−30	76
6	PhMe	Cs <sub>2</sub> CO <sub>3</sub>	−30	77
7	CH <sub>2</sub> Cl <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	−30	0
8	Et <sub>2</sub> O	Cs <sub>2</sub> CO <sub>3</sub>	−30	90
9	CHCl <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	−30	0
10	EtOAc	Cs <sub>2</sub> CO <sub>3</sub>	−30	59
11	CH <sub>3</sub> CN	Cs <sub>2</sub> CO <sub>3</sub>	−30	0
12	PhMe	RbOH·H <sub>2</sub> O	0	56
13	PhMe	RbOH·H <sub>2</sub> O	−30	64
14	THF	RbOH·H <sub>2</sub> O	−30	15
15	Et <sub>2</sub> O	RbOH·H <sub>2</sub> O	−30	79
16	<i>t</i> -BuOMe	RbOH·H <sub>2</sub> O	−30	60

<sup>a</sup> Determined via HPLC analysis of the crude product **7**.<sup>13</sup> In all cases reactions had proceeded to  $\geq 95\%$  conversion.

influence on the level of enantioselectivity obtained (e.g., compare entries 2, 6 and 13, or 5, 8 and 15), but by far the most significant factor was the nature of the organic solvent employed. Simply by switching from dichloromethane to diethyl ether resulted in an increase in the enantiomeric excess of the product by 70–90% ee (compare entries 3 and 5 or 7 and 8). This is in sharp contrast to the corresponding alkylation reactions where toluene, diethyl ether and dichloromethane all gave similar levels of enantioselectivity, and suggests that the transition state arrangements leading to an enantioselective conjugate addition are far less robust than those leading to alkylation.<sup>11</sup> This in turn indicates that asymmetric Michael additions of this type are likely to benefit from optimisation of all reaction parameters.

Significantly, this study identified conditions (Cs<sub>2</sub>CO<sub>3</sub>/Et<sub>2</sub>O) that generated the product **7** with high enantiomeric excess. A variety of other bases (K<sub>2</sub>CO<sub>3</sub>, NaOH, CsOH·H<sub>2</sub>O,<sup>3</sup> BEMP<sup>4</sup>) that have been previously employed in PTC reactions<sup>12</sup> were also investigated, but all led to reduced levels of enantioselectivity.

Inspection of Table 1 suggests that there is no simple correlation between solvent property<sup>14</sup> and enantioselectivity.

Table 2.

$5 \xrightarrow[\text{Cs}_2\text{CO}_3 (10 \text{ eq.}), \text{MVK, 2-18 h}]{1 \text{ mol\% } 4} 7$			
Entry	Solvent	Temperature (°C)	ee <sup>a</sup> (%)
1	Et <sub>2</sub> O	0	91
2	Et <sub>2</sub> O	−30	90
3	Et <sub>2</sub> O (anhydrous)	−30	90
4	<i>i</i> -Pr <sub>2</sub> O	0	92
5	<i>i</i> -Pr <sub>2</sub> O	−30	94
6	<i>t</i> -BuOMe	0	86
7	<i>t</i> -BuOMe	−30	82
8	Diethoxymethane	−30	90
9	2,2-Dimethoxypropane	−30	89
10	THF	−30	49
11	1,2-Dimethoxyethane	−30	28

<sup>a</sup> Determined via HPLC analysis of the crude product **7**.<sup>13</sup> In all cases reactions had proceeded to  $\geq 95\%$  conversion.

tivity of the reaction, however for each of the bases investigated, diethyl ether gave the highest selectivity. Because of this, we selected the best base (Cs<sub>2</sub>CO<sub>3</sub>) and examined a range of alternative ether solvents (Table 2).

Table 2 shows that a number of these solvents gave similar results (entries 1–5 and 8–9), whereas substantially reduced selectivities were obtained with THF and 1,2-dimethoxyethane. This would appear to indicate that better coordinating ethers lead to reduced selectivity and may indicate increased involvement of either water or caesium ions in the conjugate addition process when these solvents are used.<sup>15</sup> Although this may account for the lower selectivity with some other solvents, it still does not adequately account for all the solvent effects outlined in Table 1.

Overall diethyl ether and di-isopropyl ether appeared to be the solvents of choice.<sup>16</sup> Using these solvents we found that it was possible to reduce the amount of base to 50 mol % without significantly altering the enantiomeric excess or rate of reaction.<sup>17</sup>

In order to probe the generality of this process we employed these optimised conditions to a series of related transformations (Table 3). Reactions involving addition to  $\alpha,\beta$ -unsaturated ketones (entries 1–5) generally proceeded in good yields, however, the structure of both enone and imine affected the level of enantioselectivity. Reactions involving acrylate and acrylamides (entries 6–7) were unsuccessful giving low levels of conversion. This observation is interesting as acrylate esters readily participate in asymmetric PTC Michael additions with glycine imines<sup>4–7</sup> and suggests that the conditions reported here may show useful chemoselectivity.

Minor changes to the enone structure are tolerated, (compare entries 1, 4 and 5), whereas variation of the imine ester influences the level of enantioselectivity (compare entries 1–3) with benzhydryl and benzyl esters giving the best results. This latter finding again contrasts

Table 3.

Entry	R	R <sup>1</sup>	Time (h)	Yield (%)	ee <sup>a</sup> (%)
1	Ph <sub>2</sub> CH	Me	2	84	94
2	PhCH <sub>2</sub>	Me	2	94	91
3	<i>t</i> -Bu	Me	18	45	60
4	Ph <sub>2</sub> CH	Et <sup>b</sup>	18	74	92
5	Ph <sub>2</sub> CH	<i>n</i> -C <sub>5</sub> H <sub>12</sub>	18	60	94
6	Ph <sub>2</sub> CH	O- <i>t</i> -Bu	18	<10	—
7	Ph <sub>2</sub> CH	NMe <sub>2</sub>	18	<10	—

See Ref. 17.

<sup>a</sup> Determined via HPLC analysis of the crude products.<sup>13</sup><sup>b</sup> 6 equiv of enone used (added as 3 × 2 equiv over 4 h).

with observations on the corresponding reactions of glycine imines with alkyl halides using catalyst **4** where benzhydryl and *tert*-butyl esters give very similar levels of enantioselectivity.<sup>9</sup>

In conclusion, this study has demonstrated that the enantioselectivity obtained in the asymmetric Michael addition of glycine imine esters to  $\alpha,\beta$ -unsaturated ketones using quaternary ammonium salt **4** is strongly influenced by the reaction conditions employed. By careful optimisation of the reaction components, high levels of enantioselectivity can be obtained, providing efficient access to functionalised amino acid derivatives.

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- HPLC conditions for compounds reported in Table 3 are as follows: entry 1, Chiralpak AD, 95:5 (hexane–2-propanol), 0.2 mL/min, *t*<sub>R</sub> 14.0 and 16.9 min; entry 2, Chiralpak AD, 99:1 (hexane–2-propanol), 0.2 mL/min, *t*<sub>R</sub> 22.9 and 25.5 min; entry 3, Chiralcel OD-H, 97.5:2.5 (hexane–2-propanol), 0.5 mL/min, *t*<sub>R</sub> 13.7 and 16.3 min; entry 4, Chiralpak AD, 95:5 (hexane–2-propanol), 0.1 mL/min, *t*<sub>R</sub> 18.0 and 21.0 min; entry 5, Chiralcel OD-H, 99:1 (hexane–2-propanol), 0.75 mL/min, *t*<sub>R</sub> 20.0 and 23.0 min. For entries 1–4 the major enantiomer eluted second, for entry 5 the major enantiomer eluted first.
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- Representative procedure: A solution of imine **5** (0.12 mmol) and catalyst **4** (0.0012 mmol, 1 mol %) in diisopropyl ether (4 mL) was degassed with argon and then cooled to 0 °C. MVK (2.0 equiv, 0.24 mmol) was then added followed by anhydrous Cs<sub>2</sub>CO<sub>3</sub> (0.06 mmol), and the mixture stirred at 1500 rpm. After complete consumption of starting glycine imine (ca. 2 h) the reaction mixture was warmed to room temperature, filtered and concentrated under reduced pressure. If required, the crude product could be purified by flash chromatography on silica gel (petroleum ether–ethyl acetate–triethylamine 94:5:1) to give **7** as a colourless oil. *v*<sub>max</sub> (CHCl<sub>3</sub>): 3060, 3029, 2931, 1739 (s), 1715 (s), 1622 cm<sup>−1</sup>; <sup>1</sup>H NMR

(400 MHz, CDCl<sub>3</sub>):  $\delta$  7.67–7.63 (2H, m, ArH), 7.43–7.26 (16H, m, ArH), 7.10–7.06 (2H, m, ArH), 6.89 (1H, s, CHPh<sub>2</sub>), 4.19 (1H, app. t, *J* 6.0 Hz, NCH), 2.58–2.50 (1H, m), 2.44–2.36 (1H, m), 2.23–2.18 (2H, m), 2.05 (3H, s, Me); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  208.1,

171.1, 170.8, 140.0, 139.3, 136.1, 130.6, 128.9, 128.7, 128.6, 128.5, 128.1, 128.1, 127.9, 127.7, 127.4, 127.2, 127.0, 126.6, 77.2, 64.2, 39.6, 29.9, 27.6; *m/z* (CI) found [M+H]<sup>+</sup> 476.2241, C<sub>32</sub>H<sub>30</sub>NO<sub>3</sub> [M+H]<sup>+</sup> requires 476.2226.