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**CATALYTIC ASYMMETRIC MICHAEL REACTION UNDER  
PHASE-TRANSFER CATALYSIS: CONSTRUCTION OF CHIRAL  
TETRASUBSTITUTED CARBON AND ITS APPLICATION TO THE  
SYNTHESIS OF A CHIRAL PYRROLIDONE**

**Shigeru Arai,\* Fumie Takahashi, Riichiro Tsuji, and Atsushi Nishida\***

*Graduate School of Pharmaceutical Sciences, Chiba University*

1-33 Yayoi-cho, Inage-ku, Chiba, Japan 263-8522

arai@p.chiba-u.ac.jp

**Abstract** – A catalytic asymmetric Michael reaction using Schiff bases promoted by  $D_2$ -symmetrical ammonium salts as phase-transfer catalysts is described. The reaction of glycine Schiff base (**1a**) gave the Michael adduct with up to 91% ee and tetrasubstituted carbons was also constructed using alanine Schiff base (**3a**) with up to 63% ee.

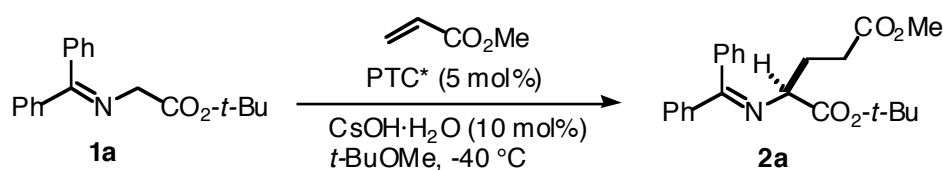
## INTRODUCTION

Phase-transfer catalysis (PTC), which is one of the most practical synthetic methodologies due to its mild conditions, operational simplicity and minimal environmental impact, has been a major topic in synthetic organic chemistry.<sup>1</sup> Since the early reports of asymmetric alkylation using chiral quaternary ammonium salts by Dolling<sup>2</sup> and O'Donnel,<sup>3</sup> many successful results have been reported regarding asymmetric PTC chemistry using alkaloid<sup>4,5</sup> and non-alkaloid<sup>6</sup> derivatives over the past decade. We have previously introduced new  $D_2$ -symmetrical ammonium salts,<sup>7,8</sup> which are easily prepared from tartrate,<sup>9</sup> to the catalytic asymmetric Michael reaction. In this communication, we describe a modification of the catalyst structure, its application to the construction of chiral quaternary carbons using  $\alpha$ -alkyl Schiff bases, a facile transformation to chiral nitrogen heterocycles and highly stereoselective [3+2] cycloaddition.

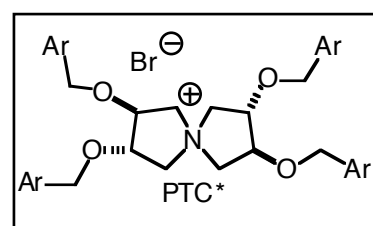
## RESULTS AND DISCUSSION

We previously reported that  $D_2$ -symmetrical quaternary ammonium salts,<sup>8</sup> which promotes the enantioselective Michael reaction to give an optically active glutamate derivative<sup>10-15</sup> with moderate ee (entry 1 vs. 2).<sup>7</sup> Based on the results with a 4- $\text{CF}_3$  group with higher catalytic activity, we performed a further catalyst survey using PTC **C-F** at  $-40\text{ }^\circ\text{C}$  (entries 2-7). For example, the reaction of **1a** with a 2- $\text{CF}_3$  derivative (PTC **D**, 5 mol%) gave **2a** with 74% ee, while lower catalytic activity or enantioselectivity was observed when PTC **B** or **C** was used (entry 5 vs. 3 and 4). Disubstituted PTCs such as 2,4- and 3,5- $(\text{CF}_3)_2$  resulted in 95% yield with 72% ee and 92% yield with 38% ee, respectively (entries 6 and 7). These results suggest that the position of the  $\text{CF}_3$  groups strongly affects the enantioselectivity. Finally, the reaction using catalyst (**D**) proceeded even at  $-60\text{ }^\circ\text{C}$  to give **2a** in 89% yield with 91% ee within 12 h (entry 8). This result indicates PTC **D** shows the maximum activity among the results reported for the catalytic Michael reaction of **1a**. These results are summarized in Table 1.

Table 1

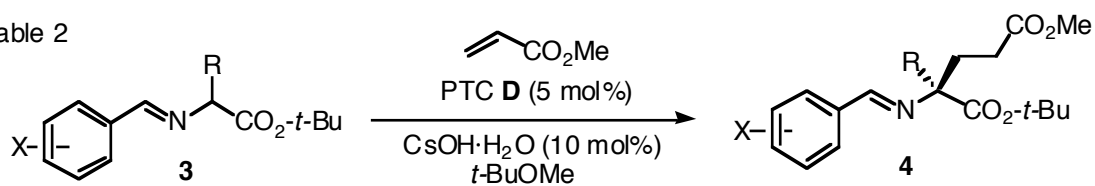


entry	PTC*	mol%	conditions	yield of <b>2a</b> (%)	ee of <b>2a</b> (%)
1	<b>A</b> : Ar = Ph	10	$-60\text{ }^\circ\text{C}$ , 70 h	86	73
2	<b>B</b> : Ar = 4- $(\text{CF}_3)$ $\text{C}_6\text{H}_4$	10	$-60\text{ }^\circ\text{C}$ , 26 h	73	77
3	<b>B</b> : Ar = 4- $(\text{CF}_3)$ $\text{C}_6\text{H}_4$	5	$-40\text{ }^\circ\text{C}$ , 24 h	45	61
4	<b>C</b> : Ar = 3- $(\text{CF}_3)$ $\text{C}_6\text{H}_4$	5	$-40\text{ }^\circ\text{C}$ , 24 h	99	52
5	<b>D</b> : Ar = 2- $(\text{CF}_3)$ $\text{C}_6\text{H}_4$	5	$-40\text{ }^\circ\text{C}$ , 24 h	95	74
6	<b>E</b> : Ar = 2,4- $(\text{CF}_3)_2$ $\text{C}_6\text{H}_3$	5	$-40\text{ }^\circ\text{C}$ , 24 h	95	72
7	<b>F</b> : Ar = 3,5- $(\text{CF}_3)_2$ $\text{C}_6\text{H}_3$	5	$-40\text{ }^\circ\text{C}$ , 35 h	92	38
8	<b>D</b> : Ar = 2- $(\text{CF}_3)$ $\text{C}_6\text{H}_4$	5	$-60\text{ }^\circ\text{C}$ , 12 h	89	91



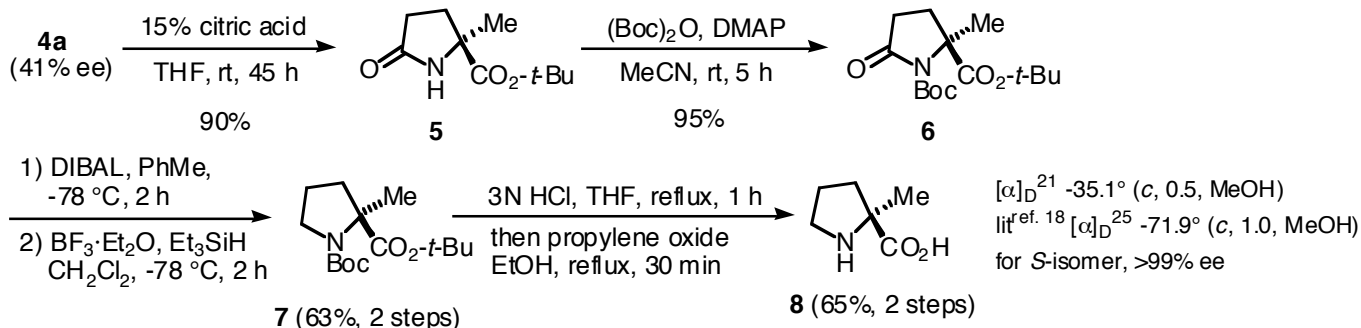
After successfully completing the highly enantioselective Michael reaction, we next investigated an alanine Schiff base (**3**) with the construction of tetrasubstituted chiral carbons. There have been no previous reports on producing quaternary glutamates *via* a catalytic asymmetric Michael reaction. We chose aldimines (**3**)<sup>16</sup> and surveyed PTCs under the optimized conditions (entries 1-4). When PTC **D** was used, **4a** was obtained in 88% yield with 45% ee.<sup>17</sup> Although other ethereal solvent effects were considered, no better results were obtained ( $\text{Et}_2\text{O}$ : 44%, 36% ee;  $n\text{-Bu}_2\text{O}$ : 83%, 37% ee;  $i\text{-Pr}_2\text{O}$ : 78%, 43% ee).

Table 2



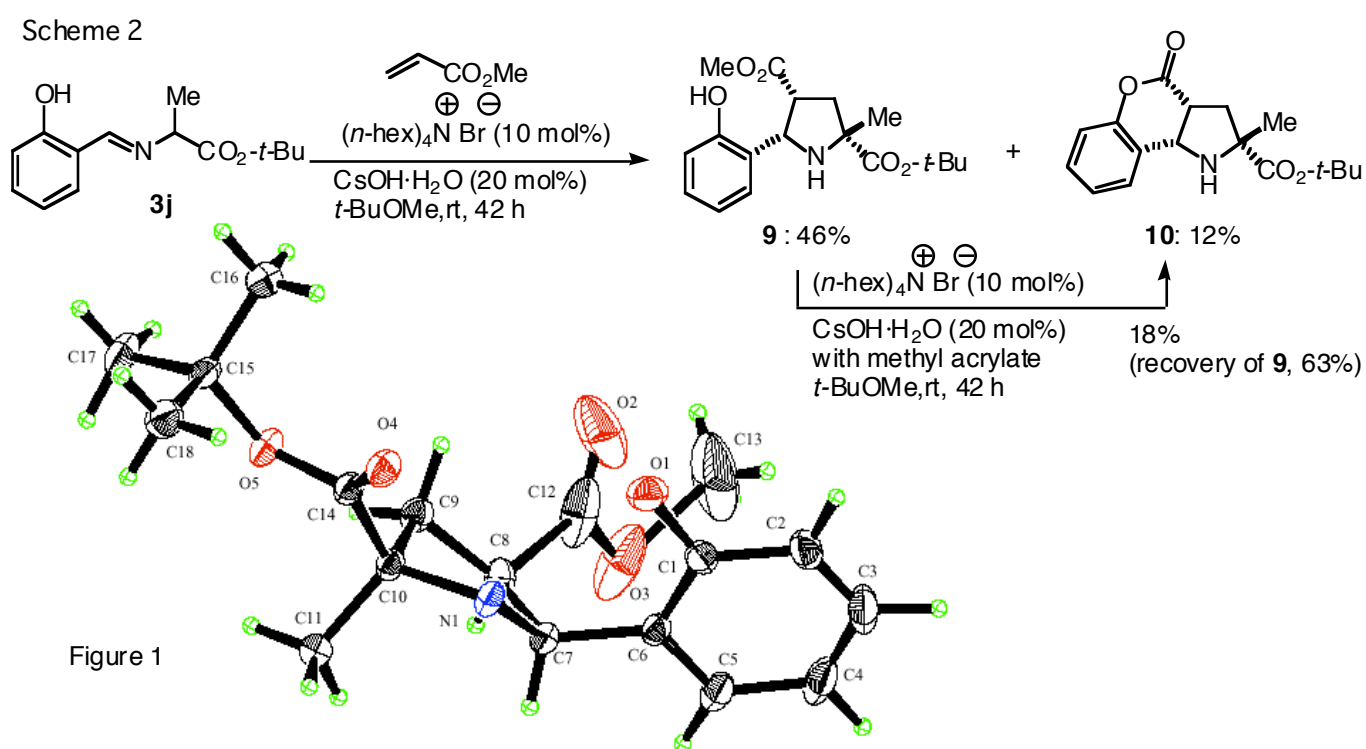
entry	PTC	Schiff base (3)	conditions	yield of 4 (%)	ee of 4 (%)
1	<b>A</b>	<b>3a</b> : X = 4-Cl, R = Me	-40 °C, 24 h	<b>4a</b> : 71	22
2	<b>B</b>	<b>3a</b> : X = 4-Cl, R = Me	-40 °C, 24 h	<b>4a</b> : 57	30
3	<b>C</b>	<b>3a</b> : X = 4-Cl, R = Me	-40 °C, 24 h	<b>4a</b> : 65	32
4	<b>D</b>	<b>3a</b> : X = 4-Cl, R = Me	-40 °C, 24 h	<b>4a</b> : 88	45
5	<b>D</b>	<b>3b</b> : X = H, R = Me	-40 °C, 24 h	<b>4b</b> : 66	54
6	<b>D</b>	<b>3c</b> : X = 4-MeO, R = Me	-40 °C, 24 h	<b>4c</b> : trace	-
7	<b>D</b>	<b>3d</b> : X = 4-CF <sub>3</sub> , R = Me	-40 °C, 24 h	<b>4d</b> : 65	25
8	<b>D</b>	<b>3e</b> : X = 3-Cl, R = Me	-40 °C, 24 h	<b>4e</b> : 56	34
9	<b>D</b>	<b>3f</b> : X = 2-Cl, R = Me	-40 °C, 24 h	<b>4f</b> : 5	28
10	<b>D</b>	<b>3b</b> : X = 4-H, R = Me	-60 °C, 60 h	<b>4b</b> : 51	45
11	<b>D</b>	<b>3a</b> : X = 4-Cl, R = Me	-60 °C, 61 h	<b>4a</b> : 45	63
12	<b>D</b>	<b>3g</b> : X = 4-Cl, R = Bn	-40 °C, 40 h	<b>4g</b> : 72	9
13	<b>D</b>	<b>3h</b> : X = 4-Cl, R = Ph	-40 °C, 24 h	<b>4h</b> : 84	0
14	<b>D</b>	<b>3i</b> : X = 4-Cl, R = <i>i</i> -Pr	-40 °C, 40 h	<b>4i</b> : 0	-

Scheme 1



While the reaction of **3b** gave **4b** in 66% yield, electron-donating group such as 4-MeO reduced the reactivity due to the lower acidity of the  $\alpha$ -proton of **3c** (entries 5 and 6). On the other hand, a 4-CF<sub>3</sub> group, which is expected to enhance proton abstraction, gave **4d** in 65% yield, although its ee was lower (entry 7). **3e** and **3f** were less effective than **3a** with regard to both chemical yield and ee (entries 8 and 9). The reaction of **3a** at -60 °C gave **4a** with 63% ee (entry 11). We observed the electron density on the aromatic rings in both the catalysts and substrates is important in achieving a higher catalytic activity and ee. Unfortunately, this asymmetric reaction is not suitable for other alkyl groups (entries 12-14). For example, while  $\alpha$ -benzyl and phenyl substrates (**3g** and **3h**) gave respective yields of 72 and 84% of **4**, no asymmetric induction was observed. In the case of *i*-Pr (**1i**), no reaction occurred. These results are summarized in Table 2.

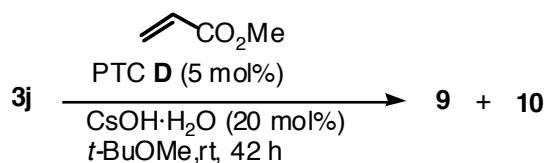
Absolute configuration of **4a** was determined as follows (Scheme 1): the acid-treatment promoted deprotection and subsequent cyclization to give **5** in 90% yield. The protection of amide (**5**) by (Boc)<sub>2</sub>O gave **6** in 95% yield, and subsequent reduction and hydrosilylation gave **7** in 63% yield. Conversion to  $\alpha$ -methylproline (**8**) was accomplished by aq. HCl in the presence of propylene oxide (65% yield in 2 steps). According to the reported value for the optical rotation, the absolute configuration of **8** was determined to be *S*.<sup>18</sup>



During our study of the asymmetric Michael reaction of **3**, we observed [3+2] cycloaddition between **3j** and methyl acrylate to give **9** and **10** (Scheme 2).<sup>19,20</sup> A hydroxyl group at the ortho position on the benzene ring promoted cycloaddition exclusively to give pyrrolidine **9** and lactone **10** in respective yields of 46 and 12%. Both 3- and 4-hydroxy derivatives also gave the desired cycloadducts, but their reactions were much slower (3-OH: 47% at 120 h, 4-OH: <30% at 120 h).<sup>21</sup> The relative configuration of **9** was determined by X-ray analysis to be all-*cis* (Figure 1) and basic treatment of **9** gave **10** in 18% yield, which suggests that the stereochemistry of **10** is similar to that of **9**. This reaction seems to include the initial abstraction of a phenolic proton, and the resulting cesium phenoxide would activate an imine carbon to promote the cyclization. We next turned to asymmetric synthesis using **3j** with PTC **D** (5 mol%), as shown in Table 3. The solvent effect indicates that *t*-BuOMe is better than non-polar

solvents (entries 1-3) and ether is a solvent of choice to give 25% ee (entry 4).<sup>22</sup> The enantioselectivity of **9** was determined by chiral HPLC analysis after *N,O*-bisbenzoylation and the absolute configuration was assigned to be similar to those in Michael adducts of **2a** and **4a**.

Table 3



entry	solvent	yield of <b>9</b> (%)	yield of <b>10</b> (%)	ee of <b>9</b> (%)
1	<i>t</i> -BuOMe	50	12	17
2	toluene	36	23	2
3	CH <sub>2</sub> Cl <sub>2</sub>	44	25	7
4	Et <sub>2</sub> O	43	13	25

Enantiomeric excess of **9** was determined by HPLC analysis (CHIRALCEL OD) after *N,O*-bisbenzoylation (BzCl, CH<sub>2</sub>Cl<sub>2</sub>, rt, 24 h, quant).

In conclusion, we succeeded in the asymmetric Michael reaction using a Schiff base catalyzed by *D*<sub>2</sub>-symmetrical PTCs. A large increase in the reaction rate using **1** was observed with up to 91% ee, and construction of a quaternary carbon was also achieved (with up to 63% ee). This method should provide chiral pyrrolidones and pyrrolidines, which are considered to be useful building blocks for biologically important compounds. We also noted the diastereospecific [3+2] cycloaddition directed by an ortho-hydroxyl group with up to 25% ee. Further studies on catalyst tuning with regard to catalytic activity and enantioselectivity are currently in progress.

## ACKNOWLEDGEMENTS

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17. Typical experimental procedure for a PTC-catalyzed asymmetric Michael reaction (synthesis of (*S*)-**4a**, Table 2, entry 4): To a solution of cesium hydroxide monohydrate (1.6 mg, 0.01 mmol), PTC **D** (4.5 mg, 0.005 mmol) and **3a** (26.7 mg, 0.1 mmol) in *t*-BuOMe (0.33 mL) was added methyl acrylate (45  $\mu$ L, 0.5 mmol) at  $-40$   $^{\circ}$ C. After being stirred for 24 h, the reaction was quenched with water and the resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL X 3). The organic layers were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ , and the solvents were removed under reduced pressure. Subsequent purification by flash column chromatography (hexane: $\text{Et}_2\text{O}$  = 2:1) gave **4a** as a colorless oil (31.1 mg, 88% yield, 45% ee). The enantiomeric excess was determined by HPLC analysis using a chiral column.  $[\alpha]_{\text{D}}^{23} -6.1^{\circ}$  (*c*, 0.3,  $\text{CHCl}_3$ , 50% ee);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 1.45 (s, 3H), 1.46 (s, 9H), 2.11 (ddd,  $J$  = 13.2, 10.4, 5.6 Hz, 1H), 2.31 (ddd,  $J$  = 14.0, 10.4, 5.6 Hz, 1H), 2.39-2.57 (m, 2H), 3.65 (s, 3H), 7.37 (d,  $J$  = 8.4 Hz, 2H), 7.68 (d,  $J$  = 8.4 Hz, 2H), 8.25 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 23.5, 27.9, 29.5, 35.0, 51.6, 67.6, 81.5, 128.7, 129.4, 134.9, 136.7, 158.4, 172.5, 174.0; IR (neat)  $\nu$ : 2922, 1737, 1644, 1118  $\text{cm}^{-1}$ ; LRMS (FAB)  $m/z$  354 ( $\text{M}^+\text{+H}$ ); HRMS (FAB) calcd for  $\text{C}_{18}\text{H}_{25}\text{NO}_4\text{Cl}$  354.1472, found 354.1500; HPLC: DAICEL CHIRALCEL OD, 254 nm, flow rate: 1.0 mL/min, hexane:*i*-PrOH = 99:1, retention time: 9.36 min (major, *S*-isomer) and 10.6 min (minor, *R*-isomer).

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21. Upon the addition of phenol (1 eq.) to the reaction of **3a** and **3b**, Michael adducts (**4a**) and (**4b**) were predominantly obtained under similar conditions (80 and 62%) with the corresponding cycloadducts in respective yields of 11 and 18%.
22. Synthesis of **9** (Table 3, entry 1): According to the procedure described in ref. 17, the reaction was performed using cesium hydroxide monohydrate (3.3 mg, 0.02 mmol), PTC **D** (4.5 mg, 0.005 mmol), **3j** (24.9 mg, 0.1 mmol), methyl acrylate (45  $\mu$ L, 0.5 mmol) and *t*-BuOMe (0.33 mL) for 24 h at  $-40$  °C to give **9** (16.7 mg, 50%) and **10** (3.5 mg, 12%), respectively. **9**; mp: 105-107 °C (Et<sub>2</sub>O);  $[\alpha]_D^{25} +11.5^\circ$  (*c*, 0.24, CHCl<sub>3</sub>, 17% ee); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.52 (s, 3H), 1.53 (s, 9H), 2.02 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.88 (dd, *J* = 13.6, 4.0 Hz, 1H), 3.30-3.35 (m, 1H), 3.33 (s, 3H), 4.78 (d, *J* = 7.6 Hz, 1H), 6.74 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.80 (dd, *J* = 16.0, 1.2 Hz, 1H), 6.94 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ : 26.5, 27.9, 39.0, 49.0, 51.6, 64.2, 65.3, 81.6, 117.2, 118.5, 121.1, 128.4, 129.0, 158.1, 172.3, 174.1; IR (neat)  $\nu$ : 3305, 2978, 1731, 1260, 1132, 752 cm<sup>-1</sup>; LRMS (FAB) *m/z* 336 (M<sup>+</sup>+H); HRMS (FAB) calcd for C<sub>18</sub>H<sub>26</sub>NO<sub>5</sub> 336.1811, found 336.1794; Anal. Calcd for C<sub>18</sub>H<sub>26</sub>NO<sub>5</sub>: C, 66.46; H, 7.51; N, 4.18, Found: C, 64.50; H, 7.47; N, 4.08.