HETEROCYCLES, Vol. 67, No. 2, 2006, pp. 495 - 501. © The Japan Institute of Heterocyclic Chemistry
Received, 25th July, 2005, Accepted, 18th November, 2005, Published online, 18th November, 2005. COM-05-S(T)41

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

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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.

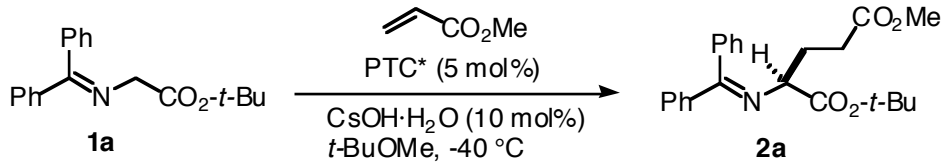
INTRODUCTION

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.[1] Since the early reports of asymmetric alkylation using chiral quaternary ammonium salts by Dolling[2] and O'Donnel,[3] many successful results have been reported regarding asymmetric PTC chemistry using alkaloid[4,5] and non-alkaloid[6] derivatives over the past decade. We have previously introduced new D_2-symmetrical ammonium salts,[7,8] which are easily prepared from tartrate,[9] 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 α-alkyl Schiff bases, a facile transformation to chiral nitrogen heterocycles and highly stereoselective [3+2] cycloaddition.

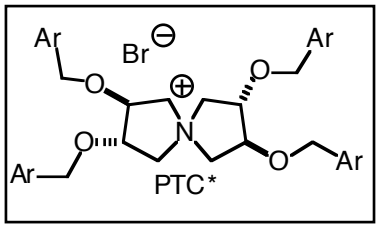
RESULTS AND DISCUSSION

We previously reported that D_2-symmetrical quaternary ammonium salts, [8] which promotes the enantioselective Michael reaction to give an optically active glutamate derivative[10-15] with moderate ee (entry 1 vs. 2).[7] Based on the results with a 4-CF_3 group with higher catalytic activity, we performed a further catalyst survey using PTC **C**-**F** at –40 °C (entries 2-7). For example, the reaction of **1a** with a 2-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-$(CF_3)_2$ resulted in 95% yield with 72% ee and 92% yield with 38% ee, respectively (entries 6 and 7). Theese results suggest that the position of the CF_3 groups strongly affects the enantioselectivity. Finally, the reaction using catalyst (**D**) proceeded even at –60 °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

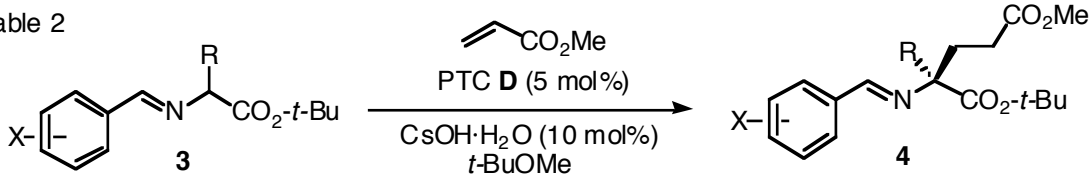


entry	PTC*	mol%	conditions	yield of **2a** (%)	ee of **2a** (%)
1	**A** : Ar = Ph	10	-60 °C, 70 h	86	73
2	**B** : Ar = 4-$(CF_3)C_6H_4$	10	-60 °C, 26 h	73	77
3	**B** : Ar = 4-$(CF_3)C_6H_4$	5	-40 °C, 24 h	45	61
4	**C** : Ar = 3-$(CF_3)C_6H_4$	5	-40 °C, 24 h	99	52
5	**D** : Ar = 2-$(CF_3)C_6H_4$	5	-40 °C, 24 h	95	74
6	**E** : Ar = 2,4-$(CF_3)_2C_6H_3$	5	-40 °C, 24 h	95	72
7	**F** : Ar = 3,5-$(CF_3)_2C_6H_3$	5	-40 °C, 35 h	92	38
8	**D** : Ar = 2-$(CF_3)C_6H_4$	5	-60 °C, 12 h	89	91



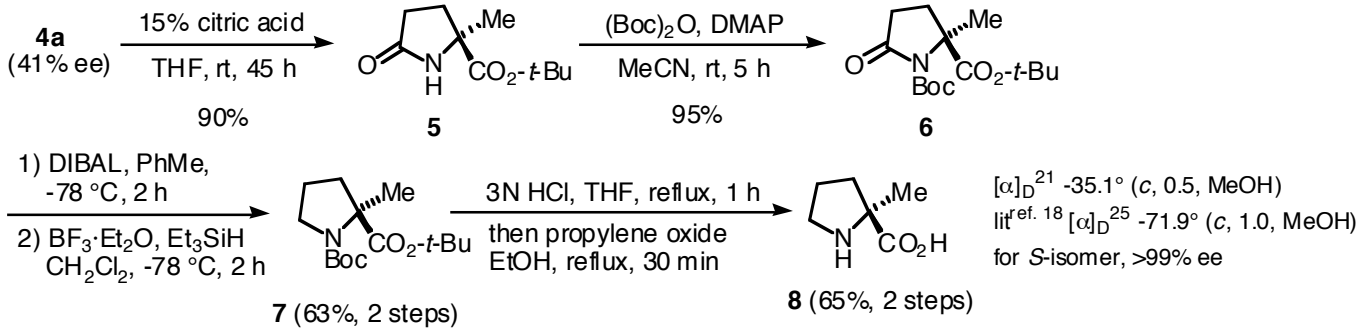
After successfully completing the highly enantioselective Michael reaction, we next investigated an alanine Schiff base (**3**) with the construction of tetrasubstituted chiral carbons. There have been no previous reports on producing quaternary glutamates *via* a catalytic asymmetric Michael reaction. We chose aldimines (**3**)[16] and surveyed PTCs under the optimized conditions (entries 1-4). When PTC **D** was used, **4a** was obtained in 88% yield with 45% ee.[17] Although other ethereal solvent effects were considered, no better results were obtained (Et_2O: 44%, 36% ee; *n*-Bu_2O: 83%, 37% ee; *i*-Pr_2O: 78%, 43% ee).

Table 2



entry	PTC	Schiff base (**3**)	conditions	yield of **4** (%)	ee of **4** (%)
1	**A**	**3a** : X = 4-Cl, R = Me	-40 °C, 24 h	**4a** : 71	22
2	**B**	**3a** : X = 4-Cl, R = Me	-40 °C, 24 h	**4a** : 57	30
3	**C**	**3a** : X = 4-Cl, R = Me	-40 °C, 24 h	**4a** : 65	32
4	**D**	**3a** : X = 4-Cl, R = Me	-40 °C, 24 h	**4a** : 88	45
5	**D**	**3b** : X = H, R = Me	-40 °C, 24 h	**4b** : 66	54
6	**D**	**3c** : X = 4-MeO, R = Me	-40 °C, 24 h	**4c** : trace	-
7	**D**	**3d** : X = 4-CF_3, R = Me	-40 °C, 24 h	**4d** : 65	25
8	**D**	**3e** : X = 3-Cl, R = Me	-40 °C, 24 h	**4e** : 56	34
9	**D**	**3f** : X = 2-Cl, R = Me	-40 °C, 24 h	**4f** : 5	28
10	**D**	**3b** : X = 4-H, R = Me	-60 °C, 60 h	**4b** : 51	45
11	**D**	**3a** : X = 4-Cl, R = Me	-60 °C, 61 h	**4a** : 45	63
12	**D**	**3g** : X = 4-Cl, R = Bn	-40 °C, 40 h	**4g** : 72	9
13	**D**	**3h** : X = 4-Cl, R = Ph	-40 °C, 24 h	**4h** : 84	0
14	**D**	**3i** : X = 4-Cl, R = *i*-Pr	-40 °C, 40 h	**4i** : 0	-

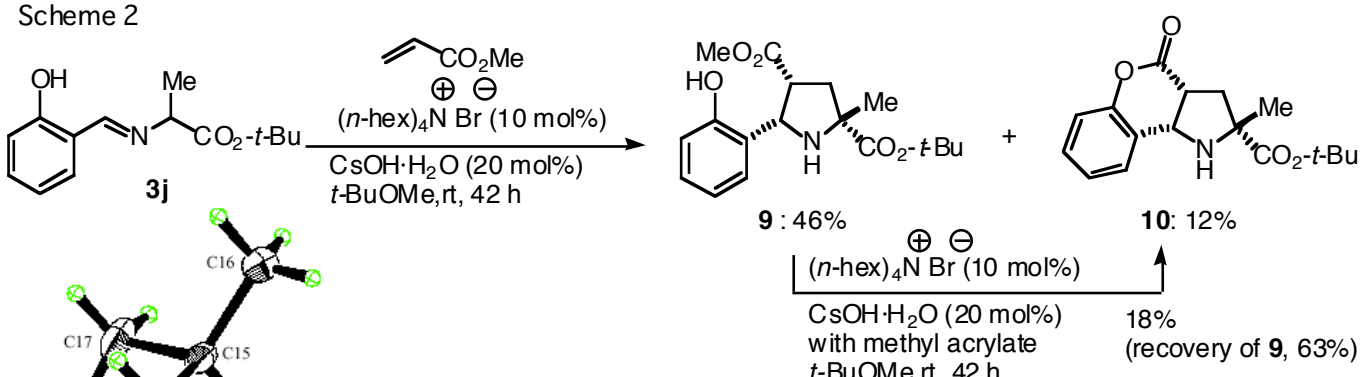
Scheme 1



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 α-proton of **3c** (entries 5 and 6). On the other hand, a 4-CF_3 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 α-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 $(Boc)_2O$ gave **6** in 95% yield, and subsequent reduction and hydrosilylation gave **7** in 63% yield. Conversion to α-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*.[18]

Scheme 2



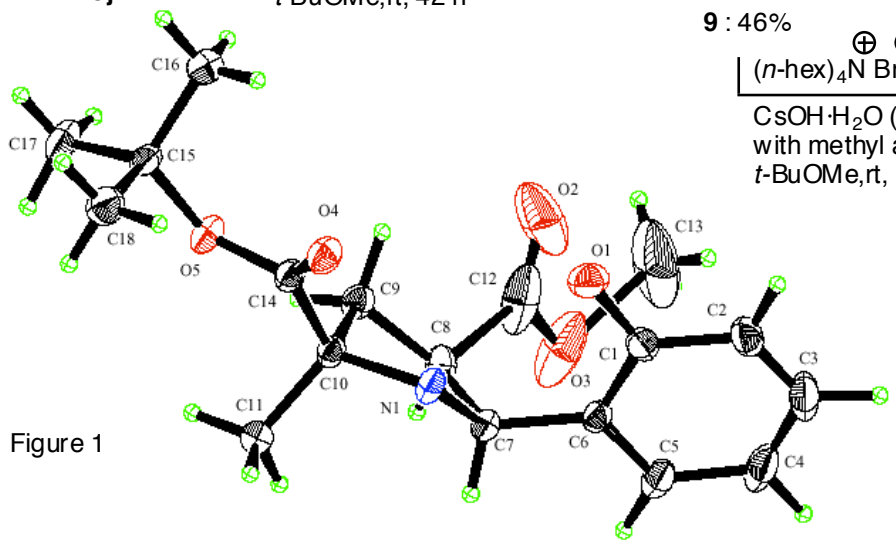
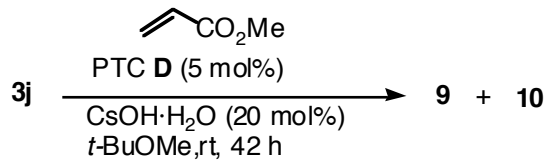


Figure 1

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).[19,20] 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).[21] 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).[22] 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 **9** (%)	yield of **10** (%)	ee of **9** (%)
1	*t*-BuOMe	50	12	17
2	toluene	36	23	2
3	CH_2Cl_2	44	25	7
4	Et_2O	43	13	25

Enantiomeric excess of **9** was determined by HPLC analysis (CHIRALCEL OD) after *N,O*-bisbenzoylation (BzCl, CH_2Cl_2, rt, 24 h, quant).

In conclusion, we succeeded in the asymmetric Michael reaction using a Schiff base catalyzed by D_2-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

We are grateful for financial support from the TAKEDA SCIENCE FOUNDATION and the Ministry of Education, Science, Sports, Culture and Technology, Japan (16790007 and 17035014).

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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 μL, 0.5 mmol) at –40 °C. After being stirred for 24 h, the reaction was quenched with water and the resulting mixture was extracted with CH_2Cl_2 (5 mL X 3). The organic layers were washed with brine and dried over Na_2SO_4, and the solvents were removed under reduced pressure. Subsequent purification by flash column chromatography (hexane:Et_2O = 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. $[\alpha]_D^{23}$ –6.1° (*c*, 0.3, $CHCl_3$, 50% ee); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 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}C NMR ($CDCl_3$, 100 MHz) δ: 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) ν: 2922, 1737, 1644, 1118 cm^{-1}; LRMS (FAB) *m/z* 354 (M^++H); HRMS (FAB) calcd for $C_{18}H_{25}NO_4Cl$ 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 μL, 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_2O); $[\alpha]_D^{25}$ +11.5° (*c*, 0.24, $CHCl_3$, 17% ee); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 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); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 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) ν: 3305, 2978, 1731, 1260, 1132, 752 cm^{-1}; LRMS (FAB) *m/z* 336 (M^++H); HRMS (FAB) calcd for $C_{18}H_{26}NO_5$ 336.1811, found 336.1794; Anal. Calcd for $C_{18}H_{26}NO_5$: C, 66.46; H, 7.51; N, 4,18, Found: C, 64.50; H, 7.47; N, 4.08.