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Rate Enhancement of Phase Transfer Catalyzed Conjugate Additions by CsCl

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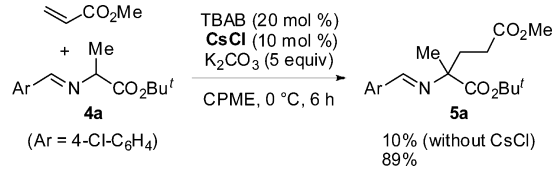
ABSTRACT



A rate enhancement of phase transfer catalyzed conjugate additions was accomplished using a catalytic amount of CsCl. The utility of this method was demonstrated in the asymmetric synthesis of glutamic acid derivatives by using a chiral phase transfer catalyst.

Asymmetric phase transfer catalysis using optically pure quaternary ammonium salts has become a field of growing importance.[1] In this area, asymmetric reactions promoted by inorganic bases were most well-known, and the inorganic base having appropriate basicity was chosen depending on the reaction system. In some cases, however, the use of a strong base to promote the reaction would lead to the loss of enantioselectivity due to a partial contribution of a racemic pathway without involving the chiral phase transfer catalyst.[2] Most phase transfer catalyzed asymmetric conjugate additions, for instance, addition of *N*-(diphenylmethylene)glycine ester to acrylates using strong bases such as $CsOH{\cdot}H_2O$ and Cs_2CO_3, were performed at low temperature to achieve high levels of enantioselectivity.[3−8] In this context, we have been interested in the development of a novel method for acceleration of the phase transfer catalyzed reaction under mild conditions without using a strong base. Herein we wish to report a rate enhancement of phase transfer catalyzed conjugate additions by adding catalytic CsCl. Using catalytic CsCl, the first highly enantioselective conjugate addition of an alanine derivative to methyl acrylate was also achieved at the synthetically useful level.[4b]

With the expectation of accelerating the reaction, metal salts were chosen as additives.[9] Thus, we first investigated the conjugate addition of *N*-(diphenylmethylene)glycine ester

(1) For reviews, see: (a) Shioiri, T. In *Handbook of Phase Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic&Professional: London, 1997; Chapter 14. (b) Ebrahim, S.; Wills, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3163. (c) Esikova, I. A.; Nahreini, T. S.; O'Donnell, M. J. In *Phase-Transfer Catalysis*; Halpern, M. E., Ed.; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997; Chapter 7. (d) Shioiri, T.; Ando, A.; Masui, M.; Miura, T.; Tatematsu, T.; Bohsako, A.; Higashiyama, M.; Asakura, C. In *Phase-Transfer Catalysis*; Halpern, M. E., Ed.; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997; Chapter 11. (e) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 10. (f) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (g) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (h) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222.

(2) For instance, the conjugate addition of *N*-(diphenylmethylene)glycine ester **1a** to methyl acrylate with Cs_2CO_3 in CPME proceeded at 0 °C to give the corresponding 1,4-addition product **2** in quantitative yield, while the reaction using a weaker base K_2CO_3 resulted in no product formation. See Supporting Informationfor details.

(3) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347.

(4) (a) Arai, S.; Tsuji, R.; Nishida, A. *Tetrahedron Lett.* **2002**, *43*, 9535. (b) Arai, S.; Takahashi, F.; Tsuji, R.; Nishida, A. *Heterocycles* **2006**, *67*, 495.

(5) (a) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539. (b) Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206. (c) Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743.

(6) Arai, S.; Tokumaru, K.; Aoyama, T. *Chem. Pharm. Bull.* **2004**, *52*, 646.

(7) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461.

(8) Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734.

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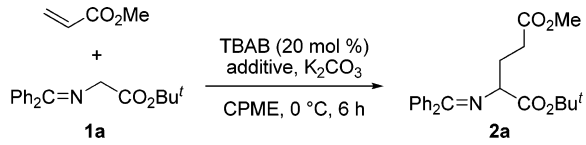
Table 1. Conjugate Addition of Glycine Ester **1a** with Various Additives under Phase Transfer Conditions[a]



entry	additive	conversion (%)	entry	additive	conversion (%)
1	–	17	8	$MgCl_2$	50
2	Li_2CO_3	22	9	$CaCO_3$	47
3	Na_2CO_3	7	10	$CaCl_2$	44
4	Cs_2CO_3	64	11	$BaCO_3$	27
5	CsCl	89	12	$BaCl_2$	23
6	CsI	24	13	18-crown-6	91
7	RbCl	12			

[a] Unless otherwise specified, the reaction was carried out with glycine derivative **1a** and 2 equiv of methyl acrylate in the presence of 20 mol % of TBAB, 10 mol % of additive, and 5 equiv of K_2CO_3 in CPME at 0 °C for 6 h.

1a to methyl acrylate in cyclopentyl methyl ether (CPME)[10] with K_2CO_3 in the presence of 20 mol % of TBAB and 10 mol % of a metal salt, and the results are shown in Table 1. To our delight, a rate enhancement of the reaction was observed in the presence of some of the metal salts tested (entry 1 vs entries 4, 5, and 8−10). Finally, the efficiency of CsCl was found to be comparable to that of 18-crown-6 (entry 5 vs entry 13).[11]

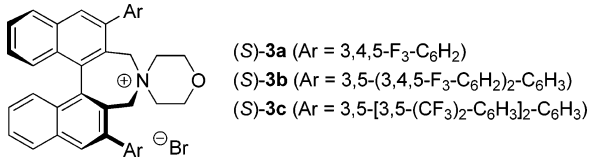
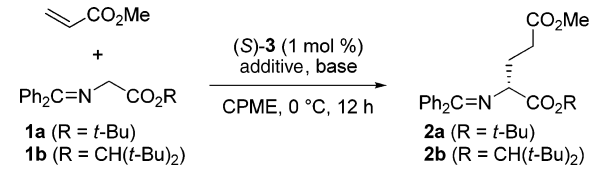


Figure 1. Chiral phase transfer catalysts.

Having identified CsCl as an effective additive for the conjugate addition of *N*-(diphenylmethylene)glycine ester **1a** to methyl acrylate, the asymmetric variant of this reaction[12−14] was examined using chiral phase transfer catalysts (*S*)-**3** (Figure 1),[3−8,15] and the representative results are summarized in Table 2. Among the catalysts examined, (*S*)-**3b** exhibited the highest yield and enantioselectivity (entry 2), and a rate enhancement of the present asymmetric conjugate addition was observed without affecting the enantioselectivity (entry 2 vs entry 4). Although the use of

Table 2. Asymmetric Conjugate Addition of Glycine Ester **1** with CsCl under Phase Transfer Conditions[a]



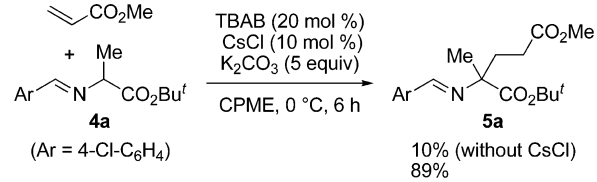
entry	cat	R	base	additive	yield[b] (%)	ee[c] (%)
1	(*S*)-**3a**	*t*-Bu	K_2CO_3	CsCl	64	80
2	(*S*)-**3b**	*t*-Bu	K_2CO_3	CsCl	88	92
3	(*S*)-**3c**	*t*-Bu	K_2CO_3	CsCl	85	80
4	(*S*)-**3b**	*t*-Bu	K_2CO_3	–	25	92
5	(*S*)-**3b**	*t*-Bu	Cs_2CO_3	–	85	86
6	(*S*)-**3b**	*t*-Bu	K_2CO_3	18-crown-6	89	84
7	(*S*)-**3b**	CH(*t*-Bu)$_2$	K_2CO_3	CsCl	88	97

[a] Unless otherwise specified, the reaction was carried out with glycine derivative **1** and 2 equiv of methyl acrylate in the presence of 1 mol % of **3**, 10 mol % of additive, and 1.2 equiv of K_2CO_3 in CPME at 0 °C for 12 h. [b] Isolated yield of **2**. [c] Enantiopurity of the conjugate adducts **2** was determined by HPLC analysis using a chiral column. Absolute configuration of **2a** was determined to be *R* by comparison of the HPLC retention time with the literature data.[13a]

the stronger base Cs_2CO_3 instead of K_2CO_3 or addition of 18-crown-6 also accelerated the reaction, the enantioselectivity was decreased (entries 5 and 6). In addition, by switching the ester moiety of glycine derivative **1a** to di(*tert*-butyl)methyl group, the enantioselectivity was improved (entry 7).

We then investigated the conjugate addition of *N*-(4-chlorobenzylidene)alanine ester **4a** to methyl acrylate in CPME with K_2CO_3 in the presence of 20 mol % of TBAB. While the reaction without CsCl proceeded slowly to give the corresponding conjugate addition product **5a** in low yield, the addition of 10 mol % of CsCl resulted in a significant increase in yield (Scheme 1).

Scheme 1. Conjugate Addition of Alanine Ester **4a** with CsCl under Phase Transfer Conditions



The asymmetric conjugate addition of alanine derivative **4** to methyl acrylate[4b] was also examined using chiral phase

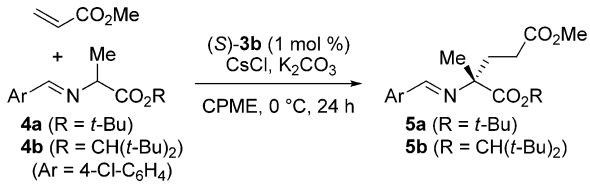
(9) The addition of K_2CO_3 slightly improves the product yield of the phase transfer catalyzed alkylation of *N*-(4-chlorobenzylidene)alanine ester **4a** with KOH. See: O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591.

(10) Use of ether, which is a common solvent for the phase transfer catalyzed conjugate addition reaction, resulted in a moderate yield of **2a** (56%) even in the presence of CsCl.

(11) Previously, we have reported that addition of achiral phase transfer catalysts involving crown ethers and quaternary ammonium salts drastically accelerated the asymmetric alkylation reaction under phase transfer conditions without affecting the enantioselectivity. See: Shirakawa, S.; Yamamoto, K.; Kitamura, M.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 625.

(12) Ma, D.; Cheng, K. *Tetrahedron: Asymmetry* **1999**, *10*, 713.

Table 3. Asymmetric Conjugate Addition of Alanine Ester **4** with CsCl under Phase Transfer Conditions[a]



entry	R	base	CsCl (mol %)	yield[b] (%)	ee[c] (%)
1	*t*-Bu	K_2CO_3	0	<5	–
2	*t*-Bu	K_2CO_3	10	45	84
3[d]	*t*-Bu	Cs_2CO_3	0	78	79
4	CH(*t*-Bu)$_2$	K_2CO_3	10	40	90
5[e]	CH(*t*-Bu)$_2$	K_2CO_3	10	82	90

[a] Unless otherwise specified, the reaction was carried out with alanine derivative **4** and 2 equiv of methyl acrylate in the presence of 1 mol % of **3b**, 10 mol % of additive, and 1.2 equiv of K_2CO_3 in CPME at 0 °C for 24 h. [b] Isolated yield of **5**. [c] Enantiopurity of the conjugate adducts **5** was determined by HPLC analysis using a chiral column. Absolute configuration of **5a** was determined to be *R* by comparison of the HPLC retention times with the literature data.[5b] [d] Stirred for 12 h. [e] With 5 equiv of K_2CO_3.

transfer catalyst (*S*)-**3b**, and the results are summarized in Table 3. In the absence of CsCl, the reaction provided only trace amounts of the desired product **5a** (entry 1). With 10 mol % of CsCl, **5a** was obtained in moderate yield with good enantioselectivity (entry 2). Using Cs_2CO_3 instead of K_2CO_3 as a base, the reaction proceeded smoothly to give **5a** in good yield; however, a decrease in enantioselectivity was observed as expected (entry 3). Replacement of *tert*-butyl group in alanine derivative **4a** by di(*tert*-butyl)methyl group improved the enantioselectivity to 90%, while the yield of **5b** was still moderate (entry 4). The use of 5 equiv of K_2CO_3 gave the improved yield of **5b** without loss of enantioselectivity (entry 5).

At present, the mechanism for the rate enhancement by CsCl is unclear. Since both reactions with Cs_2CO_3 (Table 2, entry 5, and Table 3, entry 3) as well as a mixed base of K_2CO_3 and catalytic Cs_2CO_3 (Table 1, entry 4) proceed rapidly, the nature of cesium cation might play an important role during the formation of the chiral ammonium enolate intermediate.

In summary, we have demonstrated a rate enhancement of the phase transfer catalyzed conjugate addition reaction by addition of catalytic CsCl. With respect to the enantioselectivity and cost, a combination of K_2CO_3 and catalytic CsCl is clearly superior to Cs_2CO_3 as well as to a mixture of K_2CO_3 and catalytic 18-crown-6. The present system can be applied to the asymmetric conjugate addition of glycine and alanine derivatives to methyl acrylate, thereby allowing for an efficient route to optically active glutamic acid derivatives.

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245. (b) Ryoda, A.; Yajima, N.; Haga, T.; Kumamoto, T.; Nakanishi, W.; Kawahata, M.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2008**, *73*, 133.

(14) (a) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364. (b) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321.

(15) (a) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038. (b) Lan, Q.; Wang, X.; Maruoka, K. *Tetrahedron Lett.* **2007**, *48*, 4675.