A New Class of Acetophenone-based Cinchona Alkaloids as Phase-transfer Catalysts: Application to the Enantioselective Synthesis of α-Amino Acids

Jian Lv, Liping Zhang, Lei Liu, and Yongmei Wang*
Department of Chemistry and State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

(Received August 22, 2007; CL-070895; E-mail: ymw@nankai.edu.cn)

A new class of acetophenone-based cinchona alkaloid-derived quaternary ammonium salts were prepared and evaluated as phase-transfer catalysts in the enantioselective alkylation of glycine imine ester. $^{+}R_3N$-CH_2COAr and electron-withdrawing 4′-NO_2 moieties may play an important role leading to high enantioselectivity (85–>99% ee).

Since the application of chiral PTCs to the asymmetric alkylation of glycine imine ester, which was first reported by O'Donnell et al. in 1989,[1] catalytic asymmetric alkylation has been one of the most important asymmetric methodologies.[2] A number of methods have been developed for the asymmetric alkylation of glycine imine ester.[3] Amongst them, a method utilizing chiral PTCs occupies a unique place, featuring many clear synthetic advantages for large-scale procedures including easily available and re-usable chiral catalysts and environmental benefits.[4] Recently, catalytic asymmetric PTCs alkylations by using cinchona alkaloids-derived quaternary ammonium salts as chiral PTC catalysts have been reported by several research groups.[5] Especially, the Lygo[6] and Corey[7] groups independently reported the excellent phase-transfer catalysts, respectively, by the introduction of the bulkier anthracenyl moiety instead of the phenyl group. Moreover, our group[8] and others[9] have anchored *Cinchona* alkaloids to cross-linked polystyrene or chemically modified PEG for the asymmetric alkylation of glycine imine ester.

Despite their practical potential, the high enantio-selectivity was due to the steric bulkiness of N^{+}-arylmethyl group in cinchona-derived catalysts. But we can not ignore that an electronic effect may be also another significant factor. The enantiomeric purity of the products was found to be highly dependent on the electron-withdrawing groups by Park et al.[10a,10b] and Shioiri et al.[10c] Hence, we synthesized a series of acetophenone-based cinchona ammonium salts and catalyzed the asymmetric alkylation of glycine imine ester. We expected that electron-withdrawing group (–COAr) and various functional groups on the phenyl ring might increase the enantioselectivity by the formation of a tighter binding ion pair, which would lead to a more rigid conformation.

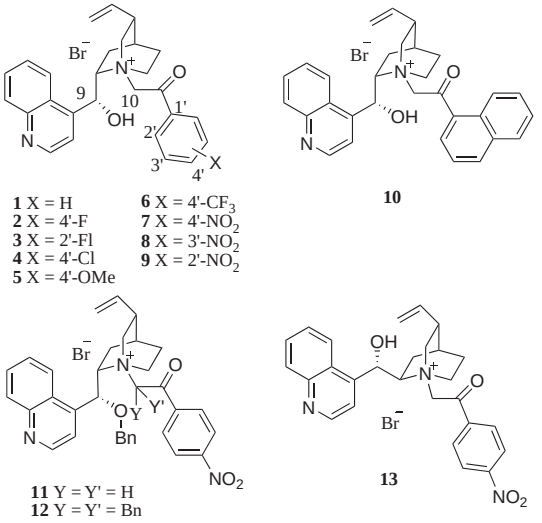
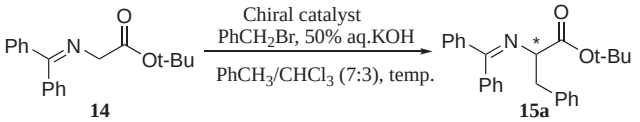


Chart 1.

First, a new class of acetophenone-based cinchona alkaloid-derived quaternary ammonium salts[11] were prepared from cinchonidine (for **1**–**10**), *O*9-benzylcinchonidine (**11**) or cinchonine (for **13**) (Chart 1), and the corresponding phenacyl bromide derivatives were stirred in refluxing ethanol for 1 h in 86%–96% yields, followed by O9 and C10-alkylation of **7** with benzyl bromide and aqueous KOH (50%) for 24 h to give quaternary ammonium salt **12** in 20% yield. Their catalytic efficiencies were evaluated by enantioselective phase-transfer alkylation, using 10 mol % catalyst, *N*-(diphenylmethylene)glycine *tert*-butyl ester **14**, benzyl bromide, and 50% aqueous KOH in toluene/chloroform (volume ratio = 7:3) at 25 °C.

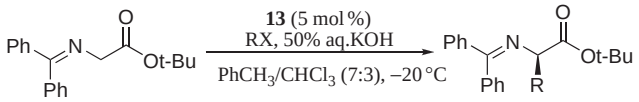
Table 1. Catalytic enantioselective phase-transfer alkylation[a]



Entry	Catalyst	Temp /°C	Time /h	Yield[b] /%	ee[c] /% (conf.)
1	**1**	25	1.0	88	60 (*S*)
2	**2**	25	0.8	90	71 (*S*)
3	**3**	25	0.8	92	73 (*S*)
4	**4**	25	0.9	93	70 (*S*)
5	**5**	25	1.3	85	48 (*S*)
6	**6**	25	0.4	95	83 (*S*)
7	**7**	25	0.2	96	84 (*S*)
8	**8**	25	0.4	89	81 (*S*)
9	**9**	25	0.3	91	83 (*S*)
10	**10**	25	1.2	90	63 (*S*)
11	**11**	25	0.4	95	83 (*S*)
12	**12**	25	2.0	91	60 (*S*)
13	**13**	25	0.05	96	85 (*R*)
14	**13**	0	0.4	95	87 (*R*)
15	**13**	−20	1.0	93	90 (*R*)
16[d]	**13**	−20	2.0	94	92 (*R*)
17[e]	**13**	−20	4.0	90	88 (*R*)

[a]Reaction was carried out with 5.0 equiv. of benzyl bromide and 13.0 equiv. of 50% aqueous KOH in the presence of 10 mol % **1**–**13** in toluene/chloroform (volume ratio = 7:3) under the given conditions. [b]Isolated yields. [c]Enantiopurity was determined by HPLC analysis of benzylated imine **15a** using a chiral column (DAICEl Chiralcel OD-H) with hexanes/2-propanol (volume ratio = 99.5:0.5) as a solvent. [d]The presence of 5 mol % **13**. [e]The presence of 1 mol % **13**.

Table 2. Catalytic enantioselective phase-transfer alkylation using catalysts **13**[a]



Entry	RX	Time/h	Yield[b]/%	ee[c]/% (conf.)
a	$PhCH_2Br$	2	94	92 (*R*)
b	*p*-$ClC_6H_4CH_2Br$	3	89	95 (*R*)
c	*m*-$ClC_6H_4CH_2Br$	3	92	95 (*R*)
d	*o*-$ClC_6H_4CH_2Br$	3	90	99 (*R*)
e	*p*-$CH_3C_6H_4CH_2Br$	2	87	94 (*R*)
f	*m*-$CH_3C_6H_4CH_2Br$	2	93	>99 (*R*)
g	*o*-$CH_3C_6H_4CH_2Br$	2	95	90 (*R*)
h	*m*-$BrC_6H_4CH_2Br$	3	91	92 (*R*)
i	*p*-$NO_2C_6H_4CH_2Br$	3	90	90 (*R*)
j	CH_3I	4	80	85 (*R*)
k		4	91	86 (*R*)

[a]Reaction was carried out with 5.0 equiv. of alkyl halides and 13.0 equiv. of 50% aqueous KOH in the presence of 5 mol % **13** in toluene/chloroform (v/v = 7:3) under the given conditions.

As shown in Table 1, there are, depending on the position substituted with different groups, quite dramatic variations in the enantioselectivity. Generally, the electronic factor is critical for enhancement of the induction, however, the steric factor is not important (**1**, 60% ee; **10**, 63% ee). The best results were obtained with an electron-withdrawing $-NO_2$ group on the 4′-position (**7**, 84% ee; **13**, 85% ee), however, an electron-donating methoxy group on the 4′-position gave lower enantioselectivity (**11**, 48% ee). It indicated that the electron-withdrawing acetophenone and 4′-NO_2 groups, caused by the overall electron deficiency of the positive charge, helped to enhance the degree of the ion pairing with enolate. The more tight ion pairing was formed, the higher enantioselective was obtained.[7a] Moreover, use of lower temperature improved the enantioselectivity (**13**, 87% ee, at 0 °C; 90% ee, at −20 °C). Notably, **13** can conserve its high catalytic efficiency in terms of both reactivity and enantioselectivity, even when present in a smaller quantity (1 mol %, 88% ee, at −20 °C). Furthermore, catalytic efficiencies of **11** and **12** were also evaluated. In agreement with our expectation, C(9)O-benzyl (**11**, 83% ee, at 25 °C) derivative of **7** gave a little lower enantioselectivity than **7** with a free C(9)OH group (84% ee, at 25 °C). Catalyst **12** obtained by O9 and C10-alkylation of **7** with benzyl bromide gave a notable decrease in the enantioselectivity (60% ee, at 25 °C).

After optimizing the reaction condition, we considered whether the catalyst could be decomposed or not during the reaction procedure. So we reclaimed the catalyst and investigated its structure. The catalyst **13** could be separated from the reaction mixture when we added diethyl ether to the reaction residue, because of the reaction product could dissolve in diethyl ether and the catalyst was insoluble in it. We found that the catalyst was not decomposed under the present conditions examined by ^{1}H NMR.[12] It indicated that the catalyst is stable under the reaction conditions.

The best enantioselectivity was obtained with catalyst **13**, which was chosen for further investigation with various alkyl halides. Satisfactory enantioselectivities (85–>99% ee) and yields were shown in Table 2. It is clear that different benzyl bromides afforded higher enantioselective than allylic bromide and methyl iodide.

In conclusion, we prepared a series of new cinchona alkaloid ammonium salt catalysts **1**–**13** by the introduction of the *N*-aromatic acyl group instead of the *N*-arylmethyl group to enhance catalytic efficiency. Among the PTC catalysts, the catalyst **13** showed the higher catalytic activity (85–>99% ee) in the alkylation of **14**.

References and Notes

1 M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353.

2 a) C. H. Stammer, *Tetrahedron* **1990**, *46*, 2231. b) H. Heimartner, *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238. c) R. M. Williams, J. A. Hendrix, *Chem. Rev.* **1992**, *92*, 889. d) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539. e) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **2000**, *11*, 645. f) C. Nájera, *Synlett* **2002**, 1388.

3 a) R. M. Williams, in *Organic Chemistry Series*, ed. by J. E. Baldwin, P. D. Magnus, Pergamon Press, Oxford, **1989**, Vol. 7. b) I. Wagner, H. Musso, *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.

4 For recent representative review, see: a) M. J. O' Donnell, in *Catalytic Asymmetric Synthesis*, ed. by I. Ojima, Verlag Chemie, **1993**, Chap. 8. b) M. J. Porter, J. Skidmore, *Chem. Commun.* **2000**, 1215.

5 a) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506. b) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518. c) A. Siva, E. Murugan, *J. Mol. Catal. A: Chem.* **2006**, *248*, 1. d) S. Elango, M. Venugopal, P. S. Suresh, Eni, *Tetrahedron* **2005**, *61*, 1443. e) S. Kumar, U. Ramachandran, *Tetrahedron* **2005**, *61*, 7022. f) N. Mase, T. Ohno, H. Morimoto, F. Nitta, H. Yoda, K. Takabe, *Tetrahedron Lett.* **2005**, *46*, 3213. g) M. B. Andrus, Z. Ye, J. Zhang, *Tetrahedron Lett.* **2005**, *46*, 3839. h) H.-G. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-J. Kim, S.-S. Jew, *Angew. Chem., Int. Ed.* **2002**, *41*, 3036. i) S.-S. Jew, B.-S. Jeong, M.-S. Yoo, H. Huh, H.-G. Park, *Chem. Commun.* **2001**, 1244. j) R. Chinchilla, P. Mazón, C. Nájera, *Tetrahedron: Asymmetry* **2002**, *13*, 927. k) H.-G. Park, B.-S. Jeong, M.-S. Yoo, H. Huh, S.-S. Jew, *Tetrahedron Lett.* **2001**, *42*, 4645. l) P. Mazón, R. Chinchilla, C. Nájera, G. Guillena, R. Kreiter, R. J. M. K. Gebbink, G. van Koten, *Tetrahedron: Asymmetry* **2002**, *13*, 2181.

6 a) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595. b) B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **1999**, *40*, 1385. c) B. Lygo, *Tetrahedron Lett.* **1999**, *40*, 1389. d) B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **1999**, *40*, 8671. e) B. Lygo, J. Crosby, T. R. Lowdon, J. A. Peterson, P. G. Wainwright, *Tetrahedron* **2001**, *57*, 2403. f) B. Lygo, B. I. Andrews, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **2002**, *43*, 8015. g) B. Lygo, B. Allbutt, *Synlett* **2004**, 326.

7 a) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414. b) E. J. Corey, M. C. Noe, F. Xu. *Tetrahedron Lett.* **1998**, *39*, 5347. c) M. Horikawa, J. Busch-Petersen, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843.

8 a) Y. Wang, Zh. P. Zhang, Zh. Wang, J. B. Meng, P. Hodge, *Chin. J. Polym. Sci.* **1998**, *16*, 356. b) Z. Zhengpu, W. Yongmer, W. Zhen, P. Hodge, *React. Funct. Polym.* **1999**, *41*, 37. c) X. Wang, L. Yin, T. Yang, Y. Wang, *Tetrahedron: Asymmetry* **2007**, *18*, 108.

9 a) R. Chinchilla, P. Mazón, C. Nájera, *Adv. Synth. Catal.* **2004**, *346*, 1186. b) R. Chinchilla, P. Mazón, C. Nájera, *Molecules* **2004**, *9*, 349. c) B. Thierry, J.-C. Plaguevent, D. Cahard, *Tetrahedron: Asymmetry* **2003**, *14*, 1671. d) T. Danelli, R. Annunziata, M. Benaglis, M. Cinquini, F. Cozzi, G. Tocco, *Tetrahedron: Asymmetry* **2003**, *14*, 461.

10 a) S.-S. Jew, M.-S. Yoo, B.-S. Jeong, I. Y. Park, H.-G. Park, *Org. Lett.* **2002**, *4*, 4245. b) M.-S. Yoo, B.-S. Jeong, J.-H. Lee, H.-G. Park, S.-S. Jew, *Org. Lett.* **2005**, *7*, 1129. c) S. Arai, H. Tsuge, T. Shioiri, *Tetetrahedron Lett.* **1998**, *39*, 7563.

11 All new compouds gave satisfactory analytical and spectral data. Selected data for **13**: mp 210–212 °C; $[\alpha]_D^{20} = +63$ ($c = 0.1$, ethanol); IR (KBr) 3441, 3149, 2987, 1694, 1653, 1600, 1530, 1496, 1455, 1027, 759 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (d, $J = 4.2$ Hz, 1H), 8.44–8.37 (t, 3H), 8.13–8.08 (t, 3H), 7.88–7.74 (m, 3H), 6.83 (d, $J = 3.3$ Hz, 1H), 6.52 (s, 1H), 6.06–5.94 (m, 1H), 5.25–5.05 (m, 3H), 4.29–3.91 (m, 3H), 3.52–3.45 (t,$J = 11.4$ Hz, 1H), 2.99 (d, $J = 9.6$ Hz, 1H), 2.61 (d, $J = 8.1$ Hz, 1H), 2.48 (t, $J = 12.3$ Hz, 1H), 1.87–1.74 (m, 3H), 1.08–0.82 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 191.9, 150.4, 147.6, 147.4, 141.2, 138.9, 136.1, 130.0, 129.8, 126.7, 124.5, 124.0, 123.6, 123.2, 118.7, 116.7, 64.9, 62.9, 61.0, 58.5, 56.8, 36.5, 26.6, 22.6, 20.8; MS(ESI): m/z 458 $[M]^+$; HRMS (ESI) calcd for $[C_{27}H_{28}N_3O_4]^+$: m/z 458.2074, found: 458.2078.

12 The recovery date for **13**: recovery yield 92%; $[\alpha]_D^{20} = +62$ ($c = 0.1$, ethanol).

Published on the web (Advance View) October 13, 2007; doi:10.1246/cl.2007.1354