JOC Notes

Highly Enantioselective Synthesis of α-Alkyl-alanines via the Catalytic Phase-Transfer Alkylation of 2-Naphthyl Aldimine *tert*-Butyl Ester by Using *O*(9)-Allyl-*N*(1)-2′,3′,4′-trifluorobenzylhydrocinchonidinium Bromide

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Abstract: Systematic investigations to develop an efficient enantioselective synthetic method for α-alkyl-alanine by catalytic phase-transfer alkylation were performed. The alkylation of 2-naphthyl aldimine *tert*-butyl ester, **1E**, with RbOH and *O*(9)-allyl-*N*-2′,3′,4′-trifluorobenzylhydrocinchonidinium bromide, **6**, at −35 °C showed the highest enantioselectivities, up to 96% ee.

Chiral α,α-dialkyl-α-amino acids (ααAAs), a class of noncoded amino acids, have been extensively studied due to their important role in the fields of synthetic and biological chemistry.[1] Their quaternary chiral centers contribute not only to the molecular stability but also to the conformational preference, by inducing a preferable helical secondary structure of the peptide backbone, when incorporated into a peptide.[2] Moreover, the biological activities of peptides containing ααAAs can be maintained longer because of their resistance against enzymatic hydrolysis. Also, the ααAAs themselves are known to be powerful enzymatic inhibitors (such as α-methyldopa, α-methyltryptophan, and α-methylaspartic acid)[3] and useful synthetic building blocks[1] via chemical transformations. Accordingly, the development of effective synthetic methods for chiral ααAAs is a very important and challenging subject in organic synthesis. Historically, a number of the enantioselective synthetic methods have been described for chiral ααAAs,[4] but only a few are practical.[5]

On the basis of the pioneering application of the *Cinchona*-derived phase-transfer catalyst[6] to the enantioselective synthesis of α-amino acids, the O'Donnell group adapted **4** to develop a new synthetic method for ααAAs via the enantioselective catalytic phase-transfer alkylation of aldimines **1** in 1992.[7] However, relatively low enantioselectivities were observed (ca. 30−50% ee). In 1999, the Lygo group improved the enantioselectivities up to 87% ee by using the more efficient catalyst **5**.[8] More recently, the Maruoka group developed an even better non-*Cinchona* phase-transfer catalyst, derived from (*S*)-binaphthol, which was successfully applied to the synthesis of ααAAs.[9] As a part of our program to develop new chiral building blocks, we were interested in developing a practical enantioselective synthetic method for the preparation of ααAAs. In this note, we describe the efficient enantioselective synthetic method of the synthesis of α-alkyl-alanine by using *O*(9)-allyl-*N*-2′,3′,4′-trifluorobenzylhydrocinchonidinium bromide **6**. Through systematic investigations of the electronic effect in the phase-transfer catalytic reaction, we recently reported that the *ortho*-F on the phenyl ring in **4** plays an integral role in enantioselectivity enhancement.[10,11] In particular, *O*(9)-allyl-*N*-2′,3′,4′-trifluorobenzylhydrocinchonidinium bromide **6** was successfully applied for the synthesis of an α-amino acid and showed the highest

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(1) (a) Bellier, B.; McCort-Tranchenpain, I.; Ducos, B.; Danascimento, S.; Meudal, H.; Noble, F.; Garbay, C.; Roques, B. P. *J. Med. Chem.* **1997**, *40*, 3947. (b) Mossel, E.; Formaggio, F.; Crisma, M.; Toniolo, C.; Broxterman, Q. B.; Boesten, W. H. J.; Kamphius, J.; Quaedflieg, P. J. L. M.; Temussi, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1305. (c) Dery, O.; Joisen, H.; Grassi, J.; Chassaing, G.; Couraud, J. Y.; Lavielle, S. *Biopolymers* **1996**, *39*, 67. (d) Benedetti, E.; Gavuzzo, E.; Santini, A.; Kent, D. R.; Zhu, Y.-F.; Zhu, Q.; Mahr, C.; Goodman, M. *J. Pept. Sci.* **1995**, *1*, 349. (e) Toniolo, C.; Formaggio, F.; Crisma, M.; Valle, G.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J.; Temussi, P. A.; Becker, E. L.; Précigoux, G. *Tetrahedron* **1993**, *49*, 3641. (f) Schiller, P. W.; Weltrowska, G.; Nguyen, T. M.-D.; Lemieux, C.; Chung, N. N.; Marsden, B. J.; Wilkes, B. C. *J. Med. Chem.* **1991**, *34*, 3125.

(2) (a) Wipf, P.; Heimgartner, H. *Helv. Chim. Acta* **1988**, *71*, 258. (b) Hodgkin, E. E.; Clark, J. D.; Miller, K. R.; Marshall, G. R. *Biopolymers* **1990**, *30*, 533. (c) Di Blasio, B.; Pavone, V.; Lombardi, A.; Pedone, C.; Benedetti, E. *Biopolymers* **1993**, *33*, 1037. (d) Toniolo, C.; Crisma, M.; Formaggio, F.; Valle, G.; Cavicchioni, G.; Précigoux, G.; Aubry, A.; Kamphius, J. *Biopolymers* **1993**, *33*, 1061. (e) Toniolo, C. *Janssen Chim. Acta* **1993**, *11*, 10. (f) Karle, I. L.; Rao, R. B.; Prasad, S.; Kaul, R.; Balaram, P. *J. Am. Chem. Soc.* **1994**, *116*, 10355. (g) Formaggio, F.; Pantano, M.; Crisma, M.; Bonora, G. M.; Toniolo, C.; Kamphius, J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1097. (h) Benedetti, E. *Biopolymers* **1996**, *40*, 3. (i) Karle, I. L.; Kaul, R.; Rao, R. B.; Raghothama, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 12048.

(3) (a) Sourkers, T. L. *Arch. Biochem. Biophys.* **1945**, *51*, 444. (b) Shirlin, D.; Gerhart, F.; Hornsperger, J. M.; Harmon, M.; Wagner, I.; Jung, M. *J. Med. Chem.* **1988**, *31*, 30. (c) Kiick, D. M.; Cook, P. F. *Biochemistry* **1983**, *22*, 375.

(4) For recent reviews, see: (a) Cativiela, C.; Diazde-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Wirth, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 225. (c) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708. (d) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(5) (a) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253. (b) Ito, Y.; Sawamura, M.; Matsuoka, M.; Matsumoto, Y.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 4849. (c) Belokon, Y. N.; North, M.; Kublitski, V. S.; Ikonnikov, N. S.; Krasik, P. E.; Maleev, V. I. *Tetrahedron Lett.* **1999**, *40*, 6105. (d) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Parmar, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851.

(6) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (d) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (e) Ooi, T.; Kaneda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.

(7) O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591.

(8) Lygo, B.; Crosby, J.; Perterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671.

(9) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

(10) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245.

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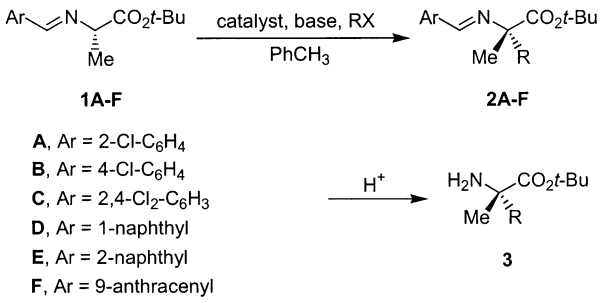
SCHEME 1



enantioselectivity for this reaction (from 94 to >99% ee).[10] We planned to use **6** in the enantioselective phase-transfer alkylation of aldimine for the synthesis of α-alkyl-alanines.

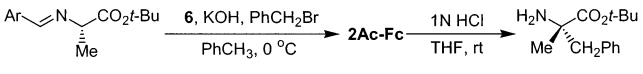
Although the optimization studies for the reaction were already performed by the O'Donnell group (reaction conditions: the mixed base, KOH + K_2CO_3; 4-chlorophenyl aldimine **1B**; room temperature), we needed to reinvestigate the reaction conditions and the imine-protecting groups of the aldimine for the best enantioselectivity for the following three reasons. (1) The optimal reaction condition could be different depending upon the structure of phase-transfer catalyst. (2) There might be some electronic effect depending upon the substituted position of the chloride in the aromatic ring of the imine. (3) There was no investigation of the optimal reaction temperature. Six aldimines (**1A**−**F**) were prepared from L-alanine *tert*-butyl ester and the corresponding aromatic aldehydes. The enantioselective benzylation reactions with the prepared aldimines were performed by using 10 mol % catalyst **6**, along with the aldimines, benzyl bromide, and KOH in toluene at 0 °C for 2−16 h (Scheme 1). The enantioselectivities of **2** were determined by a chiral HPLC analysis of the corresponding *N*-benzoyl derivatives of **3**, which were obtained by hydrolysis of **2** under acidic conditions.

As shown in Table 1, there was no considerable electronic effect depending on the substituted position of the chloride, but the dichloro group decreased the enantioselectivity (**1A**, 76% ee; **1B**, 77% ee; **1C**, 61% ee). In the case of the bulky aromatic substituents, the enantioselectivity of the 2-naphthyl derivative (**1E**, 88% ee) was higher than that of the 1-naphthyl derivative (**1D**, 75% ee), which is consistent with the previous results.[7] However, the bulkier 9-anthracenyl group (**1F**, 82% ee) did not positively influence the enantioselectivity. The 4-chlorophenyl-derived aldimine **1B**, which was mainly used in the previous studies of this type of reaction, gave lower enantioselectivity than **1E** under our reaction conditions.[7−9] Compound **1E** was chosen as a substrate for alkylation, from the viewpoint of enantioselectivity as well as chemical yield and reaction time. Further investigations to optimize the reaction conditions are summarized in Table 2.

When KOH was employed as a base, lower temperatures improved the enantioselectivity, −15 °C being the optimal. The efficiency of the catalysts for the alkylation was then examined. Among the catalysts, the enantioselectivity of *N*-trifluorobenzyl catalyst **6** (90% ee) was higher than those observed with the *N*-benzyl catalyst **4** (75% ee, entry 1) and the *N*-anthracenyl catalyst **5** (83% ee, entry 2) at −15 °C. To overcome the limitation of temperature when using KOH as a base, stronger bases were employed at temperatures below −15 °C. RbOH (92% ee, entry 7) provided higher enantioselectivity than those obtained with KOH (90% ee, entry 5) and CsOH (87% ee, entry 8) at −15 °C. By varying the reaction temperature, we finally obtained the best enantioselectivity (95% ee, entry 10) with the following reaction conditions: aldimine **1E**, catalyst **6**, RbOH, −35 °C.

Table 3 summarizes the results obtained for the alkylation of **1E** with various alkyl halides under the optimal conditions. The high enantioselectivities (up to 96% ee) with satisfactory chemical yields indicate that

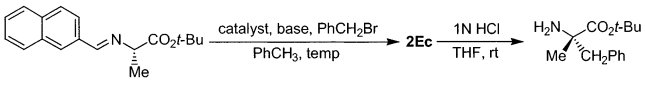
TABLE 1. Enantioselective Catalytic Phase-Transfer Benzylation of the Various Aldimines (1A−F) Using Catalyst 6[a]



entry	aldimine **1**	time (h)[b]	yield (%)[c]	% ee[d] (configuration)[e]
1	**1A**	12	76	76 (*S*)
2	**1B**	8	84	77 (*S*)
3	**1C**	10	72	61 (*S*)
4	**1D**	16	69	75 (*S*)
5	**1E**	2	93	88 (*S*)
6	**1F**	10	80	82 (*S*)

[a] Reaction was carried out with 5.0 equiv of benzyl bromide and 5.0 equiv of KOH in the presence of 10 mol % **6** in toluene under the given conditions. Reaction conditions for the deprotection of **2** and the N-benzoylation of **3c** are described in the Experimental Section. [b] Reaction time for consumption of the aldimine **1** to transform the benzylated aldimine **2**. [c] Isolated yield of purified **3c** for two steps from **1**. [d] Enantiopurity was determined by the HPLC analysis of the *N*-benzoyl derivative of **3c**, using a chiral column (Chiral Technologies Inc., Chiralcel OD). [e] Absolute configuration was assigned by the relative retention times of both enantiomers determined previously.[8,9]

TABLE 2. Enantioselective Catalytic Phase-Transfer Benzylation of 1E[a]

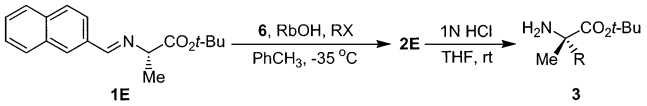


entry	catalyst	base	temp (°C)	time (h)	yield (%)	% ee (configuration)
1	**4**	KOH	−15	10	91	75 (*S*)
2	**5**	KOH	−15	9	94	83 (*S*)
3	**6**	KOH	20	0.5	96	84 (*S*)
4	**6**	KOH	0	2	93	88 (*S*)
5	**6**	KOH	−15	10	91	90 (*S*)
6	**6**	KOH	−25	24	61	64 (*S*)
7	**6**	RbOH	−15	4	93	92 (*S*)
8	**6**	CsOH	−15	2	96	87 (*S*)
9	**6**	RbOH	−25	6	93	93 (*S*)
10	**6**	RbOH	−35	10	91	95 (*S*)
11	**6**	RbOH	−45	40	67	89 (*S*)

[a] Reaction conditions were the same as those for Table 1, except for the catalyst, base, and temperature.

(11) For our recent studies on chiral phase-transfer catalysts, see: (a) Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244. (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, *42*, 4645. (c) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036.

TABLE 3. Enantioselective Catalytic Phase-Transfer Alkylation of 1E with Various Alkyl Halides in the Presence of Catalyst 6[a]



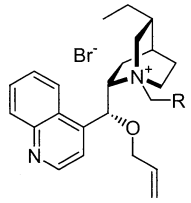
entry	alkyl halides (RX)	time (h)[b]	yield (%)[c]	% ee[d] (configuration)
a	allyl bromide	20	87	85 (*S*)
b	propargyl bromide	12	89	84 (*S*)
c	benzyl bromide	10	91	95 (*S*)
d	4-bromobenzyl bromide	24	89	90 (*S*)
e	4-*tert*-butylbenzyl bromide	40	86	90 (*S*)
f	4-trifluoromethylbenzyl bromide	24	90	88 (*S*)
g	2-fluorobenzyl bromide	12	91	90 (*S*)
h	2,6-difluorobenzyl bromide	10	92	96 (*S*)
i	2,4-dichlorobenzyl bromide	8	93	95 (*S*)
j	3-methylbenzyl bromide	40	87	92 (*S*)
k	1-chloromethylnaphthalene	24	89	86 (*S*)

[a] Reaction was carried out with 5.0 equiv of alkyl halide and 5.0 equiv of RbOH in the presence of 10 mol % **6** in toluene at −35 °C. The reaction conditions for the deprotection of **2** and the N-benzoylation of **3** are described in the Experimental Section. [b] Reaction time for consumption of the aldimine **1E** to transform the alkylated aldimine **2E**. [c] Isolated yield of **3** for two steps from **1E**. [d] Enantiopurity was determined by HPLC analysis of the *N*-benzoyl derivatives of **3**, using a chiral column [Chiral Technologies Inc., Chiralcel OD (for **3a**−**d**,**f**,**g**,**i**−**k**) and Chiralpak AD (for **3e** and **3h**)]; in each case, it was established by analysis of the racemate that the enantiomers were fully resolved.

these optimal phase-transfer reaction conditions and catalyst **6** are very effective for the preparation of chiral α-alkyl-alanine derivatives. In conclusion, we investigated the optimal reaction conditions of the enantioselective catalytic phase-transfer alkylation for α-alkyl-alanines. The alkylation of 2-naphthyl aldimine *tert*-butyl ester **1E** with RbOH and *O*(9)-allyl-*N*-2′,3′,4′-trifluorobenzylhydrocinchonidinium bromide **6** at −35 °C showed high enantioselectivities, up to 96% ee.

Experimental Section

Representative Procedure of Catalytic Enantioselective Alkylation of 1E Using Catalyst 6 Under Phase-Transfer Conditions (Benzylation). To a cooled (−35 °C) mixture of aldimine **1E** (70 mg, 0.25 mmol), catalyst **6** (14 mg, 0.025 mmol), and rubidium hydroxide (127 mg, 1.24 mmol) in toluene (1.0 mL) was added benzyl bromide (0.15 mL, 1.24 mmol). The reaction mixture was stirred vigorously at −35 °C until the starting material (**1E**) had been consumed (10 h). Then, water (5 mL) was added and the extraction was performed with dichloromethane (2 × 10 mL). The solvent was removed under reduced pressure, and the residue was dissolved in tetrahydrofuran (1.5 mL). Aqueous hydrochloric acid (1 N, 1.5 mL) was added, and the mixture was stirred at room temperature for 1 h. The resulting mixture was washed with hexanes (2 × 5 mL), and then the aqueous phase was basified with solid sodium bicarbonate and extracted with dichloromethane (3 × 10 mL). The dichloromethane extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexanes/EtOAc = 1:2) gave amine **3c** (54 mg, 91% yield) as a colorless oil. The amine **3c** (40 mg, 0.17 mmol) was dissolved in dichloromethane (0.5 mL), and then triethylamine (0.05 mL, 0.34 mmol) and benzoyl chloride (0.03 mL, 0.25 mmol) were added successively. The reaction mixture was stirred at room temperature for 30 min. The resulting mixture was extracted with dichloromethane (3 × 5 mL), and the extracts were washed with water. The dichloromethane solution was then dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexanes/EtOAc = 30:1) afforded the desired *N*-benzoyl derivative of **3c** (55 mg, 95% yield) as a white solid. The enantioselectivity was determined by chiral HPLC analysis of *N*-benzoyl derivative of **3c** (Chiral Technologies, Inc., Chiralcel OD, hexanes/2-propanol = 500:7.0, flow rate = 0.7 mL/min, 23 °C, λ = 254 nm; retention times *R* (minor) 15.9 min, *S* (major) 20.0 min, 95% ee). The absolute configuration was determined by comparison of the HPLC retention time with that of the authentic sample synthesized by the reported method.[8,9]



4, R = phenyl
5, R = 9-anthracenyl
6, R = 2,3,4-trifluorophenyl

FIGURE 1. *Cinchona*-derived phase-transfer catalysts.

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Supporting Information Available: Spectroscopic characterization of **1E**, **6**, and *N*-benzoyl derivatives of **3a**−**k** and HPLC conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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