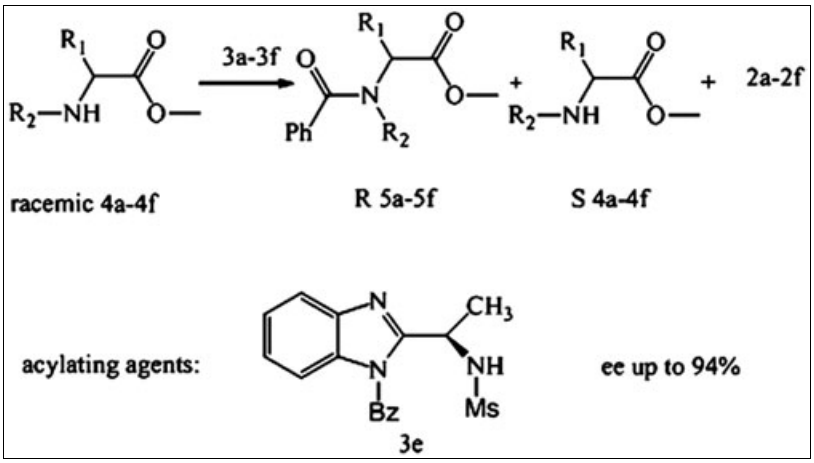
Synthesis of Chiral Benzimidazoles as Acylating Agents for Kinetic Resolution of Racemic α-Amino Esters

Hao Xu,[a] Hua Tian,[a] Liangyu Zheng,[b]* Qingwen Liu,[a] Li Wang,[a] and Suoqin Zhang[a]*

[a]College of Chemistry, Jilin University, Changchun 130012, People's Republic of China
[b]Key Laboratory for Molecular Enzymology and Engineering of Ministry of Education, Jilin University, Changchun 130012, People's Republic of China
*E-mail: lyzheng@jlu.edu.cn or suoqin@jlu.edu.cn

Received February 13, 2011
DOI 10.1002/jhet.948
Published online 29 October 2012 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel chiral 1-benzoyl-2-(α-N-substituted aminoethyl)benzimidazoles are synthesized with the improved method in high yields (72–84%) and developed as nonenzymatic acylating agents for kinetic resolution of racemic α-amino esters. The process exhibits high enantioselectivity (ee up to 94%) for α-amino esters under mild reaction conditions.

J. Heterocyclic Chem., **49**, 1108 (2012).

INTRODUCTION

Kinetic resolution is an effective category for preparing the enantiomerically pure compounds from the racemic structures. Enzymatic [1] and nonenzymatic enantioselective agents [2–5] are devoted as two main routes of kinetic resolution. Enzymes as specific and efficient agents were used widely in kinetic resolution; however, because of the expensiveness of enzymes, the development of nonenzymatic enantioselective agents has become a new hot topic. The heterocyclic compounds with nitrogen atoms such as 4-(dimethylamino)pyridine derivatives [3], nucleophilic heterocyclic carbenes [4], and imidazole derivatives [5] took an important role in the nonenzymatic enantioselective agents. Recent years, to satisfy the different structures of substrates, abundant new heterocyclic compounds were applied in kinetic resolution.

Benzimidazole and its derivatives as important heterocyclic compounds with nitrogen atoms were used widely in asymmetric organic synthesis and asymmetric organic catalysis, as a result of their rigid structure and good planarity. In these benzimidazole derivatives, (*S*)-1-benzoyl-2-(α-acetoxyethyl)benzimidazole, which was obtained and used in kinetic resolution of racemic amino compounds by Karnik and Kamath in 2007 [6,7], became facile, inexpensive, and the most effective agent for preparing enantiomerically pure amino compounds.

Amino esters as building blocks and chemical reagents are important functional compounds in organic synthesis such as peptides, proteins, and many other natural products [8]. As asymmetric synthetic intermediates, the application of enantiomerically enriched amino esters continues to enjoy widespread exposure in stereoselective functional organic synthesis. In particular, because of the importance of enantiomerically pure α-amino esters for the preparation of pharmaceuticals [9], agrochemicals [10], and food chemicals [[11], chiral α-amino esters are used as sources of chiral materials in asymmetric organic synthesis [7], [12], and considerable efforts have been devoted to their kinetic resolution *via* nonenzymatic enantioselective acylating agents. For instance, in 2002, Atkinson and coworkers [13] used quinazoline derivatives in kinetic resolution of racemic valine methyl ester with 94% ee. In 2004, Mioskowski and coworkers [14] demonstrated that (1*S*,2*S*)-cyclohexane-1,2-diamine derivatives for kinetic resolution of phenylalanine methyl ester are effective with 80% ee. Compared to the results, the method, using the benzimidazole derivative as acylating agents by Karnik and Kamath [7], is much more efficient. However, a single structure limited the further studies. For the more expected

results and the more distinct relationship between activity and structures, it is necessary that more *N*-acylbenzimidazoles with different chiral centers are investigated in kinetic resolution of α-amino esters.

Herein, six novel *N*-acylbenzimidazole derivatives (**3a**–**3f**) with various chiral centers as nonenzymatic acylating agents have been prepared efficiently with the improved method (in total yields 72–84%), and they were applied in the reaction of kinetic resolution of α-amino esters. The relationship between activity and structures was studied. The process exhibits high enantioselectivity for α-amino esters under mild reaction conditions (ee up to 94%).

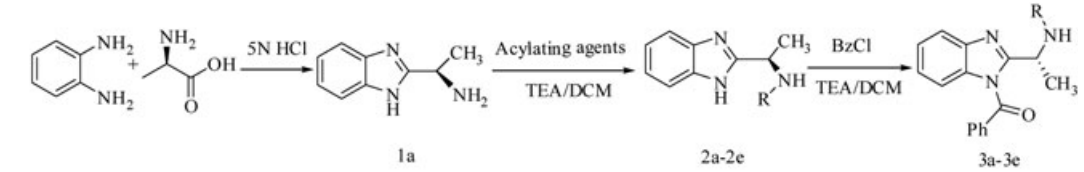
RESULTS AND DISCUSSION

Chiral 2-substituted benzimidazoles as precursors were obtained in poor yields (32–51%) by cyclization reaction of commercially available chiral amino acids with *o*-phenylene diamine *via* the methods that the literatures [15] reported. The low yields blocked synthesis of the chiral acylating agents. However, when the same reaction was heated to 130°C under N_2 atmosphere, good yields (89–94%) were obtained. Then, the benzimidazoles with chiral substituents were converted to different 2-(α-N-substituted aminoethyl)benzimidazoles (**2a**–**2f**) *via* acylation reactions with different acylating agents in good yields. When synthesis of 2-(α-acetylaminoethyl)benzimidazole (**2a**) was proceeded for 3 h, abundant diacylated byproduct and little main product were observed. However, when the reaction was allowed overnight, the diacylated byproduct disappeared, and 2-(α-acetylaminoethyl)benzimidazole (**2a**) as the only product was obtained. This diacylated byproduct could be converted to the main product *via* the reaction with 2-(α-aminoethyl)benzimidazole (**1a**), and 1-acyl-2-(α-N-substituted aminoethyl)benzimidazoles were demonstrated to be valid acylating agents. After **2a**–**2f** were prepared, the benzoylation of **2a**–**2f** was carried out in the system of dichloromethane (DCM) and triethylamine (TEA), and 1-benzoyl-2-(α-N-substituted aminoethyl)benzimidazoles (**3a**–**3f**) were obtained in good yields (Scheme 1).

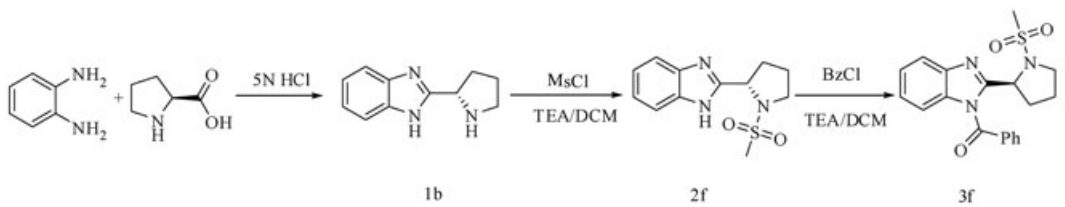
As a typical example, 1-benzoyl-2-(α-acetylaminoethyl) benzimidazole (**3a**) was to be next investigated. The reaction of 1-benzoyl-2-(α-acetylaminoethyl) benzimidazole (**3a**) with racemic phenylalanine methyl ester (**4a**) was carried out in the system of DCM and TEA (Scheme 2). Unexpectedly, *N*-benzonyl phenylalanine methyl ester (**5a**) as a reasonable product was scarcely obtained at room temperature after 120 h. Trace products were obtained in different solvents such as THF, 1,4-dioxane, DMSO, and toluene. However, when anhydrous zinc chloride was used as Lewis acid in the system of THF and TEA, the expected product was observed after 120 h in a poor enantiomeric excess (ee = 32%). Then, acylating agents (**3b**–**3e**) with bulky groups around the chiral center were readily prepared and were submitted to the reaction with racemic phenylalanine methyl ester. The results are shown in Table 1. The acylating agents with more complex acyl groups (**3b** and **3c**) gave obviously lower activity and much lower selectivity. However, acylating agents (**3d** and **3e**) including sulfonyl groups gave reasonable activity and expected selectivity. Due to the fact that acylating agent **3e** could be applied in the reaction with a good enantiomeric excess, acylating agent **3f** bearing a methylsulfonyl group was also used in the reaction with racemic phenylalanine methyl ester. To our disappointment, the product **5a** was not detected.

These results suggested that hydrogen bonding between the acylating agents and α-amino esters and the size of chiral groups may be the key interactions for attaining a high level of kinetic resolution. Acylating agent **3e** bearing a more acidic H atom as hydrogen-bond donor gave better results than **3a**–**3d**. In contrast, acylating agent **3f** without acidic H atom as hydrogen-bond donor was less active and showed almost no selectivity. On the other hand, when

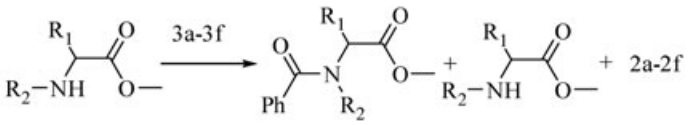
Scheme 1. Preparation of acylating agents.



a: R = acetyl; b: R = benzoyl; c: R = (2S)-N-Cbz-pyrrolidine-2-formacyl; d: R = tosyl; e: R = methylsulfonyl.



Scheme 2. Enantioselective benzoylation of α-amino esters.



4a: $R_1 = CH_2Ph$, $R_2 = H$; 4b: $R_1 = CH_3$, $R_2 = H$; 4c: $R_1 = CH_2OH$, $R_2 = H$; 4d: $R_1 = R_2 = CH_2CH_2CH_2$; 4e: $R_1 = CH_2CH_2(CH_3)_2$, $R_2 = H$; 4f: $R_1 = CH_2(CH_3)_2$, $R_2 = H$.

Table 1

Enantioselective benzoylation of racemic phenylalanine methyl ester.

Entry	Solvent	Acylating agent[a]	Time (h)	Conversion (%)[b]	%ee[c]
1	DCM	**3a**	120	8	Trace
2	Toluene	**3a**	120	–	–
3	DMSO	**3a**	120	12	11
4	THF	**3a**	120	46	32
5	1,4-Dioxane	**3a**	120	40	28
6	THF	**3b**	120	8	–
7	THF	**3c**	120	Trace	–
8	THF	**3d**	120	27	70
9	THF	**3e**	120	48	83
10	THF	**3f**	120	–	–

[a]Conditions: Acylating agent (50 mol %), 15°C.
[b]Isolated yield.
[c]Determined by chiral HPLC [Daicel Chiralpack OD-H (4.6 mm × 250 mm)].

Table 2

Enantioselective benzoylation of racemic phenylalanine methyl ester with **3e**.[g]

Entry	Base	PTC[a]	Time (h)	Conversion[b] (%)	% ee[c]
1	Na_2CO_3	–	120	–	–
2	K_2CO_3	–	120	48	82
3[d]	K_2CO_3	–	160	48	74
4[e]	K_2CO_3	–	72	48	72
5[f]	K_2CO_3	–	48	48	51
6	Cs_2CO_3	–	90	48	80
7	NaOH	–	36	–	–
8	KOH	–	36	–	–
9	K_2CO_3	BTEAC	72	48	84
10	K_2CO_3	TBAB	60	50	72

[a]PTC is phase-transfer catalysts.
[b]Isolated yield.
[c]Determined by chiral HPLC [Daicel Chiralpack OD-H (4.6 mm × 250 mm)].
[d]0°C.
[e]25°C.
[f]40°C.
[g]Conditions: Acylating agent (50 mol %), 15°C.

acylating agents (**3b**–**3d**) with bulky groups were used, *N*-benzonyl phenylalanine methyl ester was obtained in a lower enantiomeric excess. In particular, when **3c** bearing very big size of chiral groups was used, the crowded space led the reaction not to occur. The results show that **3e** exhibits high enantioselectivity for α-amino esters, as **3e** included a chiral group with a suitable size that could provide a more active hydrogen-bond donor.

Optimization of the reaction conditions of 1-benzoyl-2-(α-methylsulfonylaminoethyl)benzimidazole (**3e**) and racemic phenylalanine methyl ester (**4a**) at different temperatures with inorganic bases in THF has been shown in Table 2. Phenylalanine methyl ester (**4a**) was acylated at good conversion with a reasonable enantiomeric excess (ee = 80%), when the reactions were performed at 15°C with K_2CO_3 or Cs_2CO_3 in THF in 90 h. To reduce the reaction time, the phase-transfer catalysts (PTCs) were applied in the reactions. When benzyl triethyl ammonium chloride was used in the reaction, acylating agent **3e** gave the similar selectivity (ee = 84%) in shorter time (72 h). However, when we submitted tetrabutylammonium bromide to the reaction of acylating agent **3e** and racemic phenylalanine methyl ester, the product was obtained more speedily in 48 h with a moderate enantiomeric excess (ee = 72%).

The successful kinetic resolution of racemic phenylalanine methyl ester encouraged us to explore more racemic α-amino esters (Scheme 2), and the results are summarized in Table 3. As expected, *N*-benzonyl amino esters (**5b**–**5f**) were obtained in a reasonable enantiomeric excess. When racemic alanine methyl ester (**4b**) was submitted to the reaction with acylating agent **3e**, the most excellent result occurred in 94% ee at 48.2% conversion. As racemic α-amino esters with bulky groups (**4e**–**4f**) were used, acylating agent **3e** gave lower activity and selectivity. In particular, when valine methyl ester reacted with acylating agent **3e**, *N*-benzonyl valine methyl ester could not be obtained in the optimized condition. Compared to (*S*)-1-benzoyl-2-(α-acetoxyethyl) benzimidazole, which was developed by Karnik and Kamath [6, 7], the present acylating agents are more efficient for α-amino esters bearing small functional groups. More remarkably, abundant new acylating agents with various chiral centers are helpful for in-depth study of the relationship between activity and structures.

Table 3

Enantioselective benzoylation of racemic amino methyl esters with **3e**.

Entry	α-Amino ester	Time (h)	Conversion (%)[a]	% ee[b]	%ee[b], [c]
1	**4a**	72	48	84	78
2	**4b**	90	48	94	85
3	**4c**	90	48	78	38
4	**4d**	90	–	–	–
5	**4e**	120	45	42	37
6	**4f**	160	–	–	–

[a]Isolated yield.
[b]Determined by chiral HPLC [Daicel Chiralpack OD-H (4.6 mm × 250 mm)].
[c]Unreacted amino esters converted to *N*-benzoyl amino esters.

EXPERIMENTAL

Commercially available solvents and reagents were used as received. Melting points were obtained in a Mel-Temp II melting point apparatus and are corrected. Mass spectra were obtained on a Fison Trio 2000 quadrupole mass spectrometer. ^{1}H-NMR spectra were measured on a Varian Mercury-300 NMR spectrometer using tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm) on a δ scale and referenced to the residual solvent peak (^{1}H 7.26 ppm for $CDCl_3$, 2.49 ppm for DMSO-d_6). Coupling constants (*J*) are reported in Hertz. The elemental analysis was performed on a Perkin-Elmer 2400 analyzer. Flash column chromatography was carried out using 300- to 400-mesh silica gel. Thin-layer chromatography was used as an indicator for the completion of the reactions and was performed on silica gel 60A plates. The spots on TLC were visualized by UV. Organic solvent extracts in the isolation procedures were dried over anhydrous magnesium sulfate.

General procedure for the synthesis of 2-(α-N-substituted aminoethyl)benzimidazoles (2a–2f). (Take the synthesis of 2a for an example). A solution of **1a** (0.80 g, 5 mmol) in anhydrous DCM (20 mL) was cooled to 0°C. A solution of TEA (2 mL, 12.5 mmol) and acetic anhydride (0.52 g, 5.5 mmol) in anhydrous DCM (20 mL) was added to the reaction mixture. After 1 h, the mixture was warmed to room temperature and stirred for 5 h. After acylation was completed, the reaction mixture was washed by saturated brine. Organic phase was dried by anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by silica gel column to give **2a** (0.89 g, 43.8 mmol, 87.7%).

2-(α-N-Acetylaminoethyl)benzimidazole (2a). This compound was obtained as a white solid. Mp: 187.3–191.0°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.45 (brs, 1H), 7.54–7.51 (m, 2H), 7.24–7.21 (m, 2H), 5.40–5.30 (m, 1H), 1.88 (s, 3H), 1.76–1.73 (d, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 171.24, 155.77, 137.68, 122.80, 114.99, 44.32, 22.68, 19.15. MS (ESI) *m/z*: calcd for $(M+H)^+$ 204.24, found 203.97. Analysis calculated for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.05; H, 6.52; N, 20.76.

2-(α-N-Benzoylaminoethyl)benzimidazole (2b). General procedure was the same as **2a**. This compound was obtained as a white solid. Mp: 192.2–193.1°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.86 (d, *J* = 7.4 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.61–7.56 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.29 (dd, *J* = 6.4, 3.2 Hz, 2H), 5.57–5.56 (m, 1H), 1.94 (d, *J* = 7.1 Hz, 3H). ^{13}C-NMR (DMSO-d_6, 75 MHz) δ (ppm) 165.98, 156.05, 142.92, 131.36, 128.20, 127.61, 121.83, 118.44, 111.23, 43.96, 19.56. MS (ESI) *m/z*: calcd for $(M+H)^+$ 266.31, found 266.07. Analysis calculated for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.40; H, 5.56; N, 15.89.

2-(α-N-Tosylaminoethyl)benzimidazole (2d). General procedure was the same as **2a**. This compound was obtained as a white solid. Mp: 169.8–172.2°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.75 (d, *J* = 8.2 Hz, 2H), 7.55–7.48 (m, 2H), 7.2–7.20 (m, 2.5 Hz, 4H), 5.96–5.75 (m, 1H), 4.73–4.66 (m, 1H), 2.36 (s, 3H), 1.54 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 154.02, 144.10, 136.48, 129.98, 129.84, 127.28, 127.13, 122.80, 115.20, 48.20, 21.46, 19.83. MS (ESI) *m/z*: calcd for $(M+H)^+$ 316.10, found 316.82. Analysis calculated for $C_{16}H_{17}N_3O_2S$: C, 60.93; H, 5.43; N, 13.32. Found: C, 61.00; H, 5.45; N, 13.27.

2-(α-N-Methylsulfonylaminoethyl)benzimidazole (2e). General procedure was the same as **2a**. This compound was obtained as a white solid. Mp: 169.2–172.2°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.29 (dd, *J* = 6.4, 3.2 Hz, 2H), 7.64–7.55 (m, 2H), 5.60 (brs, 1H), 4.96–4.89 (m, 1H), 2.98 (s, 3H), 1.80 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR (DMSO-d_6, 75 MHz) δ (ppm) 155.41, 139.03, 121.55, 115.09, 47.65, 40.72, 21.03. MS (ESI) *m/z*: calcd for $(M+H)^+$ 240.30, found 240.97. Analysis calculated for $C_{10}H_{13}N_3O_2S$: C, 50.19; H, 5.48; N, 17.56. Found: C, 50.01; H, 5.43; N, 17.79.

2-(1-(Methylsulfonyl)pyrrolidin-2-yl)benzimidazole (2f). General procedure was the same as **2a**. This compound was obtained as a yellow solid. Mp: 208.8–211.1°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.61–7.58 (m, 2H), 7.26–7.22 (m, 2H), 5.02 (dd, *J* = 8.1, 2.9 Hz, 1H), 3.66–3.54 (m, 1H), 3.50–3.36 (m, 1H), 3.09–2.96 (m, 1H), 2.93 (s, 3H), 2.39–2.24 (m, 1H), 2.23–2.00 (m, 2H). ^{13}C-NMR (DMSO-d_6, 75 MHz) δ (ppm) 155.80, 138.59, 121.44, 114.96, 57.40, 48.88, 34.44, 33.10, 24.37. MS (ESI) *m/z*: calcd for $(M+H)^+$ 266.09, found 265.83. Analysis calculated for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84. Found: C, 54.26; H, 5.73; N, 15.97.

General procedure for the synthesis of 1-benzoyl-2-(α-N-substituted aminoethyl)-benzimidazoles (3a–3f). (Take the synthesis of 3a for an example). A solution of **2a** (0.41 g, 2 mmol) in anhydrous DCM (20 mL) was cooled to 0°C. A solution of TEA (2 mL, 12.5 mmol) and benzoyl chloride (0.26 mL 2.2 mmol) in anhydrous DCM (20 mL) was added to the reaction mixture. After 1 h, the mixture was warmed to room temperature and stirred for 5 h. After acylation was completed, the reaction mixture was washed by dilute hydrochloric acid (1*N*) and saturated brine. Organic phase was dried by anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by silica gel column to give **3a** (0.55 g, 18.0 mmol, 90.0%).

1-Benzoyl-2-(α-N-acetylaminoethyl)benzimidazole (3a). This compound was obtained as as colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.82–7.81 (m, 1H), 7.80–7.79 (m, 1H), 7.75–7.70 (m, 2H), 7.57–7.52 (m, 2H), 7.32–7.27 (m, 1H), 7.14–7.09 (m, 1H), 6.85 (brs, 1H), 6.70–6.67 (m, 1H), 5.64–5.55 (m, 1H), 2.00 (s, 3H), 1.68–1.66 (d, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 169.58, 168.32, 158.32, 141.67, 134.29, 133.57, 132.85, 130.20, 129.04, 124.06, 124.03, 119.48, 113.50, 44.16, 22.90, 20.70. MS (ESI) *m/z*: calcd for $(M+H)^+$ 308.35, found 308.40. Analysis calculated for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.36; H, 5.53; N, 13.57.

1-Benzoyl-2-(α-N-benzoylaminoethyl)benzimidazole (3b). General procedure was the same as **3a**. This compound was obtained as yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.82–7.68 (m, 5H), 7.60–7.36 (m, 7H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 5.88–5.79 (m, 1H), 1.76 (d, *J* = 6.7 Hz,

3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 168.39, 166.45, 157.75, 141.74, 134.33, 132.71, 131.46, 130.18, 129.04, 128.36, 127.06, 124.04, 119.73, 113.51, 44.63, 20.87. MS (ESI) *m/z*: calcd for $(M+H)^+$ 370.15, found 369.90. Analysis calculated for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37. Found: C, 74.82; H, 5.23; N, 11.07.

1-Benzoyl-2-(α-N-(2S)-N-Cbz-pyrrolidine-2-formacylaminoethyl) benzimidazole (3c). General procedure was the same as **3a**. This compound was obtained as colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.86–7.27 (m, 10H), 7.11 (d, *J* = 7.9 Hz, 4H), 6.65 (d, *J* = 8.2 Hz, 1H), 5.65–5.50 (m, 1H), 5.13 (s, 2H), 4.53–4.14 (m, 1H), 3.84–3.26 (m, 2H), 2.15–1.54 (m, 7H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 171.43, 170.88, 168.27, 157.33*, 155.79*, 141.91, 134.18, 133.66, 130.14, 128.97, 128.34*, 127.90*, 123.96, 119.93, 113.38, 67.16, 60.74*, 47.43*, 44.21*, 30.09*, 24.47*, 20.62 (*doublet due to the existence of rotamers). MS (ESI) *m/z*: calcd for $(M+H)^+$ 497.21, found 497.41. Analysis calculated for $C_{29}H_{28}N_4O_4$: C, 70.15; H, 5.68; N, 11.28. Found: C, 69.99; H, 5.83; N, 11.41.

1-Benzoyl-2-(α-N-tosylaminoethyl)benzimidazole (3d). General procedure was the same as **3a**. This compound was obtained as colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.78–7.70 (m, 2H), 7.66–7.61 (m, 4H), 7.58–7.50 (m, 2H), 7.44–7.38 (m, 1H), 7.29–7.22 (m, 1H), 7.08–7.02 (m, 3H), 6.51 (d, *J* = 8.3 Hz, 1H), 6.14 (d, *J* = 9.4 Hz, 1H), 5.22–5.03 (m, 1H), 2.19 (s, 3H), 1.64 (d, *J* = 6.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 168.26, 156.53, 143.09, 137.05, 134.32, 132.72, 129.99, 129.25, 129.03, 127.11, 124.16, 120.01, 113.54, 48.10, 22.14, 21.28. MS (ESI) *m/z*: calcd for $(M+H)^+$ 420.13, found 420.57. Analysis calculated for $C_{23}H_{21}N_3O_3S$: C, 65.85; H, 5.05; N, 10.02. Found: C, 65.29; H, 5.06; N, 10.41.

1-Benzoyl-2-(α-N-methylsulfonylaminoethyl)benzimidazole (3e). General procedure was the same as **3a**. This compound was obtained as colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.91–7.70 (m, 4H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.33–7.28 (m, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 5.83–5.74 (m, 1H), 5.39–5.29 (m, 6.84 Hz, 1H), 2.92 (s, 3H), 1.72 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 168.55, 157.21, 141.68, 134.55, 130.14, 129.17, 124.43, 120.20, 113.55, 48.20, 41.44, 22.35. MS (ESI) *m/z*: calcd for $(M+H)^+$ 344.10, found 344.26. Analysis calculated for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24. Found: C, 59.50; H, 5.06; N, 12. 41.

1-Benzoyl-2-(1-(methylsulfonyl)pyrrolidin-2-yl)benzimidazole (3f). General procedure was the same as **3a**. This compound was obtained as colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.82–7.69 (m, 4H), 7.54 (dd, *J* = 9.8, 5.6 Hz, 2H), 7.34–7.27 (m, 1H), 7.09 (dd, *J* = 11.0, 4.6 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 5.49 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.89–3.54 (m, 2H), 2.93 (s, 3H), 2.59 (dd, *J* = 9.5, 3.8 Hz, 1H), 2.38 (ddd, *J* = 25.2, 12.9, 6.5 Hz, 2H), 2.19–1.99 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 168.69, 156.90, 142.11, 134.19, 133.62, 130.29, 124.01, 120.06, 113.42, 57.02, 48.45, 38.18, 33.57, 24.97. MS (ESI) *m/z*: calcd for $(M+H)^+$ 370.10, found 370.61. Analysis calculated for $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.89; H, 5.16; N, 11. 41.

General procedure for benzoylation of racemic amino methyl esters. A solution of **4a** (6.0 mg, 0.04 mmol) in anhydrous THF (20 mL) was cooled to 0°C. Anhydrous zinc chloride (8.0 mg, 0.06 mmol), K_2CO_3 (5.4 mg, 0.04 mmol), and **3e** (6.9 mg, 0.02 mmol) in anhydrous THF (20 mL) were added to the reaction mixture under N_2. After acylation was completed, the reaction mixture was washed by dilute hydrochloric acid (1*N*) and saturated brine. Organic phase was dried by anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by silica gel column to give *N*-benzonyl phenylalanine methyl ester (4.9 mg, 0.019 mmol, 48%) as a white solid. The ee values were determined by HPLC analysis with Daicel Chiralpack OD-H (4.6 mm × 250 mm) with hexane/2-propanol = 90:10 as the eluent [7].

CONCLUSION

Six new 1-benzoyl-2-(α-N-substituted aminoethyl)-benzimidazoles including various chiral centers as acylating agents were prepared facilely and efficiently from commercially available chiral amino acids and *o*-phenylene diamine (in total yields 72–84%). Then, the acylating agents were used in kinetic resolution of racemic α-amino esters, and the reaction conditions of kinetic resolution were optimized in different solvents with various inorganic bases and PTCs. The best result of kinetic resolution was obtained in 94% ee at 48.2% conversion.

Acknowledgments. The authors are grateful for the financial support from National Natural Science Foundation of China (no. 20802025) and Jilin Provincial Science & Technology Sustentation Program (no. 20090585, 20100538).

REFERENCES AND NOTES

[1] (a) Cho, B. K.; Park, H. Y.; Seo, J. H.; Kinnera, K.; Lee, B. S.; Kim, B. G. Biotechnol Bioeng 2004, 88, 512; (b) Zhao, H.; Malhotra, S. V. Biotechnol Lett 2002, 24, 1257; (c) Brown, S. A.; Parker, M. C.; Turner, N. J. Tetrahedron: Asymmetry 2000, 11, 1687.

[2] (a) Wegler, R. Liebigs Ann Chem 1932, 498, 62; (b) Wegler, R. Liebigs Ann Chem 1933, 506, 77; (c) Wegler, R. Liebigs Ann Chem 1934, 510, 72; (d) Wegler, W.; Rüber, A. Chem Ber 1935, 68, 1055; (e) Bird, C. W. Tetrahedron 1962, 18, 1; (f) Stegmann, W.; Uebelhart, P.; Heimgartner, H.; Schmid, H. Tetrahedron Lett 1978, 19, 3091; (g) Potapov, V. M.; Dem'yanovich, V. M.; Khlebnikov, V. A.; Korovina, T. G. Zh Org Khim 1988, 24, 759 and references therein; (h) Weidert, P. J.; Geyer, E.; Horner, L. Liebigs Ann Chem 1989, 533 (i) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. Tetrahedron Lett 1996, 37, 8543; (j) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. Chem Lett 1999, 265, 4; (k) Sano, T.; Miyata, H.; Oriyama, T. Enantiomer 2000, 5, 119.

[3] (a) Vedejs, E.; Chen, X. J Am Chem Soc 1996, 118, 1809; (b) Harper, L. Chem Abstr 2001, 136, 369315; (c) Shaw, S. A.; Aleman, P.; Vedejs, E. J Am Chem Soc 2003, 125, 13368.

[4] (a) Kano, T.; Sasaki, K.; Maruoka, K. Org Lett 2005, 7, 1347; (b) Chan, A.; Scheidt, K. A. Org Lett 2005, 7, 905.

[5] (a) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. J Am Chem Soc 1998, 120, 1629; (b) Jarvo, E. R.; Vasbinder, M. M.; Miller, S. J. Tetrahedron 2000, 56, 9773; (c) Matsuoka, Y.; Ishida, Y.; Sasaki, D.; Saigo, K. Tetrahedron 2006, 62, 8199; (d) Matsuoka, Y.; Ishida, Y.; Sasaki, D. Chem Eur J 2008, 14, 9215; (e) Blay, G.; Domingo, L. R. Chem Eur J 2008, 14, 4725.

[6] Karnik, A. V.; Kamath, S. S. Tetrahedron: Asymmetry 2008, 19, 45.

[7] Karnik, A. V.; Kamath, S. S. J Org Chem 2007, 72, 7435.

[8] Humphrey, J. M.; Chamberlin, A. R. Chem Rev 1997, 97, 2243.

[9] (a) Bommarius, A. S.; Schwarm, M.; Drauz, K. J Mol Catal B: Enzym 1998, 5, 1; (b) Angle, S. R.; Henry, R. M. J Org Chem 1997, 62, 8549; (c) Paruszewski, R.; Strupinska, M.; Stables, J. P.; Czuczwar, S.; Kleinrok, Z.; Turski, W. Chem Pharm Bull 2001, 49, 629; (d) Fedi, V.; Altamura, M.; Balacco, G.; Canfarini, F.; Criscuoli, M.; Giannotti, D.; Giolitti, A.; Giuliani, S.; Guidi, A.; Harmat, N. J. S.; Nannicini, R.; Pasqui, F.; Patacchini, R.; Perrotta, E.; Tramontana, M.; Triolo, A.;

Maggi, C. A. J Med Chem 2004, 47, 6935; (e) Yurek-George, A.; Habens, F.; Brimmell, M.; Packham, G.; Ganesan, A. J Am Chem Soc 2004, 126, 1030.

[10] (a) Norris, P. E.; Blicke, F. F. J Am Pharm Assoc Sci Ed 1952, 41, 637; (b) Jones, T. E.; Wilson, C. O. J Am Pharm Assoc Sc Ed 1953, 42, 340; (c) Patel, D. V.; Gordon, E. M.; Schmidt, R. J. J Med Chem 1995, 38, 435; (d) Patel, V. F.; Andis, S. L.; Kennedy, J. H. J Med Chem 1999, 42, 2588.

[11] (a) Zamora, R.; Hidalgo, F. J. J Agric Food Chem 2006, 54, 398; (b) Rajesh, M.; Kapila, S.; Nam, P. J Agric Food Chem 2003, 51, 2461; (c) Park, E. Y.; Murakami, H.; Matsumura, Y. J Agric Food Chem 2005, 53, 8334.

[12] (a) Shiraiwa, T.; Ohta, A.; Miyazaki, H.; Gogun, Y.; Kurokawa, H. Chirality 1997, 9, 386; (b) Krasnov, V. P.; Zhdanova, E. A.; Solieva, N. Z.; Sadretdinova, L. S.; Bukrina, I. M.; Demin, A. M.; Levit, G. L.; Ezhikova, M. A.; Kodess, M. I. Russ Chem Bull Int Ed 2004, 53, 1331; (c) Marin, J.; Didierjean, C.; Aubry, A.; Casimir, J. R.; Briand, J. P.; Guichard, G. J Org Chem 2004, 69, 130; (d) Krasnov, V. P.; Levit, G. L.; Korolyova, M. A.; Bukrina, I. M.; Sadretdinova, L. S.; Andreeva, I. N.; Charushin, V. N.; Chupakhin, O. N. Russ Chem Bull Int Ed 2004, 53, 1253; (e) Katritzky, A. R.; Jiang, R.; Suzuki, K. J Org Chem 2005, 70, 4993.

[13] Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J. J Chem Soc PerkinTrans 1 2002, 257.

[14] Arseniyadis, S.; Valleix, A.; Wagner, A.; Mioskowski, C. Angew Chem Int Ed 2004, 43, 3314.

[15] (a) Reddy, K. R.; Krishna, G. G.; Rajasekhar, C. V. Synth Commun 2007, 37, 4289; (b) Alatorre-Santamaria, S.; Gotor-Fernández, V. Eur J Org Chem 2009, 15, 2533; (c) Li, Y.; Ding, K.; Sandoval, C. A. Org Lett 2009, 11, 907.