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Practical Stereoselective Synthesis of β-Branched α-Amino Acids through Efficient Kinetic Resolution in the Phase-Transfer-Catalyzed Asymmetric Alkylations

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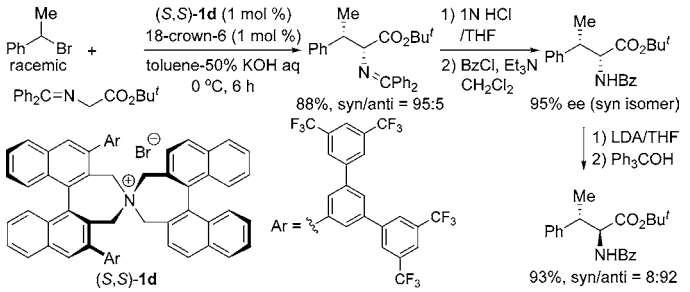
ABSTRACT



Phase-transfer-catalyzed alkylation of glycinate Schiff base with racemic secondary alkyl halides proceeded with excellent levels of syn- and enantioselectivities under the influence of chiral quaternary ammonium bromide 1d and 18-crown-6. The alkylation product can be selectively converted to the corresponding anti isomer, allowing the preparation of all the stereoisomers of β-alkyl-α-amino acid derivatives, an extremely valuable chiral building block.

Stereochemically homogeneous β-branched α-amino acids have been regarded as extremely valuable, conformationally constrained amino acids mainly because their incorporation into peptides results in a significant influence on the conformational preference, providing useful information for the understanding of structure−activity relationships and for the design of peptide analogues with enhanced pharmacological properties.[1] In addition, they are often encountered as components of naturally occurring peptides with unique biological activities.[2] Accordingly, numerous studies have been made for the synthesis of the individual stereoisomer of β-alkyl-α-amino acids (Figure 1), most of which rely on the diastereoselective transformations involving substrates with chiral auxiliaries[3] or resolution of racemates.[4] Hence, to our knowledge, the catalytic asymmetric approach toward

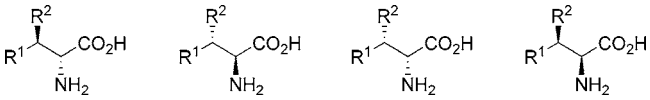


Figure 1. Four possible stereoisomers of β-branched α-amino acid.

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(1) For general reviews, see: (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. See also: (c) Qian, X.; Shenderovich, M. D.; Kövér, K. E.; Davis, P.; Horváth, R.; Zalewska, T.; Yamamura, H. I.; Porreca, F.; Hruby, V. J. *J. Am. Chem. Soc.* **1996**, *118*, 7280. (d) Hruby, V. J. *J. Med. Chem.* **2003**, *46*, 4215.

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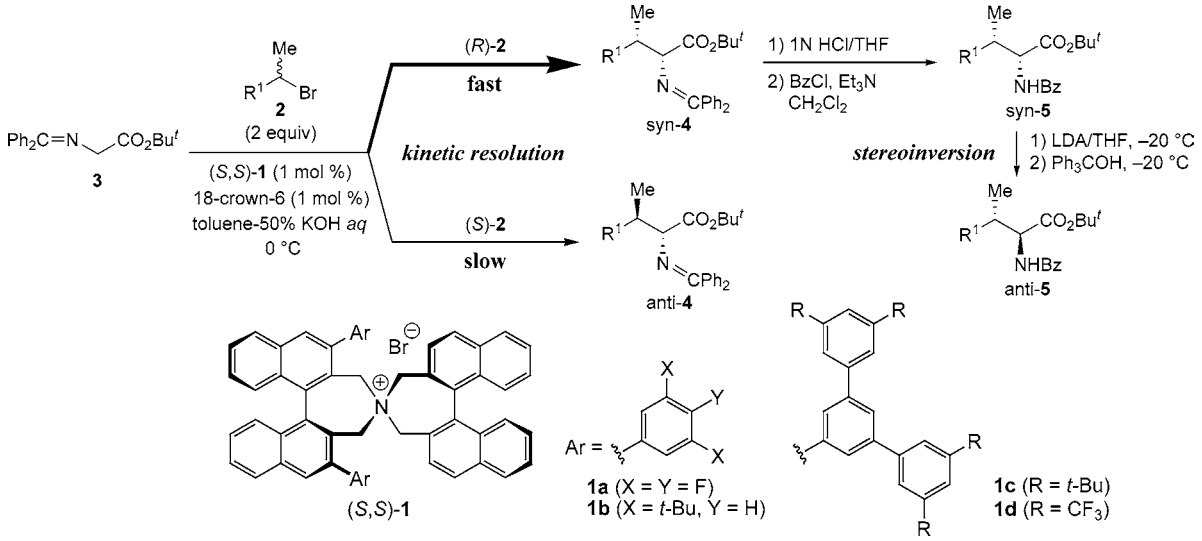
Scheme 1



this subject has been restricted to only two examples recently reported. In 1995, Burk and co-workers pioneered the enantioselective hydrogenation of β,β-disubstituted didehydroamino acids utilizing rhodium chiral bisphosphine complexes,[5] and Turner and co-workers elegantly combined it with an amino acid oxidase (AAO) stereoinversion procedure, offering a chemobiocatalytic method for the synthesis of the possible four stereoisomers of β-methyl-β-arylalanine analogues.[6] However, this strategy based on the transition-metal-catalyzed asymmetric hydrogenation inevitably requires the stereoselective, multistep preparation of (*E*)- and (*Z*)-isomers of the starting didehydroamino esters. In this context, we have been interested in the possibility of direct construction of β-alkyl-α-amino acid derivatives from a glycine unit through the alkylation with readily available *racemic* secondary alkyl halides under phase-transfer conditions in the presence of chiral quaternary ammonium salts of type **1** as catalyst.[7] If the chiral ammonium cation of appropriately modified **1** could precisely discriminate not only the enantiofaces of the prochiral enolate but also the central chirality of the halides during this bond-forming event, simultaneous establishment of relative and absolute stereochemistries of the target amino acid derivatives could be achieved. In this Letter, we wish to disclose the realization of this phase-transfer-catalyzed alkylation involving impressive kinetic resolution, together with the highly selective inversion of α-stereogenic carbon centers by a simple deprotonation−protonation sequence, thereby providing a versatile chemical process for the synthesis of all the stereoisomers of β-methyl-α-amino acid derivatives (Scheme 1).

Asymmetric alkylation of glycinate Schiff base **3** using chiral phase-transfer catalysts has been intensively studied and rapidly developed into a powerful method for the synthesis of optically active α-amino acids.[8] Surprisingly, however, the stereochemistry of the alkylation of **3** with chiral electrophiles (alkyl halides), particularly those having an asymmetric center on the electrophilic carbon itself, has never been addressed.[9] Our initial examination was therefore focused on the search for the appropriate phase-transfer conditions including catalyst structure to attain sufficient reactivity and selectivity in the reaction of **3** with commercially available, *racemic* 1-bromo-1-phenylethane (**2a**). Attempted treatment of **3** with **2a** (2 equiv) and (*S,S*)-**1a**,[10] a promising catalyst for the asymmetric alkylation of **3** with simple achiral alkyl halides, in toluene−50% KOH aqueous

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(8) For recent reviews, see: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. See also ref 7.

(9) The stereochemical outcome of the alkylation of **3** with β-chiral alkyl halides has been investigated. See: (a) Lépine, R.; Carbonnelle, A.-C.; Zhu, J. *Synlett* **2003**, 1455. (b) Armstrong, A.; Scutt, J. N. *Org. Lett.* **2003**, *5*, 2331. (c) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073.

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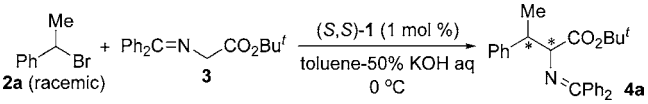
solution at 0 °C for 11 h gave rise to β-methylphenylalanine (β-MePhe) derivative **4a** in only 12% isolated yield as a 57:43 mixture of syn and anti isomers, whose enantiomeric excesses were determined to be 96% ee and 98% ee, respectively (entry 1 in Table 1). In contrast, *syn*-**4a** was

Table 1. Optimization of the Reaction Conditions in the Phase-Transfer-Catalyzed Alkylation of **3** with Racemic 1-Bromo-1-phenylethane (**2a**) Using (*S*,*S*)-**1** as Catalyst[a]



entry	catalyst (**1**)	concn (M)	time (h)	yield[b] (%)	syn/anti[c]	ee[d,e] (%)
1	**1a**	0.17	11	12	57:43	96 (98)[f]
2	**1b**		14	47	91:9	81
3	**1c**		10	30	93:7	91
4	**1d**		8	44	95:5	94
5	**1d**	0.33	8	73	>95:5	95
6[g]	**1d**		6	88	95:5	95

[a] Unless otherwise noted, the reaction was conducted with 2 equiv of **2a** and 1 mol % of (*S*,*S*)-**1** in toluene−50% KOH aqueous solution at 0 °C for the given reaction time. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Enantiopurity of *syn*-**4a**, which was determined by HPLC using a chiral column (DAICEL chiralpak AD-H) with hexane-2-propanol as solvent after derivatization to *N*-benzoate (*syn*-**5a**). [e] Absolute configuration of *syn*-**4a** was assigned to be (2*R*,3*S*). For details, see the Supporting Information. [f] Enantiomeric excess of *anti*-**4a** is shown in parentheses. [g] With 1 mol % of 18-crown-6.

obtained predominantly in higher chemical yield (47%) but with decreased enantioselectivity (81% ee) when the catalyst **1b**[9c] bearing a 3,5-di-*tert*-butylphenyl group at the 3,3′-position of one binaphthyl subunit (Ar) was employed (entry 2). Here, the importance of the steric effect of the Ar moiety for establishing kinetic resolution of **2a** as well as enantiofacial discrimination of the enolate of **3** turned out to be evident from the enhanced diastereo- and enantioselectivities of the reaction under the influence of **1c**[9c] with a radially extended 3,5-bis(3,5-di-*tert*-butylphenyl)phenyl substituent (entry 3). Furthermore, introduction of electron-withdrawing trifluoromethyl functionality in place of the *tert*-butyl group (**1d**)[11] was found to provide the highest levels of both diastereo- and enantiocontrols (entry 4), and increasing the substrate concentration delivered substantial rate acceleration without sacrificing the stereoselectivities (entry 5). Although the chemical yield was still insufficient at this stage, use of 18-crown-6 as an achiral cocatalyst fortunately solved this problem.[12] Thus, vigorous stirring of a mixture of **3**, **2a** (2 equiv), and 1 mol % each of (*S*,*S*)-**1d** and 18-crown-6 in toluene (0.33 M substrate concentration)−50% KOH aqueous solution at 0 °C for 6 h led to the almost exclusive formation of *syn*-**4a** in 88% yield with 95% ee (entry 6).

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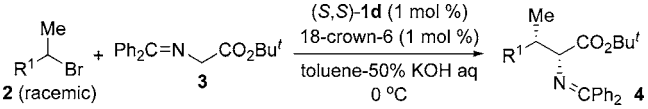
The optimized reaction condition was used for investigating the applicability of this method for the synthesis of various β-methyl-α-amino acid derivatives. As listed in Table 2, a series of 1-bromo-1-arylethanes with substituents of

Table 2. Scope of Secondary Alkyl Halides **2**[a]



entry	R^1	time (h)	yield[b] (%)	syn/anti[c]	ee[d,e] (%)	product
1	*p*-F-C_6H_4	4.5	93	>95:5	97	**4b**
2	*p*-Me-C_6H_4	3.5	82	>95:5	99	**4c**
3	2-Naph	7	65	>95:5	86	**4d**
4	PhC≡C	3.5	80	>95:5	97	**4e**
5	*t*-BuO_2C	5	45	86:14	91	**4f**

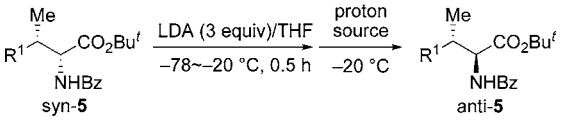
[a] The reaction was carried out with 2 equiv of **2** and 1 mol % each of (*S*,*S*)-**1d** and 18-crown-6 in toluene−50% KOH aqueous solution at 0 °C for the given reaction time. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Enantiopurity of *syn*-**4** was determined by HPLC using a chiral column (DAICEL chiralpak AD-H) after derivatization to *N*-benzoate (*syn*-**5**). For details, see the Supporting Information. [e] Assignment of the absolute configuration was deduced from that of *syn*-**4a**.

different electronic properties were employable, allowing the preparation of diverse β-MePhe analogues including β-methyl-3-(2-naphthyl)alanine (β-Me2Nal) (entries 1−3). Asymmetric construction of β-alkynyl-α-amino acid ester and β-methylaspartate can also be achieved in a similar manner with appropriate secondary alkyl bromides, though relatively lower chemical yield and diastereoselectivity were observed in the reaction with *tert*-butyl 2-bromopropionate (entries 4 and 5).

Given the present highly diastereo- and enantioselective alkylation protocol that enables the preparation of both enantiomers of *syn*-β-methyl-α-amino acid esters using either (*S*,*S*)- or (*R*,*R*)-**1d** as catalyst, we further envisaged providing a ready access to anti diastereomers by configurational inversion of the α-stereocenter of the syn isomers. Our strategy to this end is the simple deprotonation of *syn*-**5** and selective reprotonation of the resulting enolates bearing a stereochemically defined β-chiral center, and we tested the feasibility with *syn*-**5a** (95% ee, syn/anti = 95:5) as a model substrate (Table 3).[13] Complete deprotonation of *syn*-**5a** was realized by the treatment with 3 equiv of LDA in THF at −78 to −20 °C for 0.5 h, and subsequent protonation by the addition of H_2O at the same temperature furnished **5a** with high preference to the anti isomer (syn/anti = 17:83) (entry 1). While switching the proton source to methanol showed a similar degree of diastereoselectivity (entry 2), increasing the steric size of an alcohol substituent appeared beneficial for the enhancement of the anti selectivity, and *anti*-**5a** was obtained predominantly (syn/anti = 8:92) with 89% ee by the use of triphenylmethanol (entries 3 and 4).[14]

(13) For comparison of the nitrogen-protecting groups, see the Supporting Information.

Table 3. Stereoinversion of *syn*-**5** to *anti*-**5** through a Deprotonation−Protonation Sequence[a]

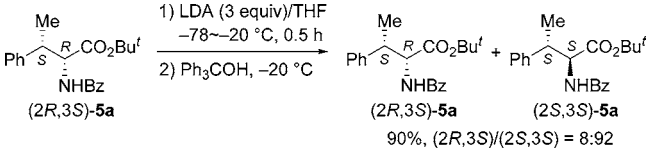


entry	R^1 (**5**, syn/anti, %ee)	proton source	yield (%)[b]	syn/anti[c]	ee[d,e] (%)
1	Ph (**5a**, 95:5, 95)	H_2O	96	17:83	88
2		MeOH	94	17:83	87
3		*t*-BuOH	96	14:86	88
4		Ph_3COH	93	8:92	89
5	*p*-F-C_6H_4 (**5b**, >95:5, 97)		87	8:92	88
6	*p*-Me-C_6H_4 (**5c**, >95:5, 99)		89	9:91	92
7	2-Naph (**5d**, >95:5, 86)		90	5:95	84

[a] The reaction was performed by the treatment of *syn*-**5** with 3 equiv of LDA at −78 to −20 °C for 0.5 h and subsequent addition of an appropriate proton source at −20 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Enantiopurity of *anti*-**5** was determined by HPLC using a chiral column. For details, see the Supporting Information. [e] The absolute configuration of *anti*-**5a** was assigned to be (2*S*,3*S*) (see the Supporting Information), and those for *anti*-**5b**−**d** were assumed in analogy.

With this information in hand, we examined the stereoinversion of various enantiomerically enriched *syn*-**5**, and typical results included in Table 3 demonstrate the effectiveness of the deprotonation−protonation procedure for the preparation of *anti*-*β*-methyl-α-amino acid esters (*anti*-**5**) with high levels of diastereo- and enantiomeric excesses (entries 5−7). It is worth noting that the decrease in the enantiomeric excess of *anti*-**5** is not due to the intervention of inversion at the *β*-stereogenic center and is primarily dependent on the stereochemical purity of the starting *syn*-**5**, i.e., stereoselectivity of the initial alkylation process. Indeed, exposure of essentially pure (2*R*,3*S*)-**5a** to similar conditions resulted in the formation of (2*R*,3*S*)- and (2*S*,3*S*)-**5a** in a ratio of 8:92 (90% isolated yield), and neither (2*R*,3*R*) nor (2*S*,3*R*) isomers were detected (Scheme 2). This observation certainly confirms that the stereoinversion occurs exclusively at the α-carbon of **5**.

Scheme 2



In conclusion, we have successfully demonstrated that the phase-transfer catalysis of chiral quaternary ammonium bromide **1d** and 18-crown-6 creates a new opportunity for the asymmetric alkylation of glycinate Schiff base, which involves an efficient kinetic resolution of racemic secondary alkyl halides, giving a straightforward entry to enantiomerically enriched *syn*-*β*-alkyl-α-amino acid esters. Moreover, a simple deprotonation−protonation procedure has been elaborated for the stereoinversion of the syn product to the corresponding anti isomer. We believe the present study paves the way to the practical chemical synthesis of all the stereoisomers of a wide range of *β*-alkyl-α-amino acid derivatives.

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Supporting Information Available: Detailed experimental procedures including stereochemical assignment and spectroscopic characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We demonstrated that **5a** can be readily derivatized to the corresponding amino acid without loss of stereochemical purity. For details, see the Supporting Information.