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Convenient preparation of chiral phase-transfer catalysts with conformationally fixed biphenyl core for catalytic asymmetric synthesis of α-alkyl- and α,α-dialkyl-α-amino acids: application to the short asymmetric synthesis of BIRT-377

Yong-Gang Wang, Mitsuhiro Ueda, Xisheng Wang, Zhenfu Han and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan

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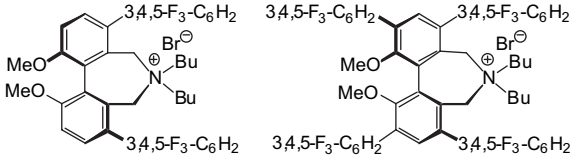
Abstract—Chiral phase-transfer catalysts (*S*)-**1a**, (*S*)-**1b**, and (*S*)-**2** with conformationally fixed biphenyl cores were conveniently prepared from the known, easily available (*S*)-6,6′-dimethylbiphenyl-2,2′-diol **3** and (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyl-2,2′-dicarboxylic acid **14**, respectively, in five steps. The catalysts, (*S*)-**1a** and (*S*)-**1b** are readily applicable to asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with excellent enantioselectivity. In particular, catalyst (*S*)-**1b** was found to exhibit the unique temperature effect on the enantioselectivity, and asymmetric alkylation of glycine derivatives at room temperature gave higher enantiomeric excess than that at 0 °C. In addition, the catalyst (*S*)-**2** exhibited the high catalytic performance (0.01–1 mol %) in the asymmetric alkylation of *N*-(diphenylmethylene)-glycine *tert*-butyl ester and *N*-(*p*-chlorophenylmethylene)alanine *tert*-butyl ester compared to the existing chiral phase-transfer catalysts, thereby allowing to realize a general and useful procedure for highly practical enantioselective synthesis of structurally diverse natural and unnatural α-alkyl-α-amino acids as well as α,α-dialkyl-α-amino acids. This approach is successfully applied to the short asymmetric synthesis of cell adhesion BIRT-377.

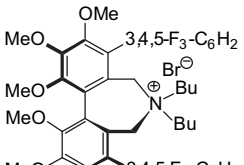
1. Introduction

Phase-transfer catalysis (PTC) has been recognized as a convenient and highly useful synthetic tool in both academia and industry because of several advantages of PTC (operational simplicity, mild reaction conditions with aqueous media and environmental consciousness, suitability for large-scale reactions, etc.), which meet the current requirement for practical organic synthesis.[1,2] Accordingly, various types of chiral phase-transfer catalysts have been developed in recent years and the chiral efficiency of such phase-transfer catalysts was examined by the application to the development of new methodologies for the asymmetric synthesis of both natural and unnatural α-alkyl- and α,α-dialkyl-α-amino acids, especially in enantiomerically pure form.[3,4] However, despite numerous studies on asymmetric amino acid syntheses, practical catalytic systems using the easily available catalysts with high enantioselection at low catalyst loading (e.g., <1 mol %) are still rare in asymmetric carbon–carbon bond formation. Major progress in terms of catalyst loading as well as the easy availability of catalysts is still most desirable for practical asymmetric synthesis.[5] In this article, we wish to report the synthesis of new phase-transfer catalysts (*S*)-**1a**, (*S*)-**1b**, and (*S*)-**2** with a chiral biphenyl backbone, and their application to asymmetric alkylation of glycine and alanine derivatives with excellent enantioselectivity.[6]



(*S*)-**1a**

(*S*)-**1b**



(*S*)-**2**

Keywords: Phase-transfer catalyst; Asymmetric alkylation; α-Amino acids; Glycine; Alanine.
* Corresponding author. Tel./fax: +81 75 753 4041; e-mail: maruoka@kuchem.kyoto-u.ac.jp

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2. Results and discussion

2.1. Synthesis of chiral phase-transfer catalysts (*S*)-1a and (*S*)-1b

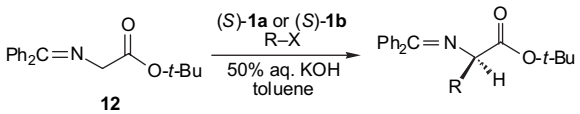
The requisite catalysts, (*S*)-**1a** and (*S*)-**1b** can be easily prepared from the known (*S*)-6,6′-dimethylbiphenyl-2,2′-diol (*S*)-**3** (>99% ee), which is conveniently derived from commercially available 4,6-di-*tert*-butyl-*m*-cresol according to the reported procedure.[7] Methylation of (*S*)-**3** and subsequent selective *para*-bromination of the resulting (*S*)-**4** afforded (*S*)-5,5′-dibromo-2,2′-dimethoxy-6,6′-dimethylbiphenyl (*S*)-**5** in 97% combined yield. Suzuki–Miyaura coupling of dibromide (*S*)-**5** and radical bromination of the resulting coupling product (*S*)-**6** gave dibromide (*S*)-**7** in 91% combined yield. Treatment of (*S*)-**7** with Bu_2NH furnished chiral quaternary ammonium salt (*S*)-**1a** in 83% overall yield from the known (*S*)-**3** (Scheme 1).

In a similar manner, chiral quaternary ammonium salt (*S*)-**1b** was prepared from the known (*S*)-**3** in moderate overall yield except the use of the initial bromination of (*S*)-**3** and subsequent methylation of the resulting (*S*)-**8** as shown in Scheme 2.

2.2. Evaluation of the reactivity and selectivity of (*S*)-1a and (*S*)-1b in the asymmetric alkylation of glycinate Schiff base 12

The chiral efficiency of these chiral phase-transfer catalysts (*S*)-**1a** and (*S*)-**1b** was examined by carrying out asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **12**, and the selected data are listed in Table 1. Thus, reaction of **12** with benzyl bromide (3 equiv) and 50% aqueous KOH in toluene was effected in the presence of 1 mol % of catalyst (*S*)-**1a** under argon atmosphere at 0 °C for 5 h to furnish

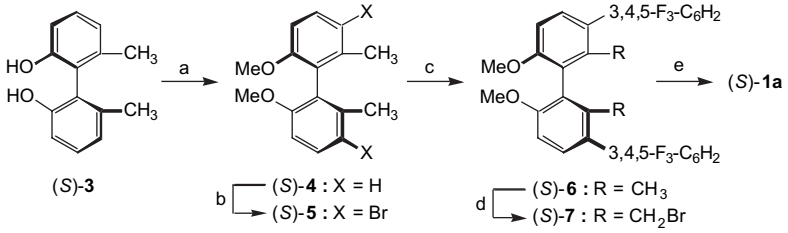
Table 1. Catalytic enantioselective phase-transfer alkylation of glycine derivative **12**[a]



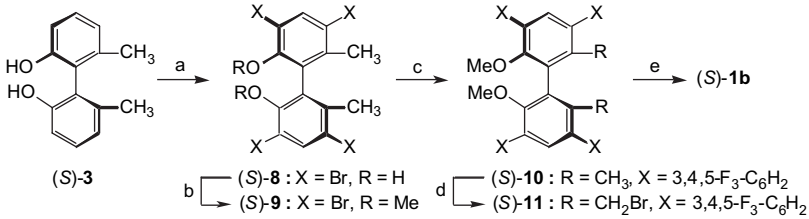
(*R*)-**13a** (R = benzyl)
(*R*)-**13b** (R = allyl)
(*R*)-**13c** (R = propargyl)
(*R*)-**13d** (R = ethyl)

Entry	Catalyst (mol %)	RX (equiv)	Condition (°C, h)	Yield[b] (%)	% ee[c] (config)[d]
1	(*S*)-**1a** (1)	$PhCH_2Br$ (3)	0, 5	97	96 (*R*)
2	(*S*)-**1a** (1)	$PhCH_2Br$ (3)	20, 3	99	91 (*R*)
3	(*S*)-**1a** (1)	$CH_2{=}CHCH_2Br$ (3)	0, 2.5	90	93 (*R*)
4	(*S*)-**1a** (1)	$HC{\equiv}CCH_2Br$ (3)	0, 4	95	86 (*R*)
5	(*S*)-**1a** (1)	EtI (8)	0, 8	92	81 (*R*)
6	(*S*)-**1b** (1)	$PhCH_2Br$ (1.5)	0, 4	94	86 (*R*)
7	(*S*)-**1b** (1)	$PhCH_2Br$ (1.5)	20, 2.5	96	98 (*R*)
8	(*S*)-**1b** (1)	$PhCH_2Br$ (1.5)	28, 5	93	95 (*R*)
9	(*S*)-**1b** (0.5)	$PhCH_2Br$ (1.2)	20, 5	93	95 (*R*)
10[e]	(*S*)-**1b** (0.1)	$PhCH_2Br$ (1.5)	20, 12	94	95 (*R*)
11	(*S*)-**1b** (1)	$CH_2{=}CHCH_2Br$ (1.5)	0, 3.5	92	88 (*R*)
12	(*S*)-**1b** (0.5)	$CH_2{=}CHCH_2Br$ (1.5)	20, 5	95	93 (*R*)
13	(*S*)-**1b** (1)	$CH_2{=}CHCH_2Br$ (1.5)	28, 4	95	90 (*R*)
14	(*S*)-**1b** (1)	$HC{\equiv}CCH_2Br$ (1.5)	0, 3	94	87 (*R*)
15	(*S*)-**1b** (0.5)	$HC{\equiv}CCH_2Br$ (1.5)	20, 6	92	91 (*R*)
16	(*S*)-**1b** (1)	$HC{\equiv}CCH_2Br$ (2)	28, 2	91	87 (*R*)
17	(*S*)-**1b** (1)	EtI (8)	0, 10	86	90 (*R*)
18	(*S*)-**1b** (1)	EtI (8)	20, 10	81	90 (*R*)

[a] Unless otherwise specified, the reaction was carried out with 1.5–8 equiv of RX in the presence of 0.1–1 mol % of (*S*)-**1a** or (*S*)-**1b** in 50% aqueous KOH/toluene (volume ratio=2:3) under the given reaction conditions.
[b] Isolated yield.
[c] Enantiopurity of (*R*)-**13** was determined by HPLC analysis of the alkylated imine using a chiral column [DAICEL Chiralcel OD] with hexane/isopropanol as solvent.
[d] Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[4b]
[e] A five-gram scale of **12** was used.



Scheme 1. Reagents and conditions: (a) MeI (20 equiv), K_2CO_3 (10 equiv), acetone, quant; (b) Br_2 (2.1 equiv), AcOH (0.2 equiv), CH_2Cl_2, 97%; (c) (3,4,5-F_3-C_6H_2)$B(OH)_2$ (4 equiv), $Pd(OAc)_2$ (0.2 equiv), P(*o*-Tol)$_3$ (0.8 equiv), $K_3PO_4{\cdot}nH_2O$ (10 equiv), DMF, reflux, quant; (d) AIBN (0.1 equiv), NBS (2.1 equiv), benzene, 91%; (e) Bu_2NH (0.9 equiv), K_2CO_3 (10 equiv), MeCN, reflux, 94%.



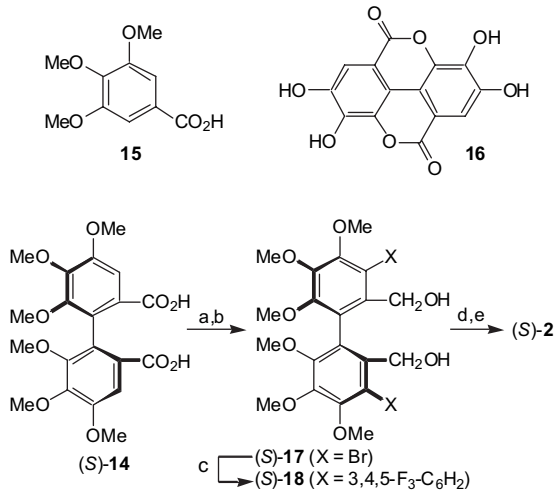
Scheme 2. Reagents and conditions: (a) Br_2 (4.1 equiv), AcOH (0.2 equiv), CH_2Cl_2, 87%; (b) MeI (20 equiv), K_2CO_3 (10 equiv), acetone, 98%; (c) (3,4,5-F_3-C_6H_2)$B(OH)_2$ (8 equiv), $Pd(OAc)_2$ (0.2 equiv), P(*o*-Tol)$_3$ (0.8 equiv), $K_3PO_4{\cdot}nH_2O$ (10 equiv), DMF, reflux, 65%; (d) AIBN (0.1 equiv), NBS (2.1 equiv), benzene; (e) Bu_2NH (0.9 equiv), K_2CO_3 (10 equiv), MeCN, reflux, 53% for two steps.

benzylation product (*R*)-**13a** (R=CH_2Ph) in 97% yield with excellent enantioselectivity (96% ee) (entry 1). As expected, the enantioselectivity is decreased upon warming to room temperature (entry 2). Asymmetric allylation, propargylation, and ethylation of **12** also proceeded smoothly at 0 °C with high enantioselectivity (entries 3–5). Based on these results, asymmetric benzylation of **12** with catalyst (*S*)-**1b** was carried out both at 0 and 20 °C (entries 6 and 7). Surprisingly, the room temperature (20 °C) reaction was found to exhibit higher enantioselectivity, although use of higher temperature slightly lowered the enantioselectivity (entry 8). This unique temperature effect on the enantioselectivity was also observed in asymmetric propargylation and allylation reactions (entries 11–16). The catalytic amount of (*S*)-**1b** can be reduced to 0.5 mol % (entries 9, 12, and 15). In particular, in a five-gram scale reaction, the catalyst loading can be further reduced to 0.1 mol % without decreasing the enantioselectivity (entry 10).

The unique temperature effect on the enantioselectivity of (*R*)-**13** as described above might be ascribed to the steric hindrance of two 3,3′-bis(3,4,5-trifluorophenyl) substituents in (*S*)-**1b** as shown in Figure 1. At lower temperature, these 3,3′-bis(3,4,5-trifluorophenyl) substituents would occupy the perpendicular position to the chiral biphenyl moiety in (*S*)-**1b**, thereby disturbing the favorable aromatic π−π interaction between the chiral biphenyl moiety of (*S*)-**1b** and the benzophenone imine part of the glycine enolate in the transition state structure. At higher temperature (20 °C), the 3,3′-bis(3,4,5-trifluorophenyl) substituents would rotate to an appropriate angle for the more effective aromatic π−π interaction to achieve the higher enantioselectivity.

2.3. Synthesis of chiral phase-transfer catalyst (*S*)-2

The chiral phase-transfer catalyst (*S*)-**2** can be conveniently prepared from the known (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyl-2,2′-dicarboxylic acid (*S*)-**14** (Scheme 3), which is readily derived from commercially available gallic acid derivative **15** or ellagic acid **16**.[8] Reduction of chiral dicarboxylic acid (*S*)-**14** with $BH_3\cdot SMe_2$ and subsequent addition of Br_2/Py gave rise to (*S*)-3,3′-dibromo-4,5,6,4′,5′,6′-hexamethoxybiphenyl-2,2′-dimethanol (*S*)-**17** in 95% yield.[9] Suzuki–Miyaura cross coupling of (*S*)-**17** with 3,4,5-trifluorophenylboronic acid in the presence of catalytic $Pd(OAc)_2$, P(*o*-Tol)$_3$, and K_3PO_4 in THF afforded (*S*)-3,3′-bis(3,4,5-trifluorophenyl)-4,5,6,4′,5′,6′-hexamethoxybiphenyl-2,2′-dimethanol (*S*)-**18** in 78% yield. Bromination of (*S*)-**18** with PBr_3 in THF and subsequent treatment with dibutylamine and K_2CO_3 in acetonitrile led to the formation of the catalyst (*S*)-**2** in 90% yield. The overall yield of (*S*)-**2** by five-step sequence from the known dicarboxylic acid (*S*)-**14** is 67%.



Scheme 3. Reagents and conditions: (a) $BH_3\cdot SMe_2$ (4 equiv), THF/$B(OMe)_3$ (2:1); (b) Br_2/Py (7 equiv), THF, 95% from (*S*)-**14**; (c) (3,4,5-F_3-C_6H_2)$B(OH)_2$ (5 equiv), $Pd(OAc)_2$ (20 mol %), P(*o*-Tol)$_3$ (80 mol %), $K_3PO_4\cdot nH_2O$ (10 equiv), THF, 78%; (d) PBr_3 (2 equiv), THF; (e) Bu_2NH (1.1 equiv), K_2CO_3 (2 equiv), CH_3CN, reflux, 90% from (*S*)-**18**.

2.4. Evaluation of the reactivity and selectivity of (*S*)-2 in the asymmetric alkylation of glycinate Schiff base 12

The chiral efficiency of the phase-transfer catalyst (*S*)-**2** was examined by carrying out asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **12** (Table 2). Thus, reaction of **12** with benzyl bromide (1.5 equiv) and 50% aqueous KOH in toluene was effected in the presence of 1 mol % of catalyst (*S*)-**2** under argon atmosphere at 0–25 °C for several hours to furnish benzylation product (*R*)-**13** (R=CH_2Ph) in 95–97% yields with excellent

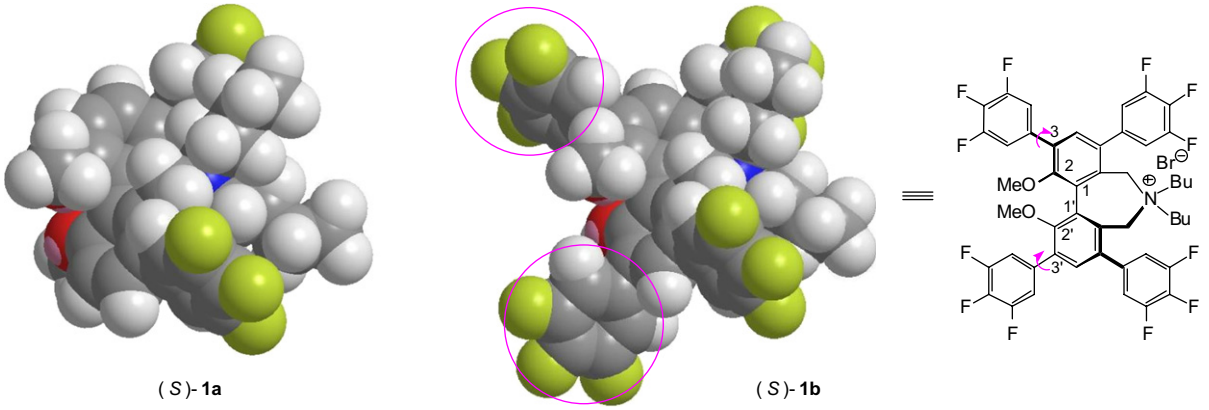
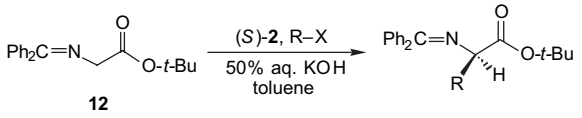


Figure 1. Space filling models of chiral phase-transfer catalysts (*S*)-**1a** and (*S*)-**1b**. In (*S*)-**1b**, two 3,3′-bis(3,4,5-trifluorophenyl) substituents are indicated by the light violet circle.

Table 2. Catalytic enantioselective phase-transfer alkylation of glycine derivative **12**[a]



(*R*)-**13a** (R = benzyl)
(*R*)-**13b** (R = allyl)
(*R*)-**13c** (R = propargyl)
(*R*)-**13d** (R = ethyl)
(*R*)-**13e** (R = *p*-bromobenzyl)

Entry	Catalyst (mol %)	RX	Condition (°C, h)	Yield[b] (%)	% ee[c] (config)
1	(*S*)-**2** (1)	$PhCH_2Br$	0, 6	95	98 (*R*)
2	(*S*)-**2** (1)	$PhCH_2Br$	25, 4.5	97	97 (*R*)
3	(*S*)-**2** (0.1)	$PhCH_2Br$	25, 11	96	97 (*R*)
4	(*S*)-**2** (0.05)	$PhCH_2Br$	25, 20	94	97 (*R*)
5	(*S*)-**2** (0.01)	$PhCH_2Br$	25, 24	95	96 (*R*)
6	(*S*)-**2** (0.05)	*p*-Br-C_6H_4-CH_2Br	25, 20	92	96 (*R*)
7	(*S*)-**2** (0.5)	CH_2=$CHCH_2Br$[d]	0, 5	99	96 (*R*)
8	(*S*)-**2** (0.5)	HC≡CCH_2Br	0, 5	97	96 (*R*)
9	(*S*)-**2** (0.1)	EtI[e]	25, 36	80	94 (*R*)

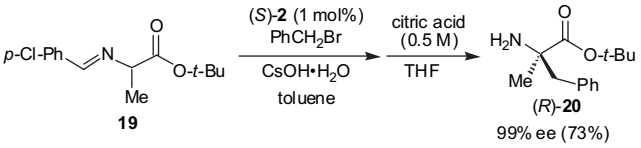
[a] Unless otherwise specified, the reaction was carried out with 1.5 equiv of RX in the presence of catalytic (*S*)-**2** in 50% aqueous KOH/toluene (volume ratio=2:3) under the given reaction conditions.
[b] Isolated yield.
[c] Enantiopurity of **13** was determined by HPLC analysis of the alkylated imine using a chiral column [DAICEL Chiralcel OD] with hexane–isopropanol as solvent.
[d] Use of 3 equiv of R–X.
[e] Use of excess ethyl iodide (8 equiv).

enantioselectivity (97–98% ee) (entries 1 and 2). Quite surprisingly (*S*)-**2** was found to be a very active catalyst among existing chiral phase-transfer catalysts, and the amount of the catalyst can be lowered to 0.1 and 0.05 mol % in the asymmetric benzylation of glycine derivative **12** without decreasing the enantioselectivity (entries 3 and 4).[5] Even 0.01 mol % of catalyst (*S*)-**2** still gave high enantioselectivity (96% ee at 25 °C for 24 h) (entry 5).

Other selected examples are also listed in Table 2. Several characteristic features of the present alkylations are as follows: (1) in contrast to the existing chiral phase-transfer catalysts, the catalyst (*S*)-**2** exhibited high catalytic performance (0.01–0.5 mol %), demonstrating the remarkable efficiency and practicability of the present approach for the enantioselective synthesis of α-alkyl-α-amino acids. (2) Not only benzylation and allylation, but also alkylation of **12** with a simple alkyl halide such as ethyl iodide proceeded smoothly under mild conditions to furnish the corresponding α-alkyl-α-amino acids in high yield and excellent enantioselectivity (entry 9).

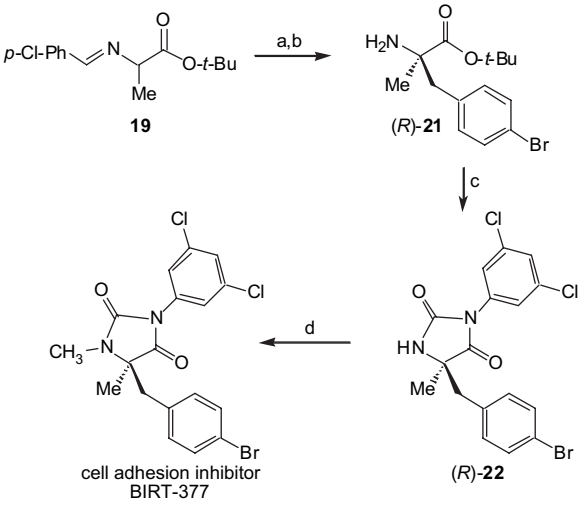
2.5. Evaluation of the reactivity and selectivity of (*S*)-2 in the asymmetric alkylation of alaninate Schiff base 19

The catalyst (*S*)-**2** is, of course, applicable to the asymmetric alkylation of aldimine Schiff base **19** derived from DL-alanine *tert*-butyl ester. Thus, reaction of **19** with benzyl bromide (1.5 equiv) and $CsOH \cdot H_2O$ (5 equiv) in toluene in the presence of 1 mol % of catalyst (*S*)-**2** under argon atmosphere at 0 °C for 10 h gave, after acidic work-up, rise to benzylation product (*R*)-**20** in 73% yield with 99% ee.



2.6. Application to the short synthesis of BIRT-377

BIRT-377 is a potent inhibitor of the interaction between intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1),[10] potential therapeutics designed to block the binding of LFA-1 and ICAM-1 for the treatment of immunological disorders,[11a] had been mostly mAb based,[11b] mainly because of the problems inherent in identifying or designing small molecules that antagonize protein–protein interactions.[11c,d] Recently, the research has found that blockade of integrin LFA-1 by monoclonal antibodies (mAbs) had shown efficacy in animal models of inflammation and autoimmune diseases such as arthritis, ischemia/reperfusion injury, and transplant rejection.[11e] Therefore, BIRT-377 may prove useful for the treatment or prophylaxis of inflammatory diseases, autoimmune diseases including Crohn′s disease,[10a] tumor metastasis, allograft rejection, and reperfusion injury.[11f] The present approach is highlighted by the short asymmetric synthesis of cell adhesion BIRT-377 (Scheme 4), which is a potent inhibitor of the interaction between intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1).[10] Thus, the asymmetric *p*-bromobenzylation of alanine derivative **19** under similar phase-transfer conditions as described above gave rise to the key intermediate of quaternary *p*-bromobenzylalanine ester (*R*)-**21** in 97% ee (83% yield). The amino ester (*R*)-**21** was treated with 3,5-dichlorophenyl isocyanate in the presence of sodium carbonate in DMSO to furnish the hydantoin (*R*)-**22** in 86% yield. N-Methylation of (*R*)-**22** was effected with lithium bis(trimethylsilyl)amide and methyl iodide in THF to afford BIRT-377 in 92% yield.[10g]



Scheme 4. Reagents and conditions: (a) (*S*)-**2** (1 mol %), *p*-Br-$C_6H_4CH_2Br$ (1.5 equiv), $CsOH \cdot H_2O$ (5 equiv), toluene; (b) citric acid (0.5 M), THF, 83%; (c) 3,5-Cl_2-C_6H_3NCO (1.1 equiv), Na_2CO_3, DMSO, 86%; (d) $LiN(SiMe_3)_2$ (1.1 equiv), CH_3I (1.5 equiv), THF, 92%.

3. Summary

Several new, efficient phase-transfer catalysts of type **1** and **2** can be readily prepared in five-step sequence from the known (*S*)-6,6′-dimethylbiphenyl-2,2′-diol and (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyldicarboxylic acid, respectively. These chiral phase-transfer catalysts are successfully utilized for asymmetric alkylation of glycine and alanine derivatives, implying the practicality of the catalysts **1** and **2** in practical asymmetric synthesis. In particular, the unique chemical behavior of catalyst (*S*)-**1b**, giving higher enantioselectivity at higher temperature, is noteworthy. The present asymmetric phase-transfer alkylation is applicable to the short asymmetric synthesis of cell adhesion BIRT-377.

4. Experimental

4.1. General information

Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-FX400 NMR instrument (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) at ambient temperature and calibrated using $SiMe_4$ (δ=0 ppm) and the central line of $CDCl_3$ triplet (δ=77 ppm) as internal references unless otherwise noted. The following abbreviations were used to express the multiplicities: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet; br=broad. High-performed liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using a Daicel CHIRALPAK OD or AD-H 4.6 mm×25 mm column. High-resolution mass spectra (HRMS) were performed on BRUKER micrOTOF focus–KR. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. All reactions were monitored by thin-layer chromatography carried out on Merck silica gel plates (0.25 mm thick, $60F_{254}$), visualized by using UV (254 nm) or dyes such as $KMnO_4$, PMA, and $CeSO_4$. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230–400 mesh). In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co. Inc. as 'dehydrated'. Toluene was dried over sodium metal. Dichloromethane (CH_2Cl_2) was stored over 4 Å molecular sieves. Other simple chemicals were purchased and used as such.

4.2. Preparation of chiral phase-transfer catalyst (*S*)-1a

4.2.1. (*S*)-2,2′-Dimethoxy-6,6′-dimethylbiphenyl (*S*)-4. To a solution of (*S*)-6,6′-dimethylbiphenyl-2,2′-diol (*S*)-**3** (89 mg, 0.42 mmol) in acetone (5.0 mL) at room temperature were added MeI (0.52 mL, 8.3 mmol) and K_2CO_3 (0.57 g, 4.2 mmol). After being stirred at room temperature for 5 h, the resulting mixture was filtered through a pad of Celite with EtOAc. The filtrate was concentrated to yield a residue, which was purified by column chromatography on silica gel (hexane/EtOAc) to furnish (*S*)-2,2′-dimethoxy-6,6′-dimethylbiphenyl (*S*)-**4** (105 mg, quantitative) as an oil: $[\alpha]_D^{32}$ −38 (*c* 0.60, $CHCl_3$); ^{1}H NMR δ 7.21 (t, *J*=8 Hz, 2H), 6.89 (d, *J*=8 Hz, 2H), 6.79 (d, *J*=8 Hz, 2H), 3.65 (s, 6H), 1.93 (s, 6H); ^{13}C NMR δ 156.9, 138.1, 127.8, 126.1, 122.1, 108.2, 55.6, 19.5; IR (neat) 2941, 1579, 1466, 1252, 1080, 777, 743 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{16}H_{19}O_2$ ([M+H]$^+$): 243.1380; found: 243.1383.

4.2.2. (*S*)-5,5′-Dibromo-2,2′-dimethoxy-6,6′-dimethylbiphenyl (*S*)-5. To a solution of (*S*)-2,2′-dimethoxy-6,6′-dimethylbiphenyl (*S*)-**4** (105 mg, 0.42 mmol) in CH_2Cl_2 (4.0 mL) at room temperature were added AcOH (0.005 mL, 0.083 mmol) and Br_2 (0.045 mL, 0.87 mmol) successively. The resulting solution was stirred at room temperature for 1 h and poured into an ice-cold saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc twice. The combined extracts were dried over Na_2SO_4, and concentrated to provide a residual oil, which was purified by column chromatography on silica gel (hexane/EtOAc) to afford (*S*)-5,5′-dibromo-2,2′-dimethoxy-6,6′-dimethylbiphenyl (*S*)-**5** (161 mg, 97%) as an oil: $[\alpha]_D^{32}$ −36 (*c* 0.68, $CHCl_3$); ^{1}H NMR δ 7.49 (d, *J*=9 Hz, 2H), 6.68 (d, *J*=8 Hz, 2H), 3.63 (s, 6H), 1.99 (s, 6H); ^{13}C NMR δ 156.0, 137.3, 131.9, 127.6, 116.3, 109.9, 55.8, 20.0; IR (neat) 2934, 2359, 1566, 146, 1429, 1281, 1254, 1080, 1230, 799 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{16}H_{16}Br_2O_2$ ([M+H]$^+$): 397.9512; found: 397.9500.

4.2.3. (*S*)-2,2′-Dimethoxy-6,6′-dimethyl-5,5′-bis(3,4,5-trifluorophenyl)biphenyl (*S*)-6. To a solution of (*S*)-5,5′-dibromo-2,2′-dimethoxy-6,6′-dimethylbiphenyl (*S*)-**5** (550 mg, 1.37 mmol) in dry DMF (15 mL) at room temperature were added 3,4,5-trifluorophenylboronic acid (868 mg, 5.50 mmol), $Pd(OAc)_2$ (62 mg, 0.28 mmol), P(*o*-Tol)$_3$ (335 mg, 1.10 mmol), and $K_3PO_4 \cdot nH_2O$ (3.93 g, 13.8 mmol) sequentially. After being refluxed under argon atmosphere overnight, the resulting mixture was filtered through a pad of Celite with Et_2O. The filtrate was poured into a mixture of H_2O and Et_2O with vigorous stirring. The organic phase was separated and the aqueous phase was extracted with Et_2O twice. The combined extracts were dried over Na_2SO_4, and concentrated to furnish a residue, which was purified by column chromatography on silica gel (hexane/EtOAc) to afford (*S*)-2,2′-dimethoxy-6,6′-dimethyl-5,5′-bis(3,4,5-trifluorophenyl)biphenyl (*S*)-**6** in quantitative yield as a white foam: $[\alpha]_D^{32}$ −8 (*c* 0.43, $CHCl_3$); ^{1}H NMR δ 7.18 (d, *J*=8 Hz, 2H), 6.97 (t, *J*=8 Hz, 4H), 6.90 (d, *J*=8 Hz, 2H), 3.76 (s, 6H), 1.86 (s, 6H); ^{13}C NMR δ 156.7, 150.7 (ddd, J_{C-F}=250, 10, 4 Hz), 138.6 (dt, J_{C-F}=251, 5 Hz), 138.2–138.5 (m), 135.2, 132.2, 129.6, 126.9, 113.82, 113.76, 113.67, 113.6, 108.4, 55.7, 17.4; IR (neat) 2940, 1614, 1516, 1477, 1261, 1244, 1084, 1042, 806, 754 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{28}H_{20}F_6O_2$ ([M+H]$^+$): 502.1362; found: 502.1381.

4.2.4. (*S*)-6,6′-Bis(bromomethyl)-2,2′-dimethoxy-5,5′-bis(3,4,5-trifluorophenyl)biphenyl (*S*)-7. To a solution of (*S*)-2,2′-dimethoxy-6,6′-dimethyl-5,5′-bis(3,4,5-trifluorophenyl)biphenyl (*S*)-**6** (690 mg, 1.37 mmol) in benzene (10 mL) at room temperature were added *N*-bromosuccinimide (509 mg, 2.9 mmol) and AIBN (23 mg, 0.14 mmol) successively. After being refluxed for 1.5 h, the mixture was cooled to room temperature and filtered through a pad of Celite with Et_2O. The filtrate was concentrated to afford a residue, which was purified by column chromatography on silica gel (hexane/Et_2O) to provide (*S*)-6,6′-bis(bromomethyl)-2,2′-dimethoxy-5,5′-bis(3,4,5-trifluorophenyl)biphenyl (*S*)-**7** (820 mg, 91%) as a white solid: mp 78–80 °C; $[\alpha]_D^{33}$ +51

(c 0.40, $CHCl_3$); ^1H NMR δ 7.26 (d, J=9 Hz, 2H), 7.16 (d, J=8 Hz, 4H), 7.04 (d, J=8 Hz, 2H), 4.08 (s, 4H), 3.77 (s, 6H); ^{13}C NMR δ 157.0, 150.7 (ddd, J_{C-F}=251, 10, 5 Hz), 139.1 (dt, J_{C-F}=253, 15 Hz), 136.2–136.5 (m), 132.8, 131.3, 125.5, 113.9, 113.8, 113.74, 113.69, 111.2, 55.7, 30.1; IR (neat) 2940, 1614, 1526, 1477, 1435, 1271, 1043, 816, 758 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{28}H_{18}Br_2F_6O_2$ ($[M+H]^+$): 657.9572; found: 657.9571.

4.2.5. Chiral ammonium salt (*S*)-1a. To a solution of dibromide (*S*)-**7** (316 mg, 0.48 mmol) in CH_3CN (5 mL) at room temperature were added Bu_2NH (0.074 mL, 0.43 mmol) and K_2CO_3 (0.60 mg, 4.4 mmol). After being stirred at 85 °C overnight, the resulting mixture was cooled to room temperature and filtered through a pad of Celite with CH_2Cl_2. The filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel (CH_2Cl_2/MeOH) to furnish chiral ammonium salt (*S*)-**1a** (290 mg, 94%) as a white solid: mp 230–232 °C; $[\alpha]_D^{32}$ −63 (c 0.37, $CHCl_3$); ^1H NMR δ 7.41 (d, J=9 Hz, 2H), 7.23 (d, J=9 Hz, 2H), 7.14 (br s, 4H), 4.74 (d, J=14 Hz, 2H), 3.90 (s, 6H), 3.66 (d, J=14 Hz, 2H), 3.18 (t, J=13 Hz, 2H), 2.65–2.80 (m, 2H), 0.90–1.18 (m, 6H), 0.73 (t, J=7 Hz, 6H), 0.20–0.38 (m, 2H); ^{13}C NMR δ 156.9, 151.6–152.4 (m), 149.2–149.8 (m), 139.3 (dt, J_{C-F}=255, 16 Hz), 134.7–135.0 (dt, J_{C-F}=16, 4 Hz), 132.5, 131.9, 126.3, 125.0, 113.5–115.5 (m), 113.3, 57.1, 56.9, 55.8, 24.2, 19.0, 12.9; IR (neat) 3400, 2965, 1614, 1528, 1489, 1287, 1045, 733 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{36}H_{36}F_6NO_2$ (M^+): 628.2645; found: 628.2642.

4.3. Preparation of chiral phase-transfer catalyst (*S*)-1b

4.3.1. (*S*)-3,3′,5,5′-Tetrabromo-2,2′-dihydroxy-6,6′-dimethylbiphenyl (*S*)-8. To a solution of (*S*)-2,2′-dihydroxy-6,6′-dimethylbiphenyl (*S*)-**3** (110 mg, 0.51 mmol) in CH_2Cl_2 (5.0 mL) at ambient temperature were added AcOH (0.006 mL, 0.10 mmol) and Br_2 (0.11 mL, 2.10 mmol) successively. After being stirred at ambient temperature for 40 min, the resulting solution was poured into a mixture of H_2O and CH_2Cl_2 with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined extracts were dried over Na_2SO_4 and concentrated to afford a residual solid, which was purified by column chromatography on silica gel (hexane/EtOAc) to furnish (*S*)-3,3′,5,5′-tetrabromo-2,2′-dihydroxy-6,6′-dimethylbiphenyl (*S*)-**8** (236 mg, 87%) as a white solid: mp 186–188 °C; $[\alpha]_D^{32}$ −38 (c 0.50, $CHCl_3$); ^1H NMR δ 7.75 (s, 2H), 5.35 (s, 2H), 2.03 (s, 6H); ^{13}C NMR δ 149.0, 137.8, 134.7, 124.5, 116.1, 107.9, 20.0; IR (neat) 3501, 1425, 1287, 1211, 1061, 1032, 758, 675 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{14}H_9Br_4O_2$ ($[M-H]^-$): 524.7331; found: 524.7337.

4.3.2. (*S*)-3,3′,5,5′-Tetrabromo-2,2′-dimethoxy-6,6′-dimethylbiphenyl (*S*)-9. To a solution of (*S*)-3,3′,5,5′-tetrabromo-2,2′-dihydroxy-6,6′-dimethylbiphenyl (*S*)-**8** (236 mg, 0.45 mmol) in acetone (10 mL) at room temperature were added MeI (0.56 mL, 8.9 mmol) and K_2CO_3 (0.62 g, 4.45 mmol). After being stirred at room temperature for 2 h, the resulting mixture was filtered through a pad of Celite with EtOAc. The filtrate was concentrated to yield a residue, which was purified by column chromatography on silica gel (hexane/EtOAc) to furnish (*S*)-3,3′,5,5′-tetrabromo-2,2′-dimethoxy-6,6′-dimethylbiphenyl (*S*)-**9** (246 mg, 98%) as an oil: $[\alpha]_D^{32}$ +7 (c 0.64, $CHCl_3$); ^1H NMR δ 7.84 (s, 2H), 3.54 (s, 6H), 2.03 (s, 6H); ^{13}C NMR δ 153.8, 136.8, 136.0, 133.6, 120.3, 115.0, 60.5, 20.5; IR (neat) 2938, 1452, 1406, 1350, 1260, 1063, 930, 866 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{16}H_{14}Br_4O_2$ ($[M+H]^+$): 553.7722; found: 553.7718.

4.3.3. (*S*)-2,2′-Dimethoxy-6,6′-dimethyl-3,3′,5,5′-tetrakis(3,4,5-trifluorophenyl)biphenyl (*S*)-10. To a solution of (*S*)-3,3′,5,5′-tetrabromo-2,2′-dimethoxy-6,6′-dimethylbiphenyl (*S*)-**9** (423 mg, 0.76 mmol) in dry DMF (10 mL) at room temperature were added 3,4,5-trifluorophenylboronic acid (1.076 g, 6.08 mmol), $Pd(OAc)_2$ (34 mg, 0.15 mmol), $P(o\text{-}Tol)_3$ (185 mg, 0.61 mmol), and $K_3PO_4 \cdot nH_2O$ (2.17 g, 7.58 mmol) sequentially. After being refluxed under argon atmosphere for 20 h, the resulting mixture was filtered through a pad of Celite with Et_2O. The filtrate was poured into a mixture of H_2O and Et_2O with vigorous stirring. The organic phase was separated, and the aqueous phase was extracted with Et_2O twice. The combined extracts were dried over Na_2SO_4, and concentrated to furnish a residue, which was purified by column chromatography on silica gel (hexane/Et_2O) to yield (*S*)-2,2′-dimethoxy-6,6′-dimethyl-3,3′,5,5′-tetrakis(3,4,5-trifluorophenyl)biphenyl (*S*)-**10** (377 mg, 65%) as a white solid: mp 245–247 °C; $[\alpha]_D^{34}$ +17 (c 0.15, $CHCl_3$); ^1H NMR δ 7.28 (d, J=8 Hz, 2H), 7.29 (d, J=9 Hz, 2H), 7.20 (s, 2H), 7.00 (d, J=8 Hz, 2H), 6.98 (d, J=8 Hz, 2H), 3.31 (s, 6H), 1.98 (s, 6H); ^{13}C NMR δ 154.8, 151.1 (ddd, J_{C-F}=251, 10, 4 Hz), 138.8 (ddt, J_{C-F}=254, 16, 4 Hz), 136.1, 135.65, 135.56 (ddt, J_{C-F}=316, 8, 5 Hz), 132.8, 131.2, 129.4, 113.8, 113.7, 113.61, 113.55, 113.2, 113.1, 113.02, 112.97, 60.4, 18.1; IR (neat) 2930, 2359, 1614, 1526, 1470, 1418, 1395, 1258, 1098, 860, 732 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{40}H_{22}F_{12}O_2$ ($[M+H]^+$): 762.1423; found: 762.1424.

4.3.4. Chiral ammonium salt (*S*)-1b. To a solution of biphenyl compound (*S*)-**10** (377 mg, 0.49 mmol) in benzene (5.0 mL) at room temperature were added *N*-bromosuccinimide (183 mg, 1.03 mmol) and AIBN (8 mg, 0.049 mmol) successively. After being refluxed for 30 min, the mixture was cooled to room temperature and filtered through a pad of Celite with Et_2O. The filtrate was concentrated to afford a residual solid, which was used for the next reaction without further purification.

To a solution of crude dibromide (*S*)-**11** in CH_3CN (5 mL) at room temperature were added Bu_2NH (0.051 mL, 0.30 mmol) and K_2CO_3 (410 mg, 2.96 mmol). After being stirred at 95 °C for 10 h, the resulting mixture was cooled to room temperature and filtered through a pad of Celite with CH_2Cl_2. The filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel (CH_2Cl_2/MeOH) to furnish chiral ammonium salt (*S*)-**1b** (254 mg, 53% for two steps) as a white solid: mp 188–190 °C; $[\alpha]_D^{34}$ −34 (c 0.48, $CHCl_3$); ^1H NMR δ 7.20–7.60 (m, 10H), 4.73 (d, J=14 Hz, 2H), 4.05 (d, J=14 Hz, 2H), 3.41 (s, 6H), 3.08 (t, J=12 Hz, 2H), 2.85 (t, J=12 Hz, 2H), 0.85–1.20 (m, 6H), 0.73 (t, J=7 Hz, 6H), 0.30 (br s, 2H); ^{13}C NMR δ 156.0, 151.2 (ddd, J_{C-F}=251, 9, 3 Hz), 139.8 (dq, J_{C-F}=256, 15 Hz), 136.6, 134.7, 134.1–134.6 (m),

133.8, 132.5–133.0 (m), 113.74, 113.67, 113.58, 113.5, 61.8, 57.5, 24.4, 19.4, 13.2; IR (neat) 3404, 2965, 2357, 1616, 1528, 1472, 1398, 1260, 1242, 1045, 862 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{48}H_{38}F_{12}NO_2$ (M^+): 880.2705; found: 880.2703.

4.4. Representative procedure for catalytic asymmetric alkylation of *tert*-butyl *N*-(diphenylmethylene)glycinate (12) under phase-transfer conditions (Table 1, entry 10)

To a mixture of glycine derivative **12** (5 g, 16.93 mmol) and chiral phase-transfer catalyst (*S*)-**1b** (17 mg, 0.017 mmol) in toluene (24 mL) were added KOH (50% aqueous, 16 mL) and benzyl bromide (3.02 mL, 25.4 mmol). After being stirred vigorously at 20 °C for 12 h, the starting material **12** was consumed. The mixture was poured into water and extracted with Et_2O twice. The combined organic layers were dried over Na_2SO_4 and concentrated to afford a residual oil, which was purified by flash column chromatography on silica gel (hexane/Et_2O=100:1 to 30:1) to furnish *tert*-butyl *N*-(diphenylmethylene)phenylalaninate (*R*)-**13a** (6.13 g, 94% yield) as an oil. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel OD, hexane/2-propanol=100:1, flow rate=0.5 mL/min, retention time: 12.0 min (*R*) and 16.3 min (*S*)). Absolute configuration was determined by comparison of the HPLC retention time with authentic sample independently synthesized by the reported procedure.[4b] ^1H NMR δ 7.56–7.58 (m, 2H), 7.26–7.38 (m, 6H), 7.13–7.21 (m, 3H), 7.04–7.06 (m, 2H), 6.60 (d, J=6 Hz, 2H), 4.10 (dd, J=9.6, 4.4 Hz, 1H), 3.23 (dd, J=13.6, 4.4 Hz, 1H), 3.15 (dd, J=13.6, 9.6 Hz, 1H), 1.44 (s, 9H); IR (neat) 2978, 1732, 1624, 1576, 1495, 1447, 1367, 1286, 1150, 1082, 1030, 849, 756, 696 cm^{-1}.

4.5. Preparation of chiral phase-transfer catalyst (*S*)-2

4.5.1. (*S*)-3,3′-Dibromo-4,5,6,4′,5′,6′-hexamethoxybiphenyl-2,2′-dimethanol (*S*)-17. To a solution of (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyl-2,2′-dicarboxylic acid (*S*)-**14** (0.422 g, 1.0 mmol) in THF/$B(OMe)_3$ (4 mL/2 mL) was added dropwise $BH_3\cdot SMe_2$ (4.0 mL, 1.0 M in THF, 4.0 mmol) at 0 °C under an argon atmosphere. The reaction was then brought to room temperature and kept stirring for 5 h. Methanol (1 mL) was added slowly to quench the reaction. The solvent was removed under reduced pressure. Then 1 N HCl was added to the residue and AcOEt was used for extraction. The organic layer was dried over Na_2SO_4 and concentrated. The residue was transferred into a solution of pyridine (0.57 mL, 7.0 mmol) in THF (5 mL). The mixture was cooled to −20 °C and bromine (0.36 mL, 7.0 mmol) was added. After the addition, the reaction was brought to 0 °C and kept stirring for 1 h. The reaction mixture was poured into saturated aqueous Na_2SO_3 solution, and AcOEt was used for extraction. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=1:1 as eluant) to furnish (*S*)-**17** (524 mg, 95%) as a white foam: $[\alpha]_D^{25}$ −7.17 (*c* 1.00, $CHCl_3$); ^1H NMR δ 4.56 (d, J=12.0 Hz, 2H), 4.18 (d, J=12.0 Hz, 2H), 3.98 (s, 6H), 3.94 (s, 6H), 3.66 (s, 6H), 3.34 (s, 2H); ^{13}C NMR δ 151.15, 150.32, 146.54, 134.10, 126.85, 115.65, 62.08, 60.99, 60.97, 60.62; IR (neat) 3292, 2939, 1458, 1388, 1313, 1088, 1005 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{20}H_{24}Br_2O_8$ ([M+Na]$^+$): 572.9730; found: 572.9723.

4.5.2. (*S*)-3,3′-Bis(3,4,5-trifluorophenyl)-4,5,6,4′,5′,6′-hexamethoxybiphenyl-2,2′-dimethanol (*S*)-18. A mixture of (*S*)-**17** (0.276 g, 0.5 mmol), 3,4,5-trifluorophenylboronic acid (0.440 g, 2.5 mmol), $Pd(OAc)_2$ (0.0225 g, 0.10 mmol), P(*o*-Tol)$_3$ (0.122 g, 0.40 mmol), and $K_3PO_4\cdot nH_2O$ (1.056 g, 5.0 mmol) in THF (5 mL) was heated at 88 °C under an argon atmosphere. The reaction was monitored by TLC until the starting material disappeared. Then the suspension was filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=2:1 as eluant) to give (*S*)-3,3′-bis(3,4,5-trifluorophenyl)-4,5,6,4′,5′,6′-hexamethoxybiphenyl-2,2′-dimethanol (*S*)-**18** (0.255 g, 78%) as a white foam: $[\alpha]_D^{24}$ +43.79 (*c* 1.00, $CHCl_3$); ^1H NMR δ 7.09 (m, 4H), 3.92–4.02 (m, 10H), 3.76 (s, 6H), 3.71 (s, 6H), 3.19 (s, 2H); ^{13}C NMR δ 151.11, 150.74, 150.27 (ddd, J_{C-F}=250.6, 9.9, 4.1 Hz), 138.91 (dt, J_{C-F}=252.2, 15.7 Hz), 133.11, 131.88 (dt, J_{C-F}=5.8, 8.2 Hz),130.26, 126.23, 114.71 (m), 61.03, 60.77, 60.72, 59.60; IR (neat) 3219, 2943, 1530, 1458, 1404, 1308, 1041 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{32}H_{28}F_6O_8$ ([M+Na]$^+$): 677.1581; found: 677.1583.

4.5.3. Chiral ammonium salt (*S*)-2. To a solution of (*S*)-**18** (0.131 g, 0.2 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added PBr_3 (0.038 mL, 0.4 mmol). The reaction mixture was stirred at room temperature for 1 h. Then it was quenched with water and extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was transferred into a suspension of K_2CO_3 (0.0553 g, 0.40 mmol) and Bu_2NH (0.037 mL, 0.22 mmol) in acetonitrile (5 mL) under an argon atmosphere. Then the mixture was heated at 80 °C for 10 h. It was quenched by pouring into 1 N HBr and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2=1:10 as eluant), affording chiral quaternary ammonium bromide (*S*)-**2** (0.153 g, 90%) as a white solid: mp 210–212 °C; $[\alpha]_D^{24}$ −121.78 (*c* 1.00, $CHCl_3$); ^1H NMR δ 7.27 (m, 2H), 7.08 (m, 2H), 4.33 (d, J=12.8 Hz, 2H), 4.04 (s, 6H), 3.90 (m, 8H), 3.75 (s, 6H), 2.97 (m, 2H), 2.78 (m, 2H), 1.86 (m, 4H), 1.09 (m, 2H), 0.77 (dd, J=7.2, 7.2 Hz, 6H), 0.23 (m, 2H); ^{13}C NMR δ 152.12, 151.75, 150.68 (ddd, J_{C-F}=253.0, 10.7, 4.1 Hz), 139.28 (dt, J_{C-F}=255.5, 14.9 Hz), 130.21 (dt, J_{C-F}=4.9, 7.4 Hz), 129.80, 126.54, 119.98, 115.48 (m), 61.58, 61.14, 60.95, 57.69, 57.15, 24.30, 19.37, 13.28; IR (neat) 2962, 2943, 1530, 1460, 1400, 1041. HRMS (ESI-TOF) Calcd for $C_{40}H_{44}F_6NO_6$ (M^+): 748.3067; found: 748.3088.

4.6. Procedure for catalytic enantioselective benzylation of alanine *tert*-butyl ester aldimine Schiff base 19

A mixture of alanine *tert*-butyl ester aldimine Schiff base **19** (80.3 mg, 0.3 mmol), (*S*)-**2** (1 mol %), benzyl bromide (54 μL, 0.45 mmol), and $CsOH\cdot H_2O$ (252 mg, 1.5 mmol) in 1.5 mL of toluene was stirred vigorously at 0 °C under an argon atmosphere. The reaction was monitored by TLC. When the reaction was over, the mixture was poured into water and extraction was performed with CH_2Cl_2. Solvents were evaporated and the residue was dissolved into

THF (5 mL). Then citric acid (5 mL, 0.5 M) was added and the mixture was stirred at room temperature for 1 h. After evaporation to remove THF, the aqueous phase was washed with hexane. It was then basified by the addition of solid Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (EtOAc/hexane=1:2 as eluant) gave the alkylation product (*R*)-**20** (49.3 mg, 73%) as an oil. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel AD-H, hexane/2-propanol=30:1, flow rate: 0.5 mL/min, retention time: 12.6 min (*R*) and 19.4 min (*S*)).

4.6.1. *tert*-Butyl (*R*)-2-amino-3-(*p*-bromophenyl)-2-methylpropanoate (*R*)-21. To an ice-cold mixture of aldimine Schiff base of alanine *tert*-butyl ester **19** (77 mg, 0.29 mmol), (*S*)-**2** (1 mol %) (2 mg, 0.0029 mmol), and *p*-$BrC_6H_4CH_2Br$ (112.5 mg, 0.45 mmol) in toluene (2 mL) were added $CsOH\cdot H_2O$ (252 mg, 1.5 mmol). After being stirred vigorously at 0 °C for 10 h, the resulting mixture was poured into water and extracted with Et_2O twice. The combined organic layers were dried over Na_2SO_4 and concentrated to afford a residual oil, which was dissolved in THF (2 mL). Then 1 N HCl (15 mL) was added and the mixture was stirred at room temperature for 2 h. The aqueous layer was separated and the pH was adjusted to 9–10 by addition of Na_2CO_3, which was extracted with EtOAc for three times. The combined organic layers were dried over Na_2SO_4 and concentrated to afford (*R*)-**21** (75 mg, 83% yield) as an oil, which was pure enough for the next reaction without further purification. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel AD-H, hexane/EtOH=50:1, flow rate=1 mL/min, retention time: 10.9 min (minor) and 19.0 min (major)): $[\alpha]_D^{23}$ +3.2 (*c* 0.95, $CHCl_3$); ^{1}H NMR δ 7.41 (d, *J*=8.4 Hz, 2H), 7.09 (d, *J*=8.4 Hz, 2H), 3.05 (d, *J*=13.6 Hz, 1H), 2.72 (d, *J*=13.2 Hz, 1H), 1.33 (br s, 2H), 1.45 (s, 9H), 1.32 (s, 3H); ^{13}C NMR δ 175.8, 135.7, 131.7, 131.0, 120.7, 81.2, 58.6, 45.7, 28.0, 26.9; IR (neat) 2974, 2359, 1721, 1487, 1368, 1152, 1111 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{14}H_{20}BrNO_2$ ([M+H]$^+$): 314.07558; found: 314.07502.

4.6.2. (*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-5-methylimidazolidine-2,4-dione (*R*)-22.[10g,h,i] A solution of α-amino ester (*R*)-**21** (69.5 mg, 0.22 mmol) and 3,5-dichlorophenyl isocyanate (41 mg, 0.22 mmol) in dry DMSO (0.5 mL) was stirred at room temperature for 1 h. Sodium carbonate (53 mg, 0.50 mmol) was then added and stirred at 120 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with brine. The organic phase was dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (hexane/ethyl acetate=2:1 to 1:1) to afford (*R*)-**22** (81 mg, 86%) as a white foam: $[\alpha]_D^{22.8}$ +131.51 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.41 (d, *J*=8.4 Hz, 2H), 7.34 (t, *J*=1.6 Hz, 1H), 7.07 (d, *J*=8.4 Hz, 2H), 7.01 (d, *J*=1.6 Hz, 2H), 5.84 (br s, 1H), 3.14 (d, *J*=13.6 Hz, 1H), 2.92 (d, *J*=13.6 Hz, 1H), 1.61 (s, 3H); ^{13}C NMR δ 174.0, 154.0, 135.2, 132.8, 132.7, 131.7, 128.5, 124.5, 122.1, 62.5, 43.7, 29.7.

4.6.3. (*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethylimidazolidine-2,4-dione (BIRT-377).[10g,h,i] To a solution of hydantoin (*R*)-**22** (74 mg, 0.18 mmol) in DMF (1.0 mL) at 0 °C, $LiN(SiMe_3)_2$ (0.216 mL, 1 M in THF) followed by iodomethane (0.02 mL, 0.324 mmol) was added, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel to give BIRT-377 (72.5 mg, 92%) as a white solid: mp 136–138 °C; $[\alpha]_D^{22}$ +132.4 (*c* 1.02, $CHCl_3$); ^{1}H NMR δ 7.42 (d, *J*=8.4 Hz, 2H), 7.29 (t, *J*=1.6 Hz, 1H), 6.94 (d, *J*=8.4 Hz, 2H), 6.84 (d, *J*=2.0 Hz, 2H), 3.10 (d, *J*=15.2 Hz, 1H), 3.08 (s, 3H), 2.97 (d, *J*=14 Hz, 1H), 1.63 (s, 3H); ^{13}C NMR δ 173.3, 153.4, 135.0, 133.0, 132.8, 131.8, 131.1, 128.3, 124.5, 121.9, 65.6, 40.7, 25.3, 21.0.

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References and notes

1. (a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993; (b) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman and Hall: New York, NY, 1994; (c) *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic and Professional: London, 1997; (d) *Phase-Transfer Catalysis*; Halpern, M. E., Ed.; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997.
2. For recent representative reviews on asymmetric phase-transfer catalysis, see: (a) Shioiri, T. *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic and Professional: London, 1997, Chapter 14; (b) O'Donnell, M. J. *Catalytic Asymmetric Syntheses*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, NY, 2000; Chapter 10; (c) Shioiri, T.; Arai, S. *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, 2000; p 123; (d) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3; (e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013; (f) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506; (g) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518; (h) Maruoka, K.; Ooi, T.; Kano, T. *Chem. Commun.*, in press. (i) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.*, in press.
3. (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353; (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414; (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595; (d) Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244; (e) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, *42*, 4645; (f) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329; (g) 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; (h) Kita, T.; Georgieva, A.; Hashimoto, U.; Nakata, T.; Nagasawa, K.

Angew. Chem., Int. Ed. **2002**, *41*, 2832; (i) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539; (j) Lygo, B.; Allbutt, B.; James, S. R. *Tetrahedron Lett.* **2003**, *44*, 5629; (k) Belokon, Y. N.; Bespalova, N. B.; Churkina, T. D.; Císarová, I.; Ezernitskaya, M. G.; Harutyunyan, S. R.; Hrdina, R.; Kagan, H. B.; Kocovsky, P.; Kochetkov, K. A.; Larionov, O. V.; Lyssenko, K. A.; North, M.; Polásek, M.; Peregudov, A. S.; Prisyazhnyuk, V. V.; Vyskocil, S. *J. Am. Chem. Soc.* **2003**, *125*, 12860; (l) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497; (m) Mase, N.; Ohno, T.; Hoshikawa, N.; Ohishi, K.; Morimoto, H.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 4073; (n) Chinchilla, R.; Mazon, P.; Najera, C. *Synlett* **2003**, 1931; (o) Kowtoniuk, W. E.; Rueffer, M. E.; MacFarland, D. K. *Tetrahedron: Asymmetry* **2004**, *15*, 151; (p) Rueffer, M. E.; Fort, L. K.; MacFarland, D. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3279; (q) Yoo, M.-S.; Jeong, B.-S.; Lee, J.-H.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1129; (r) Ayyanar, S.; Eagambaram, M. *J. Mol. Catal. A: Chem.* **2006**, *248*, 1; (S) Yonezawa, H.; Shimomoto, A.; Takizawa, S.; Sasai, H. Jpn. Kokai Tokkyo Koho, JP 2006070001, 2006.

4. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519; (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228; (c) Ooi, T.; Kameda, M.; Tannai, H.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 8339; (d) Maruoka, K. *J. Fluorine Chem.* **2001**, *112*, 95; (e) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1621; (f) Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640; (g) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139; (h) Ooi, T.; Kubota, Y.; Maruoka, K. *Synlett* **2003**, 1931; (i) Ooi, T.; Sakai, D.; Takeuchi, M.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5868; (j) Hashimoto, T.; Maruoka, K. *Tetrahedron Lett.* **2003**, *44*, 3313; (k) Hashimoto, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron: Asymmetry* **2003**, *14*, 1599; (l) Ooi, T.; Uematsu, Y.; Maruoka, K. *Tetrahedron Lett.* **2004**, *45*, 1675; (m) Shirakawa, S.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2004**, *6*, 1429; (n) Shirakawa, S.; Yamamoto, K.; Kitamura, M.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 625; (o) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073; (p) Ooi, T.; Arimura, Y.; Hiraiwa, Y.; Yuan, L. M.; Kano, T.; Inoue, T.; Matsumoto, J.; Maruoka, K. *Tetrahedron: Asymmetry* **2006**, *17*, 145.
5. Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549.
6. For preliminary communications, see: (a) Han, Z.; Yamaguchi, Y.; Kitamura, M.; Maruoka, K. *Tetrahedron Lett.* **2005**, *46*, 8555; (b) Wang, Y. -G.; Maruoka, K. *Org. Process Res. Dev.*, in press.
7. (a) Takuma, Y.; Tanaka, Y.; Nakashima, I.; Kasuga, Y.; Urata, T. Jpn. Kokai Tokkyo Koho, JP 2002069022, 2002; (b) Karen, M. T.; Thomas, J. b.; Gino, G. L.; Lavoie, W. M.; Richard, R. S. *Macromolecules* **1996**, *29*, 6114; (c) Kanoh, S.; Tamura, N.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1987**, 2307.
8. (a) Schmidt, O. T.; Demmler, K. *Justus Liebigs Ann. Chem.* **1952**, *576*, 85; (b) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577; See also: (c) Lee, K. H.; Xie, L. *J. Med. Chem.* **1995**, *38*, 3003; (d) Reitze, J. D.; Przewloka, S. R.; Shearer, B. J. *Holzforschung* **2001**, *55*, 171; (e) Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533; (f) Surry, D. S.; Fox, D. J.; Macdonald, S. J.; Spring, D. R. *Chem. Commun.* **2005**, 2589.
9. Lane, C. F.; Myatt, H. L.; Daniel, J.; Hopps, H. B. *J. Org. Chem.* **1974**, *39*, 3052.
10. (a) Kelly, T. A.; Jeanfavre, D. D.; McNeil, D. W.; Woska, J. R., Jr.; Reilly, P. L.; Mainolfi, E. A.; Kishimoto, K. M.; Nabozny, G. H.; Zinter, R.; Bormann, B.-J.; Rothlein, R. *J. Immunol.* **1999**, *163*, 5173; (b) Yee, N. K. *Org. Lett.* **2000**, *2*, 2781; (c) Napolitano, E.; Farina, V. *Tetrahedron Lett.* **2001**, *42*, 3231; (d) Frutos, R. P.; Stehle, S.; Nummy, L.; Yee, N. K. *Tetrahedron: Asymmetry* **2001**, *12*, 101; (e) Kapadia, S. R.; Spero, D. M.; Eriksson, M. *J. Org. Chem.* **2001**, *66*, 1903; (f) Yee, N. K.; Nummy, L. J.; Frutos, R. P.; Song, J. J.; Napolitano, E.; Byrne, D. P.; Jones, P.-J.; Farina, V. *Tetrahedron: Asymmetry* **2003**, *14*, 3495; (g) Chowdari, N. S.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 867; (h) Patwardhan, A. P.; Pulgram, V. R.; Zhang, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 6169; (i) Stamatia, V.; Plato, A. M. *Tetrahedron: Asymmetry* **2006**, *17*, 1754.
11. (a) Lebedeva, T.; Dustin, M. L.; Sykulev, Y. *Curr. Opin. Immunol.* **2005**, *17*, 251; (b) Fischer, A.; Friedrich, W.; Fasth, A.; Blanche, S.; Le Deist, F.; Girault, D.; Veber, F.; Vossen, J.; Lopez, M.; Griscelli, C.; Him, M. *Blood* **1991**, *77*, 249; (c) Schreiber, S. L. *Nat. Chem. Biol.* **2005**, *1*, 64; (d) Arkin, M. R.; Wells, J. A. *Nat. Rev. Drug Discov.* **2004**, *3*, 301; (e) Wattanasin, S.; Albert, R.; Ehrhardt, C.; Roche, D.; Sabio, M.; Hommel, U.; Welzenbach, K.; Weitz-Schmidt, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 499; (f) Link, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinski, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 973.