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Design of *N*-Spiro C_2-Symmetric Chiral Quaternary Ammonium Bromides as Novel Chiral Phase-Transfer Catalysts: Synthesis and Application to Practical Asymmetric Synthesis of α-Amino Acids

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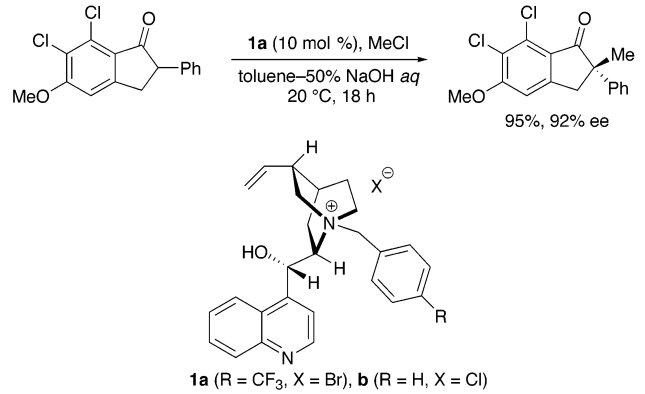
Abstract: A series of C_2-symmetric chiral quaternary ammonium bromides **10** and **11** have been designed as a new, purely synthetic chiral phase-transfer catalyst, and readily prepared from commercially available optically pure 1,1′-bi-2-naphthol as a basic chiral unit. The details of the synthetic procedures of each requisite chiral binaphthyl subunit have been disclosed, and the structures of the assembled *N*-spiro chiral quaternary ammonium bromides **11a** and **11f** were unequivocally determined by single-crystal X-ray diffraction analysis. The reactivity and selectivity of these chiral ammonium bromides as chiral phase-transfer catalysts have been evaluated in the asymmetric alkylation of the benzophenone Schiff base of glycine ester **7** under mild liquid−liquid phase-transfer conditions, and the optimization of the reaction variables (solvent, base, and temperature) has also been conducted. Further, the scope and limitations of this asymmetric alkylation have been thoroughly investigated with a variety of alkyl halides, in which the advantage of the unique *N*-spiro structure of **11** and dramatic effect of the steric as well as the electronic properties of the aromatic substituents on the 3,3′-position of one binaphthyl moiety have been particularly emphasized. Finally, the potential synthetic utility of the present method for the practical asymmetric synthesis of structurally diverse natural and unnatural α-amino acids has been demonstrated by its successful application to the facile asymmetric syntheses of (*S*)-*N*-acetylindoline-2-carboxylate, a key intermediate in the synthesis of the ACE inhibitor, and L-Dopa (L-3,4-dihydroxyphenylalanine) ester and its analogue.

Introduction

Both academic and industrial research on phase-transfer catalysis (PTC) have taken great strides forward during the past decades.[1] Their continuous growth seems to be assured by ever stronger driving forces originating from the advantages offered by PTC (operational simplicity, mild reaction conditions with aqueous media, environmental consciousness, suitability for large-scale reaction, etc.), which meet the current requirement for practical synthetic reactions. Along with this stream, development of asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral catalysts to create optically active organic molecules from prochiral substrates,[2] particularly through carbon−carbon bond formation, was triggered by the pioneering work of the Merck research group in 1984.[3] They carried out efficient and practical asymmetric methylation of the phenylindanone derivative with cinchona alkaloid-derived catalyst (Scheme 1)[3a] and made careful and systematic studies of this reaction.[3c] Five years later, this type of catalyst was successfully utilized for the asymmetric synthesis

Scheme 1

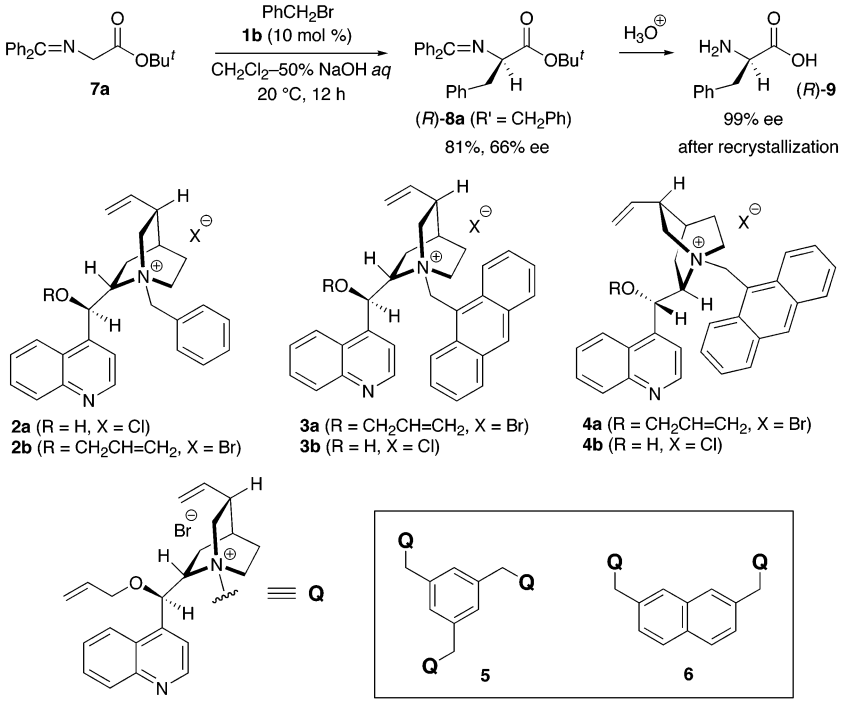


(1) (a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993. (b) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman & Hall: New York, 1994. (c) Sasson, Y.; Neumann, R., Eds. *Handbook of Phase-Transfer Catalysis;* Blackie Academic & Professional: London, 1997. (d) Halpern, M. E., Ed. *Phase-Transfer Catalysis*; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997.

(2) For reviews: (a) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Verlag Chemie: New York, 1993; Chapter 8. (b) Shioiri, T. In *Handbook of Phase-Transfer Catalysis*; Sasson, Y.; Neumann, R., Eds.; Blackie Academic & Professional: London, 1997; Chapter 14. (c) O'Donnell, M. J. *Phases—The Sachem Phase Transfer Catalysis Review* **1998**, issue 4, 5. (d) O'Donnell, M. J. *Phases—The Sachem Phase Transfer Catalysis Review* **1999**, issue 5, 5. (e) Shioiri T.; Arai, S. In *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; WILEY−VCH: Weinheim, 2000; p 123.

(3) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc*. **1984**, *106*, 446. (b) Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 476. (c) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745.

Scheme 2



of α-amino acids by O'Donnell et al. using glycine ester benzophenone Schiff base (**7**) as a key substrate.[4] Asymmetric alkylation of **7a** proceeded smoothly under mild phase-transfer conditions with cinchonine-derived catalyst **1b** to give the monoalkylation product (*R*)-**8a** in high yield with moderate enantioselectivity as exemplified by the benzylation in Scheme 2.[4a] Importantly, the remaining α-proton of **8a** has a much lower acidity compared to that of **7a** as long as the benzophenone Schiff base is employed, securing the chirality of the α-stereogenic center under the reaction conditions.[4e] By using cinchonidine-derived catalyst **2a**, the other enantiomer (*S*)-**8a** could be obtained,[4a] and the enantioselectivity was enhanced to 81% ee by optimization of the reaction parameters with hydroxy-protected **2b** as catalyst.[4f] Recrystallization and then acidic hydrolysis of **8a** afforded essentially enantiopure α-amino acids **9**.[4a] This study certainly opened the door to intensive research on the asymmetric synthesis of amino acids by means of chiral phase-transfer catalysis.

Among numerous contributions, new cinchona alkaloid-derived catalysts possessing the 9-anthracenylmethyl substituent dramatically improved the level of asymmetric induction.[5,6] Corey used **3a** as the catalyst and solid cesium hydroxide monohydrate as the basic phase to allow the reaction to be conducted at a lower temperature, and extremely high enantioselectivities were obtained for the products **8a**.[5a] At the same time, Lygo demonstrated the remarkable potential of chiral ammonium chlorides **3b** and **4b** with a free hydroxy group under liquid−liquid phase-transfer conditions.[6a] These reports have accelerated the research on the improvement and synthetic applications of the asymmetric alkylation of **7a** as represented by the recent contribution of Jew and Park[7] using the trimeric and dimeric cinchona alkaloid catalysts **5**[7b] and **6**.[7c] On the other hand, extensive studies have also been made on the development of various other asymmetric bond-forming processes (Michael addition,[5b,8] Horner−Wadsworth−Emmons reaction,[9] Darzens condensation,[8i,j,l,10] aldol reaction,[11] oxidation,[12] reduction,[13] cyclopropanation,[14] and aziridination[15]) under phase-transfer conditions.

(4) (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc*. **1989**, *111*, 2353. (b) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507. (c) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem*. **1991**, *56*, 5181. (d) O'Donnell, M. J.; Esikova, I. A.; Shullenberger, D. F.; Wu, S. In *Phase-Transfer Catalysis*; ACS Symposium Series 659, Halpern, M. E., Ed.; American Chemical Society: Washington, DC, 1997; Chapter 10. (e) O'Donnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Boldwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc*. **1988**, *110*, 8520. (f) O'Donnell, M. J.; Wu, S.; Esikova, I. A.; Mi, A. U.S. Patent, 5,554,753, 1996; *Chem. Abstr*. **1995**, *123*, 9924. (g) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3.

(5) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc*. **1997**, *119*, 12414. (b) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett*. **1998**, *39*, 5347.

(6) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett*. **1997**, *38*, 8595. (b) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett*. **1999**, *40*, 1385. (c) Lygo, B. *Tetrahedron Lett*. **1999**, *40*, 1389. (d) Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2391. (e) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403.

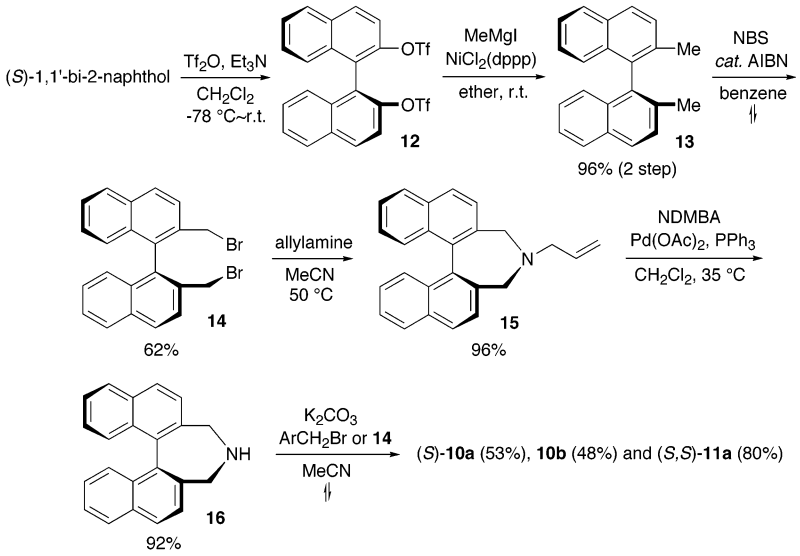
(7) (a) Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun*. **2001**, 1244. (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett*. **2001**, *42*, 4645. (c) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed*. **2002**, *41*, 3036.

(8) (a) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun*. **1981**, 625. (b) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett*. **1989**, *30*, 7229. (c) Brunet, E.; Poveda, A. M.; Rabasco, D.; Oreja, E.; Font, L. M.; Batra, M. S.; Rodríguez-Ubis, J. C. *Tetrahedron: Asymmetry* **1994**, *5*, 935. (d) Tõke, L.; Bakó. P.; Keserü, G. M.; Albert, M.; Fenichel, L. *Tetrahedron* **1998**, *54*, 213. (e) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem*. **1986**, *51*, 4710. (f) Nerinckx, W.; Vandewalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 265. (g) Loupy, A.; Zaparucha, A. *Tetrahedron Lett*. **1993**, *34*, 473. (h) Bakó, P.; Kiss, T.; Tõke, L. *Tetrahedron Lett*. **1997**, *38*, 7259. (i) Bakó, P.; Szöllõy, Á.; Bombicz, P.; Tõke, L. *Synlett* **1997**, 291. (j) Bakó, P.; Vízvárdi, K.; Toppet, S.; der Eycken, E. V.; Hoonaert, G. J.; Tõke, L. *Tetrahedron* **1998**, *54*, 14975. (k) Bakó, P.; Novák, T.; Ludányi, K.; Pete, B.; Tõke, L.; Keglevich, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2373. (l) Bakó, P.; Czinege, E.; Bakó, T.; Czugler, M.; Tõke, L. *Tetrahedron: Asymmetry* **1999**, *10*, 4539. (m) Zhang, F.-Y.; Corey, E. J. *Org. Lett*. **2000**, *2*, 1097. (n) Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hébrault, D. *Org. Lett*. **2000**, *2*, 2959. (o) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett*. **2001**, *42*, 6299. (p) Kim, D. Y.; Huh, S. C. *Tetrahedron* **2001**, *57*, 8933.

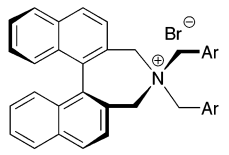
(9) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett*. **1998**, *39*, 2997.

(10) (a) Arai, S.; Shioiri, T. *Tetrahedron Lett*. **1998**, *39*, 2145. (b) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375. (c) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun*. **1999**, 49. (d) Arai, S.; Ishida, T.; Shioiri, T. *Tetrahedron Lett*. **1998**, *39*, 8299.

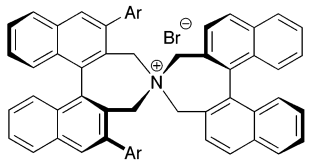
Scheme 3



Despite fruitful growth in this field, however, most of the elaborated chiral phase-transfer catalysts have been restricted to cinchona alkaloid derivatives, which unfortunately imposes obvious limitations on the structural modifications, especially upon considering fine-tuning of catalysts to attain sufficient reactivity and selectivity in various chemical transformations under phase-transfer-catalyzed conditions. Our approach to this intrinsic problem was the rational molecular design of phase-transfer catalysts using optically active binaphthyl derivatives as a basic chiral unit, namely, C_2-symmetric chiral quaternary ammonium bromide **10** and a series of *N*-spiro type chiral ammonium bromides **11**. In this article, the full synthetic schemes and structural determination of these ammonium bromides are first described. Then, the scope and synthetic utility in the chiral phase-transfer catalysis of the asymmetric alkylation of **7** are investigated in depth, unequivocally establishing the effectiveness of the catalysts for the asymmetric synthesis of both natural and unnatural α-amino acids.[16]



(*S*)-**10a** (Ar = Ph), **b** (Ar = α-Np)



(*S*,*S*)-**11a** (Ar = H), **b** (Ar = Ph), **c** (Ar = β-Np) **d** (Ar = 3,5-Ph_2-Ph), **e** (Ar = 4-F-Ph) **f** (Ar = 3,4,5-F_3-Ph)

Results and Discussion

1. Synthesis and Structural Elucidation of C_2-symmetric Chiral Quaternary Ammonium Bromides. Initially, we synthesized C_2-symmetric chiral quaternary ammonium bromides of type **10** by the alkylation of *secondary* amine **16** that was prepared from commercially available (*S*)-1,1′-bi-2-naphthol in a five-step sequence as shown in Scheme 3. Here, it is worthy of comment that the Ni-catalyzed cross coupling of **12** with MeMgI[17] proceeded at room temperature, and racemization was not observed to any detectable extent (HPLC). Since subsequent radical bromination of **13** turned out to give several side-products, recrystallization was preferable for the purification of **14**. Simple chiral *N*-spiro quaternary ammonium salt (*S*,*S*)-**11a** was also readily assembled from **14** and **16**, and its structure was successfully confirmed by single-crystal X-ray diffraction analysis (Figure 1).

For the synthesis of chiral *N*-spiro catalysts possessing aromatic substituents on the 3,3′-position of one binaphthyl subunit, 3,3′-dibromo-1,1′-bi-2-naphthol (**19**) was prepared in high yield from bis(methoxymethyl) ether **17** via lithiation−bromination and acidic deprotection as shown in Scheme 4. After derivatization to bis(trifluoromethanesulfonate) **20**, an aromatic substituent (Ph, β-Np) was installed by Suzuki−Miyaura coupling reaction[18] without affecting the triflate moiety, and a subsequent cross-coupling reaction with $NiCl_2(PPh_3)_2$ as catalyst, although relatively slow, produced **22**. Contrary to the case with **13**, radical bromination of **22** proceeded cleanly to give the requisite **23** in quantitative yield. Finally, treatment of

(11) (a) Gasparski, C. M.; Miller, M. J. *Tetrahedron* **1991**, *47*, 5367. (b) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931.

(12) Epoxidation: (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett*. **1998**, *39*, 1599. (b) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289. (c) Lygo, B.; To, D. C. M. *Tetrahedron Lett*. **2001**, *42*, 1343. (d) Corey, E. J.; Zhang, F.-Y. *Org. Lett*. **1999**, *1*, 1287. (e) Arai, S.; Tsuge, H.; Shiori, T. *Tetrahedron Lett*. **1998**, *39*, 7563. (f) Arai, S.; Oku, M.; Miura, M.; Shioiri, T. *Synlett* **1998**, 1201. (g) Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* **2002**, *58*, 1623. (h) Harigaya, Y.; Yamaguchi, H.; Onda, M. *Chem. Pharm. Bull*. **1981**, *29*, 1321. (i) Macdonald, G.; Alcaraz, L.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron Lett*. **1998**, *39*, 5433. (j) Adam, W.; Rao, P. B.; Degen, H.-G.; Saha-Möller, C. R. *Tetrahedron: Asymmetry* **2001**, *12*, 121. (k) Adam, W.; Rao, P. B.; Degan, H.-G.; Levai, A.; Patonay, T.; Saha-Möller, C. R. *J. Org. Chem*. **2002**, *67*, 259. (l) Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1994**, *116*, 6937. α-Hydroxylation: (m) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett*. **1988**, *29*, 2835. (n) de Vries, E. F. J.; Ploeg, L.; Colao, M.; Brussee, J.; van der Gen, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1123. Oxidative cyclization: (o) Brown, R. C. D.; Keily, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 4496.

(13) (a) Drew, M. D.; Lawrence, N. J.; Watson, W.; Bowles, S. A. *Tetrahedron Lett*. **1997**, *38*, 5857. (b) Hofstetter, C.; Wilkinson, P. S.; Pochapsky, T. C. *J. Org. Chem*. **1999**, *64*, 8794. (c) Pochapsky, T. C.; Hofstetter, C. PCT Int. Appl. WO 0205953 A2, 2002.

(14) (a) Arai, S.; Nakayama, K.; Hatano, K.; Shioiri, T. *J. Org. Chem*. **1998**, *63*, 9572. (b) Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K.; Shioiri, T. *Tetrahedron Lett*. **1998**, *39*, 9739. (c) Arai, S.; Nakayama, K.; Ishida, T.; Shioiri, T. *Tetrahedron Lett*. **1999**, *40*, 4215.

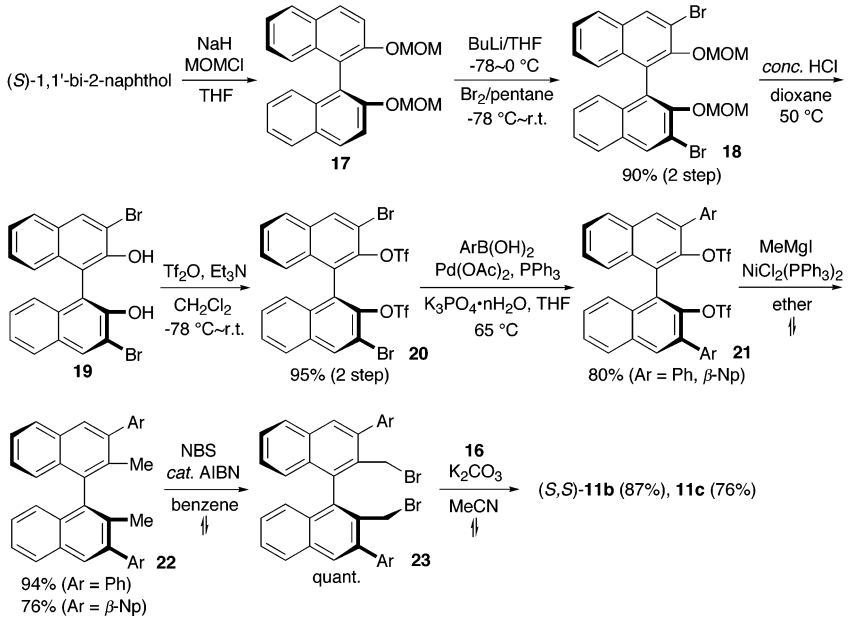
(15) Aires-de-Sousa, J.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett*. **1996**, *37*, 3183.

(16) Preliminary communication: (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc*. **1999**, *121*, 6519. See also: (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc*. **2000**, *122*, 5228. (c) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. *Synlett* **2001**, 1185. (d) Ooi, T.; Takeuchi, M.; Maruoka, K. *Synthesis* **2001**, 1716.

(17) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem*. **1992**, *57*, 4066.

(18) For review: Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147 and references therein.

Scheme 4



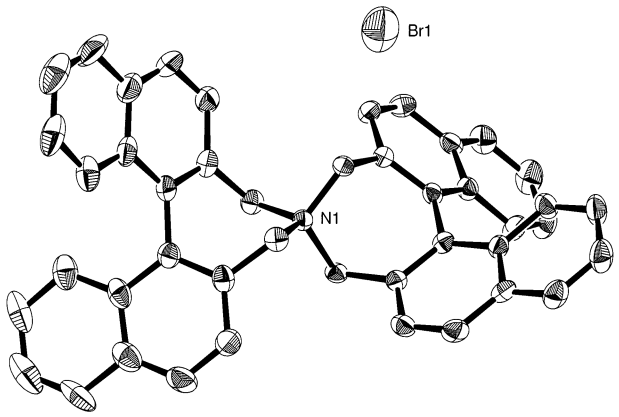
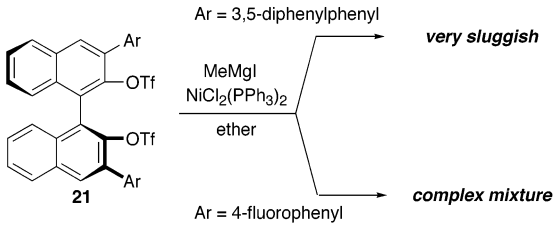


Figure 1. ORTEP diagram of the catalyst (*S*,*S*)-**11a**. The solvent molecules (MeCN) and all hydrogen atoms are omitted for clarity.

23(Ar = Ph, *β*-Np) with *secondary* amine **16** under basic conditions afforded (*S*,*S*)-**11b** or **11c**, which was purified by silica gel column chromatography.

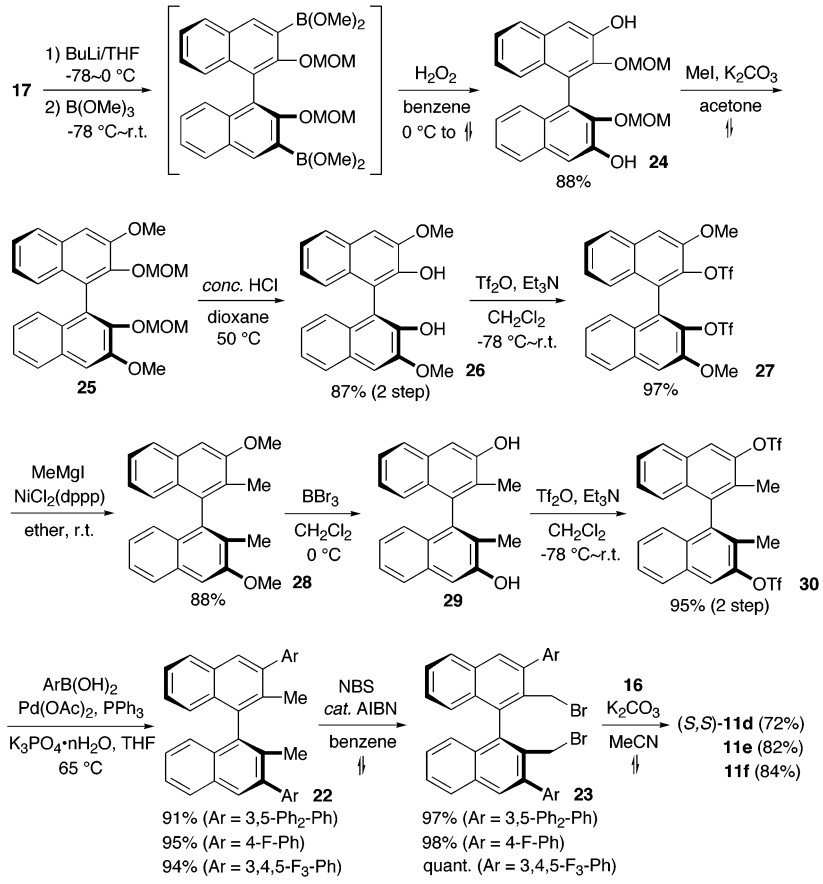
Although this synthetic scheme was thus established, we encountered a serious problem when we considered additional steric and electronic modification of the catalyst. For instance, introduction of a sterically more demanding aromatic substituent such as a 3,5-diphenylphenyl group on the 3,3′-position caused a significant rate retardation in the coupling reaction with MeMgI, suggesting the necessity of tuning the phosphine ligand of the Ni catalyst to attain higher activity. On the other hand, however, the coupling reaction of **21** containing an electron-withdrawing 3,3′-aromatic substituent (Ar) such as 4-fluorophenyl group gave rise to a complex mixture including products resulting from the intervention of C−F bond cleavage. These results strongly persuaded us to develop an entirely new route for the synthesis of catalysts that would allow a broad range of substituents. A critical point of this issue is that connection with 3,3′-substituents should be made after the formation of carbon−carbon bonds at the 2,2′-position, and this was realized via initial oxidation of the 3,3′-carbons as illustrated in Scheme 5. Lithiation of bis(methoxymethyl) ether **17** with BuLi in THF and trapping of the resulting dianion with $B(OMe)_3$ gave the



corresponding boronate, which was oxidized to **24** in one pot by H_2O_2 in benzene (88%). After protection of the hydroxy functionality as the methyl ether, selective deprotection of the methoxymethyl group was conducted under acidic conditions followed by treatment with Tf_2O and Et_3N, giving the appropriate candidate **27** for the subsequent Ni-catalyzed cross-coupling reaction. As expected, **28** was obtained in satisfactory yield, and then the triflate moiety was generated at the 3,3′-position in two steps for the next Suzuki−Miyaura reaction. Both 3,5-diphenylphenyl and 4-fluorophenyl groups were successfully introduced, and exposure of the resulting **22** (Ar = 3,5-diphenylphenyl or 4-fluorophenyl) to the radical bromination conditions furnished the requisite **23** almost quantitatively. Usual assembly of **23** (Ar = 3,5-diphenylphenyl or 4-fluorophenyl) with **16** afforded chiral *N*-spiro quaternary ammonium bromides (*S*,*S*)-**11d** and (*S*,*S*)-**11e**, respectively. Chiral ammonium bromide (*S*,*S*)-**11f** possessing the more electron-withdrawing 3,4,5-trifluorophenyl group as the Ar moiety was prepared in a similar manner. In fact, this new procedure requires 11 steps, but the chemical yield of each transformation is quite high, and no sophisticated technique is required, providing an efficient route for the synthesis of a variety of catalysts with desired steric and electronic properties (Scheme 5).

Although the attempt at X-ray analysis of the quaternary ammonium salt (*S*,*S*)-**11f** itself was unsuccessful, we were eventually able to obtain an X-ray structure by the exchange of counteranion of **11f** from Br^- to PF_6^-. As shown in Figure 2, the two 3,4,5-trifluorophenyl groups block both sides of the central nitrogen cation, creating a chiral molecular pocket. This attractive aromatic curvature, although relatively shallow, would

Scheme 5



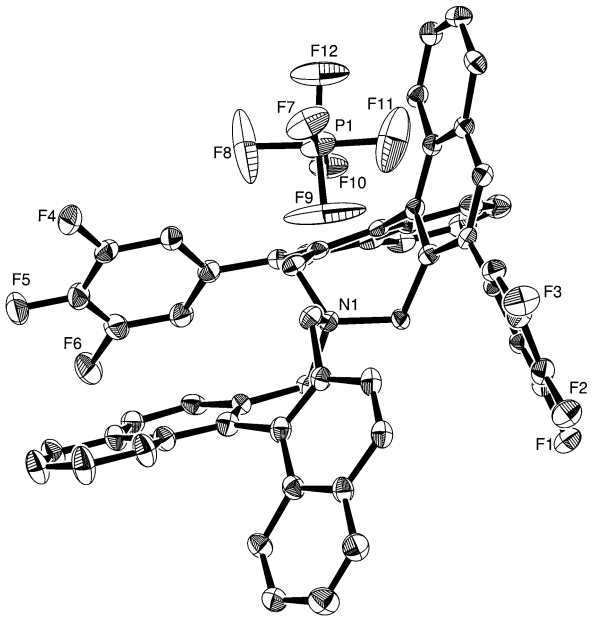


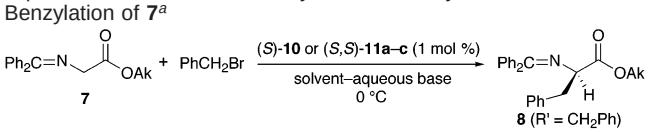
Figure 2. ORTEP diagram of the catalyst (*S,S*)-**11f** (PF_6^-). The solvent molecules (CH_2Cl_2, benzene and H_2O) and all hydrogen atoms are omitted for clarity.

contribute to precise enantiofacial differentiation of the prochiral enolate derived from **7**.

2. Application to Practical Asymmetric Synthesis of Natural and Unnatural α-Amino Acids.

2.1. Efficient Phase-Transfer Catalytic Asymmetric Alkylation of Glycine Ester Benzophenone Schiff Bases. With an efficient synthetic scheme in hand, we set out to evaluate these C_2-symmetric quaternary ammonium salts for use as chiral phase-transfer catalyst in the alkylation of glycine ester benzophenone Schiff base **7**. We chose benzylation as a benchmark reaction and first tested the quaternary ammonium salt (*S*)-**10**. The mixture of **7a**, benzyl bromide (1.2 equiv), and 1 mol % of (*S*)-**10a** in 50% aqueous NaOH−benzene (volume ratio = 1:3) was vigorously stirred at room temperature, and after 10 h, the corresponding benzylation product **8a** (R′ = CH_2Ph) was isolated in 32% yield with only 10% ee (*S*) (entry 1 in Table 1). Changing the aryl group of the catalyst to α-naphthyl [(*S*)-**10b**] brought only a slight increase of the enantiomeric excess (18% ee) (entry 2). These results might suggest that the orientation of the chiral binaphthyl moiety in the ion-paired ammonium enolate was not effectively fixed close to the reaction site due to the flexible achiral subunits of **10**, so that shielding of the prochiral enolate surface toward the approach of the carbon electrophile would be insufficient. This assumption prompted us to examine structurally rigid chiral *N*-spiro ammonium salts of type **11** consisting of two chiral binaphthyl subunits. In the presence of 1 mol % of (*S,S*)-**11a** under otherwise similar reaction conditions, the benzylation of **7a** proceeded more smoothly to furnish product **8a** (R′ = CH_2Ph) in 76% yield, and the enantiomeric excess was dramatically improved to 73% ee (entry 3). Here, use of CH_2Cl_2 as the organic solvent significantly decreased the enantioselectivity despite the increase in chemical yield, and the background reaction seemed predominant when a more polar solvent such as THF was used (entries 4 and 5). Further, the effect of the alkyl ester moiety of **7** was also examined. To our surprise, saponification was almost negligible even with the methyl ester

Table 1. Effect of Ester Moiety, Catalyst Structure, Solvent and Aqueous Base on the Reactivity and Selectivity of Phase-Transfer Benzylation of **7**[a]



entry	Ak	catalyst	solvent	base	conditions (°C, h)	yield,[b] %	% ee[c] (config)[d]
1	*t*-Bu (**7a**)	**10a**	benzene	50% NaOH	rt, 10	32	10 (*S*)
2		**10b**			rt, 10	17	18 (*S*)
3		**11a**			rt, 10	76	73 (*R*)
4			CH_2Cl_2		rt, 10	88	10 (*R*)
5			THF		rt, 1	64	16 (*R*)
6	Me (**7b**)		benzene		rt, 12	80	45 (*R*)
7	$PhCH_2$ (**7c**)				rt, 2.5	94	40 (*R*)
8	Ph_2CH (**7d**)				rt, 4	72	18 (*R*)
9	*t*-Bu (**7a**)	**11b**			rt, 10	43	81 (*R*)
10			toluene		0, 5	62	88 (*R*)
11				50% KOH	0, 0.5	82	89 (*R*)
12		**11c**			0, 0.5	95	96 (*R*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of $PhCH_2Br$ in the presence of 1 mol % of (*S*)-**10** or (*S*,*S*)-**11** under the given reaction conditions. [b] Isolated yield. [c] Enantiopurity of **8** was determined by HPLC analysis of the alkylated imine using a chiral column with hexane-2-propanol as solvent. [d] Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[4a]

7b,[4a] and the product was obtained in 80% yield with 45% ee (entry 6). In the case of the benzyl ester **7c**,[4a] the reaction proceeded faster to produce **8c** (R′ = Ak = CH_2Ph) in excellent yield after stirring for 4 h (94%), albeit with even lower enantiomeric excess (40% ee) (entry 7). Contrary to our expectation, use of the sterically more hindered benzhydryl ester **7d**[4a] reduced the enantioselectivity substantially (18% ee) (entry 8). Consequently, we decided to investigate further the use of the *tert*-butyl ester substrate **7a**. Introduction of an aromatic substituent on the 3,3′-position of one binaphthyl subunit of the catalyst (Ar) afforded a beneficial effect on the enantiofacial discrimination as the reaction with (*S*,*S*)-**11b** in 50% NaOH−benzene resulted in formation of product **8a** (R′ = CH_2Ph) in 43% yield with 81% ee (entry 9). This result led us to lower the reaction temperature to 0 °C by use of toluene as the organic solvent, which provided an even higher enantioselectivity (88% ee) (entry 10). Moreover, the benzylation of **7a** under the influence of (*S*,*S*)-**11b** was completed within 30 min at 0 °C with 50% KOH as an aqueous base, giving product **8a** (R′ = CH_2Ph) in 81% yield, whose enantiomeric purity was determined to be 89% ee (entry 11). Employment of (*S*,*S*)-**11c** as catalyst further increased the enantioselectivity to 96% ee (95% yield) (entry 12).

On the basis of these successful results, we modified the catalyst further. Interestingly, the enantioselectivity reached 98% ee with the sterically more hindered (*S*,*S*)-**11d** (entry 1 in Table 2). We also observed that the use of (*S*,*S*)-**11e** as catalyst provided enhanced selectivity (94% ee) (entry 4) compared to the case with (*S*,*S*)-**11b** (89% ee, entry 11 in Table 1). This is certainly attributable to the electronic effect of the 4-fluoro substituent, since the steric difference between **11b** and **11e** is small. Moreover, virtually complete stereochemical control was achieved using (*S*,*S*)-**11f** as catalyst (entry 5). The lower chemical yield of the benzylation with (*S*,*S*)-**11f** was probably due to the intervention of enolate oxidation by aerobic oxygen, since complete consumption of **7a** was confirmed by TLC analysis. This problem was overcome by simply performing the reaction under an argon atmosphere, yielding **8** in 90% chemical yield and 99% ee after 12 h (entry 6).[16c]

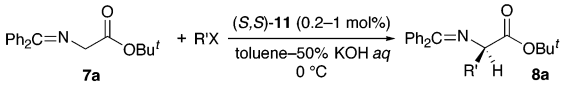
The scope and limitations of this method using a series of chiral *N*-spiro C_2-symmetric quaternary ammonium salts **11c**, **d**, and **f** were then thoroughly investigated with various alkyl halides, and the results, summarized in Table 2, reveal the following characteristic features. (1) The alkylation with **11c** as catalyst is generally fast, but the chemical yield and the enantioselectivity do not always reach a satisfactory level. (2) Chiral ammonium bromide **11d** seems to be a well-balanced catalyst in terms of reactivity and selectivity. Notably, sufficient reactivity and excellent enantioselectivity were preserved in the reaction with 0.5 mol % of the catalyst, and its loading can further be reduced to 0.2 mol % (entries 2 and 3). (3) **11f** is the catalyst of choice for the preparation of a variety of essentially enantiopure α-amino acids by this transformation. (4) By employing appropriate benzyl bromide derivatives as electrophiles, facile asymmetric synthesis of α-amino acids usually inaccessible by enzymatic processes becomes feasible. It is noteworthy that even the alkylations with ortho-disubstituted benzyl bromides worked well (entries 33−40). (5) Significant rate retardation seems inevitable in the reaction with less reactive alkyl halides such as MeI and EtI under the present conditions, although excellent enantioselectivity can be attained. However, we generally observed in such cases that the use of aqueous cesium hydroxide (CsOH) as a basic phase at lower reaction temperature greatly improved the reactivity without substantial loss of enantiomeric excess (entries 53 and 59).

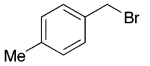
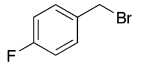
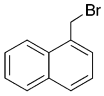
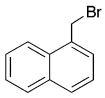
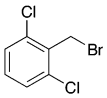
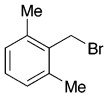
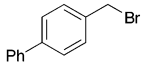
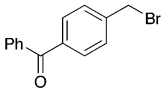
2.2. Asymmetric Synthesis of Important α-Amino Acid Esters.

(*S*)-*N*-Acetylindoline-2-carboxylic Acid *tert*-Butyl Ester (32b). Since both enantiomers of the catalyst of type **11** can be readily assembled in exactly the same manner starting from either (*R*)- or (*S*)-1,1′-bi-2-naphthol, a wide variety of natural and unnatural α-amino acids can be synthesized in an enantiomerically pure form by the phase-transfer catalytic alkylation of **7a**. To demonstrate the utility of this method, we pursued the asymmetric synthesis of (*S*)-*N*-acetylindoline-2-carboxylate **32**, a key intermediate in the synthesis of the ACE inhibitor **33**.[19] Buchwald and co-workers recently prepared **32a** by an elegant palladium-catalyzed intramolecular coupling of the optically active phenylalanine derivative **31a**, which was, in turn, prepared by a Heck coupling reaction of *o*-bromoiodobenzene with methyl 2-acetamidoacrylate followed by an efficient yet traditional rhodium-catalyzed asymmetric hydrogenation of the resulting eneamide (Scheme 6).[20] Earlier asymmetric syntheses of **33** involved either a low-yielding fractional recrystallization or an enzymatic hydrolysis of racemic **32**.[21] As we expected, however, the structure and stereochemical integrity of **31** was simultaneously constructed by the asymmetric alkylation of **7a** with commercially available *o*-bromobenzyl bromide in the presence of the catalyst (*R*,*R*)-**11f**. Subsequent hydrolysis with citric acid and *N*-acetylation afforded **31b** in 86% yield with

(19) Grundfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277.
(20) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.
(21) Tombo, G. M. R.; Schär, H. P.; Ghisalba, O. *Agric. Biol. Chem.* **1987**, *51*, 1833.

Table 2. Catalytic Enantioselective Phase-Transfer Alkylation of **7a**[a]



entry	R'X	catalyst	react. time (h)	% yield [b]	% ee [c] (config) [d]
1	$PhCH_2Br$	**11d**	0.5	91	98 (*R*)
2		**11d**	1.5	91	98 [e]
3		**11d**	12	81	98 [f]
4		**11e**	2	74	94
5		**11f**	2	79	99
6		**11f**	12	90	99 [g]
7		**11f**	36	85	99 [e,g]
8		**11f**	48	72	99 [f,g]
9		**11c**	1	84	94 (*R*)
10		**11d**	1.5	88	94
11		**11f**	4	61	99
12		**11f**	24	80	99 [g]
13		**11c**	1	82	93 (*R*)
14		**11d**	3	85	96
15		**11f**	2.5	69	99
16		**11f**	20	89	99 [g]
17		**11c**	1	90	95 (*R*)
18		**11d**	2.5	90	97
19		**11f**	4.5	70	99
20		**11f**	15	89	99 [g]
21		**11c**	0.5	80	96 (*R*)
22		**11d**	2	91	97
23		**11f**	2.5	69	99
24		**11f**	17	91	99 [g]
25		**11c**	1	81	96 (*R*)
26		**11d**	1	89	97
27		**11f**	3	83	99
28		**11f**	11	92	99 [g]
29		**11c**	1.5	60	96 (*R*)
30		**11d**	2.5	72	96
31		**11f**	3	61	99
32		**11f**	11	90	99 [g]
33		**11c**	2	61	67 (*R*)
34		**11d**	2.5	69	89
35		**11f**	6	48	96
36		**11f**	24	81	96 [g]
37		**11c**	1.5	91	82 (*R*)
38		**11d**	3	81	90
39		**11f**	6	86	99
40		**11f**	24	98	99 [g]
41		**11c**	1	86	95 (*R*)
42		**11d**	2.5	94	96
43		**11f**	1.5	83	99
44		**11f**	22	94	99 [g]
45		**11c**	1	91	91 (*R*)
46		**11d**	2.5	81	95
47		**11f**	10	77	98
48		**11f**	20	86	98 [g]
49	CH_3I [h]	**11c**	8	64	90 (*R*)
50		**11d**	33	60	91
51		**11f**	20	57	95
52		**11f**	38	72	95 [g]
53		**11f**	10	92	96 [g,j]
54	CH_3CH_2I [h]	**11c**	10	41	95 (*R*)
55		**11d**	12	41	97
56		**11f**	36	10	98
57		**11f**	48	27	98 [g]
58		**11f**	36	35	98 [g,i]
59		**11f**	10	89	98 [g,j]

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of R′X in the presence of 1 mol % of (*S*,*S*)-**11** in 50% aqueous KOH−toluene (volume ratio = 1:3) under the given reaction conditions. [b] Isolated yield. [c] Enantiopurity of **8a** was determined by HPLC analysis of the alkylated imine using a chiral column with hexane-2-propanol as solvent. [d] For the determination of absolute configuration, see the Experimental Section. [e] 0.5 mol % of catalyst loading. [f] With 0.2 mol % of the catalyst. [g] Performed under argon atmosphere. [h] Use of 5 equiv of alkyl halide. [i] With 2 mol % of the catalyst. [j] Performed at −15 °C with saturated CsOH as a basic phase.

99% ee (*S*). The above-described Buchwald procedure[20] was then used to convert almost enantiopure **31b** into **32b** (94%, 99% ee).

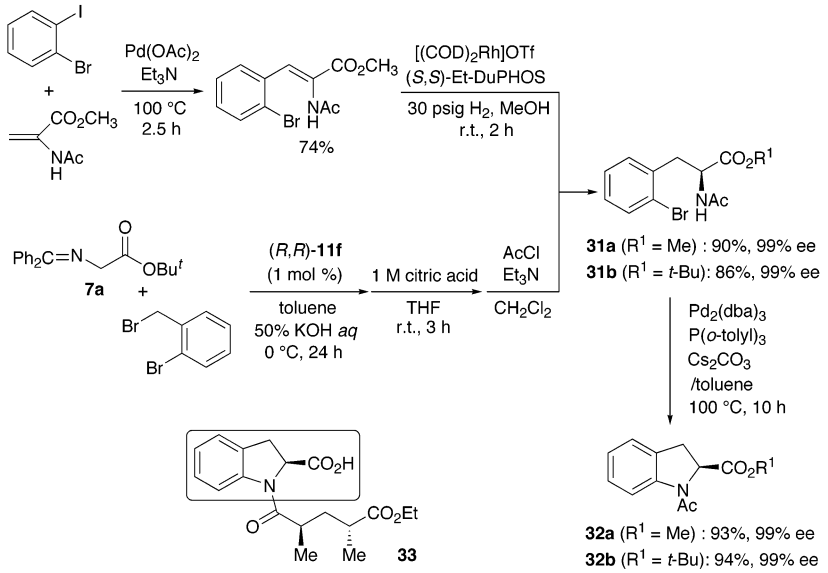
L-Dopa (L-3,4-Dihydroxyphenylalanine) *tert*-Butyl Ester (36a) and its Analogue (36b). The synthetic utility of our approach was further highlighted by the facile synthesis of L-Dopa ester and its analogue, which have usually been prepared by either asymmetric hydrogenation of eneamides[22] or enzymatic processes and tested as potential drugs for the treatment of Parkinson's disease.[23] The requisite benzyl bromide **34a** was readily prepared from 3,4-dihydroxybenzaldehyde in a three-step sequence (Scheme 7).[24] Catalytic phase-transfer alkylation of **7a** with **34a** (1.2 equiv) in toluene−50% KOH aqueous solution proceeded smoothly at 0 °C under the influence of (*R*,*R*)-**11f** (1 mol %) to furnish fully protected L-Dopa *tert*-butyl ester, which was subsequently hydrolyzed with 1 M citric acid in THF at room temperature for 10 h to afford the corresponding amino ester **35a** in 80% yield with 98% ee. Debenzylation of

(22) For review: Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1999 and references therein.

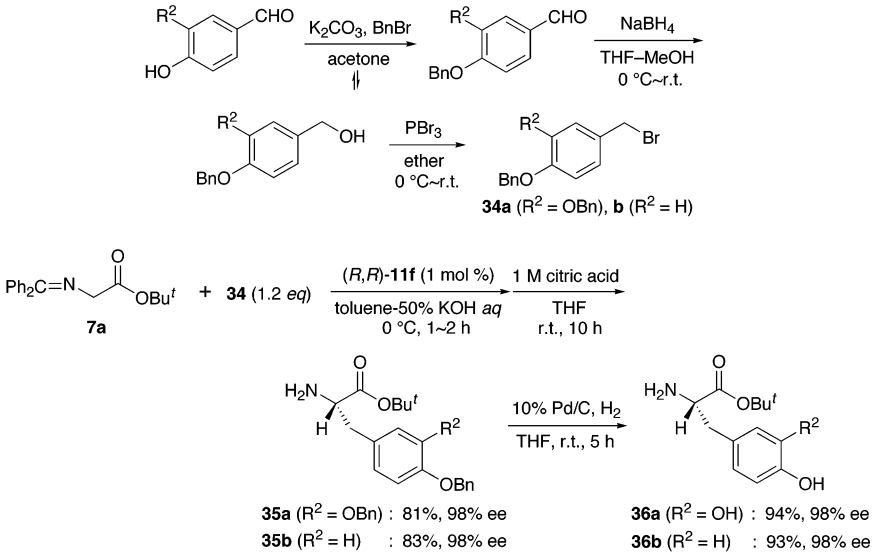
(23) (a) Marrel, C.; Boss, G.; Van De Waterbeemd, H.; Testa, B.; Cooper, D. R.; Jenner, P.; Marsden, C. D. *Eur. J. Med. Chem.* **1985**, *20*, 459. (b) Cooper, D. R.; Marrel, C.; Van De Waterbeemd, H.; Testa, B.; Jenner, P.; Marsden, C. D. *J. Pharm. Pharmacol.* **1987**, *39*, 635. (c) Vulfson, E. N.; Ahmed, G.; Gill, I.; Goodenough, P. W.; Kozlov, I. A.; Law, B. A. *Biotechnol. Lett.* **1991**, *13*, 91. (d) Ahmed, G.; Vulfson, E. N. *Biotechnol. Lett.* **1994**, *16*, 367. (e) Milewska, M. J.; Chimiak, A. *Amino Acids* **1994**, *7*, 89. (f) Brunner-Grenat, M.; Carrupt, P.-A.; Lisa, G.; Yeata, B.; Rose, S.; Thomas, K.; Jenner, P.; Ventura, P. *J. Pharm. Pharmacol.* **1995**, *47*, 861.

(24) For the preparation of **34**, see: Thakkar, K.; Geahlen, R. L.; Cushman, M. *J. Med. Chem.* **1993**, *36*, 2950.

Scheme 6



Scheme 7



35a under catalytic hydrogenation conditions produced the desired L-Dopa *tert*-butyl ester (**36a**) in 93% yield. The present practical procedure should enable highly enantioselective synthesis of various L-Dopa analogues, as exemplified by the asymmetric synthesis of natural tyrosine *tert*-butyl ester (**36b**) as also shown in Scheme 7. Furthermore, to emphasize the practicality of the method, we performed a "scale-up" experiment with 5.00 g of **7a** and 7.77 g of **34a**, providing 3.37 g of the desired L-Dopa *tert*-butyl ester (**36a**). An attractive feature of this method is that, in addition to its operational simplicity, the catalyst **11f** can be recovered and reused in the present enantioselective phase-transfer alkylation.[25,26]

Summary and Conclusions

We have designed unique C_2-symmetric chiral quaternary ammonium bromides, which can be readily synthesized starting from commercially available optically pure 1,1′-bi-2-naphthol. The full synthetic procedure of each appropriately modified binaphthyl subunit is reliable and allows the preparation of a variety of related chiral quaternary ammonium bromides with desired steric and electronic properties. Evaluation of these ammonium bromides as chiral phase-transfer catalysts in the asymmetric benzylation of the benzophenone Schiff base of glycine esters revealed that the reaction proceeded smoothly with 0.2−1 mol % of the *N*-spiro type catalysts under mild liquid−liquid phase-transfer conditions and the steric and electronic nature of the 3,3′-aromatic substituents had a significant effect on the reactivity and enantioselectivity. Thorough investigation of this asymmetric phase-transfer alkylation with *N*-spiro type catalysts of different steric and electronic properties and various alkyl halides provided a clear picture of the general applicability. A variety of essentially enantiopure α-amino acids could be obtained using the catalyst with a 3,4,5-trifluorophenyl group. By use of this practical asymmetric alkylation process as a key step, important α-amino acid esters such as (*S*)-*N*-acetylindoline-2-carboxylic acid *tert*-butyl ester and L-Dopa *tert*-butyl ester and its analogue were conveniently synthesized,

(25) Preliminary communication: Ooi, T.; Kameda, M.; Tannai, H.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 8339.

(26) The catalyst (*R*,*R*)-**11f** can be recovered by short silica gel column chromatography[27] before the acidic hydrolysis with CH_2Cl_2/MeOH = 30:1 to 10:1 as eluant (72% recovery yield). The recovered catalyst (*R*,*R*)-**11f** was reused several times without losing activity and enantioselctivity (second cycle: 80%, 98% ee; third cycle: 79%, 98% ee).

demonstrating the potential synthetic utility of the present method. We believe this study has great implications in the development of various asymmetric chemical transformations under phase-transfer-catalyzed conditions based on the rational molecular design of the chiral catalysts.

Experimental Section

General. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8200A spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 (300 MHz) spectrometer, JEOL JNM-FX400 (400 MHz) spectrometer, and JMTC-400/54/SS (400 MHz) spectrometer. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using 4.6 mm × 25 cm Daicel Chiralcel OD and OD-H. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385). High-resolution mass spectra (HRMS) were conducted at the School of Agriculture, Hokkaido University, at the School of Engineering, Kyoto University, and also performed on Applied Biosystems Mariner API-TOF workstation and JEOL JMS-HX100. Microanalyses were accomplished at School of Pharmacy, Kyoto University. Melting points were measured in open capillary tubes.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co. Inc. as "Dehydrated". Benzene and toluene were dried over sodium metal. Dichloromethane (CH_2Cl_2) was stored over 4Å molecular sieves. Triethylamine (Et_3N) was stored over potassium hydroxide (KOH) pellets. Trifluoromethanesulfonic anhydride (Tf_2O) was kindly supplied by Central Glass Co., Ltd., and also *tert*-butyl glycinate hydrochloride was supplied by Watanabe Chemical Ind., Ltd. *tert*-Butyl glycinate benzophenone Schiff base (**7a**) was prepared from *tert*-butyl glycinate hydrochloride and benzophenone imine according to the literature procedure.[28] Other simple chemicals were purchased and used as such.

Synthesis of C_2-Symmetric Chiral Ammonium Salts.

(*S*)-2,2′-Dimethyl-1,1′-binaphthyl [(*S*)-13].[17] To a solution of (*S*)-1,1′-bi-2-naphthol (5.73 g, 20 mmol) and Et_3N (8.45 mL, 60 mmol) in CH_2Cl_2 (50 mL) was added Tf_2O (7.47 mL, 44 mmol) dropwise at −78 °C, and then the cooling bath was removed. The reaction mixture was stirred for 2 h at room temperature and poured into ice-cooled 1 N HCl. After extraction with hexane, the organic extracts were washed with saturated $NaHCO_3$ and brine and then dried over Na_2SO_4. Evaporation of solvents gave the crude 2,2′-bis(trifluoromethanesulfonyloxy)-1,1′-binaphthyl [(*S*)-**12**][17] which was directly used for the following reaction without any purification. The crude (*S*)-**12** was dissolved in ether (20 mL), and the successive addition of $NiCl_2$(dppp) (325 mg, 3 mol %) and a 1 M ethereal solution of MeMgI (80 mL, 80 mmol) was performed at 0 °C under argon atmosphere followed by stirring of the mixture overnight at room temperature. This mixture was poured into ice-cooled 1 N HCl, and the whole mixture was filtered to remove the catalyst. The filtrate was extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ether/hexane = 1:100 as eluant) gave (*S*)-2,2′-dimethyl-1,1′-binaphthyl [(*S*)-**13**] (5.42 g, 19.2 mmol, 96% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (2H, d, J = 8.4 Hz, Ar−H), 7.88 (2H, d, J = 8.4 Hz, Ar−H), 7.51 (2H, d, J = 8.4 Hz, Ar−H), 7.39 (2H, ddd, J = 8.4, 6.9, 1.2 Hz, Ar−H), 7.20 (2H, ddd, J = 8.4, 6.9, 1.2 Hz, Ar−H), 7.04 (2H, d, J = 8.4 Hz, Ar−H), 2.03 (6H, s, Ar−CH_3) ppm; IR (KBr) 3049, 2918, 1506, 1352, 1026, 814, 746 cm^{-1}.

(*S*)-2,2′-Bis(bromomethyl)-1,1′-binaphthyl [(*S*)-14].[29] A mixture of (*S*)-**13** (5.42 g, 19.2 mmol), *N*-bromosuccinimide (NBS) (7.52 g, 42.2 mmol), and 2,2′-azobis(isobutyronitrile) (AIBN) (315 mg, 10 mol %) in benzene (100 mL) was heated and refluxed for 3 h. After being cooled to room temperature, this mixture was poured into water and extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by recrystallization from CH_2Cl_2/hexane to give (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl [(*S*)-**14**] (5.23 g, 11.9 mmol, 62% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (2H, d, J = 8.7 Hz, Ar−H), 7.94 (2H, d, J = 8.1 Hz, Ar−H), 7.66 (2H, d, J = 8.4 Hz, Ar−H), 7.50 (2H, ddd, J = 8.1, 6.9, 1.2 Hz, Ar−H), 7.28 (2H, ddd, J = 8.4, 6.9, 1.2 Hz, Ar−H), 7.08 (2H, d, J = 8.7 Hz, Ar−H), 4.26 (4H, s, Ar−CH_2) ppm; IR (KBr) 3047, 1595, 1506, 1433, 1360, 1329, 1211, 1026, 968, 821, 756, 721, 687 cm^{-1}.

(*S*)-Allyl-4,5-dihydro-3H-4-aza-cyclohepta[2,1-*a*;3,4-*a*′]dinaphthalene [(*S*)-15].[30] To a solution of (*S*)-**14** (4.40 g, 10 mmol) in acetonitrile (40 mL) was added allylamine (2.27 mL, 30 mmol) at room temperature. The mixture was heated to 50 °C, stirred for 5 h, and then poured into water. After extraction with CH_2Cl_2, the organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:30 as eluant) afforded (*S*)-allyl-4,5-dihydro-3H-4-aza-cyclohepta[2,1-*a*;3,4-*a*′]dinaphthalene **[**(*S*)-**15**] (3.22 g, 9.6 mmol, 96% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (4H, d, J = 8.0 Hz, Ar−H), 7.55 (2H, d, J = 8.0 Hz, Ar−H), 7.44−7.48 (4H, m, Ar−H), 7.24−7.28 (2H, m, Ar−H), 6.01 (1H, dddd, J = 17.2, 10.4, 7.2, 6.0 Hz, C$\underline{H}$=CH_2), 5.28 (1H, dd, J = 17.2, 1.6 Hz, *cis*-CH=C$\underline{H}_2$), 5.23 (1H, d, J = 10.4 Hz, *trans*-CH=C$\underline{H}_2$), 3.74 (2H, d, J = 12.4 Hz, Ar−CH_2), 3.16 (2H, d, J = 12.4 Hz, Ar−CH_2), 3.07−3.12 (2H, m, NCH_2C=C) ppm; IR (KBr) 3040, 2788, 1508, 1337, 1116, 995, 920, 826, 756 cm^{-1}.

(*S*)-4,5-Dihydro-3H-4-aza-cyclohepta[2,1-*a*;3,4-*a*′]dinaphthalene [(*S*)-16].[30] A mixture of (*S*)-**15** (3.22 g, 9.6 mmol), *N*,*N*-dimethylbarbituric acid (NDMBA) (3.72 g, 28.8 mmol), $Pd(OAc)_2$ (44.4 mg, 2 mol %), and triphenylphosphine (226 mg, 0.84 mmol) in dry, degassed CH_2Cl_2 (50 mL) was heated to 35 °C and stirred overnight under argon atmosphere.[31] After cooling, CH_2Cl_2 was removed under vacuum and replaced by benzene. This mixture was washed twice with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:10 as eluant) to give (*S*)-4,5-dihydro-3H-4-aza-cyclohepta[2,1-*a*;3,4-*a*′]dinaphthalene [(*S*)-**16**] (2.61 g, 8.8 mmol, 92% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, J = 8.8 Hz, Ar−H), 7.94 (2H, d, J = 8.8 Hz, Ar−H), 7.58 (2H, d, J = 8.4 Hz, Ar−H), 7.46 (2H, ddd, J = 8.4, 6.8, 1.2 Hz, Ar−H), 7.44 (2H, d, J = 8.4 Hz, Ar−H), 7.26 (2H, ddd, J = 8.4, 6.8, 1.2 Hz, Ar−H), 3.88 (2H, d, J = 12.4 Hz, Ar−CH_2), 3.53 (2H, d, J = 12.4 Hz, Ar−CH_2), 2.42 (1H, br, NH) ppm; IR (KBr) 3382, 3049, 2957, 2862, 1595, 1508, 1463, 1446, 1398, 1364, 817, 752 cm^{-1}.

Chiral Ammonium Salt (*S*)-10a. A mixture of (*S*)-**16** (148 mg, 0.50 mmol), benzyl bromide (122 μL, 1.1 mmol), and K_2CO_3 (104 mg, 0.75 mmol) in acetonitrile (5 mL) was heated to reflux, and stirring was maintained for 10 h. The resulting mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:30 as eluant) to furnish (*S*)-**10a** (147 mg, 0.27 mmol, 53% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, J = 8.4 Hz, Ar−H), 7.86 (2H, d, J = 8.4 Hz, Ar−H), 7.63 (2H, d, J = 8.4 Hz, Ar−H), 7.53−7.57 (6H, m, Ar−H), 7.24−7.43 (10H, m, Ar−H), 5.75 (2H, d, J = 13.2 Hz, Ar−CH_2), 5.19 (2H, d, J = 13.2 Hz, Ar−CH_2), 4.68 (2H, d, J = 13.2 Hz, Ar−CH_2), 4.29 (2H, d, J = 13.2 Hz, Ar−CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 133.8, 133.2, 130.9, 130.5, 129.3, 129.0, 128.3, 128.3, 127.6, 127.4, 127.3, 126.7, 126.4, 66.0, 62.3 ppm; IR (KBr) 3396, 3057, 1595, 1497, 1456, 1342, 1213, 1028, 860, 823, 775, 752, 702 cm^{-1}. HRMS (FAB) Calcd for $C_{36}H_{30}N$: 476.2373 (M^+), found:: 476.2377 (M^+).

(27) After completion of the reaction, neutralization with 1 N HBr is recommended to attain higher recovery yield.
(28) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.
(29) Maigrot, N.; Mazeleyrat, J. P. *Synthesis* **1985**, 317.
(30) Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1994**, *59*, 649.
(31) Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109.

Upon measuring the melting point, the crystal melted at 150 °C. However, ^{1}H NMR analysis after the measurement showed almost total decomposition. $[\alpha]^{27}_D$ 97.2° (*c* 1.00, $CHCl_3$).

Chiral Ammonium Salt (*S*,*S*)-11a. (*S*,*S*)-**11a** was prepared in a manner similar to that described above using (*S*)-**14** (0.55 mmol) instead of benzyl bromide (80% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (4H, d, J = 8.1 Hz, Ar−H), 8.17 (4H, d, J = 6.6 Hz, Ar−H), 8.11 (4H, d, J = 6.6 Hz, Ar−H), 7.64 (4H, ddd, J = 8.1, 6.6, 1.4 Hz, Ar−H), 7.26−7.44 (8H, m, Ar−H), 4.52 (4H, d, J = 13.2 Hz, Ar−CH_2), 3.92 (4H, d, J = 13.2 Hz, Ar−CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 134.5, 131.3, 131.1, 128.7, 127.7, 127.7, 127.4, 127.2, 125.2, 60.9 ppm; IR (KBr) 3647, 3400, 3053, 2361, 1624, 1595, 1508, 1458, 1346, 1030, 862, 822, 756 cm^{-1}. HRMS (FAB) Calcd for $C_{44}H_{32}N$: 574.2537 (M^+), found: 574.2526 (M^+). Melted at 278 °C with decomposition. $[\alpha]^{26}_D$ −209.2° (*c* 1.00, $CHCl_3$).

Representative Procedure for the Synthesis of Chiral Ammonium Salts 11d, 11e, and 11f.

(*S*)-3,3′-Dihydroxy-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl [(*S*)-24]. Protection of (*S*)-1,1′-bi-2-naphthol with chloromethyl methyl ether and sodium hydride in THF afforded 2,2′-bis(methoxymethoxy)-1,1′-binaphthyl [(*S*)-**17**][32] in quantitative yield. To a solution of (*S*)-**17** (6.37 g, 17 mmol) in THF (50 mL) was added a 1.6 M hexane solution of *n*-BuLi (25.5 mL, 40.8 mmol) dropwise at −78 °C under argon atmosphere. This mixture was allowed to warm to 0 °C and stirred for 1 h, then cooled back to −78 °C. Trimethoxyborane (5.81 mL, 51 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature and stirred there overnight. Removal of THF under vacuum afforded the crude borate, which was suspended in benzene (60 mL), and hydrogen peroxide (30% aqueous solution; 5 mL) was added dropwise at 0 °C. This mixture was heated and refluxed for 2 h. After cooling to room temperature, the resulting mixture was poured into ice-cooled saturated Na_2SO_3 and extracted with ethyl acetate. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ethyl acetate/hexane = 1:2 as eluant) gave (*S*)-3,3′-dihydroxy-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (*S*)-**24** (6.09 g, 15 mmol, 88% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, d, J = 8.4 Hz, Ar−H), 7.51 (2H, s, Ar−H), 7.45 (2H, s, OH), 7.34 (2H, ddd, J = 8.1, 6.9, 1.2 Hz, Ar−H), 7.12 (2H, ddd, J = 8.1, 6.9, 1.2 Hz, Ar−H), 7.04 (2H, d, J = 8.4 Hz, Ar−H), 4.72 (2H, d, J = 6.3 Hz, OCH_2O), 4.64 (2H, d, J = 6.3 Hz, OCH_2O), 3.40 (6H, s, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 144.8, 132.0, 128.2, 126.6, 125.7, 125.5, 125.3, 124.0, 111.8, 99.6, 57.5 ppm; IR (KBr) 3410, 2900, 1597, 1510, 1445, 1344, 1248, 1211, 1159, 1063, 984, 912, 876, 752, 680 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{21}O_6$: 405.1333 ([M − H]$^-$), found: 405.1351 ([M − H]$^-$). Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46; O, 23.62. Found: C, 70.71; H, 5.44; O, 23.55. Mp 120 °C. $[\alpha]^{27}_D$ 70.2° (*c* 0.28, $CHCl_3$).

(*S*)-3,3′-Dimethoxy-1,1′-bi-2-naphthol [(*S*)-26]. A mixture of (*S*)-**24** (6.09 g, 15 mmol), K_2CO_3 (6.25 g, 45 mmol) and methyl iodide (4.86 mL, 75 mmol) in acetone (200 mL) was heated and refluxed for 6 h. The resulting mixture was poured into water and extracted with ethyl acetate. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents gave the crude (*S*)-3,3′-dimethoxy-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl [(*S*)-**25**], which was directly used for the following reaction. An analytical sample of (*S*)-**25** was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:3 as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, J = 8.1 Hz, Ar−H), 7.36 (2H, ddd, J = 8.1, 6.0, 2.1 Hz, Ar−H), 7.30 (2H, s, Ar−H), 7.10−7.18 (4H, m, Ar−H), 4.97 (2H, d, J = 5.7 Hz, OCH_2O), 4.83 (2H, d, J = 5.7 Hz, OCH_2O), 4.03 (6H, s, $ArOCH_3$), 2.57 (6H, s, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 144.3, 131.2, 128.9, 126.7, 126.2, 125.2, 123.9, 107.2, 98.0, 56.0, 55.7 ppm; IR (KBr) 3003, 2959, 2895, 1594, 1462, 1429, 1342, 1248, 1201, 1159, 1115, 1074, 1020, 980, 922, 752 cm^{-1}. HRMS (ESI) Calcd for $C_{26}H_{26}NaO_6$: 457.1622 ([M + Na]$^+$), found: 457.1612 ([M + Na]$^+$). Anal. Calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03; O, 22.09. Found: C, 71.81; H, 6.05; O, 21.97. Mp 129 °C. $[\alpha]^{27}_D$ −45.6° (*c* 0.59, $CHCl_3$).

Demethoxymethylation of (*S*)-**25** was carried out with concentrated HCl in 1,4-dioxane at 50 °C. After aqueous workup, the organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residual crude product was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:1 as eluant) to afford (*S*)-3,3′-dimethoxy-1,1′-bi-2-naphthol [(*S*)-**26**] (4.50 g, 13 mmol, 87% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, d, J = 8.1 Hz, Ar−H), 7.30−7.35 (4H, m, Ar−H), 7.12−7.19 (4H, m, Ar−H), 5.89 (2H, s, OH), 4.10 (6H, s, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 143.6, 129.0, 128.8, 126.8, 124.6, 124.5, 124.0, 114.4, 106.2, 56.0 ppm; IR (KBr) 3479, 1622, 1464, 1425, 1337, 1313, 1257, 1167, 1117, 1018, 883, 831, 748 cm^{-1}. HRMS (ESI) Calcd for $C_{22}H_{17}O_4$: 345.1121 ([M − H]$^-$), found: 345.1126 ([M − H]$^-$). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24; O, 18.48. Found: C, 76.14; H, 5.23; O, 18.21. Mp 242 °C. $[\alpha]^{27}_D$ −27.6° (*c* 0.26, $CHCl_3$).

(*S*)-3,3′-Dimethoxy-2,2′-bis(trifluoromethanesulfonyloxy)-1,1′-binaphthyl [(*S*)-27]. Trifluoromethanesulfonylation of (*S*)-**26** was conducted in a manner similar to that described before. The residual crude product was purified by column chromatography on silica gel (CH_2Cl_2/hexane = 1:3 as eluant) to give (*S*)-3,3′-dimethoxy-2,2′-bis(trifluoromethanesulfonyloxy)-1,1′-binaphthyl [(*S*)-**27**] (97% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (2H, d, J = 8.4 Hz, Ar−H), 7.52 (2H, ddd, J = 8.4, 6.9, 1.2 Hz, Ar−H), 7.49 (2H, s, Ar−H), 7.24 (2H, ddd, J = 7.8, 6.9, 1.2 Hz, Ar−H), 7.14 (2H, d, J = 7.8 Hz, Ar−H), 4.12 (6H, s, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 137.6, 132.9, 127.7, 127.6, 126.8, 126.6, 125.4, 124.6, 118.0 (q, J_{C-F} = 321 Hz), 109.4, 56.4 ppm; IR (KBr) 3466, 1603, 1468, 1425, 1331, 1209, 1132, 1105, 1011, 947, 895, 813, 745 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{16}F_6NaO_8S_2$: 633.0083 ([M + Na]$^+$), found: 633.0067 ([M + Na]$^+$). Anal. Calcd for $C_{24}H_{16}F_6O_8S_2$: C, 47.22; H, 2.64; F, 18.67. Found: C, 47.06; H, 2.81; F, 18.43. Mp 139 °C. $[\alpha]^{27}_D$ 118.3° (*c* 0.24, $CHCl_3$).

(*S*)-3,3′-Dimethoxy-2,2′-dimethyl-1,1′-binaphthyl [(*S*)-28]. The cross coupling of (*S*)-**27** with MeMgI (5 equiv) using $NiCl_2$(dppp) (5 mol %) as catalyst was performed in a manner similar to that described for the conversion of (*S*)-**12** to (*S*)-**13**. (88% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (2H, d, J = 8.1 Hz, Ar−H), 7.36 (2H, ddd, J = 8.1, 6.9, 1.2 Hz, Ar−H), 7.23 (2H, s, Ar−H), 7.06 (2H, ddd, J = 8.1, 6.9, 1.2 Hz, Ar−H), 6.96 (2H, d, J = 8.1 Hz, Ar−H), 4.03 (6H, s, OCH_3) 1.92 (6H, s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 136.5, 133.1, 128.1, 127.4, 126.5, 125.7, 125.3, 123.5, 104.2, 55.4, 13.5 ppm; IR (KBr) 2953, 1599, 1456, 1421, 1323, 1232, 1194, 1165, 1115, 1022, 748 cm^{-1}. HRMS (FAB) Calcd for $C_{24}H_{22}O_2$: 342.1620 (M^+), found: 342.1608 (M^+). Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.18; H, 6.48; O, 9.34. Found: C, 83.92; H, 6.42; O, 9.31. Mp 197 °C. $[\alpha]^{27}_D$ −16.5° (*c* 0.50, $CHCl_3$).

(*S*)-3,3′-Bis(trifluoromethanesulfonyloxy)-2,2′-dimethyl-1,1′-binaphthyl [(*S*)-30]. To a solution of (*S*)-**28** (3.80 g, 11.1 mmol) in CH_2Cl_2 (40 mL) was added boron tribromide (2.50 mL, 26.6 mmol) dropwise at 0 °C. This mixture was stirred for 5 h at 0 °C, and then water was added carefully. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. After evaporation of solvents, the crude (*S*)-3,3′-dihydroxy-2,2′-dimethyl-1,1′-binaphthyl [(*S*)-**29**] was used for the following reaction without any purification. An analytical sample of (*S*)-**29** was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:1 as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (2H, d, J = 8.4 Hz, Ar−H), 7.36 (2H, ddd, J = 8.1, 6.9, 1.5 Hz, Ar−H), 7.27 (2H, s, Ar−H), 7.07 (2H, ddd, J = 8.4, 6.9, 1.5 Hz, Ar−H), 6.96 (2H, d, J = 8.1 Hz, Ar−H), 5.14 (2H, s, OH), 1.97 (6H, s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz,

(32) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett*. **1992**, *33*, 2253.

$CDCl_3$) δ 152.3, 137.0, 133.1, 128.3, 126.1, 125.8, 125.6, 125.5, 123.7, 108.8, 13.3 ppm; IR (KBr) 3385, 1622, 1601, 1570, 1508, 1437, 1383, 1331, 1234, 1161, 1101, 862, 748 cm^{-1}. HRMS (ESI) Calcd for $C_{22}H_{17}O_2$: 313.1223 ([M − H]$^-$), found: 313.1206 ([M − H]$^-$). Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77; O, 10.18. Found: C, 83.88; H, 5.99; O, 10.09. Mp 202 °C. $[\alpha]^{27}_D$ −16.8° (*c* 0.50, $CHCl_3$).

Trifluoromethanesulfonylation of (*S*)-**29** was performed as described before. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/hexane = 1:5 as eluant) gave (*S*)-3,3′-bis(trifluoromethanesulfonyloxy)-2,2′-dimethyl-1,1′-binaphthyl [(*S*)-**30**] (95% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 8.4 Hz, Ar−H), 7.94 (2H, s, Ar−H), 7.54 (2H, ddd, *J* = 8.4, 6.9, 1.2 Hz, Ar−H), 7.34 (2H, ddd, *J* = 8.4, 6.9, 1.2 Hz, Ar−H), 6.99 (2H, d, *J* = 8.4 Hz, Ar−H), 2.04 (6H, s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 137.4, 132.1, 131.5, 128.3, 128.3, 127.8, 127.0, 125.3, 119.6, 118.9 (q, J_{C-F} = 317 Hz), 13.9 ppm; IR (KBr) 3067, 1564, 1504, 1420, 1323, 1248, 1225, 1140, 1053, 988, 922, 881, 819, 779, 754 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{15}F_6O_6S_2$: 577.0209 ([M − H]$^-$), found: 577.0223 ([M − H]$^-$). Anal. Calcd for $C_{24}H_{16}F_6O_6S_2$: C, 49.83; H, 2.79; F, 19.70. Found: C, 49.79; H, 2.88; F, 19.90. Melted around room temperature. $[\alpha]^{27}_D$ −20.9° (*c* 0.58, $CHCl_3$).

(*S*)-3,3′-Bis(3,5-diphenylphenyl)-2,2′-dimethyl-1,1′-binaphthyl [(*S*)-22 (Ar = 3,5-Ph$_2$-Ph)]. A mixture of (*S*)-**30** (289 mg, 0.50 mmol), 3,5-diphenylphenylboronic acid (329 mg, 1.2 mmol), $Pd(OAc)_2$ (5.8 mg, 5 mol %), triphenylphosphine (29.4 mg, 0.11 mmol), and $K_3PO_4 \cdot nH_2O$ (429 mg, 1.5 mmol) in THF (5 mL) was heated to 65 °C and stirred for 12 h under argon atmosphere. The resulting mixture was poured into saturated NH_4Cl, and the whole mixture was filtered to remove the catalyst. The filtrate was extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/hexane = 1:20 as eluant) to afford (*S*)-3,3′-bis(3,5-diphenylphenyl)-2,2′-dimethyl-1,1′-binaphthyl [(*S*)-**22** (Ar = 3,5-Ph$_2$-Ph)] (336 mg, 0.45 mmol, 91% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, s, Ar−H), 7.92 (2H, d, *J* = 8.0 Hz, Ar−H), 7.84 (2H, t, *J* = 1.6 Hz, Ar−H), 7.70−7.74 (12H, m, Ar−H), 7.43−7.49 (10H, m, Ar−H), 7.38 (4H, ddt, *J* = 7.6, 6.4, 1.2 Hz, Ar−H), 7.28 (2H, ddd, *J* = 8.4, 6.8, 1.2 Hz, Ar−H), 7.17 (2H, d, *J* = 8.0 Hz, Ar−H), 2.08 (6H, s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 141.6, 141.0, 141.0, 136.6, 132.5, 132.1, 132.0, 128.7, 128.3, 127.9, 127.4, 127.3, 126.2, 125.7, 125.4, 124.7, 18.5 ppm; IR (KBr) 3443, 3053, 2364, 1593, 1497, 1406, 1030, 881, 758, 698 cm^{-1}. HRMS (FAB) Calcd for $C_{58}H_{42}$: 738.3287 (M$^+$), found: 738.3283 (M$^+$). Anal. Calcd for $C_{58}H_{42}$: C, 94.27; H, 5.73. Found: C, 94.33; H, 5.87. Mp 170 °C. $[\alpha]^{27}_D$ −50.4° (*c* 0.50, $CHCl_3$).

(*S*)-3,3′-Bis(4-fluorophenyl)-2,2′-dimethyl-1,1′-binaphthyl [(*S*)-22 (Ar = 4-F-Ph)]: (95% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.4 Hz, Ar−H), 7.82 (2H, s, Ar−H), 7.41−7.47 (6H, m, Ar−H), 7.25 (2H, ddd, *J* = 8.4, 6.8, 1.2 Hz, Ar−H), 7.12−7.18 (4H, m, Ar−H), 7.09 (2H, d, *J* = 8.0 Hz, Ar−H), 1.92 (6H, s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 246 Hz), 140.1, 138.0 (d, J_{C-F} = 3.3 Hz), 136.4 132.4, 131.9, 131.9, 131.0 (d, J_{C-F} = 7.4 Hz), 128.3, 127.8, 126.2, 125.5, 125.4, 114.9 (d, J_{C-F} = 21.4 Hz), 18.3 ppm; IR (KBr) 3049, 2955, 2924, 1603, 1512, 1425, 1221, 1157, 1094, 1016, 893, 835, 748 cm^{-1}. HRMS (FAB) Calcd for $C_{34}H_{24}F_2$: 470.1846 (M$^+$), found: 470.1841 (M$^+$). Mp 187 °C. $[\alpha]^{27}_D$ −69.8° (*c* 0.50, $CHCl_3$).

(*S*)-3,3′-Bis(3,4,5-trifluorophenyl)-2,2′-dimethyl-1,1′-binaphthyl [(*S*)-22 (Ar = 3,4,5-F$_3$-Ph)]: (94% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 8.1 Hz, Ar−H), 7.82 (2H, s, Ar−H), 7.47 (2H, ddd, *J* = 8.1, 6.9, 1.2 Hz, Ar−H), 7.29 (2H, ddd, *J* = 8.1, 6.9, 1.2 Hz, Ar−H), 7.12 (2H, d, *J* = 6.3 Hz, Ar−H), 7.10 (2H, d, *J* = 6.3 Hz, Ar−H), 7.06 (2H, d, *J* = 8.1 Hz, Ar−H), 1.91 (6H, s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7 (ddd, J_{C-F} = 248, 9.9, 4.1 Hz), 139.0 (dt, J_{C-F} = 250, 15.2 Hz), 138.2, 137.9 (dt, J_{C-F} = 5.0, 7.5 Hz), 136.5, 132.2, 131.8, 131.7, 128.5, 128.0, 126.9, 125.9, 125.5, 113.7 (dd, J_{C-F} = 14.9, 5.8 Hz), 18.1 ppm; IR (KBr) 3489, 3067, 2363, 1614, 1528, 1420, 1362, 1240, 1042, 866, 816, 754, 709 cm^{-1}. HRMS (FAB) Calcd for $C_{34}H_{20}F_6$: 542.1469 (M$^+$), found: 542.1479 (M$^+$). Anal. Calcd for $C_{34}H_{20}F_6$: C, 75.27; H, 3.72; F, 21.01. Found: C, 75.45; H, 3.54; F, 20.73. Mp 309 °C. $[\alpha]^{27}_D$ −58.8° (*c* 0.50, $CHCl_3$).

(*S*)-3,3′-Bis(3,5-diphenylphenyl)-2,2′-bis(bromomethyl)-1,1′-binaphthyl [(*S*)-23 (Ar = 3,5-Ph$_2$-Ph)]. Radical bromination of (*S*)-**22** (Ar = 3,5-Ph$_2$-Ph) was performed as described before. The residual crude product was purified by column chromatography on silica gel (CH_2Cl_2/hexane = 1:20 as eluant) to afford (*S*)-3,3′-bis(3,5-diphenylphenyl)-2,2′-bis(bromomethyl)-1,1′-binaphthyl [(*S*)-**23** (Ar = 3,5-Ph$_2$-Ph)] (97% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, s, Ar−H), 7.94 (2H, d, *J* = 8.4 Hz, Ar−H), 7.91 (2H, t, *J* = 1.6 Hz, Ar−H), 7.87 (2H, s, Ar−H), 7.86 (2H, s, Ar−H), 7.74−7.77 (8H, m, Ar−H), 7.54 (2H, ddd, *J* = 8.4, 7.2, 1.2 Hz, Ar−H), 7.46−7.49 (8H, m, Ar−H), 7.36−7.40 (4H, m, Ar−H), 7.33 (2H, ddd, *J* = 8.4, 7.2, 1.2 Hz, Ar−H), 7.22 (2H, d, *J* = 8.8 Hz, Ar−H), 4.38 (4H, s, Ar−CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 141.3, 140.8, 140.7, 136.4, 133.1, 132.2, 131.9, 130.4, 128.8, 127.9, 127.5, 127.3, 126.6, 125.2, 32.2 ppm; IR (KBr) 3443, 3057, 2924, 1593, 1497, 1406, 1217, 1028, 885, 758, 696 cm^{-1}. HRMS (FAB) Calcd for $C_{58}H_{40}Br_2$: 894.1497 (M$^+$), found: 894.1464 (M$^+$). Mp 185 °C. $[\alpha]^{27}_D$ −37.2° (*c* 0.50, $CHCl_3$).

(*S*)-3,3′-Bis(4-fluorophenyl)-2,2′-bis(bromomethyl)-1,1′-binaphthyl [(*S*)-23 (Ar = 4-F-Ph)]: (98% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 8.0 Hz, Ar−H), 7.89 (2H, s, Ar−H), 7.56−7.61 (4H, m, Ar−H), 7.52 (2H, ddd, *J* = 8.0, 6.8, 1.2 Hz, Ar−H), 7.30 (2H, ddd, *J* = 8.4, 6.8, 1.2 Hz, Ar−H), 7.14−7.20 (6H, m, Ar−H), 4.23 (4H, s, Ar−CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (d, J_{C-F} = 247 Hz), 139.8, 136.2, 136.2 (d, J_{C-F} = 3.3 Hz), 133.0, 132.2, 131.8, 131.1 (d, J_{C-F} = 7.4 Hz), 130.5, 127.8, 127.3, 127.2, 126.6, 115.1 (d, J_{C-F} = 21.5 Hz), 32.0 ppm; IR (KBr) 3061, 1603, 1510, 1219, 1157, 1094, 1026, 968, 893, 843, 750 cm^{-1}. HRMS (FAB) Calcd for $C_{34}H_{22}Br_2F_2$: 626.0056 (M$^+$), found: 626.0051 (M$^+$). Anal. Calcd for $C_{34}H_{22}Br_2F_2$: C, 64.99; H, 3.53; Br, 25.43; F, 6.05. Found: C, 64.53; H, 3.55; Br, 25.98; F, 6.23. Mp 218 °C. $[\alpha]^{27}_D$ −73.2° (*c* 0.50, $CHCl_3$).

(*S*)-3,3′-Bis(3,4,5-trifluorophenyl)-2,2′-bis(bromomethyl)-1,1′-binaphthyl [(*S*)-23 (Ar = 3,4,5-F$_3$-Ph)]: (quantitative yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (2H, d, *J* = 8.1 Hz, Ar−H), 7.89 (2H, s, Ar−H), 7.57 (2H, ddd, *J* = 8.1, 6.9, 1.2 Hz, Ar−H), 7.34 (2H, ddd, *J* = 8.1, 6.9, 1.2 Hz, Ar−H), 7.25−7.30 (4H, m, Ar−H), 7.13 (2H, d, *J* = 8.1 Hz, Ar−H), 4.19 (4H, s, Ar−CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7 (ddd, J_{C-F} = 249, 9.9, 4.1 Hz), 139.4 (dt, J_{C-F} = 251, 14.9 Hz), 137.7, 136.3, 136.0 (dt, J_{C-F} = 5.0, 7.9 Hz), 132.9, 132.0, 131.5, 130.6, 128.0, 127.7, 127.3, 127.0, 114.0 (dd, J_{C-F} = 15.8, 5.8 Hz), 31.1 ppm; IR (KBr) 3441, 3067, 2363, 1614, 1528, 1436, 1367, 1242, 1207, 1045, 868, 752, 712 cm^{-1}. HRMS (FAB) Calcd for $C_{34}H_{18}Br_2F_6$: 697.9679 (M$^+$), found: 697.9684 (M$^+$). Anal. Calcd for $C_{34}H_{18}Br_2F_6$: C, 58.31; H, 2.59; Br, 22.82; F, 16.28. Found: C, 58.15; H, 2.43; Br, 22.97; F, 16.48. Mp 239 °C. $[\alpha]^{27}_D$ −63.8° (*c* 0.50, $CHCl_3$).

Chiral Ammonium Salt (*S,S*)-11d. (*S,S*)-**11d** was prepared in a manner similar to that described for the preparation of (*S,S*)-**11a**. (72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (2H, br, Ar−H), 8.47 (2H, s, Ar−H), 8.18 (2H, s, Ar−H), 8.14 (2H, d, *J* = 8.4 Hz, Ar−H), 8.06 (4H, br, Ar−H), 7.75 (2H, d, *J* = 8.4 Hz, Ar−H), 7.65 (2H, t, *J* = 7.2 Hz, Ar−H), 7.43 (2H, t, *J* = 7.2 Hz, Ar−H), 7.35−7.39 (4H, m, Ar−H), 7.21 (2H, d, *J* = 8.8 Hz, Ar−H), 7.14 (2H, t, *J* = 7.2 Hz, Ar−H), 7.1−7.8 (18H, br, Ar−H), 7.06 (2H, d, *J* = 8.8 Hz, Ar−H), 6.57 (2H, d, *J* = 8.8 Hz, Ar−H), 5.06 (2H, d, *J* = 14.0 Hz, Ar−CH_2), 4.39 (2H, d, *J* = 14.0 Hz, Ar−CH_2), 4.34 (2H, d, *J* = 13.2 Hz, Ar−CH_2), 3.68 (2H, d, *J* = 13.2 Hz, Ar−CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 140.4, 139.9, 139.2, 138.8, 136.1, 133.8, 133.7, 132.9, 131.0, 130.8, 128.9, 128.8, 128.5, 128.3, 127.9, 127.8, 127.6, 127.4, 127.3, 127.2, 126.8, 126.6, 126.3, 124.6, 122.2, 62.3, 57.5 ppm; IR (KBr) 3649, 3264, 3055, 1593, 1497, 1454, 1400, 1344, 1306, 1028. 968, 885, 850, 810, 760, 698 cm^{-1}. HRMS (ESI) Calcd for $C_{80}H_{56}N$: 1030.4407 (M$^+$), found: 1030.4401 (M$^+$). Melted at 252 °C with decomposition. $[\alpha]^{27}_D$ −37.4° (*c* 0.50, $CHCl_3$).

Chiral ammonium salt (*S,S*)-11e: (82% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (2H, s, Ar−H), 8.09 (2H, d, J = 8.4 Hz, Ar−H), 7.88 (2H, d, J = 8.4 Hz, Ar−H), 7.62 (2H, ddd, J = 8.0, 6.8, 1.2 Hz, Ar−H), 7.25−7.60 (8H, br, Ar−H), 7.51 (2H, ddd, J = 8.0, 6.8, 1.2 Hz, Ar−H), 7.42 (2H, d, J = 8.4 Hz, Ar−H), 7.32 (2H, ddd, J = 8.4, 6.8, 1.2 Hz, Ar−H), 7.21 (2H, ddd, J = 8.4, 6.8, 1.2 Hz, Ar−H), 7.11 (2H, d, J = 8.4 Hz, Ar−H), 7.09 (2H, d, J = 8.0 Hz, Ar−H), 6.34 (2H, d, J = 8.4 Hz, Ar−H), 4.94 (2H, d, J = 14.0 Hz, Ar−CH_2), 4.46 (2H, d, J = 14.0 Hz, Ar−CH_2), 4.27 (2H, d, J = 13.6 Hz, Ar−CH_2), 3.75 (2H, d, J = 13.6 Hz, Ar−CH_2) ppm;^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J_{C-F} = 250 Hz), 139.1, 137.9, 136.2, 135.3 (d, J_{C-F} = 3.3 Hz), 133.8, 132.7, 132.4, 130.9 (d, J_{C-F} = 7.4 Hz), 128.6, 128.4, 128.3, 128.1, 127.4, 127.3, 126.7, 126.5, 124.7, 122.3, 116.9 (d, J_{C-F} = 21.5 Hz), 62.4, 57.4 ppm; IR (KBr) 3651, 3375, 3055, 2949, 2926, 1599, 1508, 1454, 1358, 1313, 1225, 1161, 1028, 849, 810, 750 cm^{-1}. HRMS (ESI) Calcd for $C_{56}H_{38}NF_2$: 762.2967 (M^+), found: 762.2970 (M^+). Melted at 231 °C with decomposition. $[\alpha]^{27}_D$ 77.3° (*c* 0.50, $CHCl_3$).

Chiral ammonium salt (*S,S*)-11f: (84% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (2H, s, Ar−H), 8.11 (2H, d, J = 8.4 Hz, Ar−H), 7.96 (2H, d, J = 8.7 Hz, Ar−H), 7.65 (2H, t, J = 7.8 Hz, Ar−H), 7.4−7.7 (4H, br, Ar−H), 7.52−7.58 (4H, m, Ar−H), 7.35 (2H, t, J = 7.8 Hz, Ar−H), 7.24−7.29 (2H, m, Ar−H), 7.09−7.15 (4H, m, Ar−H), 6.53 (2H, d, J = 8.4 Hz, Ar−H), 4.82 (2H, d, J = 14.1 Hz, Ar−CH_2), 4.62 (2H, d, J = 14.1 Hz, Ar−CH_2), 4.46 (2H, d, J = 13.2 Hz, Ar−CH_2), 3.74 (2H, d, J = 13.2 Hz, Ar−CH_2) ppm;^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7 (d, J_{C-F} = 253 Hz), 140.0 (dt, J_{C-F} = 255, 15.4 Hz), 139.2, 136.4, 136.0, 135.4 (dt, J_{C-F} = 4.9, 7.5 Hz), 133.9, 133.5, 132.7, 131.4, 131.0, 128.5, 128.3, 128.2, 127.9, 127.6, 127.3, 127.2, 126.9, 126.5, 126.5, 126.4, 124.7, 124.7, 122.0, 115.3, 115.2, 62.5, 57.3 ppm; IR (KBr) 3647, 3360, 3055, 2981, 2954, 1614, 1526, 1450, 1360, 1242, 1047, 854, 750 cm^{-1}. HRMS (FAB) Calcd for $C_{56}H_{34}NF_6$: 834.2597 (M^+), found: 834.2615 (M^+). Melted at 220 °C with decomposition. $[\alpha]^{27}_D$ 33.6° (*c* 0.20, $CHCl_3$).

General Procedure for Catalytic Enantioselective Alkylation of *tert*-Butyl Glycinate Benzophenone Schiff Base (7a) under Phase-Transfer Conditions (Benzylation). To a mixture of **7a** (148 mg, 0.5 mmol) and chiral catalyst (*S,S*)-**11c** (4.5 mg, 1 mol %) in toluene (3.0 mL)−50% KOH aqueous solution (1.0 mL) was added benzyl bromide (72.8 μL, 0.6 mmol) dropwise at 0 °C. The reaction mixture was stirred vigorously (approximately 1360 rpm) at the same temperature for 30 min. The mixture was then poured into water and extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:10 as eluant) gave (*R*)-*tert*-butyl *N*-(diphenylmethylene)phenylalaninate [**8a** ($R' = CH_2Ph$)][4a] (183 mg, 0.475 mmol, 95% yield). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD, hexane/2-propanol = 100:1, flow rate = 0.5 mL/min, retention time; 14.8 min (*R*) and 28.2 min (*S*)). Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[4a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.58 (2H, m, Ph), 7.26−7.38 (6H, m, Ph), 7.13−7.21 (3H, m, Ph), 7.04−7.06 (2H, m, Ph), 6.60 (2H, br d, J = 6.0 Hz, Ph), 4.10 (1H, dd, J = 9.6, 4.4 Hz, CHC=O), 3.23 (1H, dd, J = 13.6, 4.4 Hz, Ph−CH_2), 3.15 (1H, dd, J = 13.6, 9.6 Hz, Ph−CH_2), 1.44 (9H, s, *t*-Bu) ppm; IR (neat) 2978, 1732, 1624, 1576, 1495, 1447, 1367, 1286, 1150, 1082, 1030, 849, 756, 696 cm^{-1}.

Synthesis of (*S*)-*tert*-Butyl *N*-Acetylindoline-2-carboxylate (32b). (*S*)-*tert*-Butyl *N*-Acetyl-2-bromophenylalaninate (31b). To a mixture of **7a** (148 mg, 0.5 mmol) and chiral catalyst (*R,R*)-**11f** (4.6 mg, 1 mol %) in toluene (3.0 mL)-50% KOH aqueous solution (1.0 mL) was added 2-bromobenzyl bromide (159 mg, 0.6 mmol) dropwise at 0 °C under argon atmosphere. The reaction mixture was stirred vigorously at the same temperature for 24 h. The mixture was poured into water and extracted with ether. Solvents were evaporated, and the residue was dissolved in THF (5 mL). Then, 1 M citric acid aqueous solution (5 mL) was added, and the mixture was stirred at room temperature for 3 h. After removal of THF under vacuum, the aqueous phase was neutralized by addition of solid $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 (3 mL); Et_3N (106 μL, 0.75 mmol) and acetyl chloride (43.5 μL, 0.6 mmol) were added at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and poured into saturated $NaHCO_3$. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ethyl acetate/hexane = 1:1 as eluant) gave (*S*)-*tert*-butyl *N*-acetyl-2-bromophenylalaninate (**31b**) (144 mg, 0.43 mmol, 86% yield, 99% ee): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (1H, dd, J = 8.0, 1.2 Hz, Ar−H), 7.21−7.28 (2H, m, Ar−H), 7.10 (1H, ddd, J = 8.0, 6.4, 2.4 Hz, Ar−H), 5.97 (1H, br d, J = 8.0 Hz, NH), 4.85 (1H, ddd, J = 8.0, 8.0, 6.4 Hz, CHC=O), 3.25 (1H, dd, J = 14.0, 6.4 Hz, Ar−CH_2), 3.15 (1H, dd, J = 14.0, 8.0 Hz, Ar−CH_2), 1.95 (3H, s, CH_3C=O), 1.45 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.4, 136.2, 132.7, 131.1, 128.4, 127.2, 124.9, 82.2, 52.9, 38.3, 27.9, 23.1 ppm; IR (neat) 3281, 2978, 1732, 1651, 1549, 1445, 1369, 1227, 1157, 1026, 847, 754, 658 cm^{-1}. HRMS (ESI) Calcd for $C_{15}H_{20}BrNNaO_3$: 364.0519 ($[M + Na]^+$), found: 364.0523 ($[M + Na]^+$). $[\alpha]^{27}_D$ 30.2° (*c* 0.22, $CHCl_3$; 99% ee). HPLC analysis: Daicel Chiralcel OD, hexane/2-propanol = 12:1, flow rate = 0.5 mL/min, retention time; 15.7 min (*R*) and 43.5 min (*S*).

(*S*)-*tert*-Butyl *N*-Acetylindoline-2-carboxylate (32b). A mixture of **31b** (103 mg, 0.3 mmol), $Pd_2(dba)_3$ (13.7 mg, 10 mol % Pd), P(*o*-tolyl)$_3$ (18.6 mg, 20 mol %) and Cs_2CO_3 (197 mg, 0.60 mmol) in toluene (2 mL) was heated to 100 °C and stirred for 10 h. After cooling to room temperature, the resulting mixture was filtered to remove the catalyst. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:2 as eluant) to afford (*S*)-*tert*-butyl *N*-acetylindoline-2-carboxylate (**32b**) (73.7 mg, 0.28 mmol, 94% yield, 99% ee): ^{1}H NMR (400 MHz, $CDCl_3$) 1.9:1 ratio of rotamers: δ 8.22 (0.65H, d, J = 8.0 Hz, Ar−H), 7.13−7.23 (2H + 0.35H, m, Ar−H), 7.01 (1H, t, J = 7.6 Hz, Ar−H), 5.02 (0.35H, d, J = 9.2 Hz, CHC=O), 4.76 (0.65H, d, J = 9.2 Hz, CHC=O), 3.59 (0.65H, dd, J = 16.4, 10.8 Hz, Ar−CH_2), 3.45 (0.35H, dd, J = 16.4, 10.8 Hz, Ar−CH_2), 3.19 (0.65H, d, J = 16.4 Hz, Ar−CH_2), 3.03 (0.35H, d, J = 16.4 Hz, Ar−CH_2), 2.48 (1.05H, s, CH_3C=O), 2.17 (1.95H, s, CH_3C=O), 1.45 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 168.6, 168.0, 142.7, 141.3, 130.8, 128.3, 127.6, 125.5, 124.0, 123.6, 123.0, 117.0, 113.4, 82.7, 81.6, 61.8, 60.8, 33.5, 31.5, 29.7, 27.9, 24.6, 23.6 ppm; IR (KBr) 2980, 1738, 1668, 1438, 1394, 1273, 1153, 999, 856, 756 cm^{-1}. HRMS (ESI) Calcd for $C_{15}H_{19}NNaO_3$: 284.1257 ($[M + Na]^+$), found: 284.1257 ($[M + Na]^+$). $[\alpha]^{27}_D$ −122.5° (*c* 0.99, $CHCl_3$; 99% ee). HPLC analysis: Daicel Chiralcel OD, hexane/2-propanol = 12:1, flow rate = 0.5 mL/min, retention time; 21.7 min (*R*) and 28.7 min (*S*). Absolute configuration was confirmed, after cleavage of acetyl amide and *tert*-butyl ester (6 N HCl), by comparison of the optical rotation of the amino acid hydrochloride with the literature value.[33]

Representative Procedure for the Synthesis of (*S*)-*tert*-Butyl Tyrosinate (36b) and L-Dopa *tert*-Butyl Ester (36a).

(*S*)-*tert*-Butyl 4-Benzyloxyphenylalaninate (35b).[34] The alkylation of **7a** with 4-benzyloxybenzyl bromide (**34b**) using (*R,R*)-**11f** was performed according to the general procedure. After workup, the residue was treated with a 1 M citric acid aqueous solution in THF to hydrolyze benzophenone imine as described for the synthesis of **31b**. The crude product was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:1 as eluant) to furnish (*S*)-*tert*-butyl 4-benzyloxyphenylalaninate (**35b**) (83% yield, 98% ee): ^{1}H NMR (400 MHz,

(33) Gruenfeld, N. U.S. Patent, 4,479,963, 1984.
(34) Hu, L.-Y.; Ryder, T. R.; Nikam, S. S.; Millerman, E.; Szoke, B. G.; Raffery, M. F. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1121.
(35) Young, D. W. U.S. Patent 3,496,219, 1970.

$CDCl_3$) δ 7.29−7.44 (5H, m, Ph), 7.14 (2H, d, J = 8.8 Hz, Ar−H), 6.91 (2H, d, J = 8.8 Hz, Ar−H), 5.04 (2H, s, $PhCH_2O$), 3.55 (1H, dd, J = 8.0, 5.6 Hz, CHC═O), 2.97 (1H, dd, J = 14.0, 5.6 Hz, Ar−CH_2), 2.78 (1H, dd, J = 14.0, 8.0 Hz, Ar−CH_2), 1.51 (2H, br, NH_2), 1.43 (9H, s, *t*-Bu) ppm; IR (neat) 2978, 2932, 1728, 1612, 1512, 1454, 1367, 1244, 1153, 1026, 845, 736, 696 cm^{-1}.

(*S*)-*tert*-Butyl 3,4-dibenzyloxyphenylalaninate (35a): (81% yield, 98% ee): ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.44 (4H, m, Ph), 7.26−7.37 (6H, m, Ph), 6.87 (1H, d, J = 8.0 Hz, Ar−H), 6.82 (1H, d, J = 2.0 Hz, Ar−H), 6.72 (1H, dd, J = 8.0, 2.0 Hz, Ar−H), 5.13 (4H, s, $PhCH_2O$), 3.52 (1H, dd, J = 7.6, 5.6 Hz, CHC═O), 2.93 (1H, dd, J = 13.6, 5.6 Hz, Ar−CH_2), 2.72 (1H, dd, J = 13.6, 7.6 Hz, Ar−CH_2), 1.48 (2H, br, NH_2), 1.42 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 148.7, 147.8, 137.3, 137.2, 130.8, 128.3, 127.7, 127.6, 127.3, 127.2, 122.3, 116.6, 115.3, 81.1, 71.5, 71.4, 56.3, 40.8, 28.1 ppm; IR (neat) 2978, 2932, 1728, 1589, 1512, 1454, 1367, 1265, 1153, 1022, 847, 735, 696 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{32}NO_4$: 434.2326 ($[M + H]^+$), found: 434.2328 ($[M + H]^+$). $[\alpha]^{27}_D$ 4.0° (*c* 1.02, $CHCl_3$; 98% ee). HPLC analysis: Daicel Chiralcel OD, hexane/2-propanol = 4:1, flow rate = 0.5 mL/min, retention time; 24.3 min (*S*) and 28.4 min (*R*).

(*S*)-*tert*-Butyl Tyrosinate (36b).[35] To a solution of **35b** (65.5 mg, 0.2 mmol) in THF (2 mL) was added 10% palladium on activated carbon (10 mg) at 0 °C under argon atmosphere. Then, argon was replaced by H_2, and the reaction mixture was stirred for 6 h at room temperature. The resulting mixture was filtered to remove the catalyst, and the filtrate was concentrated. Purification of the residue by column chromatography on silica gel (ethyl acetate as eluant) gave (*S*)-*tert*-butyl tyrosinate (**36b**) (44.1 mg, 0.186 mmol, 93% yield, 98% ee): ^1H NMR (400 MHz, $CDCl_3$) δ 7.01−7.04 (2H, m, Ar−H), 6.65−6.68 (2H, m, Ar−H), 3.58 (1H, dd, J = 8.0, 5.6 Hz, CHC═O), 2.99 (1H, dd, J = 14.0, 5.6 Hz, Ar−CH_2), 2.78 (1H, dd, J = 14.0, 8.0 Hz, Ar−CH_2), 2.50−3.30 (3H, br, OH and NH_2), 1.45 (9H, s, *t*-Bu) ppm; IR (KBr) 3335, 2978, 2910, 2684, 2604, 1722, 1616, 1517, 1471, 1367, 1259, 1215, 1161, 1096, 1034, 849, 821 cm^{-1}. $[\alpha]^{29}_D$ 26.1° (*c* 0.5, MeOH; 98% ee).

L-Dopa *tert*-butyl ester (36a): (94% yield, 98% ee) ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (1H, d, J = 8.4 Hz, Ar−H), 6.57 (1H, s, Ar−H), 6.56 (1H, d, J = 8.4 Hz, Ar−H), 4.04 (4H, br, OH and NH_2), 3.63 (1H, dd, J = 8.4, 4.8 Hz, CHC═O), 3.02 (1H, dd, J = 13.6, 4.8 Hz, Ar−CH_2), 2.68 (1H, dd, J = 13.6, 8.4 Hz, Ar−CH_2), 1.42 (9H, s, *t*-Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 144.7, 143.8, 128.1, 120.7, 116.3, 115.4, 82.0, 55.5, 39.4, 28.1 ppm; IR (KBr) 3462, 3337, 3288, 2977, 2939, 2625, 1724, 1609, 1533, 1472, 1367, 1308, 1283, 1159, 1111, 1043, 854, 799 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{20}O_4N$: 254.1393 ($[M + H]^+$), found: 254.1384 ($[M + H]^+$). $[\alpha]^{29}_D$ 19.7° (*c* 1.06, MeOH; 98% ee).

Large-Scale Preparation of L-Dopa *tert*-Butyl Ester. A 300-mL round-bottom flask containing a magnetic stirring bar and a solution of **7a** (5.00 g, 16.9 mmol), 3,4-dibenzyloxybenzyl bromide (**34a**) (7.77 g, 20.3 mmol), and (*R*,*R*)-**11f** (155 mg, 0.169 mmol) in toluene (100 mL) was immersed in an ice−water bath. After 10 min of gentle stirring, cold 50% KOH aqueous solution (33.3 mL) was added by a pipet, and the reaction mixture was stirred vigorously for 3 h. The resulting mixture was then poured into water (100 mL) and extracted with CH_2Cl_2 (60 mL × 2). The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (60 mL), and a 1 M citric acid aqueous solution (150 mL) was added. This solution was stirred at room temperature for 15 h. After removal of THF under vacuum, the aqueous solution was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (60 mL × 3). The organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residual oil by column chromatography on silica gel (ethyl acetate/hexane = 3:2, then ethyl acetate only as eluants) gave (*S*)-*tert*-butyl 3,4-dibenzyloxyphenylalaninate (**35a**) (6.20 g, 14.2 mmol, 84% yield, 98% ee).

To a THF (45 mL) solution of **35a** (6.20 g, 14.2 mmol) in a 100-mL round-bottom flask was added 10% palladium on activated carbon (350 mg) at 0 °C under argon atmosphere. Then, argon was replaced by H_2, and the reaction mixture was stirred for 5 h at room temperature. The resulting mixture was filtered to remove the catalyst, and the filtrate was concentrated. Purification of the residue by column chromatography on silica gel (ethyl acetate as eluant) gave l-Dopa *tert*-butyl ester (**36a**) (3.37 g, 13.3 mmol, 94% yield).

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Supporting Information Available: Synthetic procedure for chiral ammonium salts (*S*,*S*)-**11b** and **11c**, spectroscopic characterization of (*S*)-**10b**, (*S*,*S*)-**11b**, **11c**, and alkylation products **8** (PDF); the crystallographic data for (*S*,*S*)-**11a** and **11f** (PF_6^-) (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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