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Design of Binaphthyl-Modified Symmetrical Chiral Phase-Transfer Catalysts: Substituent Effect of 4,4′,6,6′-Positions of Binaphthyl Rings in the Asymmetric Alkylation of a Glycine Derivative

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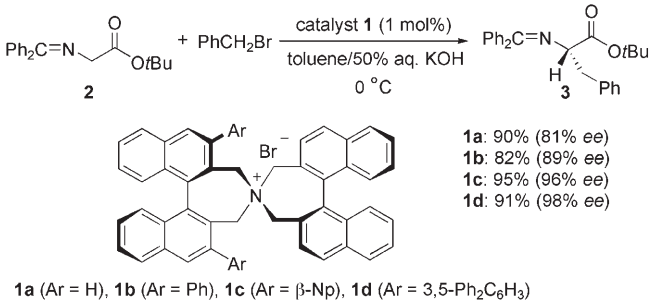
Abstract: A series of symmetrical chiral phase-transfer catalysts with 4,4′,6,6′-tetrasubstituted binaphthyl units have been designed, and these aryl- and trialkylsilyl-substituted phase-transfer catalysts, which included a highly fluorinated catalyst, were prepared. The chiral efficiency of these chiral phase-transfer catalysts was investigated in the asymmetric alkylation of *tert*-butylglycinate–benzophenone Schiff base under mild phase-transfer conditions, and the eminent substituent effect of the 4,4′,6,6′-positions of the binaphthyl units on enantioselection was observed. In particular, the $OctMe_2Si$-substituted catalyst was found to be highly efficient for the phase-transfer alkylation of *tert*-butylglycinate–benzophenone Schiff base with various alkyl halides, including *sec*-alkyl halides. The highly fluorinated catalyst was also utilized as a recyclable chiral phase-transfer catalyst by simple extraction with fluorous solvents.

Keywords: alkylation · amino acids · asymmetric catalysis · molecular design · phase-transfer catalysis

Introduction

Enantioselective reactions that use chiral phase-transfer catalysts provide one of the most useful methods for practical asymmetric synthesis because of its simple reaction procedures and mild reaction conditions.[1,2] In 1989, O'Donnell et al. reported the asymmetric synthesis of natural and non-natural α-amino acids by enantioselective alkylation of prochiral protected glycine derivatives with a *Cinchona* alkaloid derived chiral phase-transfer catalyst,[3] and recently, Corey et al.,[4] Lygo et al.,[5] Nájera and co-workers,[6] and Jew, Park, and co-workers[7] developed more efficient *Cinchona* alkaloid derived chiral catalysts for this system. However, almost all the elaborated chiral phase-transfer catalysts reported so far have been restricted to *Cinchona* alkaloid derivatives, which unfortunately constitute a major difficulty in the rational design and fine-tuning of phase-transfer catalysts. In 1999, we contributed to this area by introducing binaphthyl-modified *N*-spiro-type chiral phase-transfer catalysts of type **1**, which were applied to the highly efficient catalytic enantioselective alkylation of *tert*-butylglycinate–benzophenone Schiff base (**2**) with excellent enantioselectivity (Scheme 1).[8,9] After our report, several new types of chiral phase-transfer catalysts derived from tartaric acid[10] and others[11] have been developed, and the further development of efficient chiral phase-transfer catalysts is of great interest in the field.

In this study, the introduction of 3,3′-diaryl substituents to the chiral ammonium bromide **1a** was found to be crucially



Scheme 1. Asymmetric alkylation of glycine derivative **2** with chiral phase-transfer catalyst **1**. Np = naphthyl.

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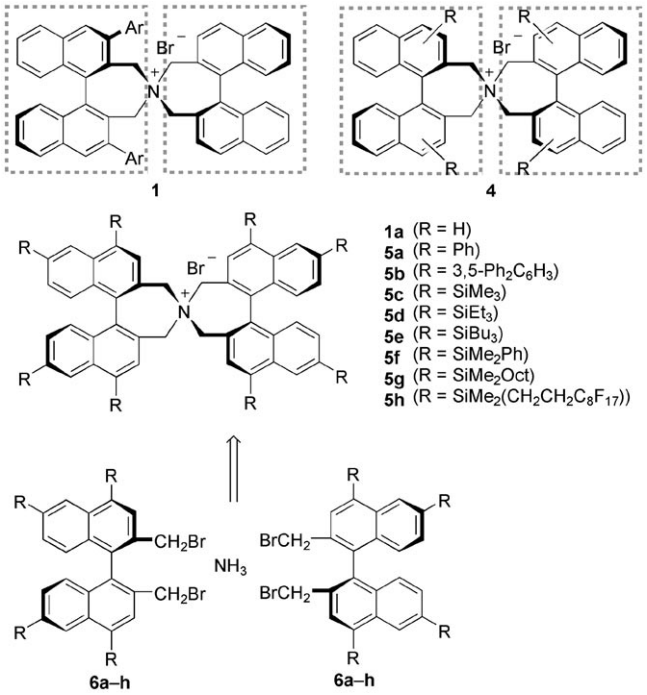
important for obtaining high enantioselectivity.[9l] However, from the viewpoint of simple catalyst design, unsymmetrical catalysts such as **1b–d** require the troublesome synthesis of both right- and left-hand parts of the molecules. Clearly, the preparation of a symmetrical chiral ammonium bromide of type **4** has a distinct advantage over unsymmetrical **1b–d** (Scheme 2). Unfortunately, however, the attempted synthesis of symmetrical 3,3′-diaryl-substituted chiral ammonium salts of type **4** was found to be totally unsuccessful in the preparation step due to steric repulsion of the tetraaryl substituents. Accordingly, we were interested in examining the effect of 4,4′-substituents, particularly 4,4′,6,6′-substituents of the symmetrical catalysts of type **5**, owing to synthetic convenience.[12,13] Easy introduction of trialkylsilyl moieties on the binaphthyl rings further expands the scope of our research. Thus, symmetrical catalysts of type **5** can be prepared from the corresponding dibromide **6** and aqueous ammonia as a most economical nitrogen source. Herein, we report the convenient synthesis of symmetrical catalysts of type **5** and their substituent effects in the asymmetric alkylation of glycine derivative **2**. Also, highly fluorinated symmetrical catalyst **5h** was conveniently prepared and applied to the recovery technique used for such fluorous catalysts.[14] This fluorinated catalyst **5h** demonstrates the first example of a recyclable fluorous chiral phase-transfer catalyst.[15]



Scheme 2. Synthesis of symmetrical catalysts **5**.

Abstract in Japanese:

ビナフチル骨格の 4,4',6,6' 位にアリール基及びトリアルキルシリル基を導入した相間移動触媒のデザイン及び合成を行い、これらの触媒活性をグリシン誘導体の不斉アルキル化によって評価したところ、ビナフチル骨格の 4,4',6,6' 位の置換基がエナンチオ選択性に顕著な影響を与えることを見出した。特にジメチルオクチルシリル基を導入した触媒 **5g** は、第二級アルキルハライドを含む各種アルキルハライドを用いたグリシン誘導体 **2** の不斉アルキル化反応において最も良好な結果を与えた。 さらに触媒 **5g** の構造を基に、フルオラス溶媒を用いた抽出によって、容易に回収及び再利用が可能なフルオラスキラル相間移動触媒 **5h** の開発も行った。

Results and Discussion

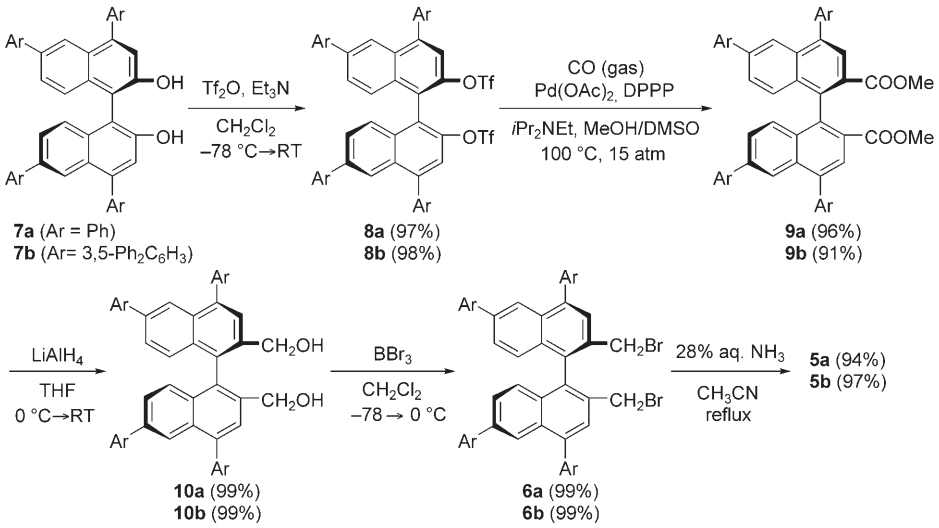
Synthesis of 4,4′,6,6′-Tetrasubstituted Symmetrical Chiral Ammonium Bromides

Initially, we synthesized 4,4′,6,6′-tetraaryl-substituted chiral ammonium bromides **5a** and **5b** from the known 4,4′,6,6′-tetraarylbinaphthols **7a** and **7b**,[13c] respectively, in a five-step sequence (Scheme 3). Thus, 4,4′,6,6′-tetraphenylbinaphthol (**7a**) was transformed with Tf_2O and Et_3N into the corresponding bistriflate **8a**, which was subjected to Pd-catalyzed carbonylation with CO (gas) and MeOH to furnish bisester **9a**. Reduction of **9a** was effected with $LiAlH_4$ to afford diol **10a**, which was further treated with BBr_3 to afford dibromide **6a**. Finally, treatment of **6a** with an excess of aqueous ammonia in CH_3CN gave directly the desired *N*-spiro-type chiral ammonium bromide **5a** in high yield. Chiral ammonium bromide **5b** was also synthesized from **7b** in a similar manner.

For the synthesis of polysilylated chiral phase-transfer catalysts **5c–h**, 4,4′,6,6′-tetrakis(trialkylsilyl)binaphthols **7c–h** were prepared from known 4,4′,6,6′-tetrabromobinaphthol (**11**)[13a] (Scheme 4). Trialkylsilyl groups of various sizes, which included a highly fluorinated trialkylsilyl group, were easily introduced in a similar manner. Thus, lithiation of 4,4′,6,6′-tetrabromobinaphthol MOM ether (**12**) with *t*BuLi in THF and subsequent trapping of the resulting tetraanion with commercially available trialkylsilyl chlorides gave the corresponding polysilylated binaphthol MOM ethers **13c–h**. Deprotection of **13c–h** was carried out with TsOH to furnish 4,4′,6,6′-tetrakis(trialkylsilyl)binaphthols **7c–h**. Further transformation to the desired polysilylated chiral ammonium bromides **5c–h** was effected from **7c–h** in a similar manner as described for the synthesis of **5a** and **5b**, except for the use of a different bromination agent.

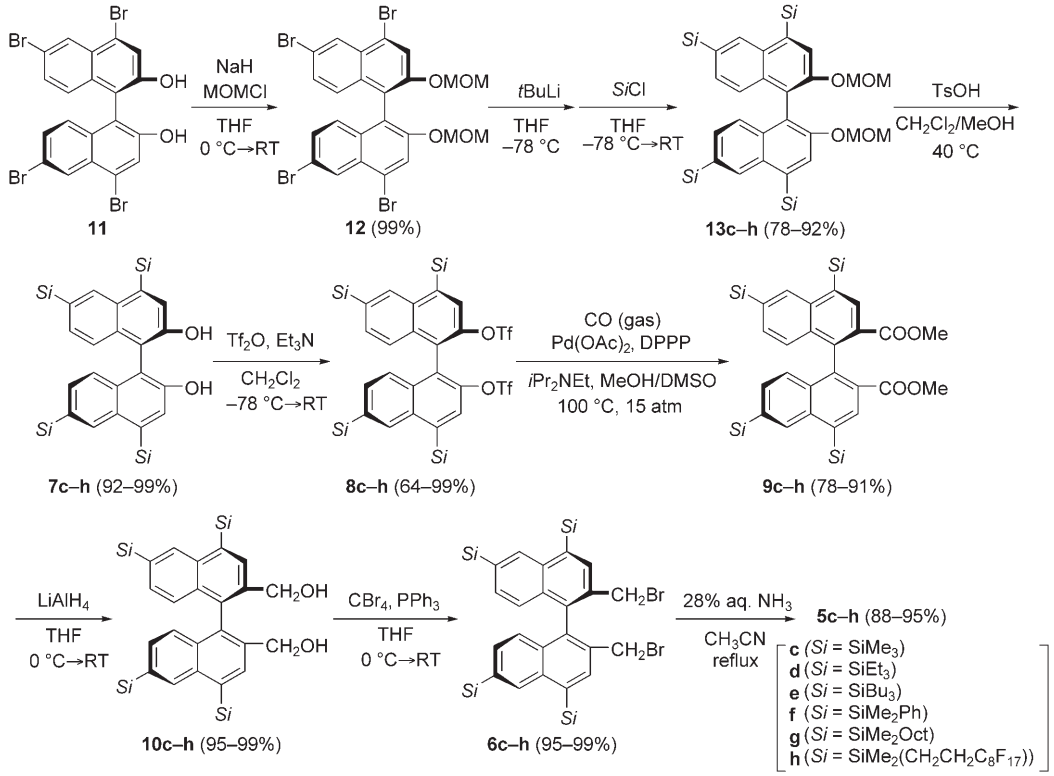
Catalytic Asymmetric Phase-Transfer Alkylation of *tert*-Butylglycinate–Benzophenone Schiff Base: Substituent Effect of the 4,4′,6,6′-Positions of Symmetrical Catalysts 5

With efficient synthetic schemes in hand, we set out to evaluate these symmetrical chiral ammonium salts as chiral phase-transfer catalysts in the asymmetric alkylation of *tert*-butylglycinate–benzophenone Schiff base (**2**). First, we examined the chiral efficiency of the symmetrical catalysts **5a–g** in comparison with nonsubstituted symmetrical catalyst **1a** by the asymmetric benzylation of glycine derivative **2**. Thus, the asymmetric benzylation of **2** with benzyl bromide in



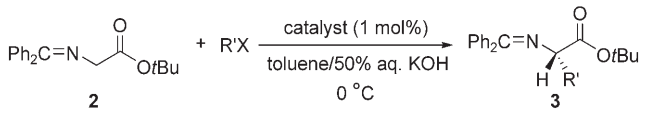
Scheme 3. Synthesis of 4,4′,6,6′-tetraaryl-substituted symmetrical chiral ammonium bromides **5a** and **5b**. DMSO = dimethyl sulfoxide, DPPP = 1,3-bis(diphenylphosphanyl)propane, Tf = trifluoromethanesulfonyl.

aqueous KOH/toluene under the influence of 1 mol% of **5a** gave the corresponding benzylation product **3** ($R' = CH_2Ph$) in 85% yield with 92% *ee* (Table 1, entry 2; 81% *ee* with 1 mol% **1a** under similar reaction conditions: entry 1). Encouraged by this positive observation, we further examined other 4,4′6,6′-tetrasubstituted catalysts **5b–g**, and benzylation product **3** ($R' = CH_2Ph$) was obtained with high enantioselectivity (94–99% *ee*; Table 1, entries 3–8). Next, we examined the methylation of **2** with symmetrical catalysts **5a–g**, because catalyst **1a** gave only low enantioselectivity (33% *ee*) in the case of methylation (Table 1, entry 9). In the reaction with methyl iodide, $CsOH·H_2O$ was employed as a base to attain sufficient reactivity.[9l] The methylation of **2** under the influence of **5a** gave the product **3** ($R' =$ Me) in 94% yield with higher enantioselectivity (52% *ee*) (Table 1, entry 10). Use of **5b** as a catalyst further increased the enantioselectivity to 72% *ee* (Table 1, entry 11). Finally, the use of polysilylated catalysts **5c–g** provided further enhancement of enantioselectivity (88–93% *ee*; Table 1, entries 12–16). The selectivities were somewhat influenced by the silyl substituents of polysilylated catalysts **5c–g** in the asymmetric benzylation and methylation of glycine derivative **2**. In the benzylation reaction, sterically less hindered silyl groups gave higher enantioselectivity ($SiMe_3$: 99% *ee*, $SiEt_3$: 97% *ee*, $SiBu_3$: 94% *ee*; Table 1, entries 4–6). On the other hand, in the reaction with a small alkyl halide such as methyl iodide, sterically



Scheme 4. Synthesis of 4,4′,6,6′-tetrasilyl-substituted symmetrical chiral ammonium bromides **5c–h**. MOM = methoxymethyl, Ts = *p*-toluenesulfonyl.

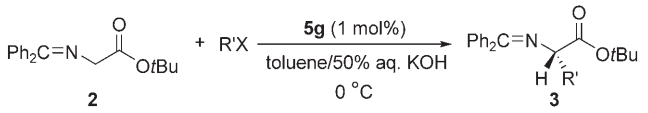
Table 1. Substituent effect of symmetrical catalysts in the enantioselective phase-transfer alkylation of **2**.[a]

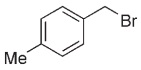
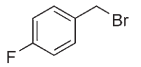


Entry	R′X	Catalyst	*t* [h]	Yield[b] [%]	*ee*[c] [%] (config.)[d]
1	$PhCH_2Br$	**1a** (R = H)	12	90	81 (*S*)
2		**5a** (R = Ph)	4	85	92 (*S*)
3		**5b** (R = 3,5-$Ph_2C_6H_3$)	24	87	97 (*S*)
4		**5c** (R = $SiMe_3$)	50	92	99 (*S*)
5		**5d** (R = $SiEt_3$)	60	96	97 (*S*)
6		**5e** (R = *Si*Bu_3)	120	97	94 (*S*)
7		**5f** (R = $SiMe_2Ph$)	26	98	98 (*S*)
8		**5g** (R = $SiMe_2Oct$)	172	96	99 (*S*)
9[e]	MeI	**1a** (R = H)	12	94	33 (*S*)
10[e]		**5a** (R = Ph)	12	83	52 (*S*)
11[e]		**5b** (R = 3,5-$Ph_2C_6H_3$)	12	86	72 (*S*)
12[e]		**5c** (R = $SiMe_3$)	10	93	88 (*S*)
13[e]		**5d** (R = $SiEt_3$)	12	90	90 (*S*)
14[e]		**5e** (R = *Si*Bu_3)	10	92	92 (*S*)
15[e]		**5f** (R = $SiMe_2Ph$)	12	92	92 (*S*)
16[e]		**5g** (R = $SiMe_2Oct$)	14	92	93 (*S*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 equivalents of R′X in the presence of 1 mol% catalyst in 50% aqueous KOH/toluene (1:3 *v*/*v*) under the given reaction conditions and argon atmosphere. [b] Yield of isolated product. [c] The enantiopurity of **3** was determined by HPLC analysis of the alkylated imine with a chiral column (Daicel Chiralcel OD or OD-H) and hexane/isopropanol as solvent. [d] The absolute configuration of **3** was determined by comparison of the HPLC retention time with that of the authentic sample, which was independently synthesized by the reported procedure.[9l] [e] 5.0 equivalents each of R′X and $CsOH{\cdot}H_2O$ as a base were used, and the reaction was performed at −20 °C.

Table 2. Catalytic enantioselective phase-transfer alkylation of **2** with **5g**.[a]



Entry	R′X	*t* [h]	Yield[b] [%]	*ee*[c] [%] (config.)[d]
1	$PhCH_2Br$	172[f]	96	99 (*S*)
2		96	98	98 (*S*)
3		32	96	99 (*S*)
4		77	90	99 (*S*)
5		168	93	98 (*S*)
6[e]	MeI	14	92	93 (*S*)
7[e]	EtI	10	87	98 (*S*)
8[e]	HexI	10	81	97 (*S*)
9[e]		15	70	95 (*S*)
10[e]		15	75	96 (*S*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 equivalents of R′X in the presence of 1 mol% **5g** in 50% aqueous KOH/toluene (1:3 *v*/*v*) under the given reaction conditions and argon atmosphere. [b] Yield of isolated product. [c] The enantiopurity of **3** was determined by HPLC analysis of the alkylated imine with a chiral column (Daicel Chiralcel OD or OD-H) and hexane/isopropanol as solvent. [d] The absolute configuration of **3** was determined by comparison of the HPLC retention time with that of the authentic sample, which was independently synthesized by the reported procedure.[9l] [e] 5.0 equivalents each of R′X and $CsOH{\cdot}H_2O$ as a base were used, and the reaction was performed at −20 °C. [f] 32% yield over 24 h.

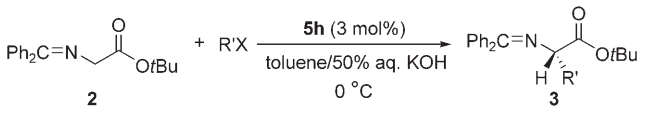
more hindered silyl groups gave higher enantioselectivity ($SiMe_3$: 88% *ee*, $SiEt_3$: 90% *ee*, $SiBu_3$: 92% *ee*; Table 1, entries 12–14). In both cases, catalyst **5g** (R = $SiMe_2Oct$) exhibited the highest asymmetric induction (Table 1, entries 8 and 16).

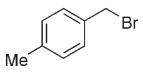
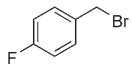
With this information in hand, we investigated the generality of catalyst **5g** (R = $SiMe_2Oct$) with various alkyl halides, and the results are summarized in Table 2. Because of the steric hindrance (or long alkyl chains) of the dimethyloctylsilyl groups in catalyst **5g**, the asymmetric alkylation of glycine derivative **2** proceeded slowly (Table 2, entries 1–5). Accordingly, the stronger base $CsOH{\cdot}H_2O$ was utilized instead of aqueous KOH for unreactive alkyl halides to accelerate the rate of alkylation (Table 2, entries 6–10). In general, uniformly high asymmetric induction was observed (93–99% *ee*). Excellent enantioselectivity (95–96% *ee*) was attained in the asymmetric alkylation with *sec*-alkyl halides (Table 2, entries 9 and 10), which is known to be the hitherto difficult catalytic asymmetric alkylation of a glycine anion equivalent.[9j,16] These results clearly demonstrate the effectiveness of catalyst **5g** for the enantioselective synthesis of both natural and nonnatural α-amino acids.

A Recyclable Fluorous Chiral Phase-Transfer Catalyst

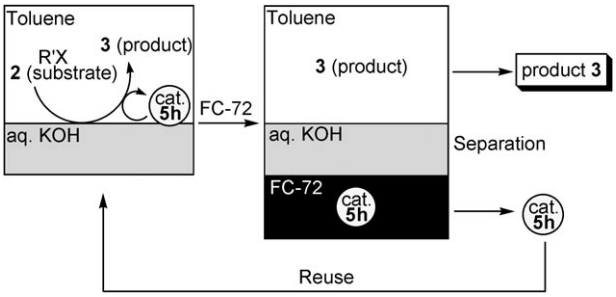
A further useful advance in the field of chiral phase-transfer catalysis would involve the design of easily recyclable catalysts. In this context, we are interested in the possibility of designing a fluorous chiral phase-transfer catalyst as a recyclable catalyst, as fluorous phase-separation techniques for the recovery of fluorinated catalysts have been found to be most useful in recently advanced catalyst-recovery techniques,[14] and some fluorous chiral metal catalysts have been developed for this method.[13b,d,17,18] We examined the chiral efficiency and reusability of the polyfluorinated phase-transfer catalyst **5h**. In the aqueous KOH/toluene biphasic system, catalyst **5h** becomes heterogeneous due to its low solubility in toluene.[19] Nevertheless, **5h** was found to promote the benzylation efficiently to give the alkylated product **3** (R′ = CH_2Ph) with good enantioselectivity (90% *ee*; Table 3, entry 1).[20] After the reaction, catalyst **5h** was easily recovered by simple extraction with FC-72[21] as a fluorous solvent (Scheme 5)[22] and could be utilized for the next run without any loss of reactivity and selectivity (Table 3, entries 1–3). Other selected examples with several alkyl halides are also listed in Table 3.

Table 3. Chiral efficiency and reusability of fluorous chiral catalyst **5h**.[a]



Entry	R′X	*t* [h]	Yield[b] [%]	*ee*[c] [%] (config.)[d]
1	$PhCH_2Br$	96	82	90 (*S*)
2[e]	$PhCH_2Br$	96	79	92 (*S*)
3[f]	$PhCH_2Br$	96	81	92 (*S*)
4		140	81	90 (*S*)
5		70	82	92 (*S*)
6		94	93	93 (*S*)
7[g]	EtI	10	83	87 (*S*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 equivalents of R′X in the presence of 3 mol% **5h** in 50% aqueous KOH/toluene (1:3 *v*/*v*) under the given reaction conditions and argon atmosphere. [b] Yield of isolated product. [c] The enantiopurity of **3** was determined by HPLC analysis of the alkylated imine with a chiral column (Daicel Chiralcel OD or OD-H) and hexane/isopropanol as solvent. [d] The absolute configuration of **3** was determined by comparison of the HPLC retention time with that of the authentic sample, which was independently synthesized by the reported procedure.[9l] [e] Use of recovered catalyst in Table 3, entry 1. [f] Use of recovered catalyst in Table 3, entry 2. [g] 10 equivalents each of R′X and $CsOH{\cdot}H_2O$ as a base and α,α,α-trifluorotoluene as a solvent were used, and the reaction was performed at −20 °C.



Scheme 5. Recovery and reuse of polyfluorinated catalyst **5h** for asymmetric alkylation of glycine derivative **2**.

Conclusions

We have developed synthetically convenient 4,4′,6,6′-tetrasubstituted symmetrical chiral phase-transfer catalysts **5a–h** and applied them to the asymmetric alkylation of *tert*-butylglycinate–benzophenone Schiff base (**2**). The substituent effect of the 4,4′,6,6′-positions of binaphthyl for chiral efficiency was observed in the asymmetric alkylation, and we found the $SiMe_2Oct$-substituted catalyst **5g** to be a very efficient chiral phase-transfer catalyst. This asymmetric phase-transfer chemistry was further extended to the design of recyclable fluorous chiral phase-transfer catalyst **5h** by the introduction of the $SiMe_2(CH_2CH_2C_8F_{17})$ group, and good chiral efficiency and reusability in the asymmetric alkylation of **2** were attained.

Experimental Section

General procedure for catalytic enantioselective alkylation of **2** under phase-transfer conditions (benzylation): Benzyl bromide (0.36 mmol) was added to a mixture of **2** (0.30 mmol) and catalyst **5g** (0.0030 mmol) in toluene (3.0 mL) at 0 °C under argon atmosphere. Next, aqueous KOH (50%, 1.0 mL) was added dropwise, and the resulting mixture was stirred vigorously for 172 h. The mixture was then poured into water and extracted with Et_2O. 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 (Et_2O/hexane = 1:10) gave the benzylation product **3** (R′ = CH_2Ph; 111 mg, 0.288 mmol, 96% yield) as a colorless oil. The enantiomeric excess was determined to be 99% *ee* by chiral HPLC analysis (Daicel Chiralcel OD, hexane/isopropanol = 100:1, flow rate = 0.5 mL min^{-1}, t_R = 14.8 (*R*) and 28.2 min (*S*)). The absolute configuration was determined by comparing the HPLC retention time with that of the authentic sample independently synthesized by the reported procedure.[9l]

Acknowledgements

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[19] Catalyst **5h** is soluble in CH_2Cl_2, $CHCl_3$, Et_2O, and perfluoro solvents, but less soluble in toluene, benzene, hexane, and so on.

[20] The reaction in the toluene/50% aqueous KOH/FC-72 (as catalyst phase) triphasic system caused a slight decrease in enantioselectivity in the asymmetric alkylation of **2**.

[21] FC-72 = perfluorohexanes.

[22] In each run, more than 95% of the catalyst **5h** was recovered by fluorous extraction.

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