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Design of new, chiral phase-transfer catalysts for practical, catalytic asymmetric synthesis

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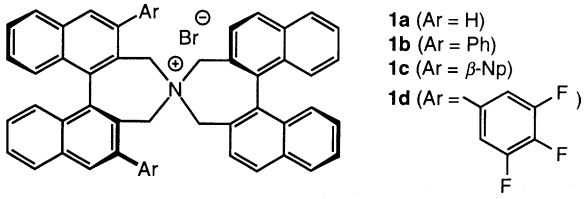
Abstract

Structurally rigid, chiral spiro ammonium salts of type **1** derived from commercially available (*S*)-binaphthol have been designed as a new C_2-symmetric chiral phase-transfer catalyst and successfully applied to the highly efficient, catalytic enantioselective alkylation of *tert*-butyl glycinate Schiff base under mild phase-transfer conditions to furnish α-alkyl-α-amino acids and α,α-dialkyl-α-amino acids with excellent enantioselectivity. These ammonium salts have been also utilized for the in situ generation of chiral quaternary ammonium fluorides. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Phase-transfer catalyst; Asymmetric alkylation; α-Amino acid; *Tert*-butyl glycinate; Quaternary ammonium fluoride

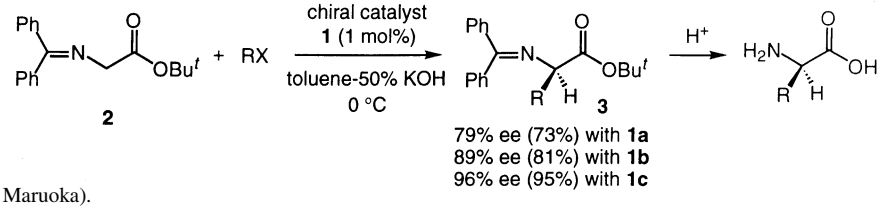
1. Introduction

Since the pioneering work of O'Donnell et al. in 1989, asymmetric synthesis of α-amino acids by phase-transfer enantioselective alkylation of a prochiral protected glycine derivative using a chiral catalyst has provided an attractive method for the preparation of both natural and unnatural amino acids [1]. Recently, the Corey and Lygo groups independently reported an impressive departure from the previous results in terms of enantioselectivity and general applicability [2–7]. However, almost all the elaborated chiral phase-transfer catalysts reported so far have been restricted to *cinchona* alkaloid derivatives, which unfortunately constitutes a major difficulty in rationally designing and fine-tuning of catalysts to attain sufficient reactivity and selectivity for various chemical transformations under phase-transfer catalyzed conditions [8–10]. Accordingly, structurally rigid, chiral spiro ammonium salts of type **1** derived from commercially available (*S*)-binaphthol have been designed as a new C_2-symmetric chiral phase-transfer catalyst and successfully applied to the highly efficient, catalytic enantioselective alkylation of *tert*-butyl glycinate-benzophenone Schiff base under mild phase-transfer conditions [11].



2. Results and discussion

The requisite catalyst **1** can be readily synthesized from commercially available (*S*)-binaphthol and the primary structure of **1a** was unambiguously determined by single-crystal X-ray diffraction analysis. The asymmetric phase-transfer alkylation of *tert*-butyl glycinate-benzophenone Schiff base (**2**) using 1 mol% of **1a**, benzyl bromide and 50% aqueous KOH/toluene proceeded smoothly at 0°C to furnish product **3** (R = CH_2Ph) in 73% after 6 h with 79% e.e. Interestingly, the profound effect of 3,3′-bisaryl



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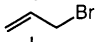
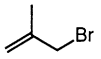
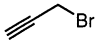
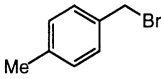
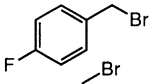
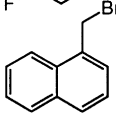
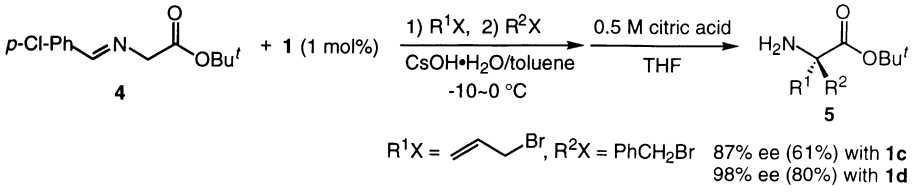
substituents of **1** on the reactivity as well as enantioselectivity was clearly observed. Thus, the benzylation of **2** under the influence of **1b** (1 mol%) was completed within 30 min at 0°C, producing the alkylation product **3** (R = CH_2Ph) in 81% yield with 89% e.e. Use of **1c** as catalyst further increased the enantioselectivity to 96% e.e. (95% yield). As revealed in Table 1, various alkyl halides (RX) were successfully employable where enantioselectivities generally exceeded 90% e.e., indicating the remarkable potential and generality of the present system for the practical α-amino acid synthesis [11].

With this basic information at hand, our attention has now been focused on the α,α-dialkyl-α-amino acid synthesis. Such non-proteinogenic α,α-dialkyl-α-amino acids have played a special role in the design of peptides with enhanced properties [12–15]. Furthermore, α,α-dialkyl-α-amino acids themselves are often effective enzyme inhibitors and also constitute a series of interesting building blocks for the synthesis of various biologically active compounds. Accordingly, development of truly efficient methods for their preparation, especially in an enantiomerically pure form, has become of great importance. In this context, we were successfully able to realize the enantioselective one-pot, double alkylation of aldimine Schiff base of glycine *tert*-butyl ester **4** under phase-transfer catalytic conditions using C_2-symmetric chiral quaternary ammonium salt **1** as catalyst [16].

Table 1
Catalytic enantioselective phase-transfer alkylation of **2** under the influence of spiro-type chiral phase-transfer catalyst **1c**[a]

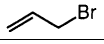
Entry	RX	Condition (°C, h)	Yield[b] (%)	Percent of e.e. (configuration)
1	$PhCH_2Br$	0, 0.5	95	96 (*R*)
2	CH_3I[c]	0, 8	64	90 (*R*)
3	CH_3CH_2I[c]	0, 10	41	95 (*R*)
4		0, 1	84	94 (*R*)
5		0, 1	82	93 (*R*)
6		0, 1	90	95 (*R*)
7		0, 0.5	80	96 (*R*)
8		0, 1	81	96 (*R*)
9		0, 1.5	60	96 (*R*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 eq. of RX in the presence of 1 mol% of **1c** in 50% aqueous KOH/toluene (volume ratio =∼ 1 : 3) under the given reaction conditions.
[b] Isolated yield.
[c] Use of 5 eq. of alkyl halide.



Initial treatment of the toluene solution of **4** and **1c** (1 mol%) with allyl bromide and commercially available $CsOH{\cdot}H_2O$ (5 eq.) at −10°C for 3.5 h and the subsequent reaction with benzyl bromide at 0°C for 30 min gave rise to, after hydrolysis, the double alkylation product **5** ($R^1 = CH_2CH{=}CH_2$; $R^2 = CH_2Ph$) in 61% yield with 87% e.e. Interestingly, use of newly designed, polyfluorinated **1d** (Ar = 3,4,5-F_3-Ph) as catalyst significantly enhanced the enantioselectivity to 98% e.e. (80% yield). Other selected examples are listed in Table 2. The distinct feature of this procedure is that it enables straightforward asymmetric synthesis of various α,α-dialkyl-α-amino acids including those otherwise inaccessible from the naturally occurring amino acids. Notably, in the double alkylation of **4** by the addition of the halides in a reverse order, the absolute configuration of the double alkylation product **5**

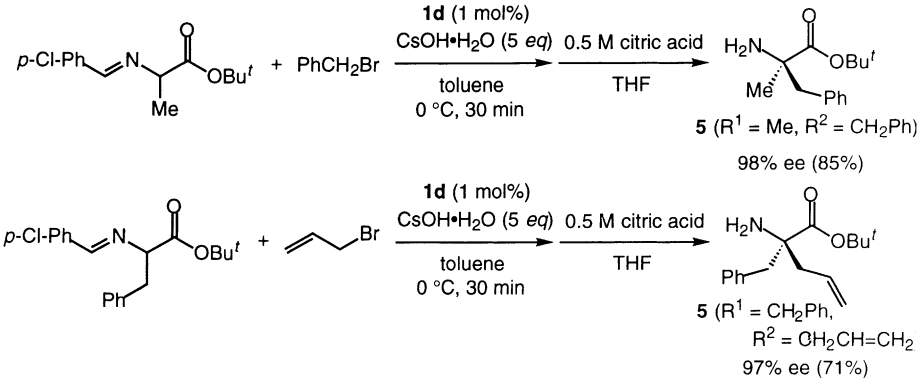
Table 2
Catalytic enantioselective double alkylation of aldimine Schiff base derived from glycine under phase-transfer conditions[a]

Entry	R^1X	First alkylation condition (°C, h)	R^2X	Second alkylation condition (°C, h)	Yield (%)	Percent of e.e. (configuration)
1	$CH_2{=}CHCH_2Br$	−10, 3.5	$PhCH_2Br$	0, 0.5	80	98 (*R*)
2				0, 0.7	60	97
3				0, 0.5	58	96
4	$PhCH_2Br$	−10, 2		0, 0.3	74	92 (*S*)

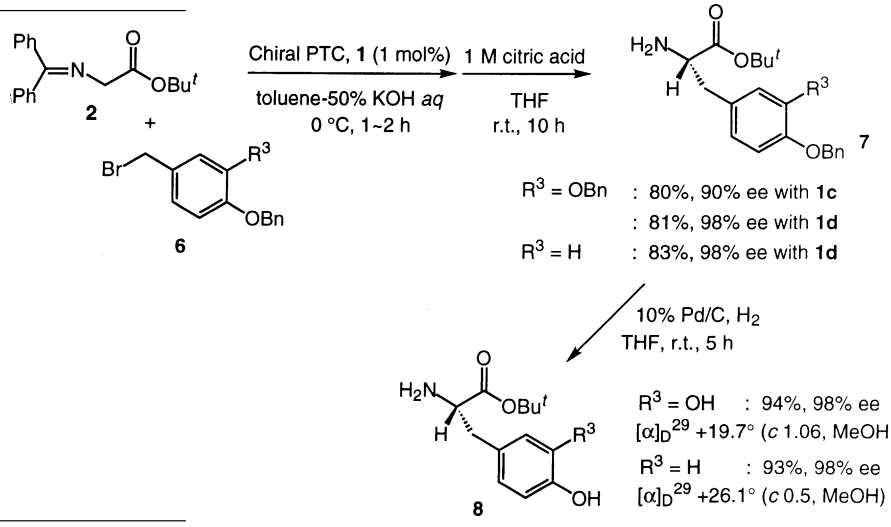
[a] The reaction was performed by the sequential treatment of aldimine Schiff base **4** with R^1X (1 eq.) and R^2X (1.2 eq.) under the indicated reaction conditions in the presence of 1 mol% of **1d** and $CsOH{\cdot}H_2O$ (5 eq.) in toluene.

was confirmed to be opposite, indicating the intervention of the expected chiral ammonium enolate in the second alkylation stage (entry 1 versus 4).

Further, our approach has been successfully applied to the catalytic asymmetric alkylation of aldimine Schiff base derived from the corresponding α-alkyl-α-amino acids, where its remarkable efficiency and general applicability have been clearly demonstrated. The present practical methods should have vast synthetic potential, being able to provide a wide variety of α,α-dialkyl-α-amino acids **5** in an enantiomerically pure form [16].



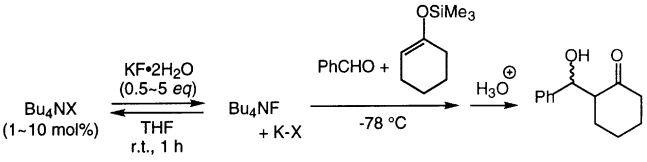
Since both enantiomers of the catalyst of type **1** can be readily assembled in exactly the same manner starting from either (*R*)- or (*S*)-binaphthol, a wide variety of natural and unnatural α-amino acids can be synthesized in an enantiomerically pure form by the phase-transfer catalytic alkylation of substrate **2**. The successful utilization of this advantage is illustrated for the facile synthesis of L-Dopa (L-3,4-dihydroxyphenylalanine) esters, which have usually been prepared in an enzymatic way and tested as potential drugs for the treatment of Parkinson's disease [17–20].



The simple synthetic route to L-Dopa esters is shown as follows [21]. Catalytic phase-transfer alkylation of **2** with benzyl bromide **6** (R^3 = OBn) (1.2 eq.) in toluene with 50% KOH aqueous solution (volume ratio = 3 : 1) proceeded smoothly at 0°C in the presence of (*R*)-**1c** (1 mol%) to furnish fully protected L-Dopa *tert*-butyl ester, which was subsequently treated with a 1 M citric acid in THF at room temperature for 10 h to afford the corresponding amino ester **7** (R^3 = OBn) in 80% isolated yield. Although the enantiomeric excess was determined to be 90% e.e. by chiral HPLC analysis, it did not seem fully satisfactory because further purification such as recrystallization would be required to increase the enantiomeric purity. Therefore, we employed (*R*)-**1d** as a catalyst and found that the alkylation of **2** with (*R*)-**1d** (1 mol%) and **6** (R^3 = OBn; 1.2 eq.) under otherwise identical conditions gave rise to the amino ester **7** (R^3 = OBn) with excellent enantioselectivity (98% e.e.). Debenzylation of **7** (R^3 = OBn) under catalytic hydrogenation conditions produced the desired L-Dopa *tert*-butyl ester (**8**; R^3 = OH) in 93% yield. Being exemplified by the feasibility of asymmetric synthesis of natural tyrosine *tert*-butyl ester (**8**; R^3 = H), the present concise and practical procedures should enable highly enantioselective synthesis of various L-Dopa analogues and related α-amino acids.

Our chiral phase-transfer chemistry has been further extended to the synthetic utility of the in situ-generated quaternary ammonium fluorides [22]. Thus, quaternary

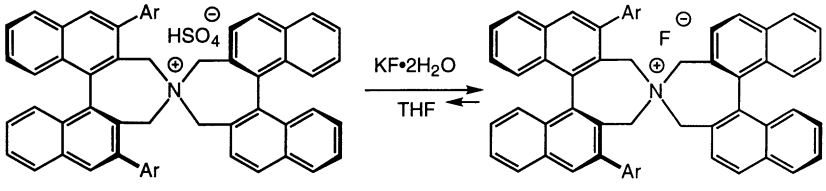
ammonium fluorides can be generated in situ from the corresponding ammonium salts by stirring with commercially available $KF{\cdot}2H_2O$ in THF, and directly used as a fluoride source for the generation of carbon nucleophiles from organosilicon compounds. We have studied the most effective ammonium salt which can generate the corresponding ammonium fluoride. The efficiency of such anion exchange is surveyed by performing aldol reaction of benzaldehyde and 1-trimethlysiloxycyclohexene. Thus, a mixture of Bu_4NX (10 mol%) and commercially available $KF{\cdot}2H_2O$ (5 eq.) in THF was well-stirred at room temperature for 1 h and then benzaldehyde (1.2 eq.) and 1-trimethlysiloxycyclohexene (1 eq.) were added sequentially at −78°C. Monitoring the reactions revealed that the efficiency of the in situ generation of Bu_4NF was profoundly influenced by the anion moiety (X) as summarized below. Use of Bu_4NX (X = I, Br, IO_4, ClO_4, BPh_4, OTf) resulted in only trace amounts of aldol products. Although the expected anion exchange was certainly achieved with Bu_4NCl to catalyze the present cross aldol reaction, the reactivity was far less than that of Bu_4NF itself. Interestingly, comparable catalytic activity was attained by use of Bu_4NHSO_4 as a precursor, where the aldol reaction was completed within 30 min at −78°C and desired β-hydroxy ketone was obtained in 91% isolated yield. Optimization of the reaction conditions showed that 0.5 eq. of $KF{\cdot}2H_2O$ was sufficient for the smooth reaction. It should be added that the aldol reaction did not proceed at all in the absence of either Bu_4NHSO_4 or $KF{\cdot}2H_2O$ under otherwise identical conditions. Noteworthy is that this phase-transfer system is advantageous especially when the reaction was conducted with a reduced amount of Bu_4NHSO_4 (1 mol%), where the catalytic activity of the in situ generated Bu_4NF was found to be markedly enhanced compared to 1 mol% of Bu_4NF itself.



X = I, Br, IO_4, ClO_4, BPh_4, OTf : *No reaction !*

X = Cl (10 mol%); $KF{\cdot}2H_2O$ (5 equiv) : 5% (*e*/*t* = 43 : 57)
F (10 mol%) : 89% (40 : 60)
HSO_4 (10 mol%); $KF{\cdot}2H_2O$ (5 equiv) : 91% (25 : 75)
HSO_4 (10 mol%); $KF{\cdot}2H_2O$ (0.5 equiv) : 91% (23 : 77)
HSO_4 (1 mol%); $KF{\cdot}2H_2O$ (0.5 equiv) : 86% (32 : 68)
F (1 mol%) : 24% (58 : 42)

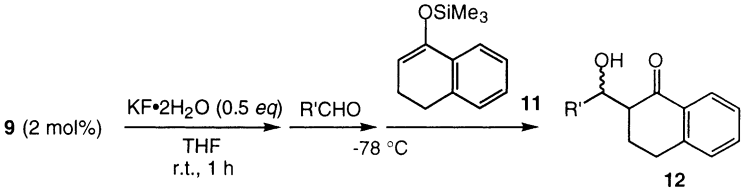
This method can be applied to the preparation of structurally well-defined, C_2-symmetric chiral quaternary ammonium fluorides of type **10** from the corresponding ammonium hydrogensulfates **9** [22]. The in situ-generated chiral ammonium fluorides **10** enhanced the reactivity of ammonium enolates and allowed catalytic enantioselective Mukaiyama-type aldol reactions under mild conditions, giving chiral β-hydroxy ketones **12** in high yields with up to 91% e.e. as illustrated in Table 3.



9a (Ar = β-Np)
9b (Ar = 3,4,5-F_3-Ph)
9c (Ar = 3,5-$(CF_3)_2$Ph)

10a~c

Table 3
Asymmetric aldol reactions of **11** with aldehydes catalyzed by in situ generated C_2-symmetric chiral quaternary ammonium fluorides **10**[a]



Entry	Aldehyde (R′)	Chiral ammonium hydrogensulfate	Yield of **12** (%)	Erythro/threo ratio	Percent of e.e.[b] (configuration)
1	Ph	**9a**	84	57:42	31 (*R*, *R*)
2		**9b**	92	70:30	76 (*R*, *R*)
3		**9c**	90	83:17	84 (*R*, *R*)
4	α-Naph	**9c**	90	94:6	91 (*R*, *R*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 eq. of aldehyde and 1 eq. of enol trimethylsilyl ether **11** in the presence of 2 mol% of **9** and 0.5 eq. of $KF{\cdot}2H_2O$ in THF at −78°C for 0.5 h.
[b] The enantiomeric excess of the major erythro isomer in **12**.

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