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New chiral phase-transfer catalysts possessing a 6,6′-bridged ring on the biphenyl unit: application to the synthesis of α,α-dialkyl-α-amino acids

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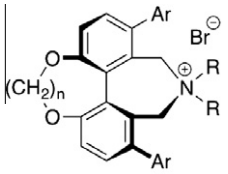
ABSTRACT

A new chiral phase-transfer catalyst possessing a 6,6′-bridged ring on the biphenyl unit has been developed for the practical synthesis of α,α-dialkyl-α-amino acids. This catalyst shows very high activity for the asymmetric alkylation of an alanine derivative to give α,α-dialkyl-α-amino acid derivatives with high enantioselectivities.

Phase-transfer catalysis (PTC) has been recognized as a powerful tool for organic synthesis because of its several advantages (i.e., simple procedure, mild reaction conditions with aqueous media and environmentally benign character, suitability for large-scale reactions, etc.), which meet the current requirements for practical organic synthesis.[1] Therefore, various types of chiral phase-transfer catalysts have been developed in recent years and the chiral efficiency of such phase-transfer catalysts was examined by application to the asymmetric synthesis of both natural and unnatural α-alkyl- and α,α-dialkyl-α-amino acids.[2] In spite of numerous studies, the search for truly efficient catalytic systems for the synthesis of α,α-dialkyl-α-amino acids is still in progress in terms of catalyst loading and reaction conditions.[3] We recently developed highly efficient chiral phase-transfer catalysts for the synthesis of α-alkyl-α-amino acids.[4] We were interested in the design of a finely tunable catalyst to improve the activity and enantioselectivity for the synthesis of α,α-dialkyl-α-amino acids. In the course of our research, the introduction of alkoxy groups to a biphenyl unit provided successful results in terms of both enantioselectivity and catalyst loading for the synthesis of α-alkyl-α-amino acids.[4b] To further improve the catalyst activity and enantioselectivity, we were interested in the introduction of an alkyl chain bridge of variable length to link the biaryl groups.[5] This new catalyst provides a rigid structure with an appropriate dihedral angle for each substrate. Herein, we report that chiral phase-transfer catalyst of type **1**, possessing a bridged ring on the biphenyl unit, can be utilized as a practical tool for the asymmetric synthesis of α,α-dialkyl-α-amino acids.



(*S*)-**1**

The chiral biphenyl core unit was easily prepared as outlined in Scheme 1. Thus, *p*-bromination of commercially available 6-*tert*-butyl-*m*-cresol, followed by oxidative coupling gave the key biphenyl core **3** in good overall yield. Optical resolution of racemic **3** using (*R*,*R*)-1,2-diphenylethylenediamine as a chiral resolving agent was performed quite successfully (88%, >99% ee). Treatment of (*S*)-**3** with TfOH in toluene gave rise to (*S*)-5,5′-dibromo-6,6′-dimethylbiphenyl-2,2′-diol [(*S*)-**4**] in 94% yield.

Reaction of (*S*)-**4** with alkyl dihalides in the presence of excess anhydrous K_2CO_3 in CH_3CN gave compounds **5a–e** having C_1–C_5 bridges linking their biaryl groups (Scheme 2). A series of new phase-transfer catalysts **6a–e** were prepared from **5a–e** in a similar

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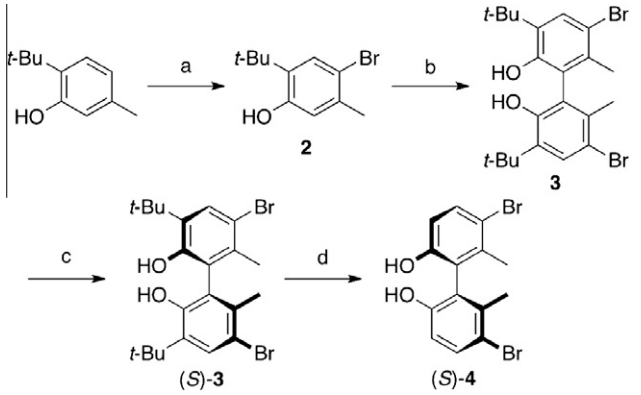
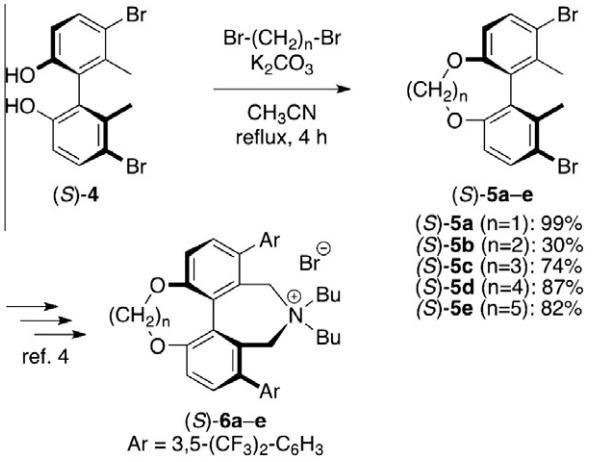


Scheme 1. Reagents and conditions: (a) NBS (1 equiv), DMF, 92%; (b) CuCl (10 mol %), TMEDA (15 mol %), O_2 (air), CH_2Cl_2, 56%; (c) (*R*,*R*)-1,2-diphenylethylenediamine (0.6 equiv), toluene–hexane, 88%; (d) TfOH (1 equiv), toluene, 94%.



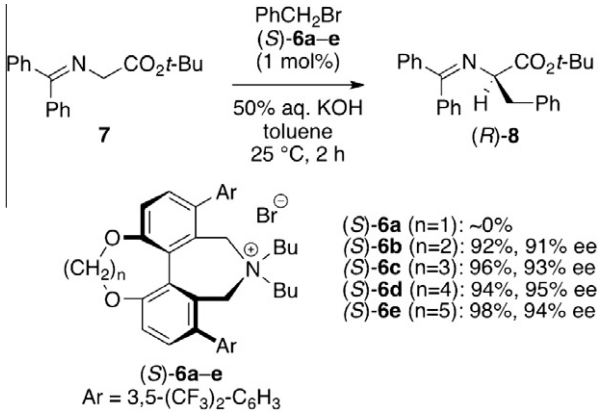
Scheme 2.

manner to the reported method.[4] Thus, Suzuki–Miyaura cross coupling[6] of (*S*)-**5a–e** with an arylboronic acid, $ArB(OH)_2$ [(Ar = 3,5-$(CF_3)_2$–C_6H_3)] in the presence of a catalytic amount of $Pd(OAc)_2$, PPh_3, and K_3PO_4 in DMF afforded the corresponding coupled products in good yields. Radical bromination of these resulting coupled products in benzene and subsequent treatment with Bu_2NH furnished (*S*)-**6a–e** in high yields.

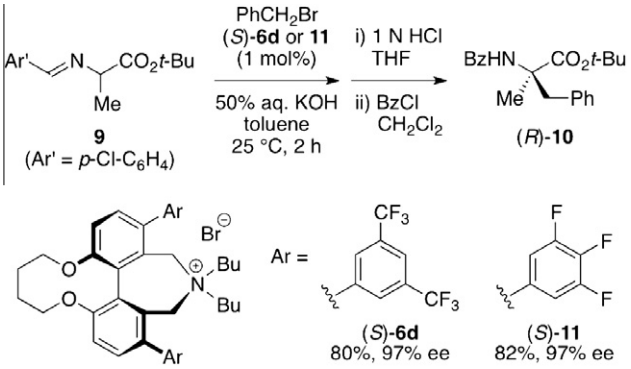
To examine the bridging effect in the catalysts **6a–e**, we studied their application in the asymmetric benzylation of glycine Schiff base **7**. Thus, reaction of **7** with benzyl bromide (1.2 equiv) and 50% aqueous KOH in toluene was carried out in the presence of 1 mol % of (*S*)-**6a–e** at 25 °C to furnish benzylation product (*R*)-**8** (Scheme 3). Unexpectedly, there was no catalytic activity with (*S*)-**6a**. However, the enantioselectivity of benzylation product (*R*)-**8** slightly increased with extension of the bridging chain. Asymmetric alkylation of **7** in the presence of (*S*)-**6d** having a four-carbon bridge led to formation of (*R*)-**8** in an excellent 94% yield with 95% ee.

With these results in hand, we applied catalyst (*S*)-**6d** to the asymmetric alkylation of aldimine Schiff base **9** derived from D,L-alanine *tert*-butyl ester. Catalyst (*S*)-**6d** was found to be quite effective for the asymmetric quaternization[7] of the aldimine Schiff base **9** of alanine *tert*-butyl ester. As shown in Scheme 4, (*S*)-**6d** and its analogue (*S*)-**11**[4] exhibited high efficiency and selectivity even in the case of using KOH as the base at room temperature.[8,9]

Prompted by this result, we examined the catalyst loading in order to optimize the catalytic system for the preparation of chiral



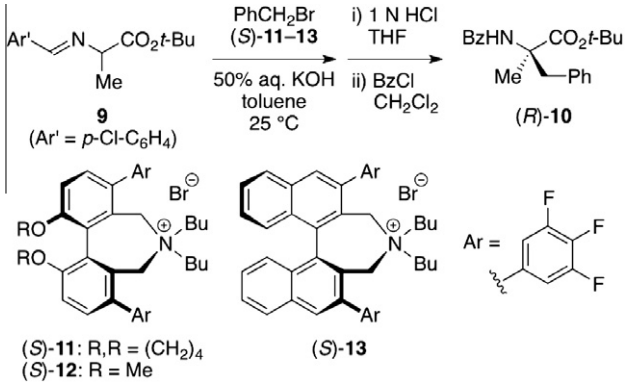
Scheme 3.



Scheme 4.

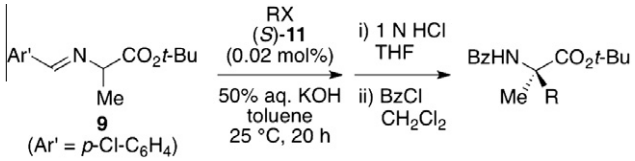
α,α-dialkyl-α-amino acids. As shown in Table 1, (*S*)-**11** was found to be an extremely useful catalyst. Catalyst (*S*)-**11** was superior to (*S*)-**12** at 0.02 mol % loading and (*S*)-**13**, which is an excellent catalyst for the preparation of chiral α-alkyl-α-amino acids,[3f,4c] under low loading conditions (below 0.1 mol %).

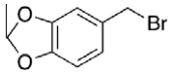
Table 1
Effect of phase-transfer catalysts at low catalyst loading



Loading/Time	(*S*)-**11**	(*S*)-**12**	(*S*)-**13**
1 mol % (2 h)	82%, 97% ee	82%, 97% ee	86%, 97% ee
0.5 mol % (2 h)	89%, 96% ee	83%, 97% ee	84%, 96% ee
0.1 mol % (20 h)	85%, 97% ee	85%, 97% ee	41%, 30% ee
0.1 mol % (60 h)	—	—	73%, 11% ee
0.02 mol % (20 h)	85%, 97% ee	82%, 94% ee	29%, 11% ee
0.01 mol % (40 h)	79%, 95% ee	71%, 73% ee	—

Table 2
Catalytic enantioselective phase-transfer alkylations of alanine derivative **9** catalyzed by (*S*)-**11**[a]



Entry	RX	Yield[b] (%)	ee[c] (%)
1	$PhCH_2Br$	85	97
2		85	95
3	$CH_2{=}CHCH_2Br$	86	96
4	$CH{\equiv}CCH_2Br$	88	89
5[d,e]	EtI	66	92

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of alkyl halide in the presence of phase-transfer catalyst (*S*)-**11** (0.02 mol %) in 50% aqueous KOH/toluene (volume ratio = 1:4) at 25 °C for 20 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Use of 0.1 mol % of (*S*)-**11**.
[e] Use of 5 equiv of alkyl halide.

We further applied catalyst (*S*)-**11** to the asymmetric synthesis of α,α-dialkyl-α-amino acids with various alkyl halides and representative results are listed in Table 2. A remarkable feature of the catalyst system is that the reaction proceeds under mild reaction conditions (KOH as base, room temperature) with extremely low catalyst loading (0.02 mol %).

The origin of the high reactivity of catalyst (*S*)-**11** in comparison with (*S*)-**13** is ascribed to the stability due to the lower acidity of the benzylic proton of (*S*)-**11**. By fixing the dihedral angle appropriately, the selectivity of (*S*)-**11** increases in contrast to the open-chain catalysts under the low loading conditions.

In conclusion, we have successfully designed very powerful chiral phase-transfer catalysts (*S*)-**6d** and (*S*)-**11** for the synthesis of α,α-dialkyl-α-amino acids. These new catalysts are effective for the practical synthesis of α,α-dialkyl-α-amino acids in terms of both high enantioselectivity with low catalyst loading under mild reaction conditions.

A typical experimental procedure is as follows: To a solution of alanine derivative **9** (0.25 mmol), alkyl halide (0.30 mmol), and catalyst (*S*)-**11** (0.00005 mmol, 0.02 mol %) in toluene (2.0 mL) was added 50% aqueous KOH (0.50 mL) at room temperature (25 °C). The reaction mixture was stirred vigorously at room temperature (25 °C) for 20 h. The mixture was then poured into H_2O and extracted with CH_2Cl_2. The solvents were evaporated, and the residue was dissolved in THF (5.0 mL). To this solution was added 1 N HCl (5.0 mL), and the mixture was stirred for 3 h at room temperature. After evaporation to remove THF, the aqueous phase was basified by the addition of solid $NaHCO_3$ and extracted with EtOAc. The organic extracts were dried over Na_2SO_4, and the solvent evaporated. The residue was dissolved in CH_2Cl_2 (3.0 mL), and to the solution was added benzoyl chloride (0.30 mmol). After stirring for 1 h at room temperature, aqueous NH_3 was added. The organic materials were extracted with CH_2Cl_2, and the organic extracts dried over Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography on silica gel (EtOAc/hexane as eluent) gave the desired product **10**.

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8. For the alkylation of the aldimine Schiff base **9** of alanine *tert*-butyl ester, CsOH (a relatively expensive base) was often used for the synthesis of α,α-dialkyl-α-amino acids. See Ref. 3.
9. A 0.02 mol % loading of (*S*)-**6d** provided (*R*)-**10** in lower selectivity (94% ee) compared with (*S*)-**11** (97% ee) in Table 1.