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Catalytic asymmetric synthesis of axially chiral 2-amino-1,1′-biaryl compounds by phase-transfer-catalyzed kinetic resolution and desymmetrization

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ABSTRACT

An efficient methodology for kinetic resolution of axially chiral 2-amino-1,1′-biaryl compounds as useful chiral building blocks was developed by means of binaphthyl-modified chiral quaternary ammonium salt-catalyzed *N*-allylations under phase-transfer conditions. The catalyst structure and reaction conditions were carefully optimized to achieve the highly selective kinetic resolutions. Various types of 2-amino-1,1′-biaryls were submitted to the kinetic resolution under the phase-transfer conditions to resolve the enantiomers with high selectivities. The synthetic utility of this method could be extended to the asymmetric desymmetrization of diamino biaryl compounds to obtain the corresponding axially chiral biaryls with high enantioselectivities.

1. Introduction

Axially chiral biaryl compounds are indispensable building blocks in modern organic synthesis. A wide variety of chiral ligands and catalysts were designed based on the biaryl scaffolds, and these chiral ligands and catalysts were utilized for various catalytic asymmetric transformations to produce important chiral compounds in optically enriched form.[1] Furthermore, axially chiral biaryl skeletons are observed in the structure of biologically active natural products.[2] Thus, the development of efficient enantioselective methods for the synthesis of axially chiral biaryls is an important task in the field of organic chemistry.[3] Among the enantioselective synthesis of axially chiral biaryls, we are interested in the catalytic asymmetric synthesis of 2-amino-1,1′-biaryls, owing to their high synthetic utility as chiral building blocks for the synthesis of important chiral ligands, catalysts, and biologically active compounds (Fig. 1).[4,5] Herein, we report our approach for the catalytic asymmetric synthesis of 2-amino-1,1′-biaryl compounds[6,7] via kinetic resolution[8,9] and desymmetrization[10] by chiral phase-transfer-catalyzed *N*-allylations (Scheme 1).[11,12]

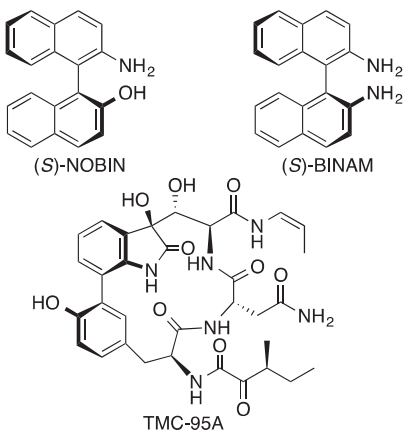

Fig. 1. Representative axially chiral 2-amino-1,1′-biaryls.

2. Results and discussion

We first investigated the effect of binaphthyl-modified chiral quaternary ammonium salts **3**–**5** in the kinetic resolution of 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) derivative (±)-**1a**, as a useful chiral building block,[4] through *N*-allylation under the

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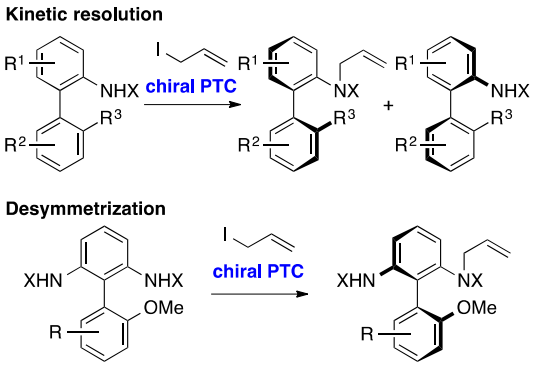


Scheme 1. Our approach for catalytic asymmetric synthesis of 2-amino-1,1′-biaryls.

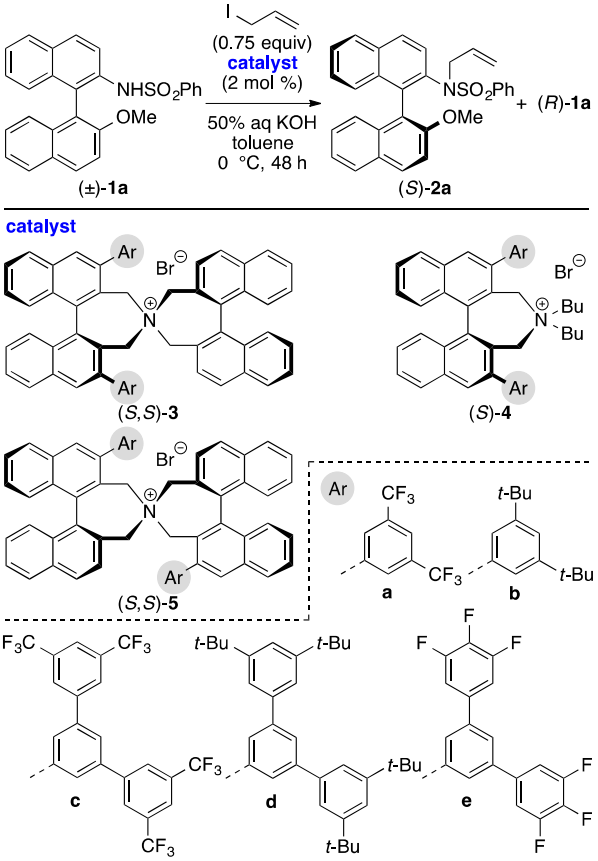
phase-transfer conditions (Table 1). The reaction of (±)-**1a** possessing a benzenesulfonamide moiety with allyl iodide (0.75 equiv) in aqueous KOH/toluene biphasic solution catalyzed by (*S*,*S*)-**3a** or **3c**, which were some of most reliable phase-transfer catalysts,[13] at 0 °C for 48 h afforded the allylation product **2a** with low to moderate selectivities (*s*=1.6–6.4, entries 1 and 2). The simplified-type catalysts (*S*)-**4a** and **4c**, which were also reliable catalysts,[14] does not improve the results (entries 3 and 4). We next employed symmetrical catalysts of the type (*S*,*S*)-**5**[15] to improve the selectivity of the kinetic resolution. Although symmetrical catalysts (*S*,*S*)-**5a** and **5b** did not show significant improvement of the results (entries 5 and 6), switching the 3,3′-aromatic substituents (Ar) of the catalyst (*S*,*S*)-**5** to radially extended substituents (**5c**–**e**) resulted in improved selectivities (*s*=11–35, entries 7–10). The best selectivity was achieved by employment of the catalyst (*S*,*S*)-**5c** (*s*=32, entry 7), and the product (*S*)-**2a** was obtained in 81% ee (53% yield) with recovery of the unreacted (*R*)-**1a** in 93% ee (43% yield). It should be noted that the further high enantioselectivity of the allylation product (*S*)-**2a** (90% ee) was obtained in the lower conversion (entry 8).

We next examined the effect of protecting groups (X) on the nitrogen of **1** in the kinetic resolution under the phase-transfer conditions (Scheme 2). Although the kinetic resolutions catalyzed by (*S*,*S*)-**5c** with substrates possessing sulfonyl groups, such as methanesulfonyl (**1b**) and *p*-nitrobenzenesulfonyl (**1c**) groups, gave the allylation products **2b** and **2c** with good selectivities (*s*=18–23), the reaction with amide-type substrates **1d** and **1e** showed low reactivities and gave only trace amount of allylation products **2d** and **2e**. The substrate **1a** possessing benzenesulfonyl group on the nitrogen was most appropriate substrate in terms of both reactivity and selectivity for the kinetic resolution under the phase-transfer conditions.

We also investigated the effect of electrophiles for the kinetic resolution of (±)-**1a** in the presence of catalyst (*S*,*S*)-**5c** (Scheme 3). The reactions with relatively reactive alkyl iodides, such as benzyl iodide and methyl iodide, gave alkylation products **2f** and **2g** in moderate conversion with good selectivities (*s*=13–19). On the other hand, Michael acceptors, such as methyl vinyl ketone and phenyl vinyl sulfone, were not appropriate electrophiles for the kinetic resolution under the phase-transfer conditions.[16] The best electrophile was allyl iodide in these trials.

With optimal phase-transfer catalyst and reaction conditions in hand, we studied the generality of the kinetic resolution of 2-amino-1,1′-biaryls (±)-**6** (Scheme 4). Although 2-amino-1,1′-binaphthyls **6a** and **6b** showed low reactivities for the phase-transfer-catalyzed *N*-allylations,[16] the kinetic resolutions with substrates **6c** and **6d** possessing a methylthio group and a dimethylamino group, respectively, were efficiently promoted by

Table 1
Effect of chiral phase-transfer catalysts[a]



Entry	Catalyst	Yield of 2a[b] (%)	ee of 2a[c] (%)	Yield of 1a[b] (%)	ee of 1a[c] (%)	*s*[d]
1	(*S*,*S*)-**3a**	15	−70	82	−12	6.4
2	(*S*,*S*)-**3c**	39	−20	57	−8	1.6
3	(*S*)-**4a**	44	−17	53	−12	1.6
4	(*S*)-**4c**	68	22	30	40	2.2
5	(*S*,*S*)-**5a**	26	60	69	22	4.9
6	(*S*,*S*)-**5b**	65	8	33	12	1.3
7	(*S*,*S*)-**5c**	53	81	43	93	32
8[e]	(*S*,*S*)-**5c**	38	90	60	61	35
9[f]	(*S*,*S*)-**5d**	47	70	50	64	11
10	(*S*,*S*)-**5e**	29	84	67	38	17

[a] Reaction conditions: (±)-**1a** (0.050 mmol), allyl iodide (0.038 mmol) in the presence of chiral phase-transfer catalyst (2 mol %) in 50% aqueous KOH (2.0 mL)/toluene (1.0 mL) at 0 °C for 48 h.
[b] Isolated yield.
[c] Enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase.
[d] The selectivity factor (*s*) was calculated as follows.[8] $s=k_{fast}/k_{slow}=\ln[1-C(1+ee\mathbf{2})]/\ln[1-C(1-ee\mathbf{2})]=\ln[(1-C)(1-ee\mathbf{1})]/\ln[(1-C)(1+ee\mathbf{1})]$; $C=ee\mathbf{1}/(ee\mathbf{1}+ee\mathbf{2})$.
[e] The reaction was performed for 16 h.
[f] Allyl iodide (0.028 mmol) was used.

catalyst (*S*,*S*)-**5c** to provide allylation products **7c** and **7d** in moderate to high selectivities (*s*=4.7–27). These results indicate that the heteroatoms at 2′-position of the binaphthyl core are important for efficient promotion of the present kinetic resolution.[17] Substrate **6e** possessing tetraline backbone, which was also useful building block,[18] was resolved with high selectivity (*s*=37). Other 2-amino-1,1′-biaryls **6f**–**j** possessing different biaryl skeletons were also resolved with moderate to high selectivities (*s*=5.7–43). Notably, introduction of an additional methoxy group onto the phenylamino moiety improved the selectivities (substrates **6g**, **6h** vs **6f**).

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