Asymmetric Synthesis

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Kinetic Resolution of Axially Chiral 2-Amino-1,1′-Biaryls by Phase-Transfer-Catalyzed N-Allylation**

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Kinetic resolution of racemic compounds is one of the most reliable methods for producing a variety of optically enriched compounds.[1] In particular, the kinetic resolution of amino compounds has become a topic of great scientific interest in recent years (Scheme 1).[2–4] Various kinds of racemic primary and secondary amines have been submitted to non-enzymatic kinetic resolutions through N-acylation promoted by chiral nucleophilic catalysts to produce optically active amines (Schemes 1 a,c).[3] In contrast, examples of catalytic kinetic resolutions of axially chiral amino compounds of type **1** (Scheme 1 b) are quite limited,[5–7] despite the high synthetic utility of these compounds as chiral building blocks for the synthesis of chiral ligands, catalysts, and biologically active compounds (Figure 1).[8,9] Although nucleophilic-catalyst-promoted N-acylation has also been applied to the kinetic resolution of 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) derivatives, the acylations showed only modest selectivities ($s = 1.4$–4.4, Scheme 1 c)[5] and the catalytic kinetic resolution of these axially chiral compounds still remains a challenging task. To achieve this important task, we have been interested in the chiral phase-transfer-catalyzed approach as shown in Scheme 1 d.[10] In the conventional N-acylation approach, the chiral catalyst, which is the activating acylation reagent, must recognize the chiral amino compounds from a remote place (Scheme 1 c). In contrast, a phase-transfer catalyst may directly interact with the axially chiral amino compound by the formation of an ion pair, which gives rise to opportunities for efficient chiral recognition of the amino compound. Herein we report a valuable example of a highly selective kinetic resolution of axially chiral 2-amino-1,1′-biaryls by phase-transfer-catalyzed N-allylation.[11,12]

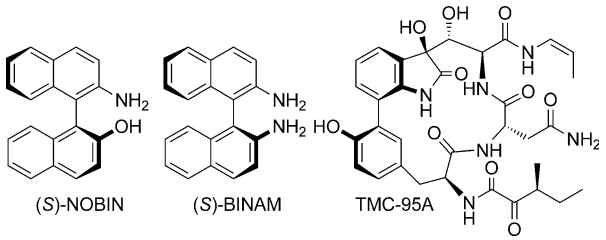
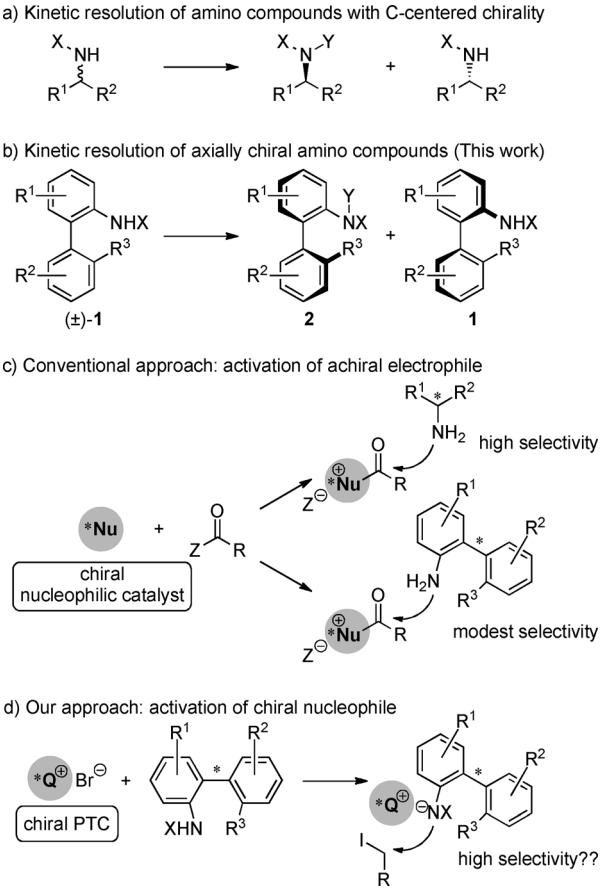


Figure 1. Axially chiral 2-amino-1,1′-biaryls.



Scheme 1. Kinetic resolution of amino compounds.

We first examined the kinetic resolution of the NOBIN derivative (±)-**1a** by asymmetric alkylation promoted by the binaphthyl-modified chiral quaternary ammonium salts **3**–**5** (Table 1). Attempted reactions of (±)-**1a** ($X = SO_2Ph$) with allyl iodide (0.75 equiv) in aqueous KOH/toluene under the influence of catalysts of type (*S*)-**3**[13] or (*S*,*S*)-**4**[14] (2 mol%), which were some of the most reliable phase-transfer catalysts in our previous studies,[10] at 0 °C for 48 hours afforded the allylation product **2a** with low to moderate selectivities ($s =$ 1.6–6.4, entries 1–4). To improve the selectivity of this reaction, we next examined symmetrical catalysts of the type (*S*,*S*)-**5**.[15] Although (*S*,*S*)-**5a** did not show significant improvement of the selectivity ($s = 4.9$, entry 5), the use of

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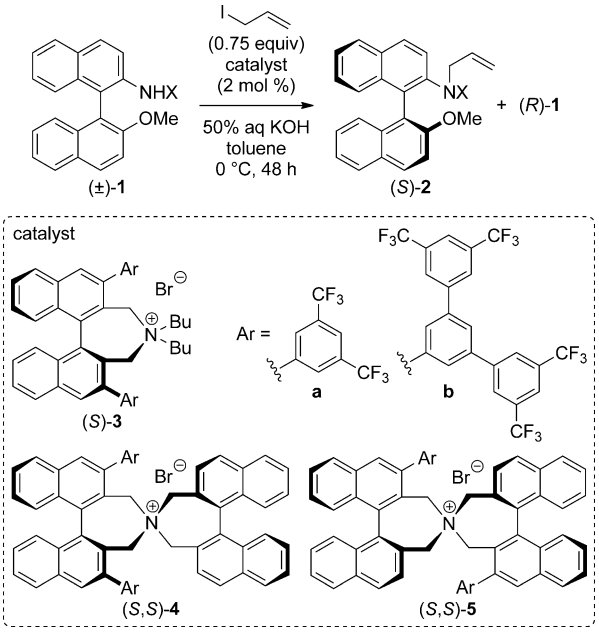
Table 1: Optimization of the reaction conditions.[a]



Entry	Cat.	X	2	*ee* [%][b]	Yield [%][c]	1	*ee* [%][b]	Yield [%][c]	*s*[d]
1	(*S*)-**3a**	SO_2Ph (±)-**1a**	(*R*)-**2a**	−17	44	(*S*)-**1a**	−12	53	1.6
2	(*S*)-**3b**	SO_2Ph (±)-**1a**	(*S*)-**2a**	22	68	(*R*)-**1a**	40	30	2.2
3	(*S*,*S*)-**4a**	SO_2Ph (±)-**1a**	(*R*)-**2a**	−70	15	(*S*)-**1a**	−12	82	6.4
4	(*S*,*S*)-**4b**	SO_2Ph (±)-**1a**	(*R*)-**2a**	−20	39	(*S*)-**1a**	−8	57	1.6
5	(*S*,*S*)-**5a**	SO_2Ph (±)-**1a**	(*S*)-**2a**	60	26	(*R*)-**1a**	22	69	4.9
6	(*S*,*S*)-**5b**	SO_2Ph (±)-**1a**	(*S*)-**2a**	81	53	(*R*)-**1a**	93	43	32
7[e]	(*S*,*S*)-**5b**	SO_2Ph (±)-**1a**	(*S*)-**2a**	90	38	(*R*)-**1a**	61	60	35
8	(*S*,*S*)-**5b**	SO_2Me (±)-**1aa**	(*S*)-**2aa**	78	46	(*R*)-**1aa**	73	53	18
9	(*S*,*S*)-**5b**	COPh (±)-**1ab**	**2ab**	–	≈0	**1ab**	–	99	–
10[f]	(*S*,*S*)-**5b**	SO_2Ph (±)-**1a**	(*S*)-**2ac**	83	16	(*R*)-**1a**	21	78	13
11[g]	(*S*,*S*)-**5b**	SO_2Ph (±)-**1a**	(*S*)-**2ad**	75	36	(*R*)-**1a**	40	61	10

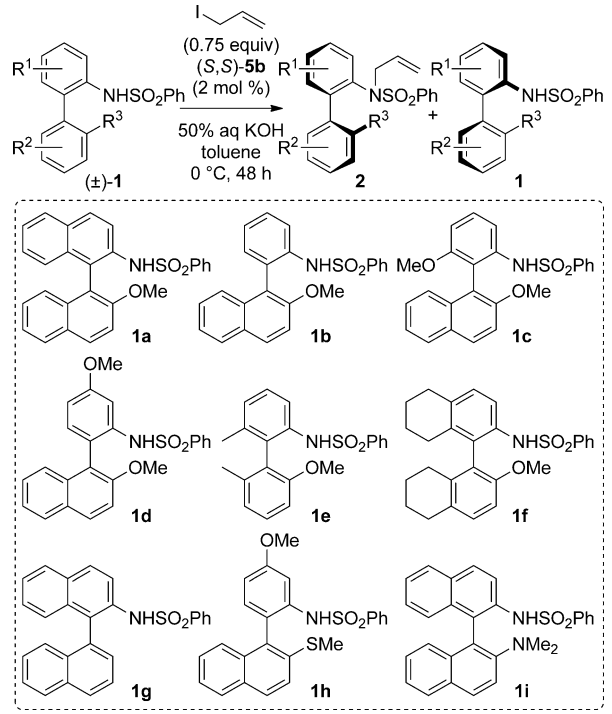
[a] Reaction conditions: **1** (0.050 mmol), allyl iodide (0.038 mmol) in the presence of chiral phase-transfer catalyst (2 mol%) in 50% aqueous KOH (2.0 mL)/toluene (1.0 mL) at 0°C for 48 h. [b] Enantiomeric excess (*ee*) was determined by HPLC analysis using a chiral stationary phase. [c] Yield of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

(*S*,*S*)-**5b**, possessing radially extended aromatic substituents (Ar), proved to be effective ($s = 32$, entry 6), 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 enantioselectivity of the allylation product **2a** could be improved with lower conversion (90% *ee*, 38% yield, entry 7). Switching the benzenesulfonyl group of **1a** to a methanesulfonyl group (X = SO_2Me, **1aa**) caused a decrease in selectivity ($s = 18$, entry 8), and low reactivity was observed when the reaction was performed with a substrate possessing an N-benzoyl group (X = COPh, **1ab**, entry 9). The reactions with other alkyl iodides, such as benzyl iodide and methyl iodide, were also examined (entries 10 and 11), and we found that allyl iodide gave best selectivity.

With the optimal reaction conditions in hand, we next studied the substrate generality of the kinetic resolution of the 2-amino-1,1′-biaryls (±)-**1** by phase-transfer-catalyzed N-allylation (Table 2). The substrates possessing a biaryl structure of the type (±)-**1b–d** were resolved with good to high selectivities ($s = 9.2$–43, entries 2–4). Notably, introduction of an additional methoxy group onto the phenylamino moiety improved the selectivities (entries 3 and 4 versus entry 2). The substrates containing a biphenyl structure ((±)-**1e** and (±)-**1f**) were also examined for this kinetic resolution. Although (±)-**1e** gave the allylation product **2e** with moderate selectivity ($s = 5.7$, entry 5), (±)-**1f**, possessing the octahydro structure of (±)-**1a**, which was also useful chiral building block,[16] was resolved with high selectivity ($s = 37$, entry 6). 2-Amino-1,1′-biaryls possessing other functional groups were also tolerated for this kinetic resolution. Although the simple 2-amino-1,1′-binaphthyl compound (±)-**1g** ($R^3 = H$) showed low reactivity, the reactions with compounds having methylthio and dimethylamino substituents ((±)-**1h** and (±)-**1i**) proceeded to give the allylation products **2h** and **2i**, respectively, with good to high selectivities ($s = 9.7$–27, entries 8 and 9).

The protecting groups of the resulting optically enriched starting materials **1** and allylation products **2** could be readily removed (Scheme 2). For example, the benzenesulfonyl group of (*R*)-**1a** was removed by treatment with a low-valent titanium reagent, which was generated in situ from titanium(IV) isopropoxide, trimethylsilyl chloride, and magnesium powder.[17] Subsequent treatment of the resulting 2-amino-2′-methoxy-1,1′-binaphthyl with boron tribromide gave (*R*)-NOBIN without any loss of enantiomeric purity.[18] Furthermore, (*S*)-NOBIN was obtained from the allylation product (*S*)-**2a** by treatment with diisobutylaluminum hydride (DIBAL-H) in the presence of a nickel catalyst,[19] and subsequent reaction with a low-valent titanium reagent.

Table 2: Kinetic resolution of 2-amino-1,1′-biaryls.[a]

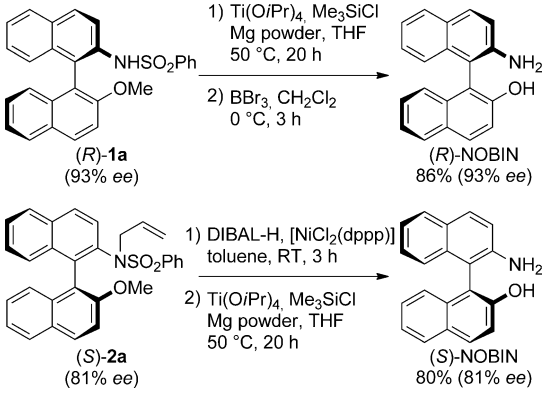


Entry	(±)-**1**	**2**	*ee* [%][b]	Yield [%][c]	**1**	*ee* [%][b]	Yield [%][c]	*s*[d]
1	(±)-**1a**	**2a**	81	53	**1a**	93	43	32
2	(±)-**1b**	**2b**	62	51	**1b**	74	41	9.2
3	(±)-**1c**	**2c**	85	53	**1c**	94	45	43
4	(±)-**1d**	**2d**	82	43	**1d**	60	51	19
5	(±)-**1e**	**2e**	60	40	**1e**	37	57	5.7
6	(±)-**1f**	**2f**	80	56	**1f**	97	40	37
7	(±)-**1g**	**2g**	–	< 5	**1g**	–	> 95	–
8[e]	(±)-**1h**	**2h**	72	41	**1h**	47	56	9.7
9[f]	(±)-**1i**	**2i**	86	41	**1i**	67	55	27

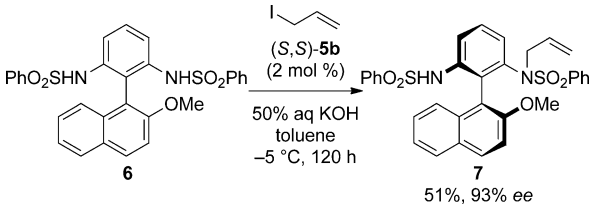
[a] Reaction conditions: **1** (0.050 mmol), allyl iodide (0.038 mmol) in the presence of chiral phase-transfer catalyst (*S*,*S*)-**5b** (2 mol%) in 50% aqueous KOH (2.0 mL)/toluene (1.0 mL) at 0°C for 48 h. [b] Enantiomeric excess (*ee*) was determined by HPLC analysis using a chiral stationary phase. [c] Yield of isolated product. [d] The selectivity factor (*s*) was calculated as follows.[1] $s = k_{fast}/k_{slow} = \ln[1-C(1+ee\mathbf{2})]/\ln[1-C(1-ee\mathbf{2})] = \ln[(1-C)(1-ee\mathbf{1})]/\ln[(1-C)(1+ee\mathbf{1})]$; $C = ee\mathbf{1}/(ee\mathbf{1}+ee\mathbf{2})$. [e] The reaction was performed for 96 h with 1 equivalent of allyl iodide (0.050 mmol). [f] The reaction was performed for 96 h with 2 equivalents of allyl iodide (0.10 mmol).

To expand the utility of this catalytic asymmetric method for the synthesis of axially chiral amino compounds, we also examined the enantioselective desymmetrization of the diamino compound **6** (Scheme 3).[20] Attempted reaction of **6** with allyl iodide in aqueous KOH/toluene in the presence of (*S*,*S*)-**5b** (2 mol%) at −5°C for 120 hours afforded the monoallylation product **7** in moderate yield with high enantioselectivity (93% *ee*).[21]

In summary, we have successfully developed an efficient methodology for the kinetic resolution of 2-amino-1,1′-biaryl compounds by an asymmetric allylation promoted by binaphthyl-modified chiral quaternary ammonium salts. Furthermore, this synthetic method could be extended to the



Scheme 2. Deprotection of (*R*)-**1a** and (*S*)-**2a**. DIBAL-H = diisobutylaluminum hydride, dppp = 1,3-bis(diphenylphosphino)propane, THF = tetrahydrofuran.



Scheme 3. Catalytic enantioselective desymmetrization of **6**.

desymmetrization of a biaryl compound with a high level of enantiocontrol. These are valuable examples of a highly selective catalytic asymmetric synthesis of axially chiral compounds containing an amino group.

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[21] Diallylation product was also obtained in this reaction; for details see the Supporting Information.

