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Switchable Smiles Rearrangement for Enantioselective *O*-Aryl Amination

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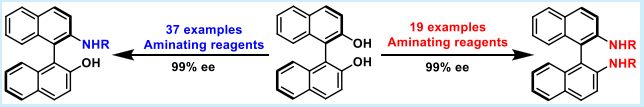
Supporting Information

ABSTRACT: Asymmetric assembly of atropisomeric anilines from abundant and readily available precursors is one of the most challenging but valuable processes in organic synthesis. The use of highly efficient Smiles rearrangement to accomplish switchable enantioselective amination reactions of *O*-arenes provides access to nonsymmetric 2′-amino[1,1′-binaphthalen]-2-ol (i.e., NOBIN-type) and [1,1′-binaphthalene]-2,2′-diamine (i.e., BINAM-type) derivatives. This transition metal-free strategy provides a powerful way to access a wide range of advanced highly functionalized enantioenriched anilines.



Axially chiral biaryl compounds[1] are versatile building blocks for catalysts,[2] functional materials,[3] and natural products.[4] Atropisomeric anilines,[5] as represented by 2′-amino[1,1′-binaphthalen]-2-ol (NOBIN) and [1,1′-binaphthalene]-2,2′-diamine (BINAM), are widely used as powerful chiral ligands or auxiliaries in asymmetric synthesis.[6−13] However, asymmetric synthetic methods for atropisomeric anilines, especially nonsymmetric NOBIN derivatives, remain elusive.[14] Moreover, the development of more general strategies for construction of enantioenriched axially chiral aniline derivatives with functional diversity is highly desirable.[15]

C−N bond formation has emerged as a powerful strategy for generating anilines, which can be used to construct enantioenriched organic frameworks.[16] While great achievements have been realized, the development of regiodivergent protocols for common precursors in a rational and predictable manner remains a formidable challenge, offering a unique opportunity to develop diversity-oriented synthesis.[15] Furthermore, given the great importance of atropisomeric anilines, obtaining versatile reaction intermediates from readily available starting materials is very appealing and of great synthetic value. The development of transition metal-free protocols would offer an eco-friendly alternative for chiral C−N bond construction.[17] New methods and strategies for direct functionalization of unactivated C−O bonds are beginning to reshape the field of retrosynthetic analysis,[18] which affects the synthesis of axially chiral anilines (Figure 1). Early reports of racemic amination of phenols by Smiles rearrangement reactions with amide-based reagents indicate that this class of bromoacetamides might be a suitable starting point for the development of highly selective rearrangement of axially chiral *O*-arenes.[19] However, general and selective amination using more common unactivated axially chiral phenols remains elusive, although methods for the enantioselective synthesis of 1,1′-bi-2-naphthol (BINOL) are well-established.[20]

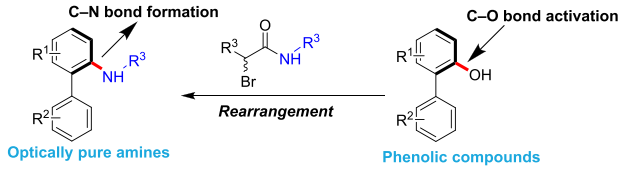


Figure 1. New Smiles rearrangement approach for the enantioselective synthesis of axially chiral anilines.

In this study, we aimed to develop an alternative strategy using easily accessible axially chiral phenols as novel reaction partners for aminating reagents in asymmetric Smiles rearrangement reactions. There are several challenges associated with the development of this reaction: (1) the ability to match these bulky phenol derivatives with aminating reagents in the rearrangement reaction, (2) control of the selectivity of the axially chiral aniline products (NOBIN or BINAM), and (3) determination of the reaction conditions that give excellent regio- and enantioselectivity. Careful selection of the reaction conditions can profoundly affect the reaction outcome, leading to the formation of axially chiral anilines with different regioisomers in a highly enantiomerically enriched form. We suggest that the use of aminating reagents, which are capable of effectively discerning the sensitive steric bias between the mono- and dialkylation processes, would be the key to the successful implementation of our proposed

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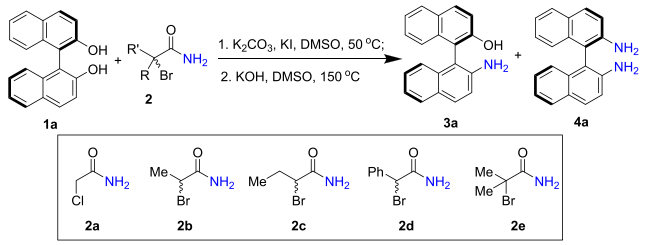
chemo- and enantioselective rearrangement. Herein, we report the highly enantioselective and regiodivergent Smiles rearrangement reactions of BINOLs with aminating reagents, providing NOBIN and BINAM derivatives with excellent regio- and enantioselectivity.

We began our study by investigating the enantioselective Smiles rearrangement of unprotected enantiopure **1a** using aminating reagent **2** as the model substrate (Table 1). We

Table 1. Optimization of the Switchable Smiles Rearrangement Reaction[a]



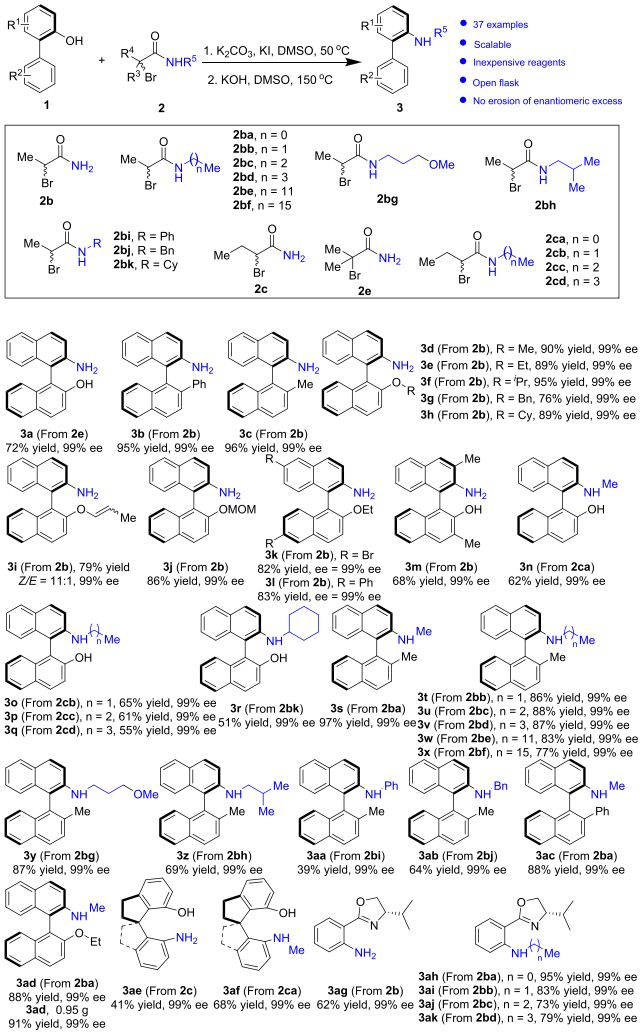
entry	2	3a:4a[b]	3a (%)	ee of 3a	4a (%)	ee of 4a (%)
1	**2a**	<1:20	not detected	not detected	12	99
2	**2b**	<1:20	not detected	not detected	82	99
3	**2c**	1:6	11	not detected	65	99
4	**2d**	1:4	8	not detected	35	99
5[c]	**2e**	9:1	35	99	4	not detected
6[d]	**2e**	12:1	72	99	6	not detected

[a]Unless otherwise specified, all of the reactions were performed using (*R*)-BINOL **1a** (0.2 mmol) and **2** (0.6 mmol) with K_2CO_3 (0.6 mmol), KI (0.02 mmol), and DMSO (2 mL) at 50 °C for 24 h. After the disappearance of **1a** from the reaction mixture, KOH (2.5 mmol) was added to the reaction mixture and the temperature was increased to 150 °C. [b]Determined by crude ^{1}H NMR spectroscopy. [c]The first step was performed at 110 °C. [d]Acetone was used as the solvent for the first step under the refluxing condition.

found that using KOH as the base at 150 °C gave desired product **4a** in 12% yield with a 99% enantiomeric excess (ee), demonstrating that there was no decrease in the ee during the rearrangement process (entry 1). We then evaluated aminating reagents **2**. Of the aminating reagents tested, desired product **4a** was obtained in 82% yield with a 99% ee when racemic 2-bromopropanamide **2b** was used (entry 2). Further attempts were made to switch the chemoselectivity to give **3a** using various other aminating reagents (entries 2−5). Significantly, using sterically hindered 2-bromo-2-methylpropanamide **2e**, we achieved regiochemical switching of the monorearrangement, leading to formation of **3a** in 72% yield with a 99% ee (entry 6). From the results, it is clear that this aminating reagent scaffold is multifunctional because it can be easily modified to control the selectivity.

NOBIN is a structural unit of natural products and the architectures of chiral transition metal catalysts and organocatalysts.[14] Most currently used methods for the preparation of NOBIN are by oxidative coupling[21] or the Bucherer reaction[22] in the racemic form. New and powerful synthetic strategies are needed to complement existing methods.[23] We envision the direct Smiles rearrangement of BINOL is an alternative route for preparing a diverse range of NOBIN derivatives.[24] With the optimized conditions established (Table 1, entries 2 and 6), the scope of the reaction for the synthesis of NOBIN derivatives was explored (Scheme 1). A number of BINOLs

Scheme 1. Scope of the NOBIN Derivatives in the C−N Coupling Reaction[a]



[a]Unless otherwise specified, all of the reactions were performed using **1** (0.2 mmol, 1.0 equiv) and **2** (0.4 mmol, 2.0 equiv) with K_2CO_3 (0.4 mmol, 2.0 equiv) and KI (0.02 mmol, 0.1 equiv) at 50 °C for 24 h. KOH (2.5 mmol) was then added to the reaction mixture, and it was stirred at 150 °C for 4 h. The ee was determined by chiral high-performance liquid chromatography (HPLC) analysis. The yields are for the isolated materials. See the Supporting Information for the experimental details.

with diverse substituents at different ring positions gave the desired products, typically in good yields with complete enantiospecificity. Initial screening showed that the process extends the range of functional groups that are compatible with the new protocol (**3a−3m**). The utility of this chemistry was further evaluated by stereospecific rearrangement of BINOL-based diaryl- and arylalkylamines. Direct amination of **1** gave the desired rearrangement process without the need for protection of the hydroxyl group (**3n−3r**), which shows that the methodology tolerates steric hindrance of the amines and is compatible with amine functionalities. Furthermore, a set of substituted amides **2** also effectively coupled with 2′-methyl-[1,1′-binaphthalen]-2-ol in good yields with complete enantiospecificity (**3s−3ab**). To demonstrate the practicality of the method, the asymmetric C−N coupling reaction was performed on a gram scale, and a high yield with complete

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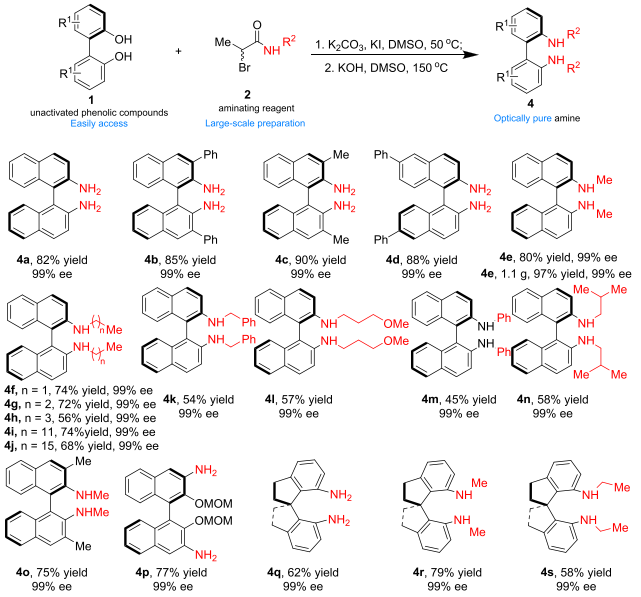
diastereospecificity was achieved (Scheme 1, **3ad**). Remarkably, the reaction was effective even for a set of spiro-phenols, giving the corresponding products **3ae** and **3af** in good yields and optical purities. Furthermore, using readily available (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol as the starting material gave the corresponding products (**3ag**−**3ak**), demonstrating the power of the new methodology.

Given the abundance of axially chiral biaryl compounds in nature and their importance in asymmetric catalysis and materials science, it is surprising that relatively few methods are available for atroposelective amine synthesis. Recently, Kürti and co-workers[25] and List and co-workers[26] independently reported benzidine rearrangement of hydrazine catalyzed by chiral phosphoric acid for the synthesis of BINAMs. Encouraged by the results described above (Table 1 and Scheme 1), we turned our attention to more challenging processes that make use of double rearrangement using aminating reagent **2** (Scheme 2). Under the optimized

Scheme 2. Synthesis of BINAM Derivatives[a]

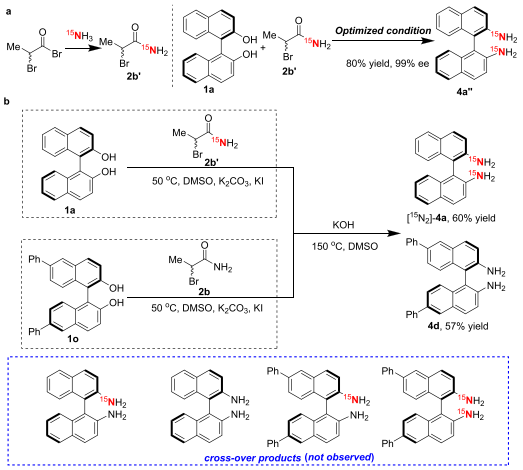


[a]Unless otherwise specified, all of the reactions were performed using **1** (0.2 mmol, 1.0 equiv) and **2** (0.6 mmol, 3.0 equiv) with K_2CO_3 (0.6 mmol, 3.0 equiv) and KI (0.02 mmol, 0.1 equiv) at 50 °C for 24 h. KOH (2.5 mmol) was then added to the reaction mixture, and it was stirred at 150 °C for 4 h. The ee was determined by chiral HPLC analysis. The yields are for the isolated materials. See the Supporting Information for the experimental details.

rearrangement reaction conditions (Table 1, entry 2), a wide range of **1** and aminating reagents **2** were investigated (Scheme 2). In general, 3,3′- or 6,6′-diaryl substituted aromatic rings smoothly underwent this rearrangement transformation with excellent chemoselectivities and optically pure enantioselectivities (**4b**−**4d**). In addition, a variety of aminating reagents were well tolerated to give the corresponding products (**4e**−**4o**) with complete enantiospecificity and without a distinct steric effect. Importantly, the reaction with methyl aminating reagent **2ba** proceeded without any difficulty to give methyl-BINAM **4e** in a gram scale (97% yield, 99% ee), which is highly desirable but has previously been achieved only by resolution of racemic biaryls.[27] 3,3′-Disubstituted binaphthalene also gave the corresponding adduct with a good yield with 99% ee (**4p**). Importantly, a variety of aminating reagents (**2**) were also investigated for amination of spiro-phenol, and they gave the designed chiral adducts with complete enantioselectivity (**4q**−**4s**).

A series of experiments were performed to elucidate the asymmetric amination mechanism. To determine whether aminating reagent equilibration occurs under the reaction conditions, ^{15}N-aminating reagent **2b′**, which is typically prepared from [^{15}N]ammonia and 2-bromopropanoyl bromide, was substituted for **2b** in the rearrangement reaction (Scheme 3a). BINAM with the ^{15}N isotope **4a″** formed, which

Scheme 3. Mechanistic Studies



was confirmed by mass spectrometry. Importantly, selective introduction of ^{15}N can now be accomplished using axially chiral phenols as starting materials, and this process provides access to ^{15}N-labeled compounds that cannot be accessed by conventional chemistry. In addition, reaction of a mixture of $^{15}N_2$-etherified **1a** and N_2-etherified **1o** produced only the expected isotopologues, [$^{15}N_2$]-**4a** and **4d**, without any crossover products (Scheme 3b). C−N coupling was then performed in the presence of the radical quencher TEMPO or BHT, and coupling product **4a** was isolated without a decrease in the yield, suggesting no involvement of a radical intermediate in the rearrangement amination process (see the Supporting Information for details).[28] Combined with the optical purity of the products, these factors suggest ionic intramolecular rearrangement is favored in the reaction.

In summary, we have developed a general method for coupling axially chiral phenolic compounds with achiral aminating reagents to give NOBIN and BINAM derivatives, which are of great importance in synthetic chemistry. Using this methodology, structurally diverse axially chiral anilines can be produced in good yields with a broad scope, allowing the straightforward preparation of anilines from the corresponding aryl phenols. The reaction involves the initial formation of an alkylation complex leading to the synthesis of functionalized axially chiral anilines with complete stereospecificity. The process is a convenient, safe, transition metal-free, and user-friendly method for large-scale preparation. We anticipate that this strategy will have extensive applications in the synthesis of complex target molecules and provide new enthusiasm for asymmetric aryl functionalization.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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