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Ruthenium-Catalyzed Atropoenantioselective Synthesis of Axial Biaryls via Reductive Amination and Dynamic Kinetic Resolution

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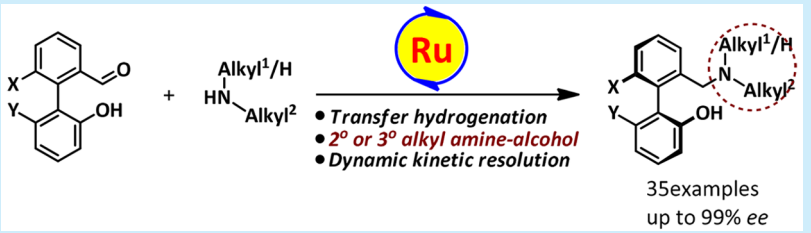
Supporting Information



ABSTRACT: The unprecedented ruthenium-catalyzed atropoenantioselective reductive amination of aldehydes with alkylamines via a cascade transfer hydrogenation and dynamic kinetic resolution strategy is described. This protocol features broad substrate scope and good functional group tolerance and allows the rapid assembly of axially chiral biaryls in good to high yields with high to excellent enantioselectivities. In addition, such structural motifs may have potential applications in enantioselective catalysis as chiral ligands or catalysts.

Axially chiral biaryls[1] are ubiquitously important scaffolds because of their unique molecular architecture and conformational behavior. A variety of synthetic protocols for their atroposelective construction have been widely explored during the past few decades.[1a,2] Among the well-known axial biaryl structures, 1,1′-bi-2-naphthol (BINOL) and 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (BINAP) have been recognized as privileged chiral backbones for the further design of new catalysts.[3] Despite established outstanding transformations, progress in preparing these chiral biaryl molecules remains less explored. Although chiral resolution of racemates is conventionally used for the preparation of atropisomerically enantiopure compounds,[4] enantioselective catalysis seems to meet the standards of high efficiency and economic value.[1a,4,5] Unfortunately, only a handful of enantioselective catalytic strategies have been reported regarding chiral biaryl synthesis,[6] including enantioselective C−C cross-couplings,[6b,c] atroposelective transformations of prostereogenic compounds,[1a] and enantioselective synthesis via aromatic ring formation.[6b−h]

Recently, chiral biaryl amino−alcohols as priority skeletons have been extensively implemented as ligands or catalysts in enantioselective catalysis (Figure 1a).[7] In 2016, Akiyama and co-workers reported an elegant example of the atropoenantioselective synthesis of chiral biaryl arylamine−alcohols promoted by chiral phosphoric acid.[8] Later on, our group successfully exploited an iridium-catalyzed atropoenantioselective amination that also provided chiral biaryl arylamine−alcohols in good yields with excellent enantioselectivities.[9] However, the above methods are applied for aromatic amine substrates. In sharp contrast, chiral biaryl alkylamine−alcohols reflect outstanding merits in catalytic performance and stereocontrol. For example, chiral alkylamine−alcohol catalysts **5** and **6** (Figure 1a) can efficiently promote the addition of zinc reagents to aldehydes to give the corresponding chiral products with good to high enantioselectivities.[10] We then envisioned that either primary or secondary alkylamines could be utilized as raw materials to assemble the target biaryl alkylamine−alcohols via catalytic reductive amination[11] (Figure 1b). In this scenario, two major challenges might be encountered: (1) the unpredictable reactivity of reductive amination, as there are not enough data to guarantee the success of the use of alkylamines as nucleophiles; (2) successful examples of the atropoenantioselective construction of axially chiral biaryls are still in high demand.

Dynamic kinetic resolution (DKR)[12] of bridged biaryl lactone systems, uncovered by the Bringmann group[13] and then expanded by the groups of Yamada,[14a,b] Wang,[14c] and Zhang,[14d] has proven to be an efficient tool for the enantioselective synthesis of chiral biaryls. Later on, the expanded bridged biaryl mixed cyclic *N,O*-acetal was reported by Akiyama and then used by our group to accomplish the assembly of chiral biaryls.[8,9] Inspired by these achievements, we report herein the unprecedented ruthenium-catalyzed atropoenantioselective synthesis of axial biaryl alkylamine−alcohols via a reductive amination and DKR strategy (Figure 1c). Although the reductive amination of carbonyls is a powerful and versatile strategy for the creation of amine motifs, only a limited enantioselective version exists.[15]

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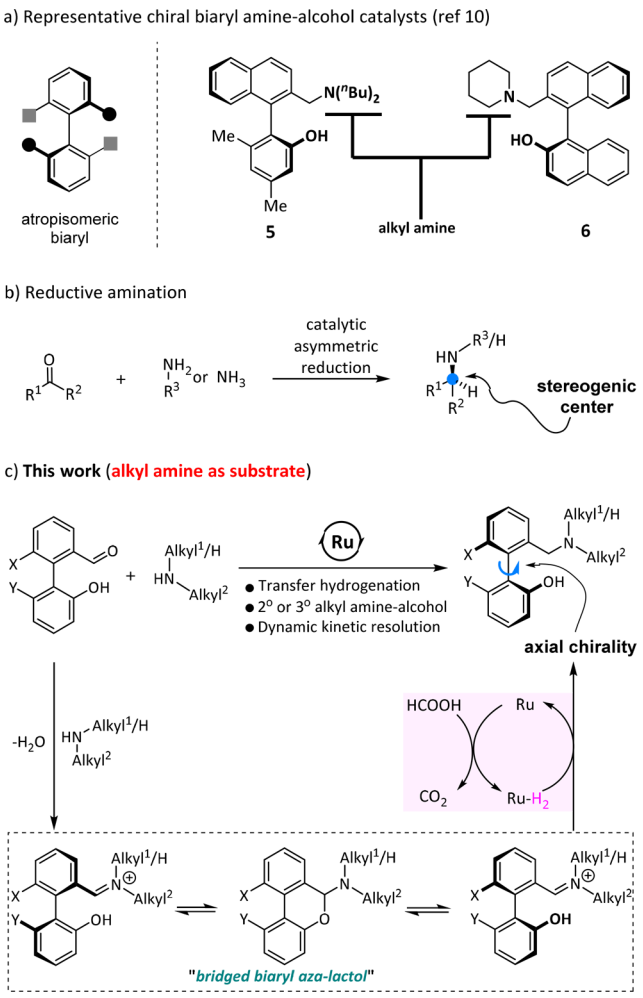
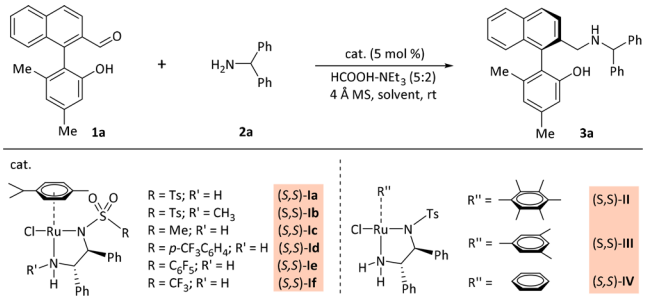


Figure 1. Atropoenantioselective strategies in the synthesis of axially chiral biaryls.

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	solvent	yield (%)[b]	*ee* (%)[c]
1	none	DCM	0	–
2	(*S*,*S*)-**Ia**	DCM	87	93
3	(*S*,*S*)-**Ib**	DCM	37	92
4	(*S*,*S*)-**Ic**	DCM	82	70
5	(*S*,*S*)-**Id**	DCM	76	96
6	(*S*,*S*)-**Ie**	DCM	89	98
7	(*S*,*S*)-**If**	DCM	77	98
8	(*S*,*S*)-**II**	DCM	<5	–
9	(*S*,*S*)-**III**	DCM	67	90
10	(*S*,*S*)-**IV**	DCM	91	91
11	(*S*,*S*)-**Ie**	toluene	76	94
12	(*S*,*S*)-**Ie**	THF	27	88
13	(*S*,*S*)-**Ie**	MeCN	91	50
14[d]	(*S*,*S*)-**Ie**	DCM	82	98
15[e]	(*S*,*S*)-**Ie**	DCM	89	98
16[f]	(*S*,*S*)-**Ie**	DCM	89	99

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.05 mmol), catalyst (5.0 mol %), HCOOH–NEt_3 (5:2, 30 μL), 4 Å MS (50 mg), solvent (2.0 mL), room temperature, 24 h. [b]Yields of isolated products. [c]The enantiomeric excesses (*ee*) were determined by HPLC with a chiral AD-H column. [d]10 μL of HCOOH–NEt_3 was added in one portion. [e]20 μL of HCOOH–NEt_3 was added in one portion. [f]20 μL of HCOOH–NEt_3 was added in five portions.

We commenced our study with the reaction of biaryl *rac*-**1a** with benzhydrylamine (**2a**) (Table 1). No reaction happened in the absence of catalyst, indicating that a catalyst is essential for achieving the bottom line of reactivity (Table 1, entry 1). Variation of the R group as well as the R′ and R″ groups at the sulfonamide moiety led to the identification of catalyst (*S*,*S*)-**Ie** as a superior facilitator, producing **3a** with excellent results for both chemical yield and enantiocontrol (Table 1, entries 2–10). With these promising data in hand, we then turned our attention to solvent screening. The reaction medium had a significant influence on controlling the reactivity as well as the enantioselectivity (Table 1, entries 10–13). Further fine-tuning revealed that the feeding mode affected the stereocontrol to some degree (Table 1, entries 14–16). Finally, the optimal conditions consisted of 5.0 mol % (*S*,*S*)-**Ie**, 4 Å MS (50 mg), HCOOH–NEt_3 (20 μL, added in five portions), 2.0 mL of DCM, and room temperature (Table 1, entry 16).

Having identified the optimal protocol, we next explored the substrate scope by examining various primary and secondary alkylamines. Pleasingly, the reductive amination of **1a** with primary alkylamines proceeded in high yields with high to excellent enantioselectivities (Scheme 1, **3a–d** and **3f–j**). Remarkably, even a chiral amino ester as the substrate was well-tolerated with excellent diastereoselectivity (Scheme 1, **3e**, dr >20:1). Encouraged by these results, we also investigated the scope of the atropoenantioselective reductive amination of **1a** with secondary amines (Scheme 1, **3k–r**). A number of symmetric *N*,*N*-disubstituted alkylamines were efficiently promoted to the corresponding biaryl amino–alcohols in high yields with excellent enantioselectivities (Scheme 1, **3k** and **3n–r**). Gratifyingly, unsymmetric *N*,*N*-disubstituted amines were also well-tolerated (Scheme 1, **3l** and **3m**). As shown in Scheme 1, good results (83% yield, 85% *ee*) were found for unsymmetric butylmethylamine (Scheme 1, **3l**). *N*-Methylaniline as a substrate also provided the corresponding product in 91% yield with 90% *ee* (Scheme 1, **3m**).

Next, we turned our focus to biaryl substrates. Substituted 2-formyl-2′-hydroxy-1,1′-biaryls bearing electron-donating groups (Me or OMe) or an electron-withdrawing group (Cl) on the upper aromatic ring, were obtained with high to excellent enantioselectivities (83 to >99% *ee*; Scheme 2). Overall, the substitution pattern and electronic effects of the substituents had limited influence on the enantiocontrol and reactivity. Biaryls bearing substituents (e.g., Me, OMe, Br, or CN) on the lower aromatic ring were also found to be suitable substrates, affording the corresponding biaryl amine–alcohols in high yields with high to excellent enantioselectivities (Scheme 2, **4a–g**, **4i–p**, and **4r–t**). This atropoenantioselective method was not limited to the phenyl–naphthyl derivatives. Both phenyl–phenyl and binaphthyl derivatives also participated in the reaction and afforded the corresponding products in acceptable yields with high *ee* values (Scheme

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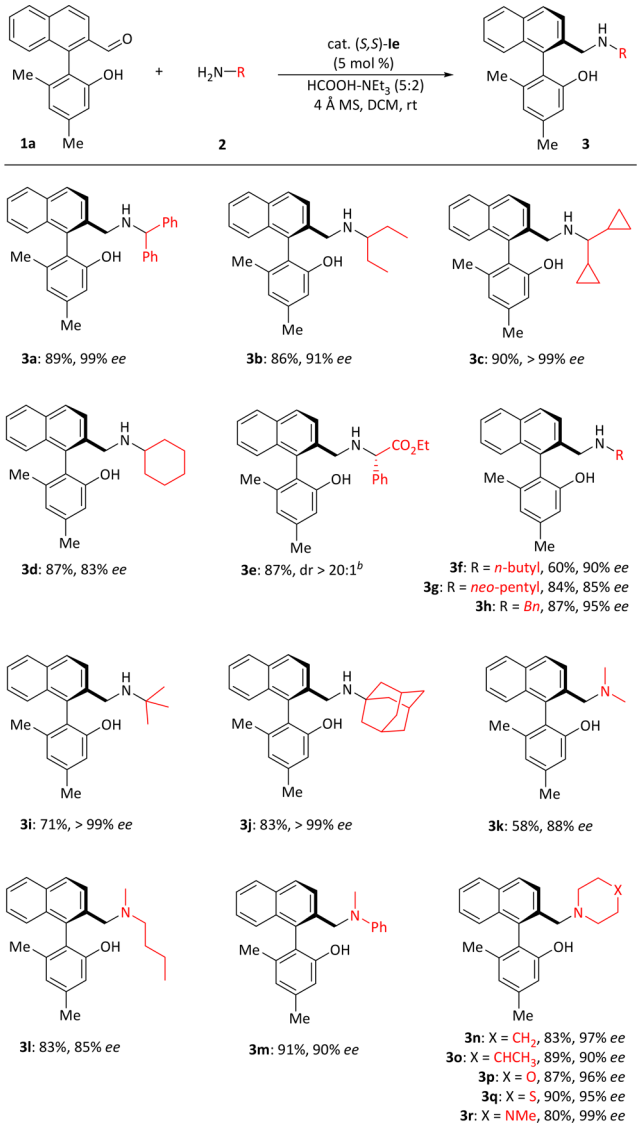
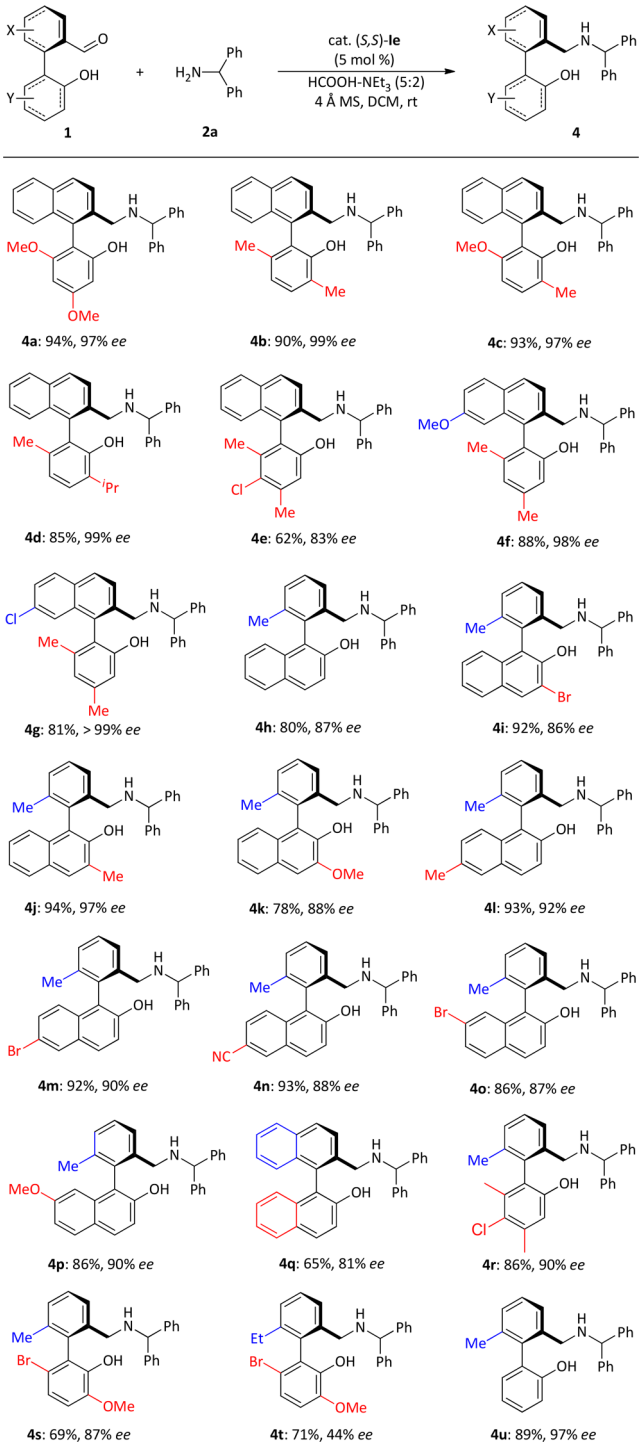
Scheme 1. Scope of Amines 2[a]



[a]Reaction conditions: **1a** (0.05 mmol), amine **2** (0.05 mmol), cat. (*S*,*S*)-**Ie** (5.0 mol %), HCOOH−NEt_3 (5:2, 20 μL), 4 Å MS (50 mg), DCM (2.0 mL), room temperature, 24 h. [b]The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy.

Scheme 2. Scope of 1[a]



[a]Reaction conditions: *rac*-**1** (0.05 mmol), **2a** (0.05 mmol), (*S*,*S*)-**Ie** (5 mol %), HCOOH−NEt_3 (5:2, 20 μL), 4 Å MS (50 mg), DCM (2.0 mL), room temperature, 24 h.

2, **4q**−**u**). The absolute configurations of **3** and **4** were determined by comparison of the optical rotations to the literature-reported data (also see the Supporting Information).[16]

To demonstrate the synthetic utility of this protocol, the products were subjected to further transformations. Under the standard conditions, the mixture of **1a** and **2s** afforded axially chiral biaryl catalyst **5** in an acceptable yield (82%) with high enantioselectivity (83% *ee*) (Scheme 3, eq 1). Axially chiral catalyst **6** was smoothly prepared from **1r** via a transfer hydrogenation (Scheme 3, eq 2). Furthermore, hydrogenation of **3a** offered chiral biaryl amino−alcohol **7** in 84% yield with unchanged *ee*.

A postulated mechanism is depicted in Scheme 4. The catalyst precursor (*S*,*S*)-**Ie** reacts with formic acid to form complex **I** in the presence of triethylamine,[17] and **I** releases CO_2 to afford active Ru hydride **II**. In addition, the condensation of biaryl phenol−benzaldehyde *rac*-**1** with alkylamine **2** affords iminium species **8** or **11**.[18] The subsequent reduction proceeds through a pathway wherein the 18-electron Ru hydride **II** undergoes hydride transfer to iminium species **8** or **11** to generate the final product **3** or **4** and form unsaturated 16-electron Ru species **III**. Meanwhile, the enantioselective reduction and the subsequent supply of consumed iminium species **11** via the rapid interconversion (**11** ⇄ **10** ⇄ **9** ⇄ **8**) occurs faster than the plausible reduction

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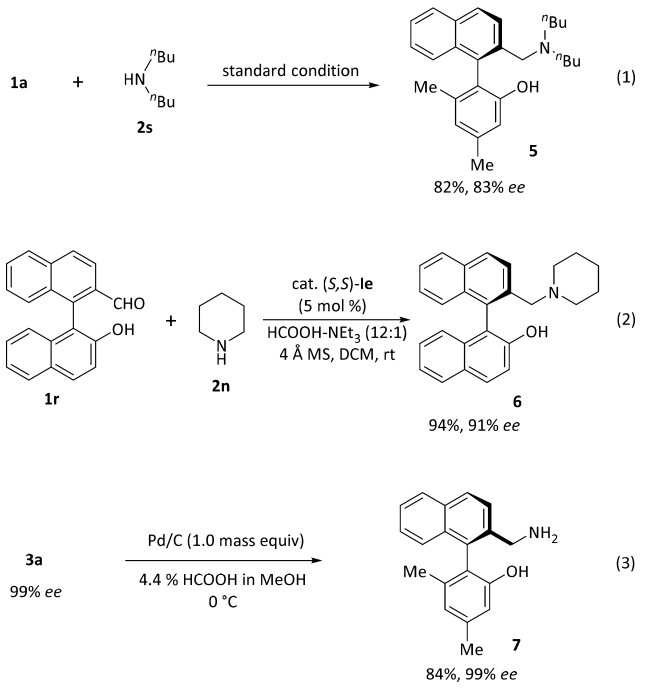
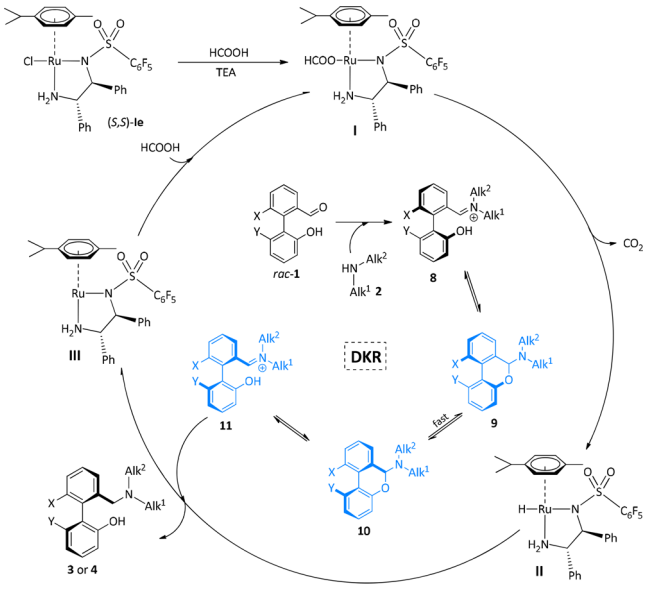
Scheme 3. Synthetic Applications



Scheme 4. Postulated Mechanism



of iminium species **8**. In other words, the key point of this successful DKR process is supported by the appropriate reaction rate difference between the equilibrium of **8** and **11** and the enantioselective reduction (transfer hydrogenation). Finally, with formic acid, Ru hydride **II** is regenerated from the unsaturated 16-electron Ru species **III**. In short, the biaryl axis in the mixed cyclic *N*,*O*-acetal is configurationally unstable and provides atropoenantiomers in equilibrium (Scheme 2, **8**−**11**). The subsequent enantioselective reductive amination of the mixed cyclic *N*,*O*-acetal leads to the formation of the chiral biaryl amine−alcohol with high stereoselectivity.

In conclusion, we have developed an unprecedented Ru-catalyzed atropoenantioselective synthesis of axially chiral biaryl amine−alcohols via reductive amination and DKR. This new protocol features several advantages, including mild reaction conditions, broad substrate scope, and operational simplicity, making it an attractive synthetic method for axially chiral biaryls. Further investigations of the synthesis of other relevant biaryl targets as well as a detailed mechanistic study are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02785.

Experimental procedures, NMR spectra, and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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