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Palladium-Catalyzed Asymmetric Hydrogenolysis of Aryl Triflates for Construction of Axially Chiral Biaryls

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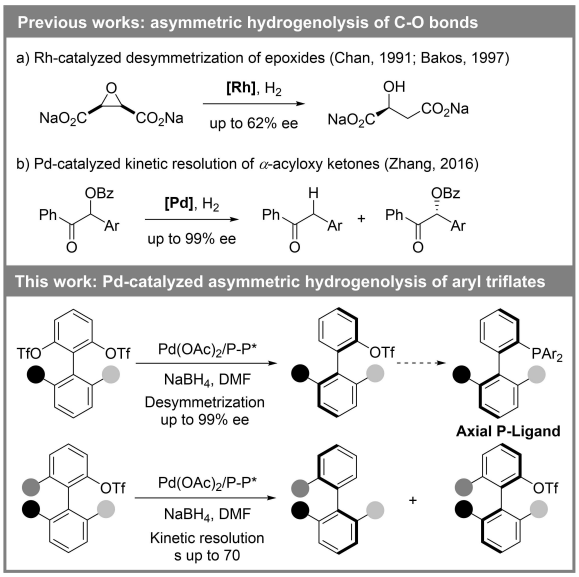
Abstract: Here we report the first palladium-catalyzed asymmetric hydrogenolysis of readily available aryl triflates via desymmetrization and kinetic resolution for facile construction of axially chiral biaryl scaffolds with excellent enantioselectivities and s selectivity factors. The axially chiral monophosphine ligands could be prepared from these chiral biaryl compounds and were further applied to palladium-catalyzed asymmetric allylic alkylation with excellent ee values and high branched and linear ratio, which demonstrated the potential utility of this methodology.

Hydrogenolysis has been seemed as an appealing synthesis method which is widely applied in organic synthesis[1] and industrial procedures.[2] However, the hydrogenolysis was mainly focused on the synthesis of racemic or achiral compounds, and relatively few studies on the asymmetric version were reported. The main challenges are as follows: 1) serious side reactions; 2) difficulty in coordination of substrate and chiral catalyst; 3) poorly chemo- and stereoselective control. In recent years, a few examples have been reported in asymmetric hydrogenolysis of C–O bonds. In 1991, the homogeneous asymmetric hydrogenolysis of sodium *cis*-epoxysuccinate was reported by Chan[3a] with the chiral rhodium complex as the catalyst, and moderate 62 % ee was obtained (Scheme 1a). Later, Bakos' group performed asymmetric hydrogenolysis of this substrate with the same rhodium catalyst system containing a water-soluble sulfonated ligand.[3b] In 2016, Zhang and co-workers developed a palladium-catalyzed asymmetric hydrogenolysis of C–O bonds of *α*-acyloxy ketones with *ortho*-substituted aryl groups through the kinetic resolution (Scheme 1b).[3c] Meanwhile, asymmetric hydrogenolytic desymmetrization of *meso* dihalides[4] and formal hydrogenolysis of the racemic tertiaryl alcohols[5] were also investigated. Although considerable efforts have been devoted in this field, these protocols are limited primarily to special substrates and



Scheme 1. Metal-catalyzed asymmetric hydrogenolysis of C–O bonds.

hydrogenolysis conditions. Therefore, the development of new catalyst system and expanding of substrate scope will further promote application of asymmetric hydrogenolysis in organic synthesis.

Axially chiral biaryl motifs are a class of important skeletons, which widely exist in natural products, drugs and ligands.[6] Recently, there have been significant advances made in the synthesis of axially chiral biaryl compounds through desymmetrization,[7] kinetic resolution,[8] dynamic kinetic resolution[9] and so on.[10] As we know, the aryl triflates are useful reaction partners for the further molecular structure modification.[11] Considering the importance of aryl triflate motif in organic chemistry, we envisioned weather 2-aryl substituted aryl triflates would be the candidates for asymmetric hydrogenolysis. Herein, we reported a palladium-catalyzed asymmetric hydrogenolysis of C–O bonds of aryl triflates to construct axially chiral biaryl scaffolds via desymmetrization and kinetic resolution. In addition, the elaboration of the axially chiral biaryl compounds was conducted, such as arylation and phosphination for synthesis of axially chiral monophosphine ligands. The applications of these monophosphine ligands were also demonstrated in palladium-catalyzed asymmetric allylic alkylation.

The investigation was initially evaluated by exploring desymmetrization of **1a** in DMF under nitrogen atmosphere using palladium(II) acetate/(*R*)-DTBM-SegPhos (**L1**) and

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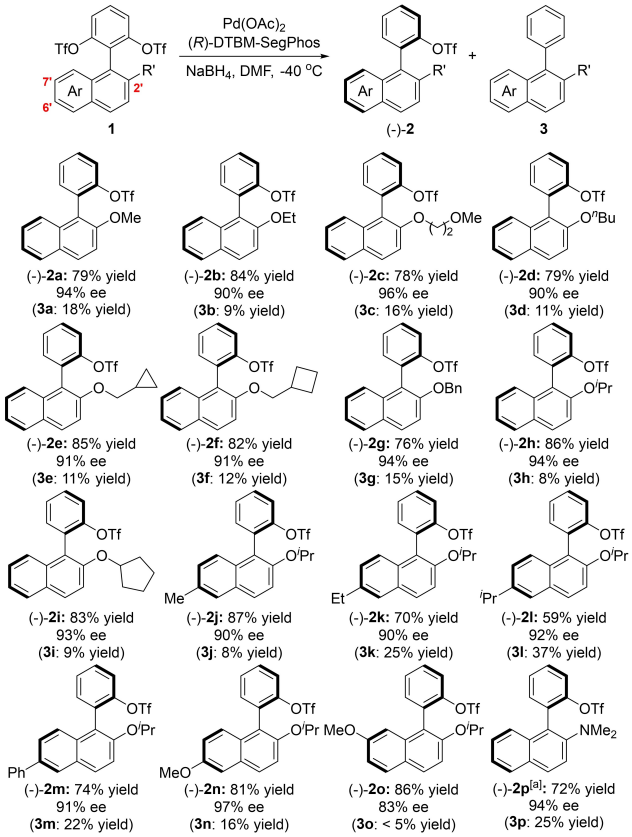
$NaBH_4$ as catalyst and hydrogen source, respectively. Pleasingly, the hydrogenolysis proceeded smoothly in 83% yield with 90% ee. Following this lead, a series of reaction parameters were screened (Please refer to Supporting Information for detailed conditions optimization). Ultimately, the optimal conditions were established as $Pd(OAc)_2$ (5 mol%)/(*R*)-DTBM-SegPhos (7.5 mol%)/$NaBH_4$/DMF/−40 °C. Under the optimal conditions, the substrate **1a** was conducted smoothly to afforded product (−)-**2a** in 79% yield and 94% ee with 18% side product **3a** (Scheme 2). Encouraged by this result, the substrate applicability was further verified (Scheme 2). Considering the influence of steric hindrance on the reaction, we first investigated the substituent at the 2′-position of the substrates. The desirable products could be successfully obtained with good yields and excellent enantioselectivities, whether it was small-steric hindered ethyl (**1b**), long-chain methoxyethyl (**1c**), or *n*-butyl (**1d**). In many cases, drug molecules containing small ring skeletons usually exhibit special pharmacological properties. So, cyclopropylmethyl (**1e**) and cyclobutylmethyl (**1f**) were introduced into the 2′-position. Happily, axially chiral biaryl compounds containing small ring skeletons with 91% ee could be obtained in 85% and 82% yield, respectively. Excellent results were also observed when the substrates contained benzyl (**1g**), isopropyl (**1h**), and cyclopentyl (**1i**) groups. In view of yields and ee values, the substituent at 2′-position was chosen to be isopropoxy, and the substituents at 6′- and 7′-position on naphthalene ring were further investigated. The results indicated that the corresponding products could be obtained with excellent enantioselectivities and moderate to good yields (**1j**–**1n**). The substrate with methoxy group at 7′-position was also explored (**1o**), affording the product in 86% yield and 83% ee with trace amount of side product **3o**. Slightly lower reactivity was observed when the dimethylamino group (**1p**) was introduced, and the reaction was carried out at −20 °C, giving the product with 72% yield and 94% ee. In addition, a small amount of over hydrogenolysis side product **3p** was generated.



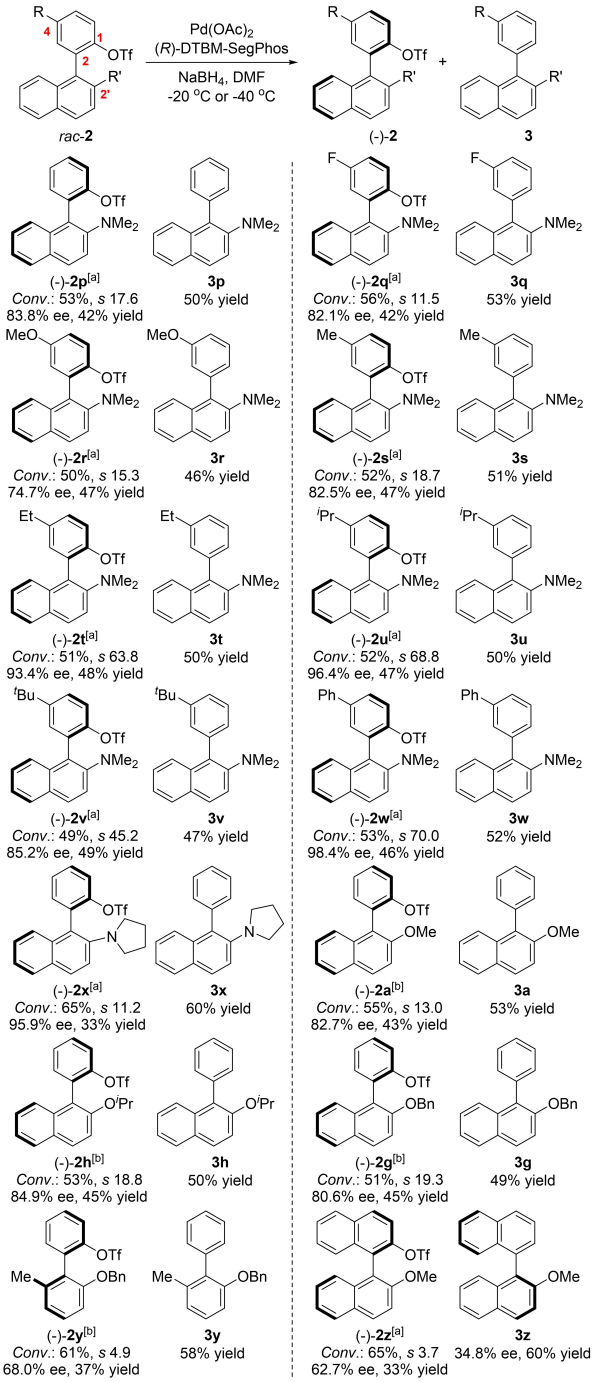
Scheme 2. The substrate scope for desymmetrization of aryl triflates **1**. Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), (*R*)-DTBM-SegPhos (7.5 mol%), $NaBH_4$ (2.0 equiv), DMF (2.0 mL), −40 °C. [a] The reaction of substrate **1p** was conducted at −20 °C.

Based on the successful examples of desymmetrization, the kinetic resolution experiments were screened using *rac*-**2p** as the model substrate (Please see Supporting Information for detailed conditions optimization). Excitingly, the selectivity factor could reach 17.6 under the slightly modified conditions. On this basis, the hydrogenolysis kinetic resolution of substrates *rac*-**2** was carried out (Scheme 3). Firstly, the influence of the steric and electronic properties of substituents on the 4-position of the phenyl ring was exploited. As expected, a variety of substituents were tolerated including electron-withdrawing (*rac*-**2q**) and electron-donating (*rac*-**2r**–**2v**) groups. It was worth noting that large steric alkyl substituents could afford high selectivity factors, such as isopropyl and *tert*-butyl groups.

Fortunately, the highest kinetic resolution selectivity factor (*s* 70) was obtained when the phenyl was introduced (*rac*-**2w**). In addition, 2′-position substituents on naphthalene ring were also investigated. The selectivity factors slightly decreased for pyrrolidin-1-yl (*rac*-**2x**) and methoxy (*rac*-**2a**) substituents. The isopropoxy (*rac*-**2h**) and benzyloxy (*rac*-**2g**) substituents were further exploited, and the selectivity factors could be maintained. Next, *ortho*-substituted phenyl ring instead of naphthalene ring as substrate was investigated (*rac*-**2y**), giving moderate selectivity factor. Lastly, the binaphthyl triflate was checked (*rac*-**2z**), and 3.7 selectivity factor was observed. The absolute configuration of the recovered substrate (−)-**2z** was determined to be *R* by comparison with the value of optical rotation reported in the literature.[12]

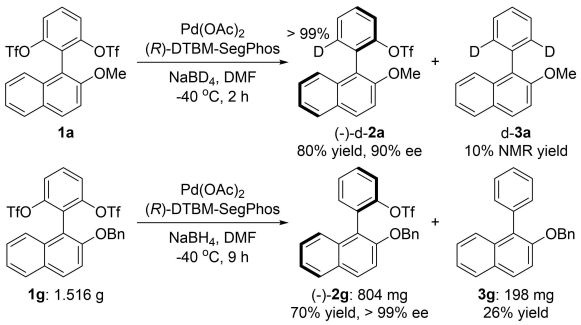
The success of the palladium-catalyzed asymmetric hydrogenolysis with sodium borohydride provided an opportunity for site-specific incorporation of deuterium atom due to easy availability of the deuterium source sodium borodeuteride. When sodium borodeuteride was used, the deuterium labelled product ((−)-d-**2a**) was given in 80% yield, 90% ee and >99% deuteration, which provided a good solution to site-specific incorporation of deuterium in chiral small molecules (Scheme 4). To further demonstrate the practicability of the hydrogenolysis methodology, gram scale experiment was carried out. Fortunately, (−)-**2g** was observed with 70% yield and >99% ee value (Scheme 4).

It is well known that monophosphine ligands containing axially chiral biaryl skeleton have a wide range of practicability.[6b,13] Therefore, the chiral monophosphine ligands were successfully synthesized through two step



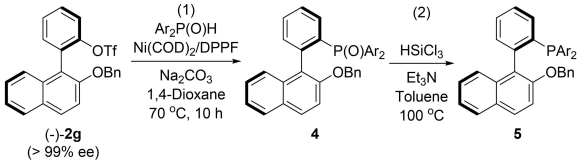
Scheme 3. The substrate scope for kinetic resolution of aryl triflates *rac*-**2**. Reaction conditions: *rac*-**2** (0.35 mmol), $Pd(OAc)_2$ (5 mol%), (*R*)-DTBM-SegPhos (7.5 mol%), $NaBH_4$ (1.5 equiv), DMF (3.5 mL), −40 °C or −20 °C. [a] The reaction was conducted at −20 °C. [b] The reaction was conducted at −40 °C.

procedures (Table 1). Firstly, the coupling reaction of chiral substrate (−)-**2g** (>99% ee) with different phosphine oxides as reaction partners were performed in the presence of $Ni(COD)_2$/DPPF, and four axially chiral phosphine oxides **4** were obtained with moderate yields and slightly decreased enantioselectivities.[14a] Due to the small steric hindrance of the substrate (−)-**2g**, it was partially racemized during the



Scheme 4. Deuterium and gram-scale experiments.

Table 1: The synthesis of monophosphine ligands.[a]

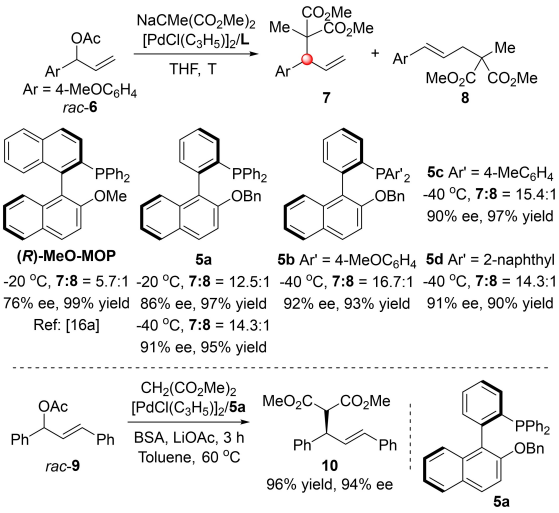


Entry	4	Ar	Yield [%][b]	ee [%][c]	5	Yield [%][b]
1	**4a**	Ph	61	96.8[d]	**5a**	94
2	**4b**	4-$MeOC_6H_4$	65	94.2[d]	**5b**	95
3	**4c**	4-MeC_6H_4	62	97.2	**5c**	93[e]
4	**4d**	2-Naphthyl	61	97.3[d]	**5d**	96

[a] Reaction conditions: (1) (−)-**2g** (1.0 equiv), $Ar_2P(O)H$ (1.2 equiv), $Ni(COD)_2$ (1.0 equiv), DPPF (1.0 equiv), Na_2CO_3 (1.0 equiv), 1,4-dioxane (0.1 M), 70 °C, 10 h. (2) **4** (1.0 equiv), $HSiCl_3$ (5.0 equiv), Et_3N (7.0 equiv), toluene (10 mL), 100 °C. [b] Isolated yield. [c] Determined by the chiral HPLC analysis. [d] The >99% ee of **4** was obtained through recrystallization, and was used in the next step. [e] The >99% ee of **5c** was obtained through recrystallization.

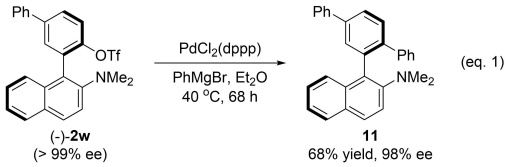
coupling process at high temperature, which led to a slight decrease in the enantioselectivity of the coupling product. Then, the phosphine oxides **4** (upgrade to >99% ee by single recrystallization) were reduced to axially chiral monophosphine ligands in excellent yields and without loss of optical purity.[14b]

The application of these axially chiral monophosphine ligands has been proved in palladium-catalyzed asymmetric allylic alkylation,[15] and the results were shown in Scheme 5. Preferable regioselectivity and enantioselectivity were obtained with ligand **5a** for asymmetric allylic alkylation of 1-(4-methoxy-phenyl)allyl acetate (*rac*-**6**) in comparison with (*R*)-MeO-MOP.[16a] When the reaction temperature was further decreased to −40 °C, the improved branched and linear ratio (14.3:1) and enantioselectivity (91%) were provided. Under the above standard reaction conditions, other chiral monophosphine ligands (**5b–5d**) were also performed well. Among them, apparent improvement of the regioselectivity was achieved with ligand **5b**. To our delight, ligand **5a** was also suitable in palladium-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenylallyl acetate (*rac*-**9**)[16b] and **10** was produced in excellent reactivity and stereoselectivity (96% yield, 94% ee). The charm of the new ligands depends on their excellent chiral induction and



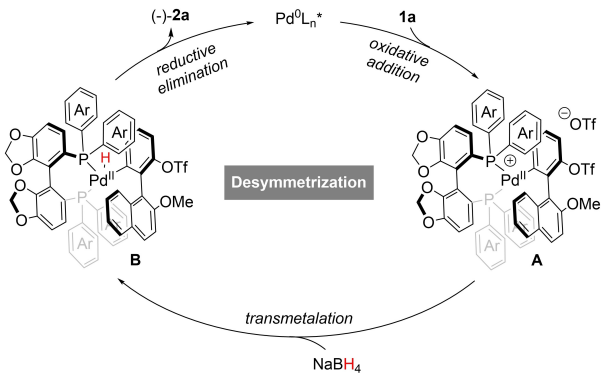
Scheme 5. The applications of monophosphine ligands.

the potential to improve the regioselectivity of the reaction.



In order to further demonstrate the utility of axially chiral biaryl compounds, a palladium-catalyzed Kumada coupling reaction of (−)-**2w** (>99 % ee) with phenylmagnesium bromide was carried out, providing the coupling product **11** with 68 % yield and excellent 98 % ee [Eq. (1)].[17] The axially chiral biaryldimethylamine could be further converted to ammonium salt, which is a useful candidate for further coupling reactions.[18]

Based on the above experimental results and the putative literature reports on the palladium-catalyzed hydrogenolysis,[4c] a plausible mechanism was proposed in Scheme 6. Firstly, the oxidative addition of chiral Pd^0 complex with aryl triflate **1a** generated the Pd^{II} species **A**, which subsequently underwent transmetallation with sodium borohydride to afford the Pd^{II}-H species **B**. Then, the chiral hydrogenolysis product (−)-**2a** were obtained via reductive elimination, the Pd^0 species was regenerated to complete catalytic cycle. As noted, the oxidative addition is the enantio-determining step.



Scheme 6. Plausible mechanism.

In summary, we have developed the first palladium-catalyzed asymmetric hydrogenolysis of C–O bond of aryl triflates through desymmetrization and kinetic resolution, giving a series of axially chiral biaryl scaffolds with high yields and enantioselectivities. These axially chiral compounds could be further transferred into chiral monophosphine ligands, which were successfully applied into palladium-catalyzed asymmetric allylic alkylation, delivering the desired product with excellent regio- and enantioselectivities. The axially chiral biaryl triflate was also converted into chiral multi-aryl compound through Kumada coupling. When sodium borodeuteride was used, the deuterium incorporated product could be prepared with excellent yield and >99 % deuteration, which provided a good solution to site-specific incorporation of deuterium of small molecules. Further studies in this area are actively explored in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords: Aryl Triflates · Asymmetric Hydrogenolysis · Axially Chiral Biaryls · Desymmetrization · Palladium

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Communications

Asymmetric Catalysis

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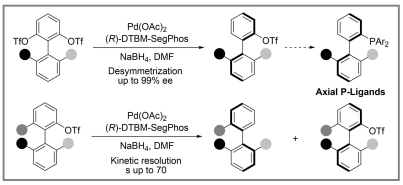
Palladium-Catalyzed Asymmetric Hydrogenolysis of Aryl Triflates for Construction of Axially Chiral Biaryls



We have developed the first palladium-catalyzed asymmetric hydrogenolysis of aryl triflates through desymmetrization and kinetic resolution that allows the facile construction of axially chiral biaryl scaffolds with excellent results. These chiral compounds could be further converted into chiral monophosphine ligands, which were then used in asymmetric allylic alkylation to produce the desired product with high regio- and enantioselectivities.