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Directing Group Enabled Ruthenium-Catalyzed Asymmetric Hydrogenation of Naphthalenes and Related Carbocyclic Aromatics

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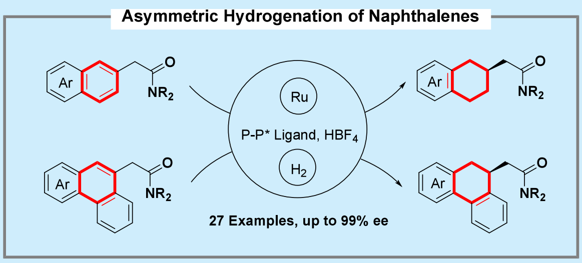
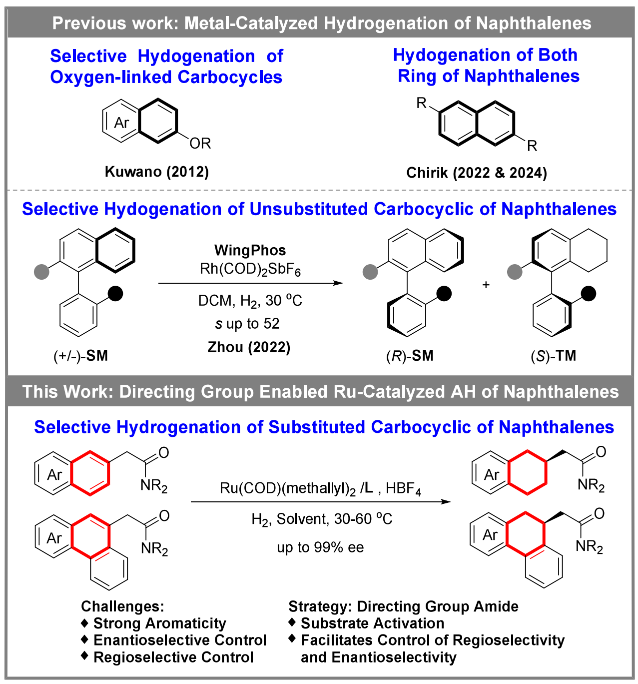
ABSTRACT: Among the aromatic carbocyclic rings, the highly regio- and enantioselective hydrogenation of nonsymmetrical naphthalenes has remained a long-standing challenge in asymmetric catalysis. Herein, we reporte an amide-directed asymmetric hydrogenation of nonsymmetrical naphthalenes with a ruthenium catalyst with up to 99% ee. This strategy was also successfully applied in the asymmetric hydrogenation of polycyclic aromatic hydrocarbons.



Chiral carbocyclic scaffolds are important structural motifs found frequently in natural products, pharmaceuticals and agrochemicals.[1] Homogeneous asymmetric hydrogenation (AH) of carbocyclic aromatics provides the most efficient, straightforward, and simple retrosynthetic route to various chiral carbocyclic scaffolds. With the success in AH of heteroarenes, the field of asymmetric hydrogenation of carbocyclic aromatics has witnessed some growth recently, especially for the aromatics containing no heteroatoms.[2−6] Compared to other aromatics, the AH of naphthalenes not only faced the challenge of strong aromaticity and enantioselective control but also had the difficulty of regioselective control. Therefore, only a few studies on the AH of naphthalenes have been completed. In 2012, Kuwano and co-workers disclosed the first successful asymmetric hydrogenation of 2-alkoxy-naphthalenes with a good to excellent ee values. The oxygen atom played a very important role in the coordination interaction between the catalyst and the naphthalene ring.[4] Obviously, the AH of unactivated naphthalenes is more difficult. Ten years later, a molybdenum-catalyzed AH of alkyl-substituted naphthalenes for the synthesis of decalins was developed by the Chirik's group.[5] The substrate scope was mainly focused on 2,6-dimethyl/ethylnaphthalene, which avoided the problem of poor differentiation between the two aromatic rings in naphthalene, thus providing excellent enantioselectivity. Very recently, our group developed a method for hydrogenative kinetic resolution of 1,2-disubstituted naphthalenes employing Rh/WingPhos as the catalyst, which constructs an axially chiral biaryl compound through hydrogenation of the unsubstituted carbocycle of naphthalenes (Scheme 1).[6] Despite the preceding successes, it has remained a long-standing challenge to date to carry out highly regio- and enantioselective asymmetric hydrogenation of simple naphthalenes

Scheme 1. Transition-Metal-Catalyzed Asymmetric Hydrogenation of Naphthalenes



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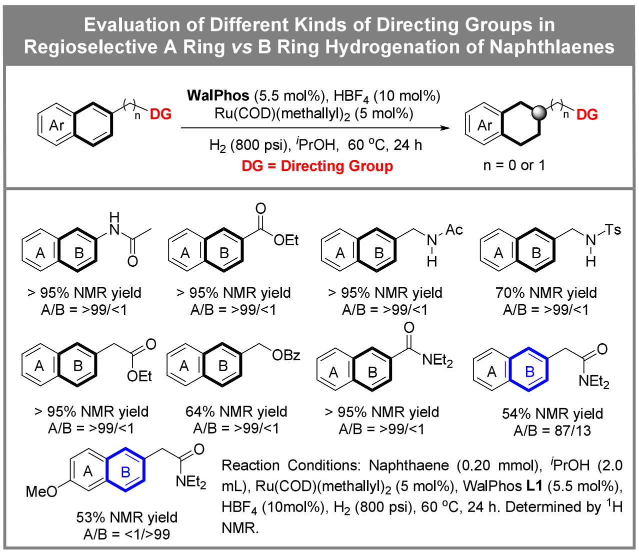
Within the past few decades, the substrate-directed method has developed into an indispensable tool in the field of asymmetric synthesis.[7] In this approach, the directing group inside the substrate could preassociate with the chiral catalyst, which directed the other reactant toward the single enantiotopic face of the reaction site. Those reactions usually result in excellent enantioselectivity through an orderly transition states. The development of substrate directed asymmetric oxidations,[8] fluorinations,[9] C−H functionalizations,[10] hydrogenations, etc.,[11,12,13] which were controlled by plentiful and common directing groups such as hydroxy, amide, and sulfonamide groups, have been described in recent years. Up to now, AH of alkenes bearing a directing group were the most widespread reactions among the numerous AH reactions.[11] Recently, a rhodium-catalyzed AH of phenanthrenes bearing a directing group for the construction of central-chiral cyclic compounds was reported by our group.[6] Encouraged by previous studies, we attempted to explore the asymmetric hydrogenation of naphthalenes based on the directing group strategy.

Inspired by the previous work, asymmetric hydrogenation of naphthalenes with different directing groups was tested with $Ru(COD)(methallyl)_2$/WalPhos as a catalyst in ^{i}PrOH under hydrogen gas (800 psi) at 60 °C (Scheme 2). When the

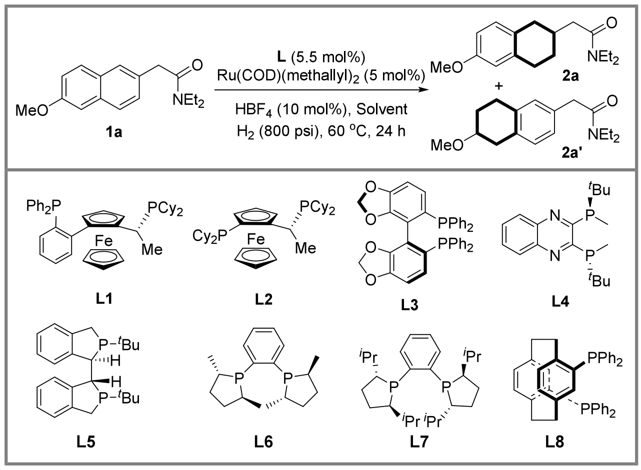
Scheme 2. Evaluation of Directing Groups in Ru-Catalyzed Regioselective Hydrogenation of Naphthalenes



directing group was −NHAc, −NHTs, C(O)OEt, −OBz, or $CONEt_2$, the hydrogenation only occurred on the benzene ring bearing no substituents (A ring). The catalyst selected the aromatic ring with a lower energy, indicating that these directing groups did not work as expected. It is worth noting that using amide ($-C(O)NEt_2$) as the directing group resulted in the hydrogenation reaction with 54% conversion. Although the regioselectivity was unsatisfactory and most of the product was hydrogenated on the benzene ring without a substituent (A ring), a small amount of the desired product hydrogenated on the benzene ring with substituents (B ring) could be obtained, and the ratio was 87:13. This observation suggested that the amide-directed AH of naphthalenes was feasible. To our delight, 53% conversion and a single regioisomer hydrogenation product were obtained (hydrogenation of B ring/hydrogenation of A ring = 99:1) using (2-(6-methoxynaphthalen-2-yl)-*N*,*N*-dimethyl-acetamide) containing methoxy at the 6-position as the substrate. In this context, we began to study the regio- and enantioselective hydrogenation of nonsymmetrical 2-substituted naphthalenes bearing an amide group.

We started our investigation with nonsymmetrical (2-(6-methoxynaphthalen-2-yl)-*N*,*N*-dimethylacetamide) **1a** as the model substrate to explore the optimal conditions of ruthenium-catalyzed asymmetric hydrogenation (Table 1). Initially, the effects of some commercially available chiral bisphosphine ligands (**L1**−**L8**) on the reactivity, enantioselectivity, and regioselectivity were evaluated. Using **L1**−**L7** as the ligand, the reaction showed moderate conversions and ee

Table 1. Evaluation of Reaction Parameters[a]



entry[a]	ligand	solvent	additives	X	conversion %[b]	2a ee %[c]
1	**L1**	^{i}PrOH	HBF_4	5	53	14
2	**L2**	^{i}PrOH	HBF_4	5	32	17
3	**L3**	^{i}PrOH	HBF_4	5	9	53
4	**L4**	^{i}PrOH	HBF_4	5	16	35
5	**L5**	^{i}PrOH	HBF_4	5	7	50
6	**L6**	^{i}PrOH	HBF_4	5	28	9
7	**L7**	^{i}PrOH	HBF_4	5	44	17
8	**L8**	^{i}PrOH	HBF_4	5	55	91
9	**L8**	DCE	HBF_4	5	52	87
10	**L8**	EA	HBF_4	5	37	87
11	**L8**	1,4-dioxane	HBF_4	5	60	85
12	**L8**	THF	HBF_4	5	82	82
13	**L8**	MeOH	HBF_4	5	37	92
14	**L8**	^{i}PrOH	HPF_6	5	26	88
15	**L8**	^{i}PrOH	TfOH	5	44	89
16	**L8**	^{i}PrOH	TFA	5	<5	
17[d]	**L8**	^{i}PrOH	HBF_4	7.5	64	88
18[e]	**L8**	^{i}PrOH	HBF_4	10	95 (91)[e]	92

[a]Reaction conditions: **1a** (0.20 mmol), solvent (2.0 mL), $Ru(COD)(methallyl)_2$ (5 mol %), **L** (5.5 mol %), additive (10 mol %), H_2 (800 psi), 60 °C, 24 h. DCE denotes 1,2-dichloroethane. EA denotes ethyl acetate. THF denotes tetrahydrofuran. TFA denotes trifluoroacetic acid. [b]Determined by ^{1}H NMR; in all the reactions, only **2a** was detected. [c]Determined by chiral HPLC. [d]$Ru(COD)(methallyl)_2$ (7.5 mol %), **L8** (8.3 mol %), additive (15 mol %), the reaction time was extended to 72 h. [e]$Ru(COD)(methallyl)_2$ (10 mol %), **L8** (11 mol %), additive (20 mol %), 72 h, isolated yield based on the **1a**.

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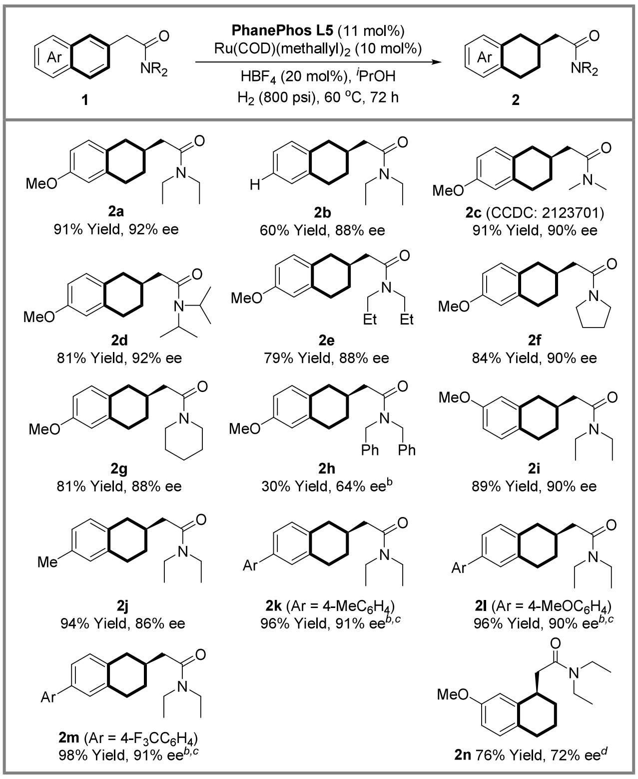
values but give excellent regioselectivities, leading to almost exclusive formation of the product tetralin **2a** (**2a**/**2a′** > 99/1, entries 1−7). To our delight, when [2,2]paracycophane-based PhanePhos **L8** with a rigid structure and large steric bulkiness was used, the desired hydrogenation product **2a** was obtained with 91% ee with extensive regioselectivity as well as moderate conversion (entry 8). To further improve the reactivity, we performed a screening of different solvents (entries 6−9). The reactions with 1,2-dichloroethane (DCE) or ethyl acetate (EA) exhibited excellent regioselectivities and enantioselectivities but showed moderate conversions (entries 9 and 10). Reactions conducted in 1,4-dioxane and THF proceeded with good conversions (60% and 82%) and ee values (85% and 82%), as well as excellent regioselectivities (entries 11 and 12, respectively). The reaction in methanol delivered 92% ee and excellent regioselectivity but only 37% conversion (entry 13). A survey of solvents indicated that isopropanol was still the best choice, albeit with moderate activity (entry 8). To further improve the reaction efficiency, an enhanced survey of the additives was conducted. Unfortunately, higher conversions have not been achieved (entries 14−16). When we increased the catalyst loading to 7.5 or 10 mol %, full conversion was obtained without loss of enantioselectivity (entries 17 and 18). To ensure the AH of other substrates proceeded smoothly, we chose 10 mol % as the optimal catalyst loading. Thus, the conditions in the entry 18 were selected as the optimized conditions.

Under the optimized conditions, we tested substrate generality on nonsymmetrical naphthalenes in asymmetric hydrogenation with a chiral ruthenium catalyst (Scheme 3). For the *N*,*N*-diethyl-2-(naphthalen-2-yl)acetamide substrate, the target product **2b** was obtained in 60% yield and 88% ee value. At the same time, a 3% yield of the side **2b′** was generated by hydrogenation on the benzene ring without substituents. Subsequently, the substituents on the amides were tested. Substrate with an ethyl group (**1a**) or methyl group (**1c**) gave the desired products with high yield and enantioselectivity. The absolute configuration of product **2c** was unambiguously assigned to be *S* by X-ray crystallographic analysis.[14] Additional steric hindrances close to the amide were also tolerated. Isopropyl (**1d**) and allyl (**1e**) substitution produced the desired products with satisfactory results (81% yield with 92% ee and 79% yield with 88% ee, respectively). It is worth noting that the double bonds of the allyl group were also hydrogenated. Meanwhile, five- and six-membered cyclic amides (**1f** and **1g**) were tested, and the corresponding products were obtained in good yields and enantioselectivities. However, both enantioselectivity and reaction rate decreased significantly when **1h** was used with two benzyl groups as the substrate. Additionally, the influence of the substituent on the aromatic ring was also screened. A substrate with methoxy in the 7-position (**1i**) or methyl in the 6-position (**1j**) was also hydrogenated successfully. In addition, excellent results for substrates bearing diverse aryl substituents in position 6 (**1k**−**1m**) were also achieved. The 1-substituted naphthalene *N*,*N*-diethyl-2-(7-methoxynaphthalen-1-yl)acetamide (**1n**) also reacted well to produce **2n** (72% ee and 76% yield) in the presence of WalPhos **L1** as a ligand.

To further prove the generality of this strategy, the next step of scope studies focused on some other polycyclic aromatic hydrocarbons (PAHs). Having adjusted the optimal reaction conditions, the substrate scope and the results are depicted in Scheme 4. Hydrogenation of phenanthrenes was first

Scheme 3. Substrate Scope: 2-Substituted Naphthalenes[a]

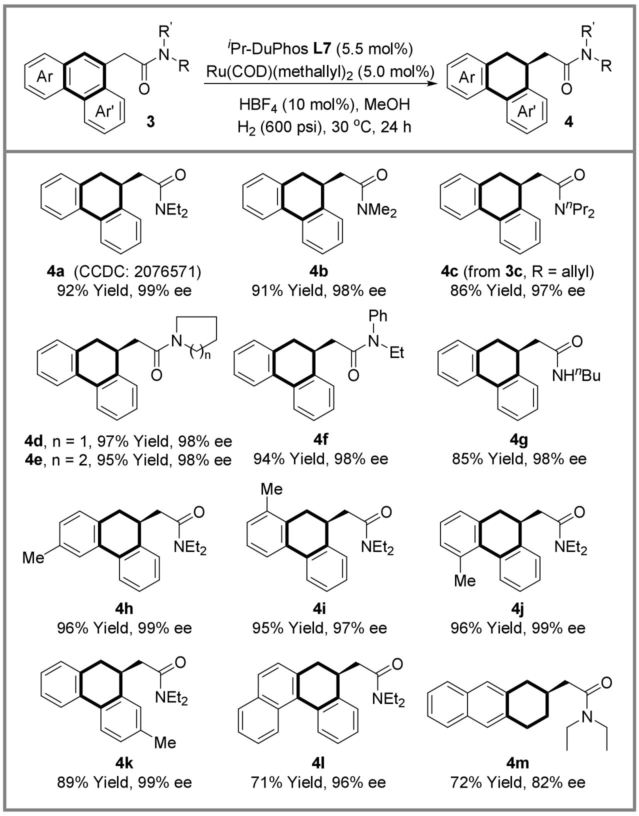


[a]Conditions: **1** (0.20 mmol), Ru(COD)(methallyl)$_2$ (10 mol %), PhanePhos **L5** (11 mol %), HBF_4 (20 mol %), ^{i}PrOH (2.0 mL), H_2 (800 psi), 60 °C, 72 h. [b]The temperature was raised to 80 °C. [c]The reaction time was 120 h. [d]Using **L1** as ligand

attempted. When the ethyl groups were introduced to the amide (**3a**), the excellent yield (92%) and ee value (99%) were obtained, and the absolute configuration was determined by the X-ray structure of the product **4a**.[15] In addition, the other substituents on the amides did not have an effect on the reactivities and enantioselectivities (**3b**−**3g**). The catalyst was not sensitive to the position of methyl on the phenanthrene, as demonstrated by the high yields and enantioselectivities obtained from the hydrogenation of substrates **3h**−**3k**. Moreover, the substrate with benzo[*c*]phenanthrene smoothly underwent hydrogenation to the corresponding product (**4l**) in 71% yield with 96% ee. Amide-directed enantioselective hydrogenation of anthracene (**3m**) was also evaluated. The desired 1,2,3,4-tetrahydroanthracene (**4m**) was formed with 72% yield and 82% ee. However, the reaction did not occur when *N*,*N*-diethyl-2-(10-methylphenanthren-9-yl)acetamide[6] was used as the substrate.

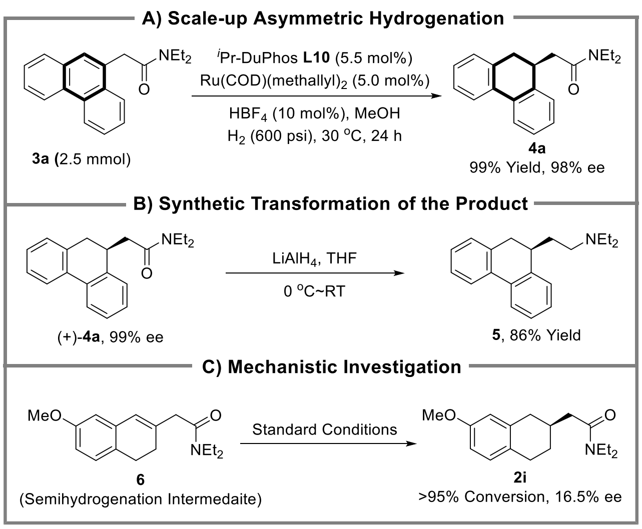
To demonstrate the efficiency of this catalytic system, a 2.5 mmol scale experiment on asymmetric hydrogenation of **3a** was conducted under the standard conditions, furnishing the product **4a** with 99% yield and 98% ee (Scheme 5A) without loss of activity and enantioselectivity. Additionally, the synthetic utility of the obtained product was highlighted by the reduction of amide (Scheme 5B). To elucidate the mechanism of the hydrogenation, the hydrogenation of 3,4-dihydronaphthalene **6** was carried out under the standard conditions (Scheme 5C). Although 3,4-dihydronaphthalene **6** converted completely, hydrogenation product **2i** was obtained

Scheme 4. Substrate Scope: Polycyclic Aromatic Hydrocarbons[a]



[a]Conditions: **3** (0.25 mmol), Ru(COD)(methallyl)$_2$ (5.0 mol %), ^{i}Pr-DuPhos **L7** (5.5 mol %), HBF_4 (10 mol %), MeOH (3.0 mL), H_2 (600 psi), 30 °C, 24 h.

Scheme 5. Scalability, Diverse Transformation, and Mechanistic Investigation



with a low 16.5% ee, which indicated that 3,4-dihydronaphthalene **6** was not the reaction intermediate.

In conclusion, we have reported the ruthenium-catalyzed amide-directed asymmetric hydrogenation of nonsymmetrical naphthalenes and polycyclic aromatic hydrocarbons, which provided effectual and practical access to the chiral exocyclic amides with up to 99% ee. This method was scalable, operationally simple, and synthetically useful. Further mechanistic studies and the development of methods that achieve asymmetric hydrogenation of more challenging benzenes are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c00014.

Experimental procedures, characterization data, crystal data and NMR spectra (PDF)

Accession Codes

Deposition Numbers 2076571 and 2123701 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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(14) CCDC 2123701 contains supplementary crystallographic data of compound (−)-**2c**.

(15) CCDC 2076571 contains supplementary crystallographic data of compound (+)-**4a**.

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