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Palladium/Lewis Acid Co-catalyzed Divergent Asymmetric Ring-Opening Reactions of Azabenzonorbornadienes with Alcohols

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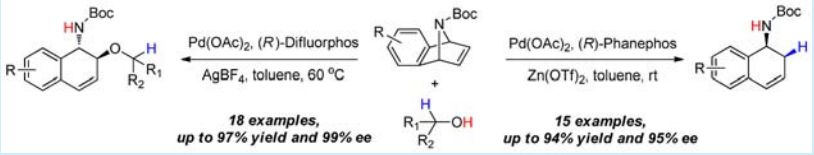
Supporting Information

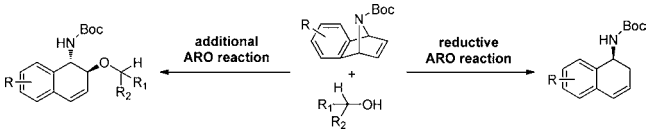


ABSTRACT: By fine tuning the combinations of chiral palladium catalysts and Lewis acids, both the additional and reductive asymmetric ring-opening reactions of azabenzonorbornadienes with alcohols were accomplished with good chemoselectivity, regioselectivity, and enantioselectivity. It was proven that the reductive ring-opening products were generated through a transfer-hydrogenation process with alcohols as hydrogen source.

The asymmetric ring-opening (ARO) reactions of oxa/azabenzonorbornadienes can directly generate substituted chiral dihydronaphthalenes, which are ubiquitous substructures in natural products and pharmaceuticals, as products.[1] Pioneered by Lautens, the ARO reactions of oxabenzonorbornadienes have been greatly developed in the past decades, and various nucleophiles have been successfully applied as effective ring-opening reagents.[2] Though the products of the ARO reactions of azabenzonorbornadienes have great application potential in organic synthesis, the corresponding achievements were relatively fewer. Before our studies, only the ARO reactions of azabenzonorbornadienes with amines[3] and organic zinc reagents[4] were well established, generating the corresponding products for a wide range of substrates and with high enantioselectivities. Aryl boronic acids[5] and terminal alkynes[6] had been applied to react with azabenzonorbornadienes to generate the ring-opening products smoothly. However, bulky steric hindrance in nucleophiles seemed necessary to ensure high enantioselectivities. Catalyzed by iridium complexes, the ARO reactions of azabenzonorbornadienes with alcohols[7] and phenols[8] were also reported, but the results were not satisfactory due to low to moderate ee's obtained in many cases. The development of new and efficient catalysts or catalytic systems for ARO reactions of azabenzonorbornadienes is still interesting and necessary.

As a part of our ongoing research in the asymmetric chemistry of oxa/azabenzonorbornadienes, we have proven that the combinations of different chiral transitional-metal complexes with some Lewis acids could form highly efficient co-catalytic systems for the ARO reactions of not only oxabenzonorbornadienes[9] but also azabenzonorbornadienes.[10] During our study of the ARO reactions of azabenzonorbornadienes with alcohols, we serendipitously found that the reductive ring-opening products[11] were generated along with the additional ring-opening products. The reductive ring-opening products were found to be generated via a transfer-hydrogenation reaction with alcohols as the hydrogen source. Although the asymmetric transfer-hydrogenation reactions had been extensively studied by many groups,[12] the successful applications of primary alcohols as hydrogen source are still rare.[13] By fine-tuning the catalytic conditions, we realized the highly chemo-, regio-, and enantioselective control for these two ring-opening reactions. Herein, we describe the palladium/Lewis acid co-catalyzed divergent ARO reactions of azabenzonorbornadienes using a wide range of alcohols as nucleophiles and reductants, respectively (Scheme 1).

Scheme 1. Divergent ARO Reactions of Azabenzonorbornadienes with Alcohols



Our journey commenced with the ARO reactions of azabenzonorbornadienes **1a** with methanol by screening a suitable chiral ligand in the presence of $AgBF_4$ as a co-catalyst (Table 1). The initial test was carried out by (*R*)-Binap and gave the desired additional ring-opening product **3aa** in 89% yield with an enantiomeric excess of 92% (Table 1, entry 1). Surprisingly, a small amount of reductive ring-opening product **4a** was also generated in this reaction. By employing other bidentate chiral ligands, we noted that (*R*)-P-Phos led to an excellent reaction yield for **3aa** but lowered the enantiose-

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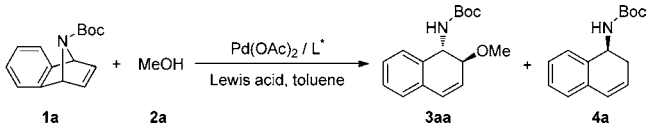
Table 1. Reaction Conditions Screening for the Divergent ARO Reactions[a]



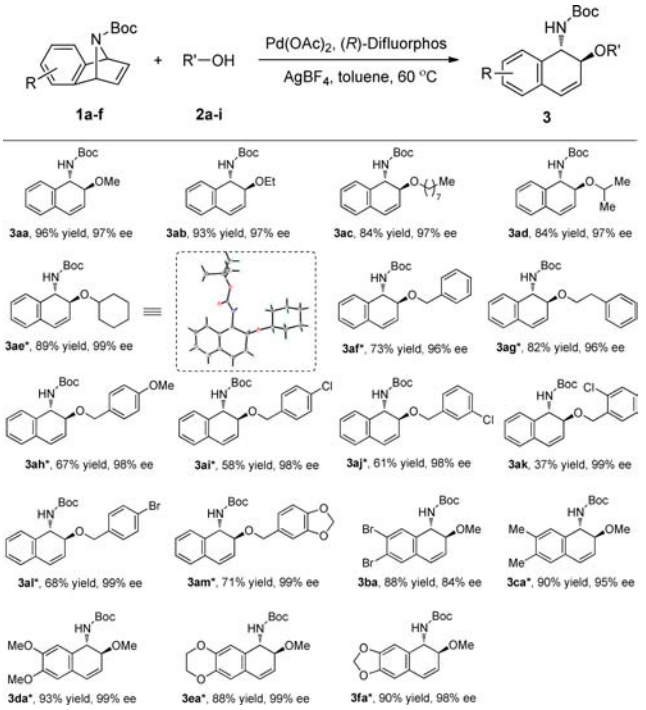
				3aa		4a	
entry	ligand	Lewis acid	time (h)	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)
1	(*R*)-Binap	$AgBF_4$	8	89	92	5	
2	(*R*)-P-Phos	$AgBF_4$	7	95	72	2	
3	(*R*)-SDP	$AgBF_4$	3	63	70	29	59
4	(*R*,*R*)-BDPP	$AgBF_4$	48	68	75	13	46
5	(*R*,*R*)-DIOP	$AgBF_4$	1.5	60	0	36	4
6	(*R*)-Phanephos	$AgBF_4$	1	34	79	65	60
7	(*R*)-Difluorphos	$AgBF_4$	5	96	97	trace	
8	(*R*)-Difluorphos	AgOTf	15	61	98	32	69
9	(*R*)-Difluorphos	CuOTf	48	20	97	76	68
10	(*R*)-Difluorphos	$Cu(OTf)_2$	8	83	97	16	70
11	(*R*)-Difluorphos	$Zn(OTf)_2$	26	42	96	55	71
12	(*R*)-Phanephos	$Zn(OTf)_2$	0.6	trace		94	93
13[d]	(*R*)-Phanephos	$Zn(OTf)_2$	1.5	trace		94	96

[a]Reaction conditions: $Pd(OAc)_2$ (0.01 mmol), Lewis acid (0.02 mol), and chiral ligand (0.012 mol) in toluene (1 mL) was stirred at room temperature for 30 min under Ar. **1a** (0.2 mmol) and **2a** (0.6 mmol) were added, and the reaction mixture was stirred at 60 °C for indicated period of time. [b]Yields were calculated on the basis of ^{1}H NMR using 1,3-benzodioxole as internal standard. [c]Determined by HPLC analysis. [d]The reaction was performed at 40 °C.

lectivity of the reaction (Table 1, entry 2), and the use of (*R*)-SDP, (*R*,*R*)-BDPP, and (*R*,*R*)-DIOP led to a dramatic decrease in both the yield and the enantioselectivity along with the generation of reductive ring-opening product **4a** (Table 1, entries 3−5). It is worth noting that when (*R*)-Phanephos was used as the chiral ligand the chemoselectivity of the reaction was reversed and **4a** became to the major product (Table 1, entry 6). To our delight, an excellent result was achieved by (*R*)-Difluorphos and afforded the asymmetric ring-opening product **3aa** exclusively in 96% yield with 97% ee (Table 1, entry 7). When the Lewis acid was switched to AgOTf and $Cu(OTf)_2$, **3aa** remained the major product (Table 1, entries 8 and 10). However, when CuOTf or $Zn(OTf)_2$ was used as the co-catalyst, the yields of **4a** increased to 76% and 55%, respectively (Table 1, entries 9 and 11). It could be seen that both the chiral ligand and Lewis acid can greatly affect the selectivity of the present reaction. (*R*)-Phanephos was then tested again in this reaction by employing $Zn(OTf)_2$ as the Lewis acid, since $Zn(OTf)_2$ is more economical than CuOTf. It was a delight that **4a** was afforded exclusively with excellent yield and enantioselectivity (Table 1, entry 12). Further experiments were carried out by screening other reaction parameters, such as reaction temperature and the amount of methanol, and a reaction temperature of 40 °C with 3 equiv of methanol were found to be the optimal conditions (Table 1, entry 13, see the Supporting Information for additional condition screening results and the chemical structures of the chiral ligands).

To investigate the scope of the additional ARO reaction, a set of alcohols were examined in the reaction of **1a**. As the results summarized in Scheme 2 show, excellent enantioselectivities were achieved and the reaction yields were generally moderate to high. For example, high yields were obtained by using simple primary alcohols, and the long-chain alcohols or secondary alcohols slightly lowered the reaction yields (Scheme 2, **3aa**−**ae**). The absolute configuration of the product **3ae** was assigned as 1*S*,2*S* by X-ray crystallographic analysis.[14] The aryl alcohols such as benzyl alcohol and 2-phenylethanol were also suitable nucleophiles for the present reaction (Scheme 2, **3af**−

Scheme 2. Scope of the Additional ARO Reactions[a]



[a]Reaction conditions: $Pd(OAc)_2$ (0.01 mmol), (*R*)-Difluorphos (0.012 mmol), and $AgBF_4$ (0.02 mmol) in toluene (1 mL) were stirred at room temperature for 30 min under Ar. **1a**−**f** (0.2 mmol) and **2a**−**i** (0.6 mmol) were added, and the reaction mixture was stirred at 60 °C. Yields refer to isolated yields of purified products. The enantiomeric excesses were determined by HPLC analysis using chiral stationary phases. *The reaction was performed at 40 °C.

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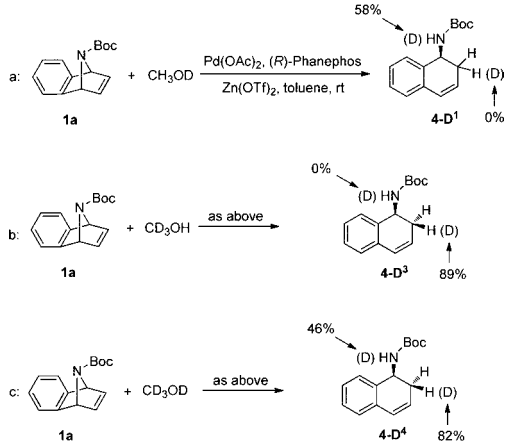
ag). Benzyl alcohols with different substitutions on the phenyl ring gave moderate yields, whereas 2-chlorobenzyl alcohol gave a low yield probably due to steric effects (Scheme 2, **3ah−am**). Various electronically modified azabenzonorbornadienes were synthesized and used for the substrate scope study of this additional ARO reaction. Except for dibromo-substitued azabenzonorbornadiene **1b** which gave a good yield but a relatively lower ee, all of the azabenzonorbornadienes were transformed to the corresponding ring-opening products in good yields and high ee's (Scheme 2, **3ba−fa**).

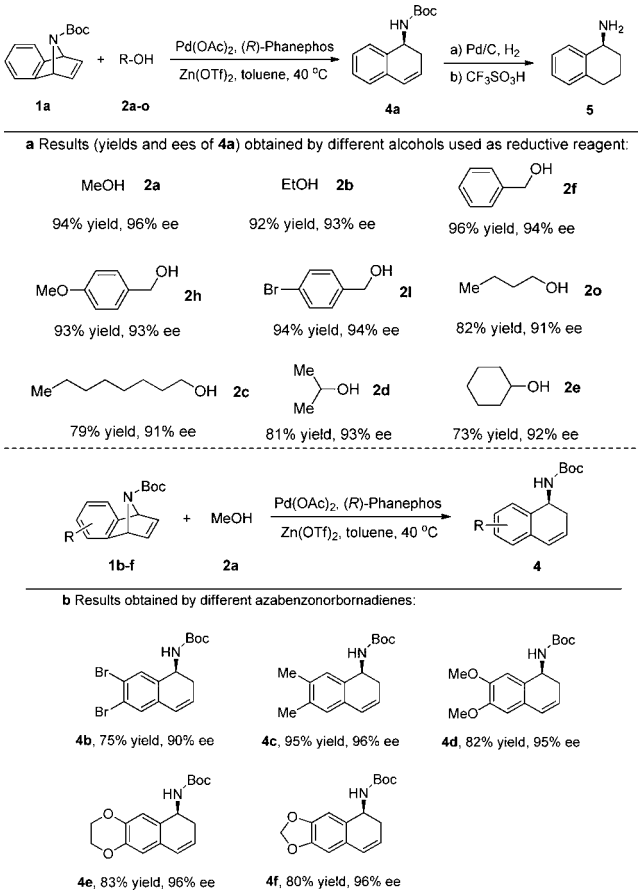
To shed light on the hydrogen source of the asymmetric ring-opening reaction that gives **4a**, several deuterium-labeling experiments were performed (Scheme 3). When CH_3OD was employed, deuterium was only incorporated into the amine group of the product (Scheme 3, a). When this reaction was performed with CD_3OH, about 89% deuterium was found in the 1,2-dihydronaphthalene structure of the product (Scheme 3, b). This result indicates that the hydrogen atom on the 1,2-dihydronaphthalene moiety was derived exclusively from the methyl group of CH_3OD. Another deuterium-labeling experiment that was carried out with CD_3OD showed 82% deuterium incorporated into the 1,2-dihydronaphthalene moiety and 46% deuterium incorporated into the amine group; this result was inconsistent with the former experiments (Scheme 3, c). Thus, was proven that the product **4a** was generated from a transfer-hydrogenation process employing methanol as hydrogen source. To the best of our knowledge, this represents the first example of a highly enantioselective transfer-hydrogenation reaction with methanol as reductant.

Scheme 3. Deuterium-Labeling Experiments



With the optimal reaction conditions of reductive ARO reaction of azabenzonorbornadiene in hand (Table 1, entry 13), a wide range of alcohols were subsequently tested as hydrogen sources. As shown in Scheme 4, simple primary alcohols (methanol and ethanol) and benzyl alcohols reacted with **1a** smoothly to generate the reductive product **4a** in good yields and with high enantioselectivities. It should be noted that benzaldehyde (19 mg, 0.18 mmol), which was the oxidative product of benzyl alcohol, was also isolated from the reaction mixtures when benzyl alcohol was used as reductant. Primary alcohols with long chains, as well as secondary alcohols, could also serve as suitable hydrogen sources with high enantioselectivities. To determine the absolute configuration of product **4a**, it was converted to **5**, which agreed with the commercially available chemical (*S*)-1,2,3,4-tetrahydro-1-naphthylamine by

Scheme 4. Scope of the Reductive ARO Reactions[a]



[a]Reaction conditions: $Pd(OAc)_2$ (0.01 mmol), (*R*)-Phanephos (0.012 mmol), and $Zn(OTf)_2$ (0.02 mmol) in toluene (1 mL) was stirred at room temperature for 30 min under Ar. **1a** (0.2 mmol) and **2a** (1.0 mmol) were added, and the reaction mixture was stirred at 40 °C. Yields refer to isolated yields of purified products. The enantiomeric excesses were determined by HPLC analysis using chiral stationary phases.

HPLC analysis. To study the substituent effects on azabenzonorbornadiene substrates, derivatives with various substituted groups on the phenyl ring were subsequently tested by employing methanol as reductant. In general, high enantioselectivities were obtained for all of the substrates, and the features of substitution groups mainly affected reaction yields. For example, an excellent result was obtained by using dimethyl-substituted azabenzonorbornadiene (Scheme 4, **4c**), and the bromo groups remained intact in the product, enabling further elaboration (Scheme 4, **4b**). Although the dimethoxy-substituted substrate **1c** showed good performance (Scheme 4, **4c**), strong electron-donating groups slightly reduced the reaction yields (Scheme 4, **4d−f**).

In conclusion, the additional ring-opening products and the reductive ring-opening products were generated, respectively, by the reactions of azabenzonorbornadienes with alcohols in high yields with high enantioselectivities. The two corresponding ARO reactions showed wide substrates scope and good functional group tolerance. A transfer-hydrogenation procedure was proven in this reductive reaction, and alcohols played the role of reductants.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02300.

Optimization tables, experimental details, proposed mechanism, characterization data, and X-ray analyses (PDF)

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Author Contributions

†F.Y. and J.C. contributed equally.

Notes

The authors declare no competing financial interest.

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(14) X-ray crystallographic data of **3ae** have been deposited with the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk/) under accession code CCDC 1436042.

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