JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Asymmetric Dearomatization of Naphthols via a Rh-Catalyzed C(sp^2)−H Functionalization/Annulation Reaction

Jun Zheng, Shao-Bo Wang, Chao Zheng, and Shu-Li You*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

Supporting Information

ABSTRACT: A Rh-catalyzed enantioselective dearomatization of 1-aryl-2-naphthols with internal alkynes via C−H functionalization reaction was achieved. In the presence of a chiral Cp/Rh catalyst and combined oxidants of $Cu(OAc)_2$ and air (oxygen), various highly enantioenriched spirocyclic enones bearing an all-carbon quaternary stereogenic center could be synthesized in 33−98% yields with up to 97:3 er.

Phenol and naphthol derivatives are among the most abundant chemical feedstocks in industry and serve as versatile building blocks for the synthesis of complex target molecules.[1] In contrast to the traditional transformations of phenols and naphthols based on aromatic substitutions, which generally lead to planar aromatic products, catalytic asymmetric dearomatization (CADA) reactions of phenols and naphthols have attracted considerable attention and emerged as novel enabling methods for rapid construction of highly functionalized three-dimensional structures, which significantly increased the chemical diversity.[2] Although great efforts have been devoted to development in this area, most dearomatization reactions of phenols and naphthols still rely on the transformation of certain functional groups which inevitably require additional steps for pre-functionalization.[3] To the best of our knowledge, no catalytic asymmetric dearomatization reaction initiated by direct functionalization of inert C−H bonds has appeared.[4]

In 2013, Luan and co-workers[5] reported the first Ru-catalyzed C−H functionalization/vinylative dearomatization of naphthols for the synthesis of various spirocyclic molecules in good yields and excellent regioselectivity (Figure 1, eq 1). Later, Mascareñas and Gulías[6a] and Lam [6b] independently developed Rh-catalyzed annulative dearomatization of *ortho*-vinylphenols triggered by terminal C−H functionalization of the alkenyl moiety (Figure 1, eq 2). More recently, the Luan group[7] described a Pd-catalyzed [2+2+1] spiroannulation reaction between β-naphthols and 2 equiv of alkynes (Figure 1, eq 3). Despite these elegant advances, the reports on transition-metal-catalyzed annulative dearomatization of phenols and naphthols initiated with C−H functionalization step are still limited to racemic reactions.

In 2014, we reported an asymmetric C−H functionalization/dehydrogenative Heck coupling between biaryl compounds and alkenes to synthesize axially chiral products.[8] The chiral Rh catalysts developed by the Cramer group were found capable of inducing good enantioselective control under relatively harsh conditions required for the C−H bond functionalization step.[9] Herein, we describe the first asymmetric annulative dearomatization reaction of β-naphthols with alkynes initiated with C−H functionalization by chiral Rh catalyst (Figure1, eq 4).[10]

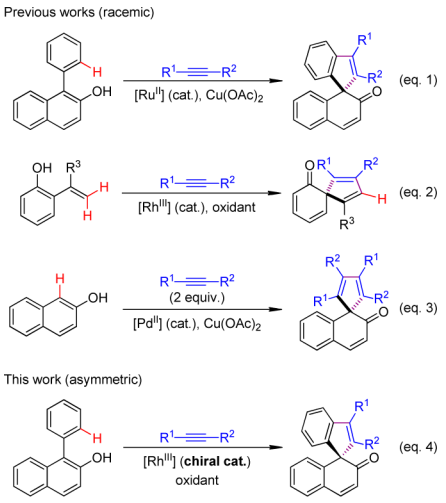


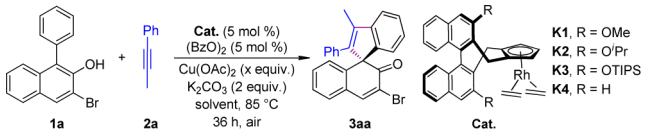
Figure 1. C−H bond functionalization/dearomatization reactions.

The study was launched by utilizing 3-bromo-1-phenylnaphthalen-2-ol (**1a**) and prop-1-ynylbenzene (**2a**) as the model substrates to optimize the reaction conditions (Table 1). In the presence of 5 mol % of chiral Rh complex **K1** and $(BzO)_2$, and 3 equiv of $Cu(OAc)_2$, the C−H functionalization/annulation reaction could proceed to provide **3aa** in 45% NMR yield and 92:8 er (entry 1). Interestingly, similar results were obtained when the reaction was conducted under air (entry 2). Lowering the reaction temperature to 85 °C led to an increase of yield and enantioselectivity (entry 3), and 1 equiv of $Cu(OAc)_2$ was found to be sufficient (entry 4). Varying the solvents showed great influence on the reactivity of the reaction, but less impact on the enantioselective control (entries 6−9). Toluene was found to be optimal solvent (entry 7), affording **3aa** in 93% yield, 95:5 er, and 17:1 regioselectivity (rr). Further examination of different chiral Cp/Rh complexes and reaction temperature did not provide better results (entries 10−13). The yield of the reaction was decreased dramatically in the absence of $Cu(OAc)_2$ (entry 14). No

Received: February 14, 2015
Published: April 8, 2015

DOI: 10.1021/jacs.5b01707
J. Am. Chem. Soc. 2015, 137, 4880−4883

Table 1. Optimization of the Reaction Conditions[a]



entry	x	solvent	cat.	yield (%)[b]	er[c]
1[d]	3	1,4-dioxane	**K1**	45	92:8
2[e]	3	1,4-dioxane	**K1**	49	92:8
3	3	1,4-dioxane	**K1**	74	95:5
4	1	1,4-dioxane	**K1**	80 (72)	95:5
5	0.5	1,4-dioxane	**K1**	70	94:6
6	1	DME	**K1**	29	92:8
7[f]	***1***	***toluene***	***K1***	***93 (81)***	***95:5***
8	1	DCE	**K1**	19	92:8
9	1	*t*-AmylOH	**K1**	21	87:13
10	1	toluene	**K2**	47	88:12
11	1	toluene	**K3**	31	88:12
12	1	toluene	**K4**	88	69:31
13[g]	1	toluene	**K1**	80	95:5
14	0	toluene	**K1**	19	89:11

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), cat. (5 mol %), $(BzO)_2$ (5 mol %), K_2CO_3 (2 equiv), and $Cu(OAc)_2$ in solvent at 85 °C for 36 h under air (open flask), unless otherwise noted. [b]Determined by ^1H NMR analysis with CH_2Br_2 as an internal standard. Isolated yields are reported in parentheses. [c]Determined by HPLC analysis. [d]Reflux under Ar. [e]At 110 °C. [f]Regioselectivity was determined as 17:1. [g]At 70 °C for 58 h.

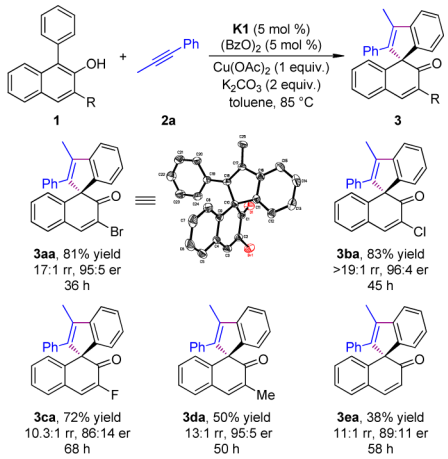
reaction occurred without the addition of Rh catalyst. Finally, the optimal reaction conditions were identified as the following: 5 mol % of **K1**, 5 mol % of $(BzO)_2$, 1 equiv of $Cu(OAc)_2$ and 2 equiv of K_2CO_3 at 85 °C in toluene under air (entry 7). The absolute configuration of product **3aa** was assigned as *S* by an X-ray crystallographic analysis (for details, see the Supporting Information).

With the optimized reaction conditions in hands, we next investigated the substrate scope of the reaction. The effects of various substituents on the 3-position of naphthols were first evaluated (Scheme 1). The reactions worked well with naphthols bearing Cl and F atoms, affording **3ba** (83% yield, >19:1 rr, 96:4 er) and **3ca** (72% yield, 10.3:1 rr, 86:14 er), respectively. However, when a methyl group was introduced (**1d**) or simple naphthol (**1e**) was used, the reactions proceeded with good regio- and enantioselectivity but moderate yields.

Next, various alkynes (**2b**−**2j**) were examined in the reaction with 3-chloro-1-phenylnaphthalen-2-ol (**1b**) (Scheme 2). Unsymmetrical alkynes bearing ethyl and cyclopropyl groups (**2b**, **2c**) both led to their corresponding dearomatized products in excellent enantioselectivity (96:4−97:3 er), moderate to good yields (74−88%), and good regioselectivity (7.1:1−14.5:1 rr). Symmetrical alkynes bearing various aromatic groups in spite of electronic property were tolerated well, and the corresponding spirocyclic products (**3bd**−**3bi**) were obtained in moderate to good yields (54−86%) with excellent enantioselectivity (96:4−97:3 er). Satisfactorily, a gram-scale reaction between **1b** and **2d** proceeded smoothly without affecting the reaction outcome. Notably, dialkylacetylene (**2j**) could undergo this transformation, leading to **3bj** in excellent yield (98%) and good enantioselectivity (92:8 er).

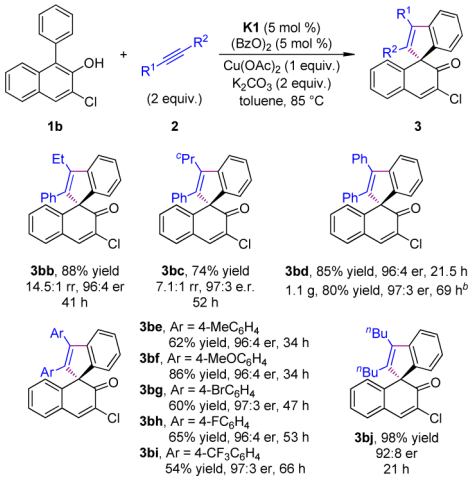
In addition, various substituted 1-aryl-2-naphthol derivatives (**1f**−**1q**) were examined with diphenylacetylene (**2d**) as the

Scheme 1. Substrate Scope: 3-Substituted *β*-Naphthols[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), **K1** (5 mol %), $(BzO)_2$ (5 mol %), K_2CO_3 (2 equiv), and $Cu(OAc)_2$ (1 equiv) in toluene at 85 °C under air (open flask). Regioselectivity (rr) was determined by ^1H NMR analysis of the crude reaction mixture. Yields of isolated products are reported. Enantioselectivity (er) was determined by HPLC analysis.

Scheme 2. Substrate Scope: Alkynes[a]

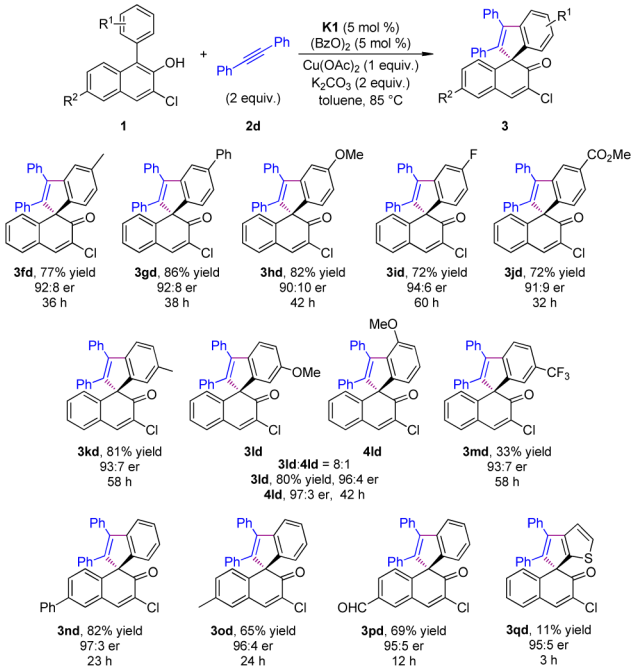


[a]Reaction conditions: **1b** (0.2 mmol), **2** (0.4 mmol), **K1** (5 mol %), $(BzO)_2$ (5 mol %), K_2CO_3 (2 equiv) and $Cu(OAc)_2$ (1 equiv) in toluene at 85 °C under air (open flask). Regioselectivity (rr) was determined by ^1H NMR analysis of the crude reaction mixture. Yields of isolated products are reported. Enantioselectivity (er) was determined by HPLC analysis. [b]3.2 mmol **1b** and 6.4 mmol **2d** were used.

coupling partner (Scheme 3). Either an electron-donating or electron-withdrawing group (Me, Ph, OMe, F, and CO_2Me) at the *para*-position of the phenyl ring (**1f**−**1j**) was well tolerated, and the desired products were obtained in good yields (72−86%) and enantioselectivity (90:10−94:6 er). While substrate **1k**, bearing 3-methylphenyl, led to the desired product in 81% yield, substrate **1m**, bearing 2-(trifluoromethyl)phenyl, gave only 33% yield. In both cases, good enantiomeric ratio was obtained (**3kd**, **3md**, 93:7 er). Notably, because of the secondary directing effect of the methoxyl group,[9d] substrate **1l**, containing 3-methoxylphenyl substituent, gave 8:1 regioselectivity with excellent enantioselectivity (96:4 and 97:3 er) for both regioisomers. To our delight, the introduction of varied

DOI: 10.1021/jacs.5b01707
J. Am. Chem. Soc. 2015, 137, 4880−4883

Scheme 3. Substrate Scope: Substituted β-Naphthols[a]

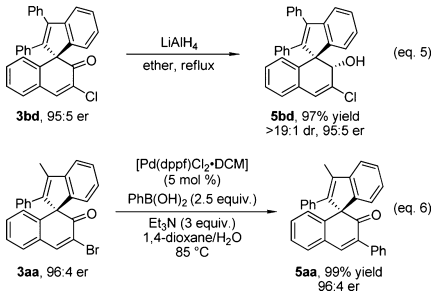


[a]Reaction conditions: **1** (0.2 mmol), **2d** (0.4 mmol), **K1** (5 mol %), $(BzO)_2$ (5 mol %), K_2CO_3 (2 equiv), and $Cu(OAc)_2$ (1 equiv) in toluene at 85 °C under air (open flask). Yields of isolated products are reported. Er was determined by HPLC analysis.

substituents (Ph, Me, CHO) on the 6-position of the naphthalene ring (**1n**−**1p**) were tolerated well, affording products in good yields and excellent enantiomeric ratios. The compatibility of the formyl group further enhanced potentials of the diverse transformation of the product. The reaction involving heterocycle substrate containing a thienyl ring (**1q**) could also provide the expected product (**3qd**) with excellent enantiomeric ratio (95:5 er), albeit in low yield.

To demonstrate the synthetic utility of the method, several transformations of the 2-naphthalenone products were carried out (Scheme 4). The ketone group in **3bd** could be reduced

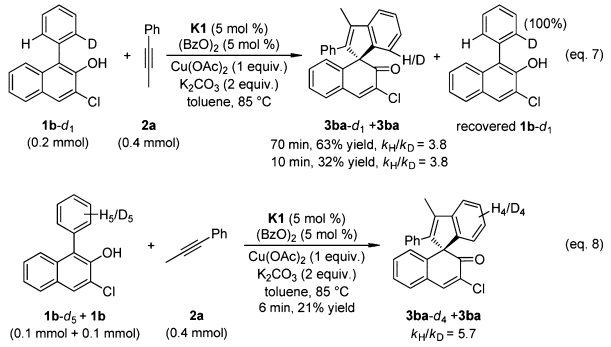
Scheme 4. Transformations of the Products



with $LiAlH_4$ to afford allylic alcohol **5bd** in excellent yield and diastereoselectivity (eq 5). The Suzuki−Miyaura coupling between bromo-containing product **3aa** and $PhB(OH)_2$ gave **5aa** in quantitative yield (eq 6).

To shed light on the mechanism of the Rh-catalyzed asymmetric annulative dearomatization reaction, deuterium-labeling experiments were performed (Scheme 5). The intramolecular competitive experiment of monodeuterated analogue **1b**-d_1 with prop-1-ynylbenzene (**2a**) under standard

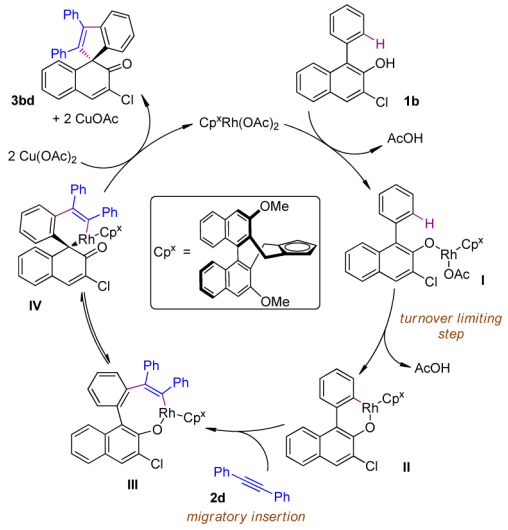
Scheme 5. Deuteration Experiments



conditions resulted in no H/D scrambling in the recovered starting material, which suggested that the C−H bond cleavage step is irreversible. A kinetic isotope effect ($k_H/k_D \approx 3.8$) was observed at different reaction stages (eq 7). In addition, the kinetic isotope effect ($k_H/k_D \approx 5.7$) was also observed in an intermolecular competitive experiment (eq 8). These observations indicate that C−H bond cleavage is most likely involved in the rate-limiting step.

Based on the above mechanistic information and previous reports,[5,6] a putative mechanism for the reaction is proposed (Scheme 6). The catalytic cycle likely begins with the

Scheme 6. Proposed Mechanism



deprotonation of the β-naphthol substrates by the Rh catalyst. The obtained intermediate **I** subsequently undergoes C−H bond activation, leading to the rhodacycle **II**. Alkyne coordination and migratory insertion gives a rather strained eight-membered rhodacycle **III**, which might be in equilibrium with a six-membered isomer **IV**. Finally, the dearomatized product is obtained after reductive elimination, and the released Rh(I) species is concomitantly oxidized by $Cu(OAc)_2$ and oxygen to the activated Rh(III) catalyst, completing the catalytic cycle.

In summary, we have achieved the first asymmetric C−H functionalization/dearomatization reaction of β-naphthol derivatives by a chiral Rh catalyst. The reaction allows the transformation of simple naphthol derivatives into chiral spirocyclic β-naphthalenones bearing an all-carbon quaternary

DOI: 10.1021/jacs.5b01707
J. Am. Chem. Soc. 2015, 137, 4880−4883

stereogenic center in good to excellent yields and regio- and enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data, including spectra and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*slyou@sioc.ac.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Basic Research Program of China (973 Program 2015CB856600) and the National Natural Science Foundation of China (21421091 and 21332009) for generous financial support. We are also greatly indebted to Prof. Tian-Sheng Mei and Prof. Guosheng Liu for their helpful discussions. This paper is dedicated to Prof. Xue-Long Hou on the occasion of his 60th birthday.

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