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Communication

Asymmetric Dearomatization of Naphthols via a Rh-Catalyzed C(sp2)–H Functionalization/Annulation Reaction

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

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Supporting Information Placeholder

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, the catalytic asymmetric dearomatization 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 the development in this area, yet 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, catalytic asymmetric dearomatization reaction initiated with direct functionalization of inert C–H bonds has not appeared.[4]

In 2013, Luan and coworkers[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] as well as Lam[6b] independently developed Rh-catalyzed annulative dearomatization of *ortho*-vinyl phenols 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 two equivalents 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 within 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 wish to 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]

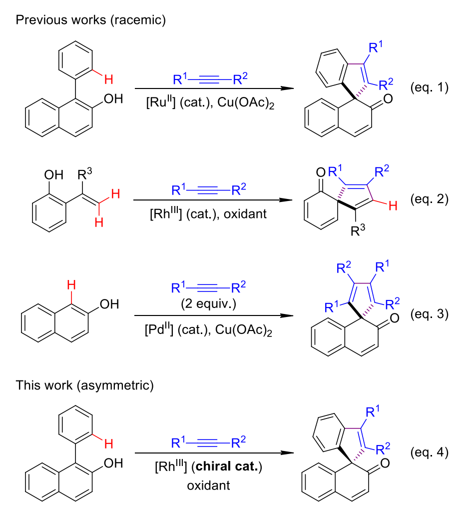
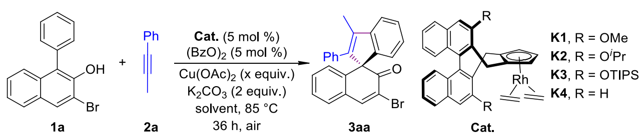


Figure 1. C–H bond functionalization/dearomatization reactions.

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 equivalents 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 ℃ led to an increase of yield and enantioselectivity (entry 3), and 1 equivalent 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 affording **3aa** in 93% yield, 95:5 er and 17:1 regioselectivity (entry 7). 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 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 equivalent of $Cu(OAc)_2$ and 2 equivalents of K_2CO_3 at 85 ℃ in toluene under air (entry 7). The absolute configuration of product **3aa** was assigned as *S* by an Xray crystallographic analysis (for details, see the Supporting Information).

Table 1. Optimization of the reaction conditions.[a]

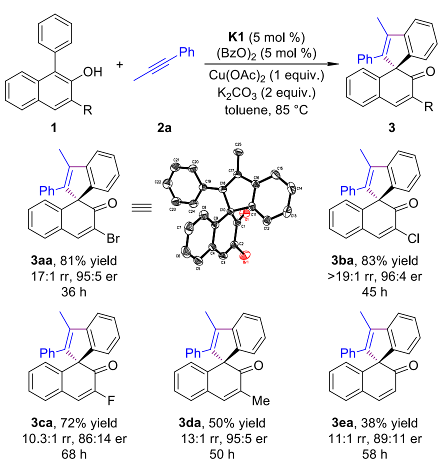


entry	x	solvent	**Cat.**	yield (%)[b]	er[c]
1[d]	3	1,4-dioxane	**K1**	45	92:8
2[e]	3	1,4-dioxane	**K1**	49	92:8
3	3	1,4-dioxane	**K1**	74	95:5
4	1	1,4-dioxane	**K1**	80 (72)	95:5
5	0.5	1,4-dioxane	**K1**	70	94:6
6	1	DME	**K1**	29	92:8
7[f]	**1**	**toluene**	**K1**	**93 (81)**	**95:5**
8	1	DCE	**K1**	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 ℃ for 36 h under air (open flask), unless otherwise noted. [b] Determined by ^{1}H 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.

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 in good regio- and enantioselectivity but moderate yields.

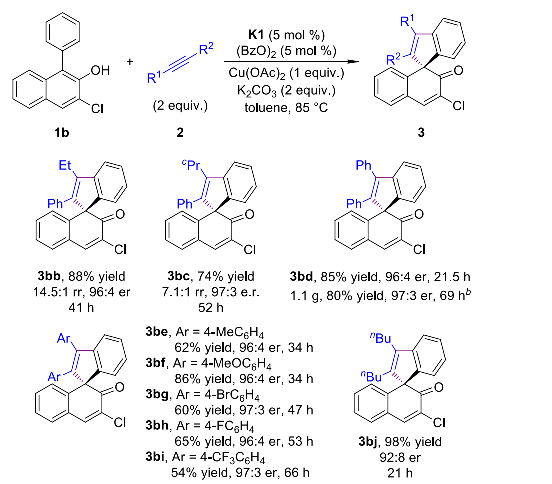
Scheme 1. Substrate scope: 3-substituted *β*-naphthols.[a]



[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 ℃ under air (open flask). Regioselectivity (rr) was determined by ^{1}H NMR analysis of the crude reaction mixture. Yields of isolated products are reported. Er was determined by HPLC analysis.

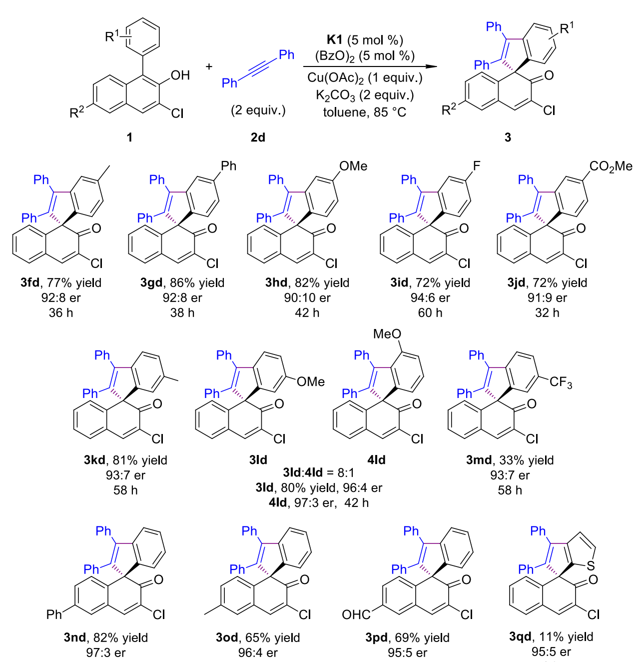
Next, various alkynes (**2b**-**2j**) were examined in the reaction with 3-chloro-1-phenylnaphthalen-2-ol (**1b**) (Scheme 2). Unsymmetrical alkynes bearing ethyl and cyclopropyl groups (**2b** and **2c**) both led to their corresponding dearomatized products in excellent enantioselectivity (96:4-97:3 er), moderate to good yields (74-88%) and good regioselectivity (7.1:1-14.5:1). 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 enantioselective control (92:8 er).

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 ℃ under air (open flask). Regioselectivity (rr) was determined by ^{1}H NMR analysis of the crude reaction mixture. Yields of isolated products are reported. Er was determined by HPLC analysis. [b] 3.2 mmol **1b** and 6.4 mmol **2d** were used.

Scheme 3. Substrate scope: substituted *β*-naphthols.[a]

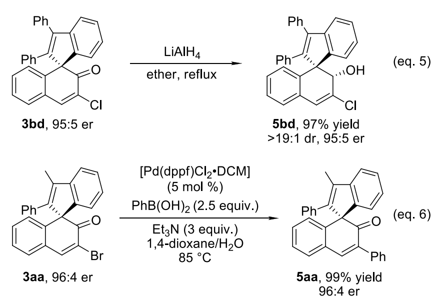


[a] Reaction conditions: **1** (0.2 mmol), **2d** (0.4 mmol), **K1** (5 mol %), $(BzO)_2$ (5 mol %), K_2CO_3 (2 equiv.) and $Cu(OAc)_2$ (1 equiv.) in toluene at 85 ℃ under air (open flask). Yields of isolated products are reported. Er was determined by HPLC analysis.

In addition, various substituted 1-aryl-2-naphthol derivatives (**1f**-**1q**) were examined with diphenylacetylene (**2d**) as the coupling partner (Scheme 3). Either electron-donating or electron-withdrawing group (Me, Ph, OMe, F and CO_2Me) at the *para*-position of 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-methyl phenyl led to the desired product in 81% yield, substrate **1m** bearing 2-trifluoromethyl phenyl only gave 33% yield. In both cases, good enantiomeric ratio was obtained (**3kd**, **3md**, 93:7 er). To be noted, because of the secondary directing effect of methoxyl group,[9d] substrate **1l** containing 3-methoxyl phenyl substituent gave 8:1 regioselectivity with excellent enantioselectivity (96:4 and 97:3 er) for both regioisomers. To our delight, the introduction of varied substituents (Ph, Me, CHO) on the 6-position of naphthalene ring (**1n**, **1o, 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 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).

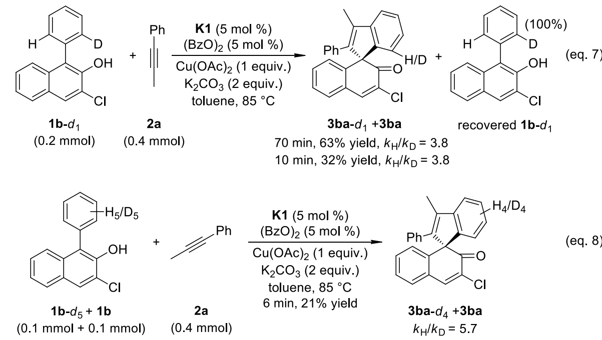
Scheme 4. Transformations of the products.



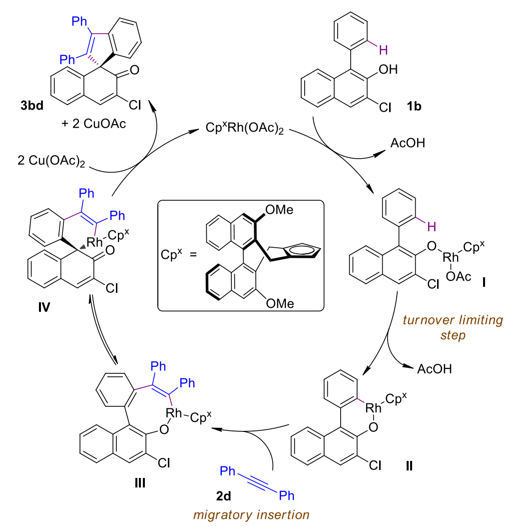
To shed light on the mechanism of the Rh-catalyzed asymmetric annulative dearomatization reaction, deuterium-labeling experiments were performed (Scheme 5). The intramolecular competitive experiment of monodeuterated analogue **1b**-d_1 with prop-1-ynylbenzene (**2a**) under standard conditions resulted 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~3.8) was observed at different reaction stages (eq. 7). In addition, the kinetic isotope effect (k_H/k_D~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 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, furnishing the catalytic cycle.

Scheme 5. Deuteration Experiments.



Scheme 6. Proposed mechanism.



In summary, we have achieved the first asymmetric C–H functionalization/dearomatization reaction of β-naphthol derivatives by a chiral rhodium catalyst. The reaction allows the transformation of simple naphthol derivatives into chiral spirocyclic β-naphthalenones bearing an all-carbon quaternary stereogenic center in good to excellent yields, regio- and enantioselectivity.

ASSOCIATED CONTENT

Supporting Information

Text, figures, and CIF files giving experimental procedures, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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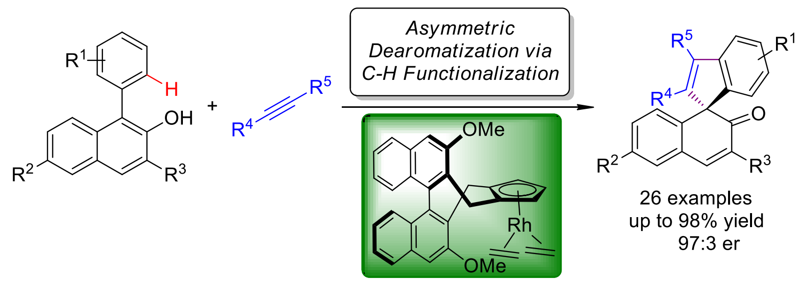
TOC Graphic


Asymmetric
Dearomatization via
C-H Functionalization
26 examples
up to 98% yield
97:3 er