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Rhodium(III)-Catalyzed Synthesis of Naphthols via C−H Activation of Sulfoxonium Ylides

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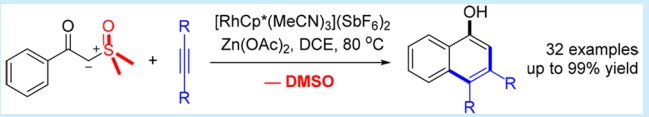
Supporting Information

ABSTRACT: Direct and efficient synthesis of 1-naphthols has been realized via Rh(III)-catalyzed C−H activation of sulfoxonium ylides and subsequent annulation with alkynes, where the sulfoxonium ylide functioned as a new traceless bifunctional directing group. This reaction occurred under redox-neutral conditions with a broad substrate scope.



Naphthols are among the most versatile organics in organic synthesis,[1] and they are ubiquitously embedded in a large number of natural products and pharmaceuticals such as korupensamine A,[2] mollugin,[3] and gossypol (Figure 1).[4] As a consequence, general methods for the synthesis of such molecules have long been regarded as an important objective in synthetic organic chemistry.[5] Despite the well-established methodologies, it is attractive to employ the C−H activation strategy for straightforward and atom-economic access to naphthols.

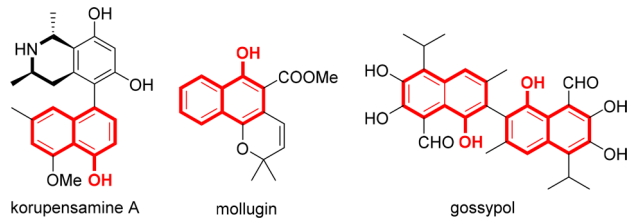
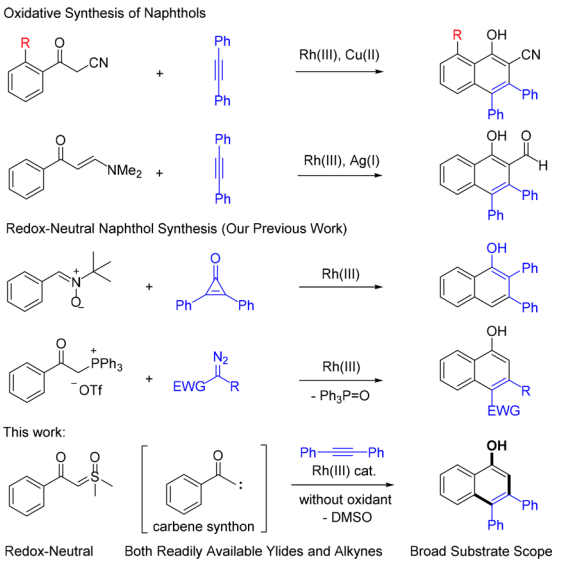


Figure 1. Bioactive compounds containing a 1-naphthol moiety.

Transition metals, especially Cp*Rh(III) complexes, represent state-of-the-art catalysts for activation of inert C−H bonds[6] en route to eventual annulation and construction of heterocycles[7] and carbocycles.[8] However, approaches to synthesize naphthols via C−H activation are still limited. Wang and co-workers reported Rh(III)-catalyzed oxidative annulation of *ortho*-substituted benzoylacetonitrile with alkynes for 1-naphthol synthesis (Scheme 1).[9] Zhu's group applied enaminones as an effective arene in the coupling with alkynes to access 2-formylnaphthol derivatives under oxidative conditions.[10] Despite these important advances, both reaction systems are limited to the employment of stoichiometric metal oxidants. Very recently, our group has described redox-neutral coupling of nitrones with cyclopropenones under redox-neutral Rh(III) catalysis for efficient construction of 2,3-substituted 1-naphthols.[11] However, access to cyclopropenones is not trivial. Thereafter, we achieved redox-neutral annulation of phosphonium ylides with reactive diazo compounds.[12] To overcome these limitations and to realize the construction of naphthols in an economic and green fashion, development of efficient methods using readily available starting materials is of great significance. Our strategy is to employ a carbene synthon for the arene. We now report Rh(III)-catalyzed C−H activation of sulfoxonium ylides[13] and annulation with simple alkynes as a practical and general method for the synthesis of 3,4-substituted 1-naphthols.

Scheme 1. Rh-Catalyzed 1-Naphthol Synthesis



We initiated our studies by exploring the coupling of ylide **1a** with diphenylacetylene **2a** in the presence of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ (Table 1). The coupling in DCE at 100 °C afforded the desired product **3aa** in 62% yield (entry 1). With CsOAc or HOPiv being an additive, the yields of **3aa** decreased dramatically

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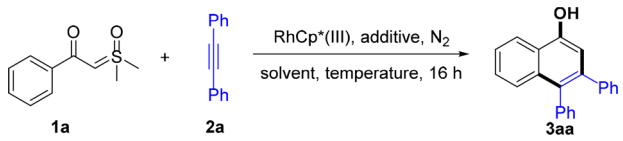
Table 1. Optimization of Reaction Conditions.[a]



entry	catalyst (mol %)	additive (mol %)	solvent	t (°C)	yield (%)[b]
1	$[Cp^*RhCl_2]_2$ (4)	$AgSbF_6$ (16)	DCE	100	62
2	$[Cp^*RhCl_2]_2$ (4)	$AgSbF_6$ (16)/CsOAc (200)	DCE	100	15
3	$[Cp^*RhCl_2]_2$ (4)	$AgSbF_6$ (16)/HOPiv (200)	DCE	100	37
4	$[Cp^*RhCl_2]_2$ (4)	$AgNTf_2$ (16)	DCE	100	56
5	$[Cp^*RhCl_2]_2$ (4)	$AgSbF_6$ (16)	DCE	80	75
6	$[Cp^*RhCl_2]_2$ (4)	$AgSbF_6$ (16)	DCM	80	68
7	$[Cp^*RhCl_2]_2$ (4)	$AgSbF_6$ (16)/$Zn(OAc)_2$ (10)	DCE	80	85
8	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (8)	$Zn(OAc)_2$ (10)	DCE	80	92
9	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (8)	$Cu(OAc)_2$ (10)	DCE	80	60
10	**$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (6)**	**$Zn(OAc)_2$ (10)**	**DCE**	**80**	**94**
11	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (4)	$Zn(OAc)_2$ (10)	DCE	80	89
12		$Zn(OAc)_2$ (10)	DCE	80	NR[c]
13	$[Cp^*RhCl_2]_2$ (4)	$Zn(OAc)_2$ (10)	DCE	80	58

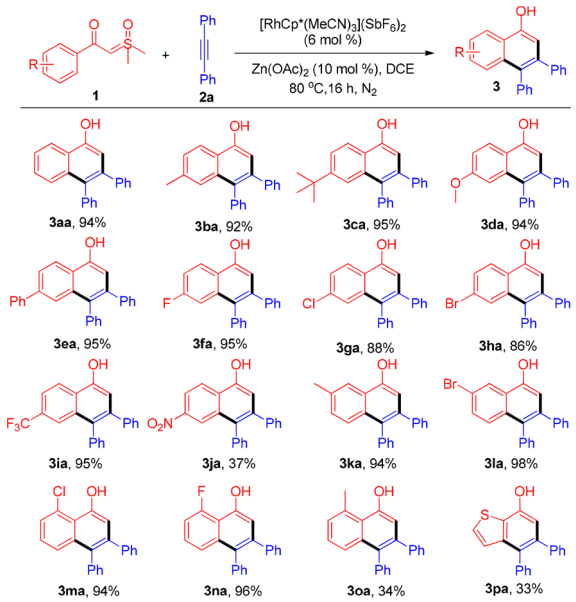
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), catalysis, additives, in solvent (4 mL), sealed tube under N_2 for 16 h. [b]Yield of isolated product. [c]No reaction.

(entries 2 and 3). A lower yield was delivered when $AgNTf_2$ was used as a halide scavenger (entry 4). Lowering the reaction temperature to 80 °C afforded **3aa** in 75% yield (entry 5). Then the effect of the solvent was examined, and DCE gave the best yield. Introduction of $Zn(OAc)_2$ (10 mol %) as an additive increased the yield to 85% (entry 7), which likely facilitates C−H activation and activates the sulfoxonium ylide. Delightfully, switching the catalyst to $[Cp^*Rh(MeCN)_3](SbF_6)_2/Zn(OAc)_2$ afforded **3aa** in 92% yield (entry 8), whereas a similar yield was still obtainable when the catalyst loading was lowered to 6 mol % (entries 10 and 11). A control experiment revealed that no reaction occurred in the absence of a rhodium catalyst (entry 12). Moreover, SbF_6^- proved to be an optimal counterion in this system (entry 13).

With the optimal reaction conditions in hand, we next sought to evaluate the scope and generality of the sulfoxonium ylides in this catalytic system. As given in Scheme 2, a wide range of sulfoxonium ylides underwent smooth annulation under the optimal conditions. Ylides with electron-donating and -withdrawing substituents (including alkyl, halides, nitro and trifluoromethyl substituents) at the 4-position all reacted with excellent efficiencies (37−95%). The coupling occurred at the less hindered *ortho* site for *m*-methyl and -bromo-substituted arenes (**3ka** and **3la**). In addition, the reaction has been extended to *o*-substituted sulfoxonium ylides (**3ma**, **3na**, and **3oa**), indicating tolerance of steric hindrance. Furthermore, a thiophene ring also coupled, albeit in lower yield.

The scope of alkynes was next examined (Scheme 3). Symmetric diarylacetylenes bearing various electron-donating and -withdrawing substituents such as methyl, methoxy, halogen, and trifluoromethyl groups at the 4-position all coupled smoothly with **1a** in excellent yields (**3ab**−**3ag**). This reaction is also compatible with *meta*-fluoro- or *meta*-methyl-substituted diarylacetylene, from which products **3ah** and **3ai** were isolated in 91 and 96% yields, respectively. Notably, 1,2-bis(2-fluorophenyl)ethyne gave an excellent yield (**3aj**, 99%). The alkynes can also be extended to heteroaryl substitution, including 1,2-di(thiophen-2-yl)ethyne in good yield (**3ak**). In addition, unsymmetric alkyl−aryl alkynes were also applicable, mostly with

Scheme 2. Scope of Sulfoxonium Ylide[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.22 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (6 mol %) and $Zn(OAc)_2$ (10 mol %) in DCE (4 mL) at 80 °C for 16 h under a N_2 atmosphere. [b]Isolated yields.

good to excellent regioselectivity (**3al**−**3aq**). Unfortunately, alkyl−alkyl alkyne failed to undergo any desired reaction.

To demonstrate synthetic utility of the reaction, a gram-scale reaction between **1a** and **2a** has been performed (Scheme 4), and the product **3aa** was isolated in an excellent yield (Scheme 4a). Moreover, naphthol **3aa** was readily converted to the corresponding triflate **4a** in 94% yield, which proved to be a useful building block in transition-metal-catalyzed cross-couplings. Thus, both the alkynyl (**5a**) and alkenyl (**5b**) groups could be efficiently installed into the naphthyl motif in excellent yields via Sonogashira and Heck reactions, respectively (Scheme 4b).

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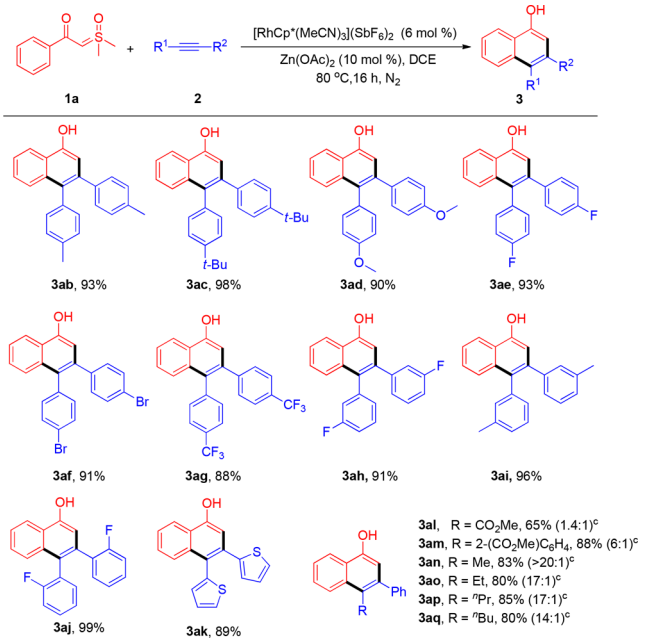
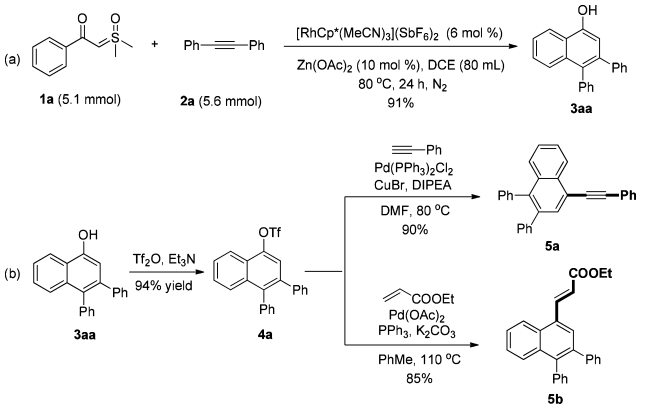
Scheme 3. Scope of Alkynes[a,b]



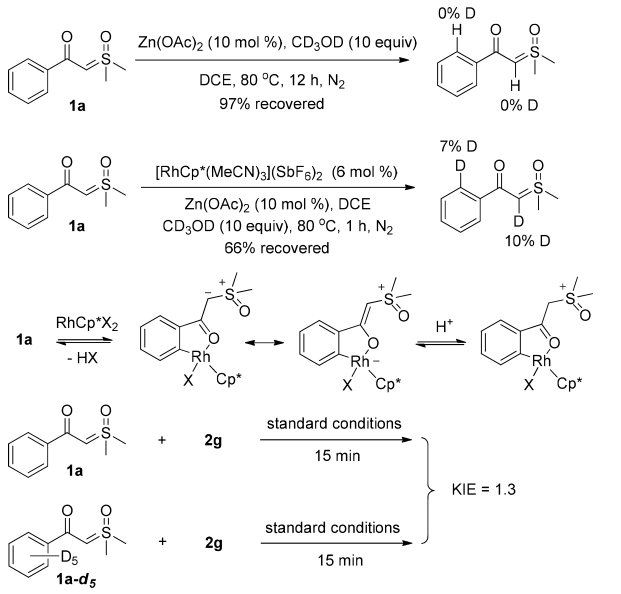
[a]Reaction conditions: **1a** (0.2 mmol), alkyne (0.22 mmol), [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ (6 mol %) and Zn(OAc)$_2$ (10 mol %) in DCE (4 mL) at 80 °C for 16 h under N$_2$. [b]Isolated yields. [c]Only the major isomer was shown.

Scheme 4. Gram-Scale Synthesis and Synthetic Applications



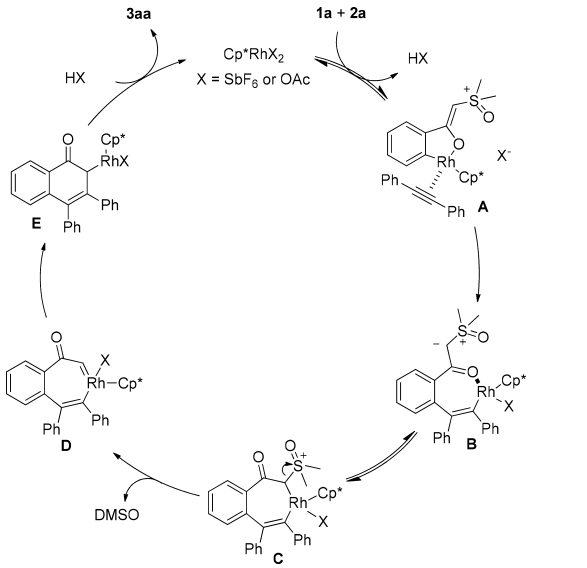
Having established the substrate scope and utility of the product, we next conducted preliminary mechanistic studies. Several H/D exchange experiments have been carried out (Scheme 5). Essentially no deuterium incorporation occurred at the 2-position of the phenyl ring or the α-position of carbonyl when **1a** was allowed to undergo exchange with CD$_3$OD in the absence of a Rh(III) catalyst. In contrast, both the *ortho*-CH and the methine proton underwent slight H/D exchange in the presence of the Rh(III) catalyst, indicating the reversibility of the C(aryl)−H bond cleavage. The observed deuterium incorporation at the methine position may also suggest cyclometalation and reversible protonation due to the enhanced basicity at this position. To further probe the C−H activation process, kinetic isotope effect was measured, and a small value of kinetic isotope effect (k_H/k_D = 1.3) obtained from parallel reactions suggests that C−H bond cleavage is likely not involved in the turnover-limiting step.

Scheme 5. Mechanistic Studies



On the basis of the preliminary mechanistic studies and previous literature reports on related systems,[8e,10,14] a plausible catalytic cycle for the annulation of **1a** and **2a** is proposed in Scheme 6. First, oxygen coordination of **1a** is followed by

Scheme 6. Proposed Reaction Mechanism



cyclometalation to deliver a five-membered rhodacyclic intermediate. Subsequent coordination of alkyne **2a** gives an alkyne species **A**, which then undergoes migratory insertion of the aryl group into alkyne to afford a seven-membered intermediate **B**. O-bound to C-bound tautomerization produces an intermediate **C**. The intermediate **C** undergoes α-elimination[8e] of DMSO to afford an α-oxo carbenoid species **D**. The Rh−alkenyl bond should readily insert into the resultant carbenoid to produce a Rh(III) alkyl species **E**. Protonolysis of the Rh−C bond by HX releases the final product with the regeneration of the active catalyst.

In summary, we have developed an efficient Rh(III)-catalyzed annulation of sulfoxonium ylides with alkynes, leading to the

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concise synthesis of 1-naphthols via a C−H activation pathway. This catalytic system features mild conditions and a wide range of both ylides and internal alkynes. This new process may add to the growing arsenal of methods for carboannulation reactions, with particular application to the increasing demand for the synthesis of highly functionalized naphthol motifs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01974.

Detailed experimental procedures, characterization of new compounds, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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