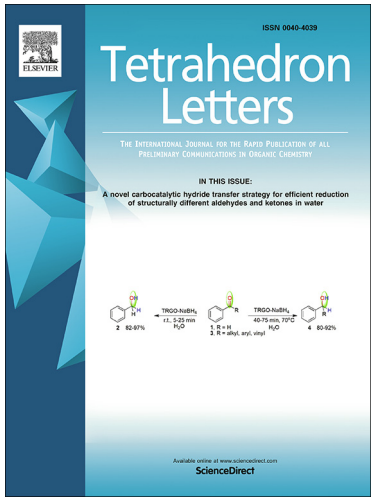

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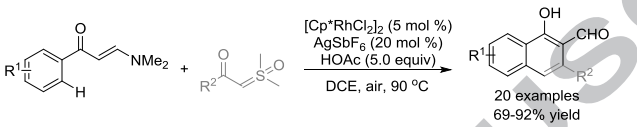

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ABSTRACT

A rhodium-catalyzed ortho-C–H functionalization and annulation between enaminones and sulfoxonium ylides was developed, affording a series of multi-substituted naphthalenes in good to moderate yields with excellent functional group compatibility. The procedure featured with enaminone acting as both a directing and cyclization bifunctional group, and the application of sulfoxonium ylide in C–H functionalization.

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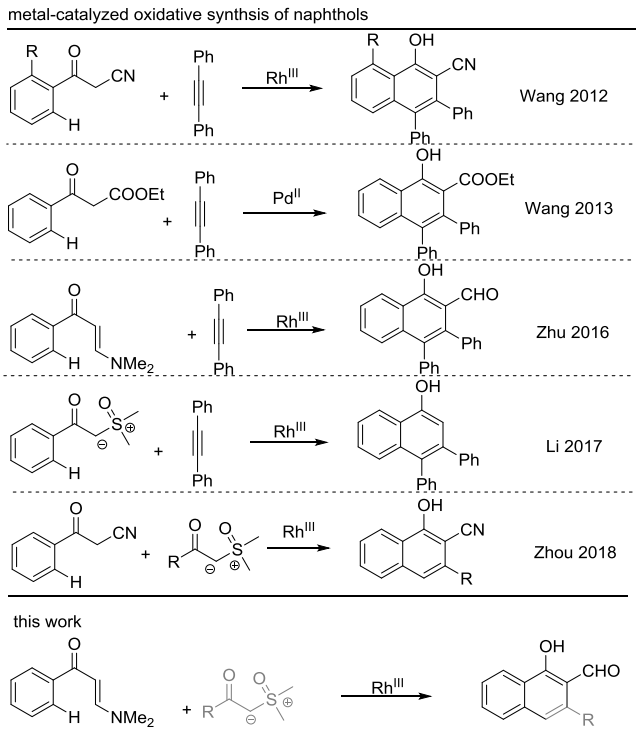
Naphthols are not only widely found in natural products and drug molecules, but also commonly used as raw materials in pesticides, dyes, and pharmaceutical industries.[1] Thus, the construction of these special frameworks has attracted the continuous attention of organic chemists by many universal and efficient synthetic routes.[2] Compared with the traditional pathways to access naphthols, C–H activation strategies are more attractive,[3, 4] in terms of atomic economy, stereoselectivity or efficiency.

Past decades have made considerable strides in transition-metal-catalyzed *ortho*-C–H activation reactions leading to the construction of C–C bonds efficiently and straightforwardly as a significant measure widely used in the field of organic chemistry.[5] This practical strategy has been successfully applied to access heterocycles and carbocycles such as naphthols,[4] through the further cyclization process.

In 2012, Wang[6] reported Rh(III)-catalyzed oxidative synthesis of 1-naphthols through ortho-C–H activation of ortho-substituted benzoylacetonitrile with alkynes (Scheme 1). Next year, Wang[7] and co-workers developed the direct access to highly substituted 1-naphthols through palladium-catalyzed oxidative annulation of benzoylacetates and internal alkynes. In 2016, Zhu[8]pioneered enaminone as a directing synthon for Rh(III)-catalyzed C−H coupling with α-diazo-β-ketoester, alkyne to access 2-formylnaphthol derivatives under oxidative conditions. As a newly-developed synthon, sulfoxonium ylide has made remarkable

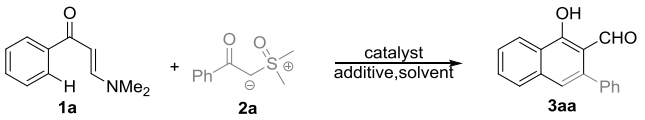


Scheme 1. The construction of naphthols frameworks through *ortho*-C–H functionalization.

advances in C–H functionalization in recent years,[9] serving as multiple roles such as C2 carbene synthons and traceless bifunctional directing groups. Such frameworks were reported by Li[10] and Zhou[11] to access 3,4-disubstituted naphthols and 2,3-disubstituted naphthols, respectively.

Although chemists strived to open up new synthetic routes continuously, methods of synthesizing naphthols through C–H activation is still finite. In view of present methodologies[9-12] on C-H activation with sulfoxonium ylide as a block for synthesizing cyclic compounds, we propose to use enaminones[13] to access 2,3-disubstituted naphthols with sulfoxonium ylides through metal-catalyzed C–H activation/cyclization pathway.

Table 1. Screening the optimized reaction condition.[a]

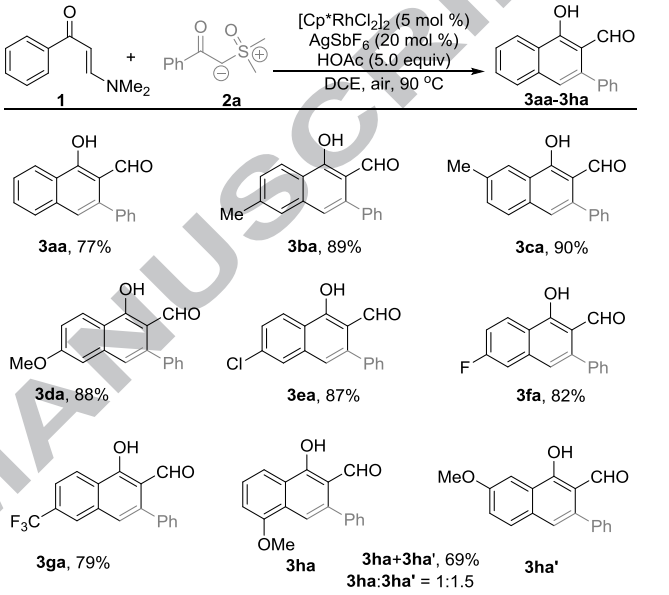


entry	additive (equiv)	solvent	**3aa**(%)[b]
1	--	dioxane	nr
2	--	toluene	nr
3	--	MeCN	23
4	--	THF	nr
5	--	DMF	nr
6	--	EtOH	nr
7	--	HOAc	trace
8	--	DCE	49
9	$Cu(OAc)_2$ (2.0)	DCE	nr
10	NaOAc (2.0)	DCE	nr
11	LiOAc (2.0)	DCE	nr
12	H_2O (2.0)	DCE	32
13	HOAc (2.0)	DCE	63, trace [c], 29 [d], trace [e], nr [f], nr [g]
14	HOAc (5.0)	DCE	77, 56 [h], 70 [i], 76 [j]

[a] Reaction conditions: (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one **1a** (0.1 mmol), dimethyloxosulfonium benzoylmethylide **2a** (0.15 mmol), catalyst: $[Cp^*RhCl_2]_2$ (5 mol %), Cp* = 1,2,3,4,5-pentamethylcyclopenta-1,3-diene, $AgSbF_6$ (20 mol %), solvent (2.0 mL), under air, at 90 °C for 12 h, in a sealed Schlenk tube, unless otherwise noted. [b] Isolated yield. [c] Without $AgSbF_6$. [d] $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgSbF_6$ (20 mol %). [e] $Cp^*Rh(OAc)_2$ (5 mol %), $AgSbF_6$ (20 mol %). [f] $[Cp^*IrCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %). [g] $CoCp^*(CO)I_2$, $AgSbF_6$ (20 mol %). [h] 80 °C. [i] 100 °C. [j] Under N_2.

We initially chose (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**1a**), α-benzoyl sulfoxonium ylide (**2a**) as model substrates to explore the *ortho*-C−H functionalization/cyclization reaction. In the presence of catalytic amount of $[Cp^*RhCl_2]_2$ (5 mol %) and $AgSbF_6$ (20 mol %), no reaction took place at all in some solvents such as dioxane, toluene (Table 1, entries 1-2), THF, DMF, EtOH, and AcOH (Table 1, entries 4-7). However, in MeCN, the desired product 1-hydroxy-3-phenyl-2-naphthaldehyde (**3aa**) was detected at 90 °C, albeit in a low yield (23%, Table 1, entry 3). The effect of solvents is particularly important that the Rh(III)/Ag catalytic system perform better in DCE, leading to **3aa** in a barely acceptable yield (49%). We also found that neither acetates nor water had no effect on promoting the conversion of products (Table 1, entries 9-12); while acetic acid increased the yield to a satisfactory level (Table 1, entry 13). The $AgSbF_6$ improved the reaction efficiency, and $[RuCl_2(p\text{-cymene})]_2$ was superior to $Cp^*Rh(OAc)_2$, $[Cp^*IrCl_2]_2$ and $CoCp^*(CO)I_2$. To our delight, the 1-hydroxy-3-phenyl-2-naphthaldehyde (**3aa**) was isolated in 77% yield in the presence of 5.0 equivalent of HOAc (Table 1, entry 14). Meanwhile, high temperature is not beneficial to the transformation.

Scheme 2. Substrates scope of substituted enaminones.[a, b]



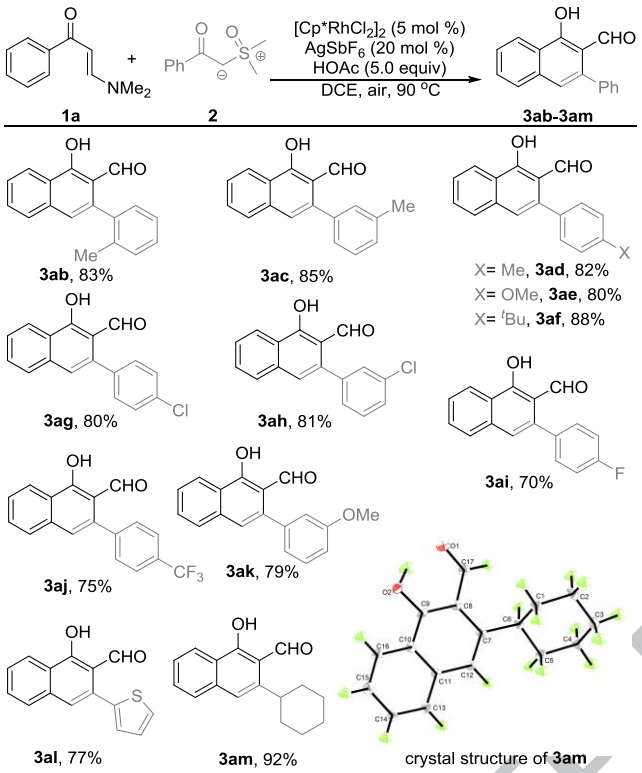
[a] Reaction conditions: substituted enaminones **1** (0.1 mmol), sulfoxonium ylide **2a** (0.15 mmol), catalyst: $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), HOAc (0.5 mmol), DCE (2.0 mL), under air, at 90 °C for 12 h, in a sealed Schlenk tube, unless otherwise noted. [b] Isolated yield. [c] It is difficult to isolate the corresponding cross-coupling mixture (**3ha** and **3ha'**), their ratio data was determined by ^1H NMR spectrum.

With the optimized reaction conditions in hand, the scope and limitation of enaminones were studied as shown in Scheme 2. Generally, the reaction efficiency was not sensitive to the electron nature of the substituents on the aryl as substrates bearing both electron-donating (**3ba-da,** 88-90%) and electron-withdrawing groups (**3ea-ga,** 79-87%) all worked well to deliver the desired products in good to excellent yields. Specially, substrate with a *meta*- substituent in phenyl resulted in a mixture of two regioselective isomers (**3ha**/**3ha'**, 69%, 1/1.5). However, *ortho*-substituted aryl enaminones failed to work under this procedure.

Next, the scope of sulfoxonium ylides was investigated (Scheme 3). Generally, α- aroyl sulfoxonium ylides bearing both electron-donating (**3ab-af**, and **3ak** 79-88%) or withdrawing groups (**3ag-aj**, 70-81%) all worked well to deliver the desired products in moderate to good yields. The position of substituent on sulfoxonium ylide has little effect on the reaction process obviously that *ortho*-(**3ab**), *meta*-(**3ac**, **3ah**, and **3ak**), *para*-substituted (**3ad-3ag**, and **3ai-3aj**) showed satisfactoryyields. Besides, this procedure were also applicable for heterocyclic

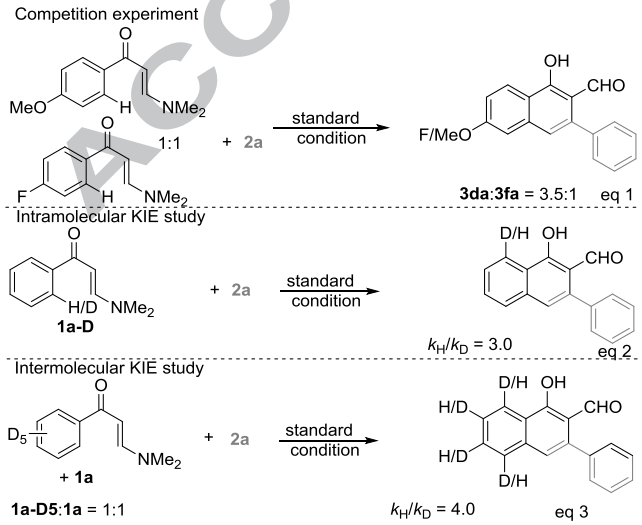
(**3al**) and alkyl (**3am**) sulfoxonium ylides. In addition, the structure of **3am** was further confirmed by X-ray crystallography (for details, see Supporting Information). [14]

Scheme 3. Scope of sulfoxonium ylides.



[a] Reaction conditions: (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one **1a** (0.1 mmol), sulfoxonium ylides **2** (0.22 mmol), catalyst: $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), HOAc (0.5 mmol), DCE (2.0 mL), under air, at 90 °C for 12 h, in a sealed Schlenk tube, unless otherwise noted. [b] Isolated yield.

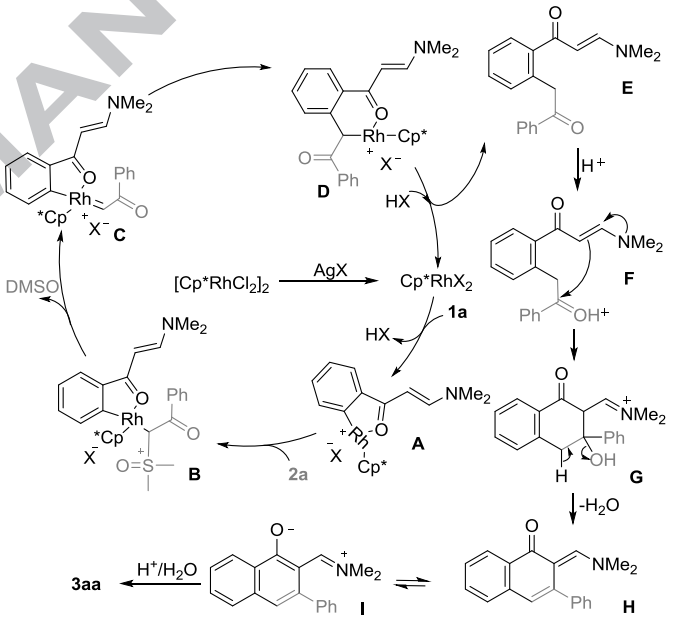
Scheme 4. Mechanism study



The competition reaction between an electron-rich and an electron-poor enaminone with **2a** shows a higher reactivity for the electron-rich substrate (Scheme 4, eq 1), which is consistent with an electrophilic aromatic substitution C−H activation pathway. The intra- and inter- molecular KIEs of deuterium-labeled substrates and **2a** identified a high value (k_H/k_D = 3.0 and 4.0, Scheme 4, eqs 2 and 3), suggesting that C−H activation is the rate-determining step.

Based on the above deuterium-labeling experiments and previous literatures,[8-9, 12-13, 15] a catalytic cycle for the *ortho*-C−H functionalization and cyclization of enaminone is proposed (Scheme 3). Initially, dedimeriation of $[Cp^*RhCl_2]_2$ and C−H activation of enaminone (**1a**) produce a rhodacyclic intermediate **A**, which then coordinated with **2a** leading to a Rh(III) intermediate **B**. Then, the key intermediate carbene species **C** was produced from **B** by α- elimination of DMSO. After the migratory insertion and protonolysis, acylmethylated intermediate **E** was generated, and Rh(III) catalyst was released, completing a catalytic cycle. The intermediate **E** transformed into an oxonium salt **F** under acidic conditions, which went through a Michael addition-type C−C coupling to furnish a hexatomic ring **G**. Then, the intermediate **H** was formed through the dehydration process of **G**. The target product **3aa** was obtained by hydrolysis of imine (intermediate **I**) to aldehyde.

Scheme 5. Proposed mechanism



In conclusion, we have developed a rhodium-catalyzed *ortho*-C−H functionalization and annulation between enaminones and α- aroyl sulfoxonium ylides toward a series of multi-substituted naphthalenes in good to moderate yields. Enaminone played a dual role as a directing group and a cyclization group, and widened the meaningful application of sulfoxonium ylide in C-H functionalization.

Acknowledgments

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Highlights

1. The readily available starting material
2. Enaminone acted as a directing and cyclization bifunctional group.
3. Safe and mild reaction conditions.