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Ruthenium-catalyzed coupling of α-carbonyl phosphoniums with sulfoxonium ylides *via* C–H activation/Wittig reaction sequences†

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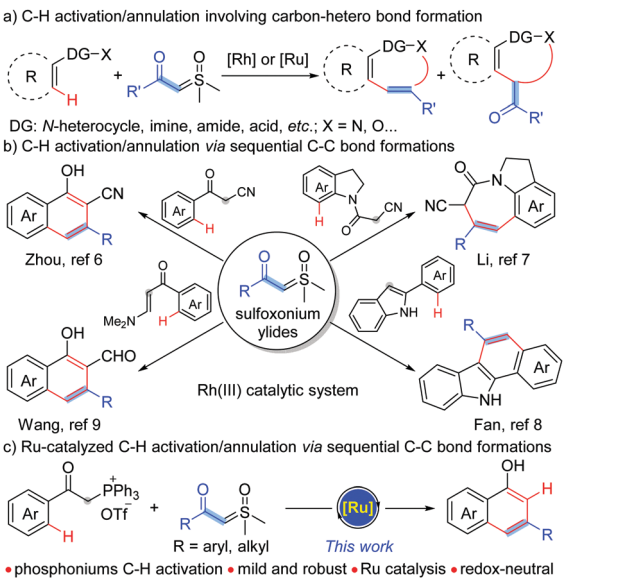
A Ru(II)-catalyzed coupling of various α-carbonyl phosphoniums with sulfoxonium ylides has been realized for the facile synthesis of 1-naphthols in good to excellent yields. This oxidant-free transformation proceeds through Ru-catalyzed C–H activation of phosphoniums, Ru-carbene insertion, and intramolecular Wittig reaction processes.

Transition-metal-catalyzed C–H activation/annulation reactions have stood out as a highly efficient protocol endowing structurally diverse cyclic architectures from simple starting materials.[1] A variety of substrates with different directing groups (DGs) and coupling partners have been disclosed to explore new types of C–H activation/annulation reactions, which are significant in organic synthesis. α-Carbonyl sulfoxonium ylides are one such example and have received increasing attention due to their unique reactivities and reaction patterns, which have been widely employed in synthetic chemistry in recent years.[2] Since the pioneering work of Li on the employment of α-carbonyl sulfoxonium ylides as the C–H activation substrate in the Rh(III)-catalyzed C–H activation/annulation with alkynes,[3] many efforts have been devoted to the exploration of different reaction patterns of such compounds either as a C–H activation substrate or as a coupling partner.[4] As to C–H activation/annulation with sulfoxonium ylides as the coupling partner, a number of elegant studies have been reported involving C–C and C–Hetero bond formations to generate heterocycles (Scheme 1a).[5] In contrast, only limited examples in terms of sequential C–C bond formations to generate carbocyclic compounds with sulfoxonium ylides have been reported owing to the immanent difficulty of constructing two distinct C–C bonds in a single step. For example, Zhou[6] and Li[7] independently reported the Rh(III)-catalyzed annulation of benzoylacetonitriles or *N*-(cyanoacetyl)indolines with sulfoxonium ylides through sequential C–C bond formations (Scheme 1b); Fan[8] disclosed the reaction of 2-arylindoles with sulfoxonium ylides *via* Rh(III)-catalyzed C–H activation/annulation; Wang[9] developed Rh(III)-catalyzed C–H functionalization and annulation between enaminones and sulfoxonium ylides to generate a series of multi-substituted naphthalenes. Although progress has been achieved in this chemistry, the room for further development of efficient strategies in the synthesis of carbocyclic compounds with α-carbonyl sulfoxonium ylides through consecutive C–C bonds formation is significant for synthetic chemistry.

On the other hand, 1-naphthols are highly desirable building blocks and of great importance in the biological, agricultural, pesticides, and dyestuff industries.[10] For example, 1-naphthol-



Scheme 1 Transition-metal-catalyzed C–H activation/annulation with sulfoxonium ylides as the coupling partner.

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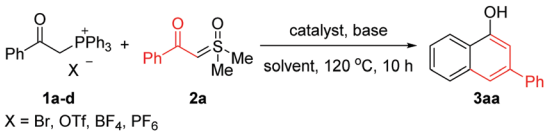
containing compounds rubilactone and mollugin are potent anti-HIV reagents,[11] and korupensamine A[12] is a promising antimalarial. Besides, 1-naphthols could be conveniently transformed into numerous useful compounds, such as VANOL, which is a famous catalyst in organic chemistry.[13] Consequently, developing convenient methods to generate 1-naphthols has attracted much attention.[14] Among them, the C–H activation/annulation strategy has drawn a special attention, because of avoiding the additional operations for preparing high-activity substrates. In this vein, a few examples have been developed and in most cases alkynes were employed as the coupling partners, including Rh(III),[3,15] Pd(II)[16] and Co(III)[4g] catalysts. In the case of sulfoxonium ylides, the relatively expensive Rh(III)-catalyst was needed to promote the corresponding C–H activation process (Scheme 1b).[6,9] Therefore, the exploration of practical and efficient methods to generate 1-naphthols *via* C–H activation/annulation enabled by less expensive catalysts is of great significance. Moreover, the Ru-catalyzed C–H activation/annulation reactions have drawn increasing attention due to their low cost, high compatibility and selectivity compared to Rh(III)-catalysis.[17] Thus, considering that phosphonium ylides could be facilely generated through the easily available phosphonium salts upon deprotonation and they are compatible in the Rh(III)-catalyzed C–H functionalization reactions,[18] together with promoting the development of Ru(II)-catalyzed C–H activation/annulation reactions, herein, we report our findings toward the coupling of various phosphoniums with sulfoxonium ylides to construct a series of structurally diverse 1-naphthols (Scheme 1c).

Our study began with the annulation between phenacyl phosphonium salts (**1a–d**) and sulfoxonium ylides **2a** to optimize the reaction conditions (Table 1). As shown in entry 1 to entry 4, the counterpart anions have a dramatic effect on the reactivity. **1a** with a bromide anion failed to generate the desired 1-naphthol **3aa** while phosphonium salts (**1b–d**) bearing OTf^-, BF_4^-, or PF_4^- anions could produce the product with good to excellent yields in ethanol by employing $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%) as the catalyst and NaOAc as the base. Next, an array of solvents were investigated, including 1,2-dichloromethane (DCE), dioxane, CH_3CN, and toluene (entries 5–8), and the initially used EtOH delivered the best result of 96% yield. Other bases, such as K_2CO_3, K_3PO_4, and KO^{t}Bu failed to give a higher yield (entries 9–11). Notably, the reactivity deteriorated in the absence of any basic additives (entry 12), and the addition of silver salt $AgSbF_6$ had little effect on the reactivity (entry 13). Other Ru(II) complexes, such as $Ru(PPh_3)_3Cl_2$, failed to achieve a higher reactivity. Further lowering the reaction temperature or reducing the reaction time resulted in a slightly lower yield, thus, the optimized reaction conditions were established as: $[Ru(p\text{-cymene})Cl_2]_2$, NaOAc, 120 °C, 10 h in EtOH.

With the optimal conditions in hand, we then explored the scope of phosphonium salts **1** in coupling with **2a** and the results are summarized in Scheme 2. Generally, a variety of phosphoniums were smoothly converted into the corresponding 1-naphthols **3** in 54–96% yields. Various functional groups, including methoxyl, halogen, trifluoromethyl, and cyano-groups, are tolerated in this reaction. It was noted that

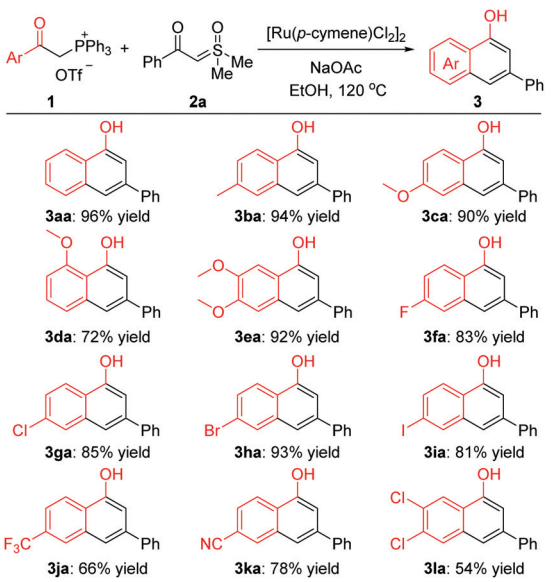
Table 1 Conditions optimization



Entry[a]	X	Base	Solvent	Yield[b] (%)
1	Br	NaOAc	EtOH	<5
2	OTf	NaOAc	EtOH	96
3	BF_4	NaOAc	EtOH	74
4	PF_6	NaOAc	EtOH	90
5	OTf	NaOAc	DCE	35
6	OTf	NaOAc	Dioxane	12
7	OTf	NaOAc	CH_3CN	21
8	OTf	NaOAc	Toluene	24
9	OTf	K_2CO_3	EtOH	15
10	OTf	K_3PO_4	EtOH	8
11	OTf	KO^{t}Bu	EtOH	<5
12	OTf	—	EtOH	<5
13[c]	OTf	NaOAc	EtOH	92
14[d]	OTf	NaOAc	EtOH	<5

[a] Reaction conditions: **1a–d** (0.1 mmol), **2a** (0.15 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), base (2.0 equiv.), solvent (1 mL), under a N_2 atmosphere at 120 °C for 10 h. [b] Isolated yields after column chromatography. [c] $AgSbF_6$ (20 mol%). [d] $Ru(PPh_3)_3Cl_2$ (5 mol%) instead of $[Ru(p\text{-cymene})Cl_2]_2$.

a substrate with less steric hindrance could afford the product with a higher yield (**3ca** *vs.* **3da**). The electronic properties of substituted groups in the phenyl group at the *para*-position of phosphonium salts had a little effect on the activities and substrates bearing electron-donating groups showed slightly higher reactivities (**3ca** *vs.* **3fa–3la**). Moreover, the substrates with di-substituents on the phenyl group were also viable, providing **3ea** and **3la** with 92% and 54% yields, respectively.

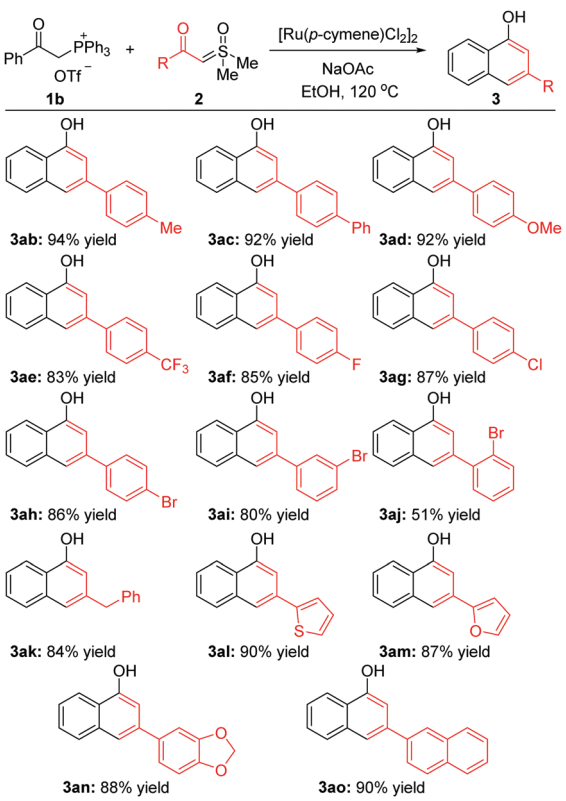


Scheme 2 Scope of phosphonium salts. Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), NaOAc (2.0 equiv.), EtOH (1 mL), under a N_2 atmosphere at 120 °C for 10 h.

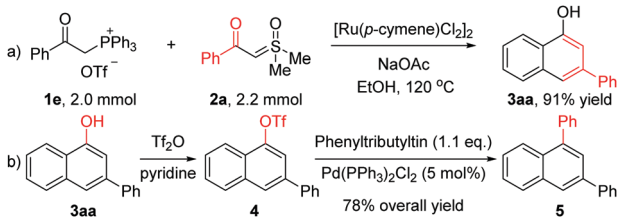
Subsequently, the generality of α-carbonyl sulfoxoniums was investigated (Scheme 3). The scope of sulfoxonium ylides, including electron-donating groups (**3ab–ad**), electron-withdrawing substituents (**3ae**), and halides (**3af–aj**), proved to be broad, and all of the corresponding 1-naphthols were isolated in 51–94% yields. Substrates bearing electron-donating groups (**3ad** *vs.* **3ae**) and less sterically hindered groups (**3ah** *vs.* **3aj**) contributed to the formation of products. In addition, the scope of sulfoxonium ylides also worked well when the alkyl-substituted sulfoxonium ylide (**3ak**) was introduced. Heterocyclic ring systems, such as furan (**3al**), thiophene (**3am**) and polycyclic rings (**3an–ao**), were also tolerated in this transformation, affording the desired products in good yields.

Finally, to further estimate the application possibility of this strategy, a larger-scale synthesis of 1-naphthol **3aa** was conducted, and a good yield of 91% was obtained on a 2 mmol scale reaction (Scheme 4a). Moreover, **3aa** could be easily transformed into triflates **4**, which then underwent Migita–Kosugi–Stille coupling with phenyltributyltin and further generated the 1,3-diphenylnaphthalene **5** product in 78% overall yield (Scheme 4b).

To gain insight into the mechanism of this chemistry, several experiments have been conducted and depicted in Scheme 5. First, deuterium experiments were performed in ethanol-d_6 with 10 equivalent of D_2O (Scheme 5A). The methylene proton of **1b** was acidic and was fully deuterated under these conditions, and the *ortho* CH of phenyl was deuterated (>95% D)



Scheme 3 Scope of sulfoxonium ylides. Reaction conditions: **1b** (0.1 mmol), **2** (0.15 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), NaOAc (2.0 equiv.), EtOH (1 mL), under a N_2 atmosphere at 120 °C for 10 h.



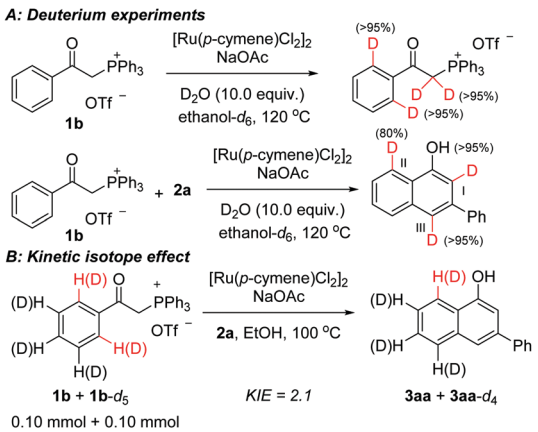
Scheme 4 Larger-scale synthesis and derivatization of **3aa**.

in the presence of the Ru(II) catalyst, suggesting the *ortho* C–H activation. When **2a** was introduced, the H/D exchange was observed at three positions (I–III) of product **3aa**; the deuteration of position I was attributed to the acidity of the methylene proton of **1b**; deuteration of position II further verified the *ortho* C–H activation; deuteration of position III suggested that keto–enol tautomerism existed in the annulation process. Finally, a preliminary kinetic isotope effect study revealed a k_H/k_D value of 2.1 at 100 °C, indicating that the C–H bond cleavage may be involved in the rate-determining step.

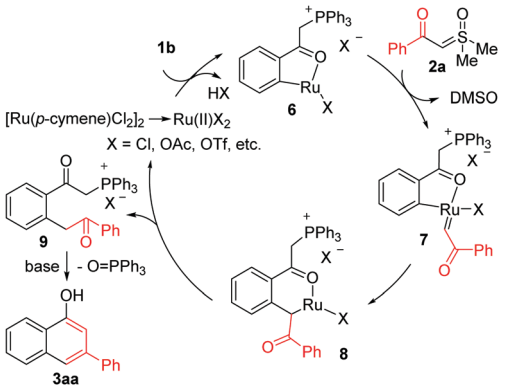
On the basis of these mechanistic studies and literature reports,[5,18] a plausible catalytic cycle was proposed to depict the synthesis of 1-naphthols (Scheme 6).

First, anion exchange may occur between [Ru(*p*-cymene)Cl_2]$_2$ and NaOAc or OTf^-, generating an active cationic Ru(II) species. Then, cyclometalation of **1b** afforded a chelating Ru(II) intermediate **6**, which was supposed to undergo insertion of an incoming sulfoxonium ylide **2a** to afford a five-membered metallacyclic species **7** and release a molecule of the dimethyl sulfoxide (DMSO) co-product. Migratory insertion of the Ru-carbene produced 6-membered metallacyclic species **8**. Protonolysis of the Ru–alkyl bond regenerates the active catalyst to deliver **9**, which was followed by a base promoted intramolecular Wittig reaction, furnishing the desired product **3aa** and generating $OPPh_3$. In addition, it should be mentioned that other possible pathways could not be excluded at this stage.[19]

To sum up, we have developed an efficient method for the construction of various 1-naphthols *via* Ru(II)-catalyzed α-carbonyl phosphoniums coupling with sulfoxonium ylides. This oxidant-free



Scheme 5 Mechanistic studies.



Scheme 6 Proposed catalytic cycle.

and silver-free transformation occurred through C–H activation, Ru-carbene insertion, and base promoted Wittig reaction processes. This method employed cost-effective $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst, and utilized the easily available phosphonium salts as the starting material. A broad substrate scope with respect to both coupling components worked efficiently with up to 96% yield.

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Conflicts of interest

There are no conflicts to declare.

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