ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, **55**, 7339

Received 16th April 2019,
Accepted 28th May 2019

DOI: 10.1039/c9cc02949d

rsc.li/chemcomm

Access to 2-naphthols *via* Ru(II)-catalyzed C–H annulation of nitrones with α-diazo sulfonyl ketones†

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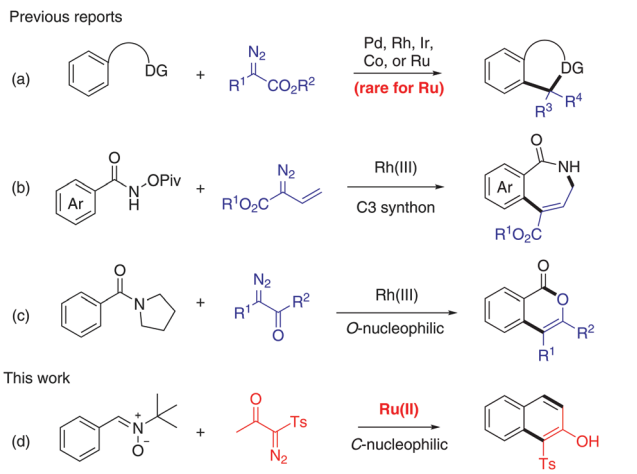
Efficient synthesis of 2-naphthols was realized by Ru(II)-catalyzed C–H activation of aryl nitrones and intermolecular [3+3] annulation with α-diazo sulfonyl ketones under redox-neutral conditions. Easily available α-diazo sulfonyl ketones act as a three-carbon component in the reaction.

2-Naphthols are synthetically important carbocycles and are ubiquitously embedded in a large number of bioactive natural products, pharmaceuticals, and agrochemicals.[1] As a result, numerous synthetic methods have been developed to access 2-naphthols over the past decades. 2-Naphthols are typically synthesized *via* intramolecular cyclization (such as oxidative cyclization, electrophilic cyclization, photo- or thermal-promoted cyclization, and intramolecular Aldol or Dieckmann condensation) and intermolecular cyclization reactions.[2] These cyclization systems generally suffer from lengthy synthetic steps, harsh reaction conditions, and the necessity of highly functionalized starting materials. Therefore, more efficient synthesis of 2-naphthols using readily available starting materials is in great demand.

In the past decades, metal-catalyzed C–H activation has been established as an effective strategy for C–C bond formation.[3] In particular, metal-catalyzed carbenoid functionalization has emerged as a straightforward and powerful strategy to construct C–C bonds under Pd^{II}-, Rh^{III}-, Ir^{III}-, Co^{III}-, and Ru^{II}-catalysis.[4] A series of elegant works have been reported by the groups of Yu,[5] Glorius,[6] Ackermann,[7] Wang,[8] Chang,[9] and others (Scheme 1a), where the carbene reagents often function as C1 or C2 synthons.[10] Occasionally, diazo reagents can act as three-atom synthons. Thus, Cui and co-workers reported Rh(III)-catalyzed [4+3] cycloaddition of amides and vinyl diazo reagents under mild conditions (Scheme 1b).[11] On the other hand, Liu and others developed Rh(III)-catalyzed *O*-nucleophilic [3+3] annulation between benzamides and diazo compounds for lactone synthesis, with the amide being an electrophilic directing group (Scheme 1c).[12] Despite the progress, diazo reagents have been rarely applied as C3 coupling reagents, especially when catalyzed by cost-effective Ru(II) complexes. Therefore, it is necessary to explore [*n*+3] annulation using easily available new three-carbon reagents.

We reasoned that α-diazo α-sulfonylacetone might serve as a C3 synthon in catalytic C–H activation assisted by an electrophilic directing group, and the subsequent annulation reaction can be chemoselective owing to the strong electron-withdrawing nature of the sulfonyl group that increases the α′-carbon nucleophilicity while weakens the *O*-nucleophilicity. What's more, examples of Ru(II)-catalyzed arene C–H activation and intermolecular coupling with diazo compounds remain limited.[13] We now report Ru(II)-catalyzed [3+3] annulation of nitrones with α-diazo sulfonyl ketones, leading to the efficient synthesis of 2-naphthols (Scheme 1d). Of note, although the synthesis of 1-naphthols has been well-studied by following the C–H activation strategy,[14] 2-naphthols have been rarely accessed *via* this method.[2e]



Scheme 1 Transition metal-catalyzed C–H activation of arenes with diazo compounds.

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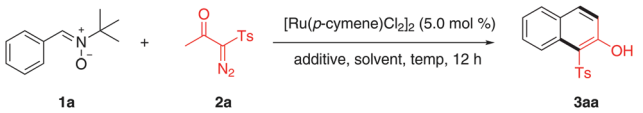
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of all compounds. See DOI: 10.1039/c9cc02949d

Table 1 Optimization of the reaction conditions[a]



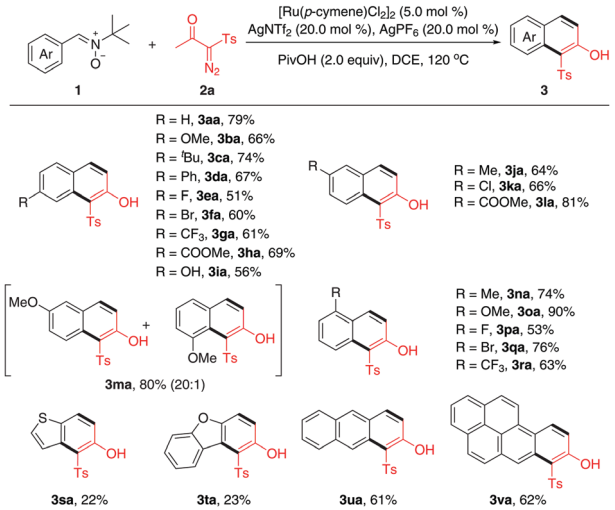
1a 2a 3aa

Entry	Additive	Acid	Solvent	T (°C)	Yield[b] (%)
1	$AgSbF_6$	MesCOOH	Ph-CF_3	100	45
2	$AgSbF_6$	PivOH	Ph-CF_3	100	48
3	$AgSbF_6$	AcOH	Ph-CF_3	100	40
4	$AgSbF_6$	PivOH	Ph-CF_3	115	54
5	$AgSbF_6$	PivOH	Ph-CF_3	130	60
6	$AgNTf_2$	PivOH	Ph-CF_3	130	66
7	AgOAc	PivOH	Ph-CF_3	130	62
8	AgOTf	PivOH	Ph-CF_3	130	30
9	$AgBF_4$	PivOH	Ph-CF_3	130	63
10	$AgPF_6$	PivOH	Ph-CF_3	130	54
11[c]	$AgNTf_2$	PivOH	Ph-CF_3	130	69
12[c]	$AgNTf_2$	PivOH	DCE	130	64
13[c]	$AgNTf_2$	PivOH	DCE	120	63
14[c]	$AgNTf_2$ + $AgBF_4$	PivOH	DCE	120	78
15[c]	$AgNTf_2$ + $AgPF_6$	PivOH	DCE	120	82 (79)[d]
16[c,e]	$AgNTf_2$ + $AgPF_6$	PivOH	DCE	120	73
17[c,f]	$AgNTf_2$ + $AgPF_6$	PivOH	DCE	120	55
18[c,g]	$AgNTf_2$ + $AgPF_6$	PivOH	DCE	120	<5

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%), additive (20.0 mol%), acid (2.0 equiv.), solvent (2.0 mL), 16 h under N_2 in a sealed tube. [b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c] **1a** (0.3 mmol) and **2a** (0.2 mmol) were used. [d] Isolated yield after chromatography. [e] $[Cp^*RhCl_2]_2$ (4.0 mol%). [f] $[Cp^*IrCl_2]_2$ (4.0 mol%). [g] $[Cp^*Co(CO)I_2]$ (10.0 mol%).

We initiated our studies with the coupling of aryl nitrone **1a** with 1-diazo-1-tosylpropan-2-one **(2a)** using $[Ru(p\text{-cymene})Cl_2]_2$ as a catalyst in trifluorotoluene at 100 °C. The desired 2-naphthol **3aa** was obtained in 45% yield in the presence of $AgSbF_6$ and MesCOOH additives (Table 1, entry 1). The yield of **3aa** was slightly improved when PivOH was used (entries 2 and 3). The reaction turned out to be temperature sensitive, and the isolated yield was improved to 60% when the reaction was performed at 130 °C (entries 4 and 5). $AgNTf_2$ proved to be the optimal silver salt; switching to other silver salts such as AgOAc, AgOTf, $AgBF_4$ or $AgPF_6$ led to a slightly or significantly lower coupling efficiency (entries 6–10). A yield of 69% was secured when the diazo compound **2a** was used as the limiting reagent (entry 11). The yields slightly decreased when using DCE as a solvent at 130 °C or 120 °C (entries 12 and 13). To our delight, switching the silver salt to an equimolar mixture of $AgNTf_2$ and $AgPF_6$ (DCE, 120 °C) gave rise to 79% isolated yield (entry 15). The Lewis acidic mixed silver salts $AgNTf_2/AgPF_6$ might facilitate the intramolecular cyclization step. Moderate yields were obtained when $[Cp^*RhCl_2]_2$ or $[Cp^*IrCl_2]_2$ was used as a catalyst, while a trace of product was observed when $Cp^*Co(CO)I_2$ was used (entries 16–18).

With the optimized reaction conditions in hand, the scope and generality of aryl nitrones in this process were next employed (Scheme 2). A range of aryl nitrones bearing electron-donating, -withdrawing and halogen substituents at the *para* position reacted smoothly with **2a**, affording the desired products **3aa–3ia** in 51–79% yields. A *para*-hydroxyl group, which can often be problematic in the C–H activation process, was also compatible

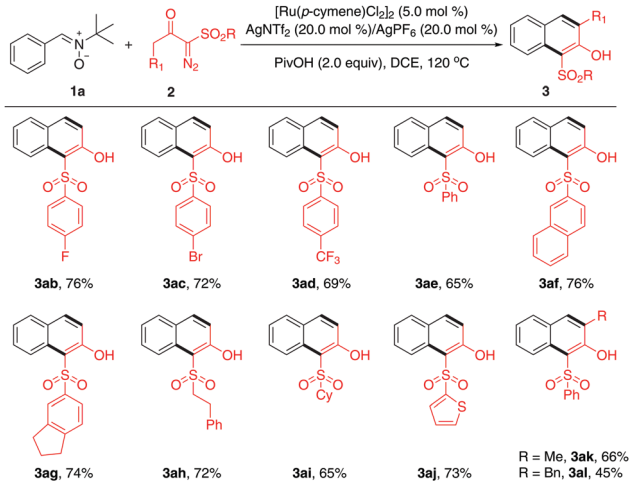


Scheme 2 Scope of arylnitrones. Reaction conditions: nitrone **1** (0.3 mmol), **2a** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%), $AgNTf_2$ (20.0 mol%), $AgPF_6$ (20.0 mol%), and PivOH (2.0 equiv.) in DCE (2.0 mL) at 120 °C for 16 h in a sealed tube under N_2. Isolated yield.

(**3ia**). The reaction also worked well for *meta* methyl-, chloro-, and ester-substituted nitrones (**3ja**, **3ka**, and **3la**) giving moderate to high yields and excellent regioselectivity (>25 : 1). Exception was found for a *meta* methoxy-substituted nitrone (**3ma**, 20 : 1 rr). To our delight, a few *ortho*-substituted nitrones (**3na–3ra**) coupled with **2a** in enhanced efficiency compared with *para*- or *meta*-substituted nitrones, suggesting that the reaction was insensitive to the steric effect. Furthermore, heterocycle-containing nitrones (**3sa** and **3ta**), 2-naphthyl nitrone (**3ua**), and fused ring nitrone (**3va**) all coupled efficiently to provide the annulated products in moderate yields.

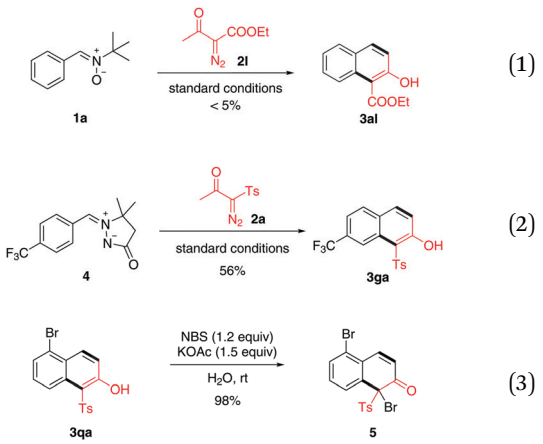
The coupling of aryl nitrone **1a** with various α-diazocarbonyl-α-sulfonyl compounds was next examined (Scheme 3). *para*-Substituted benzenesulfonyl α-diazos bearing a halogen or a CF_3 group coupled to afford the desired products **3ab–3ad** in good yields (69–76%). Meanwhile, the sulfonyl substituents were also extended to phenyl (**3ae**) and 2-naphthyl (**3af**) with moderate to high yields. In the case of 3,4-disubstituted (**3ag**), alkyl-substituted (**3ah** and **3ai**), and heterocycle-containing (**3aj**) sulfonyl diazos, the coupling also proceeded smoothly to give the target products in 65–74% yields. To our delight, 1-diazo-1-(phenylsulfonyl)butan-2-one and 1-diazo-4-phenyl-1-tosylbutan-2-one were also applicable (**3ak** and **3al**), indicating that the steric effect at the alkyl position was tolerated.

Additional experiments have been carried out to further define the scope and limitations of this reaction. Traces of products were observed using ethyl 2-diazo-3-oxobutanoate (**2l**) as a coupling partner under the standard conditions (eqn (1)), indicating the significance of the sulfonyl group. What's more, the arene substrate was not limited to aryl nitrones, and the 2-naphthol product **3ga** was obtained in 56% yield with azomethine imine **4** as an arene substrate (eqn (2)). To demonstrate the synthetic utility of this method, a derivatization reaction was carried out for a 2-naphthol product **3qa**, and a dearomative

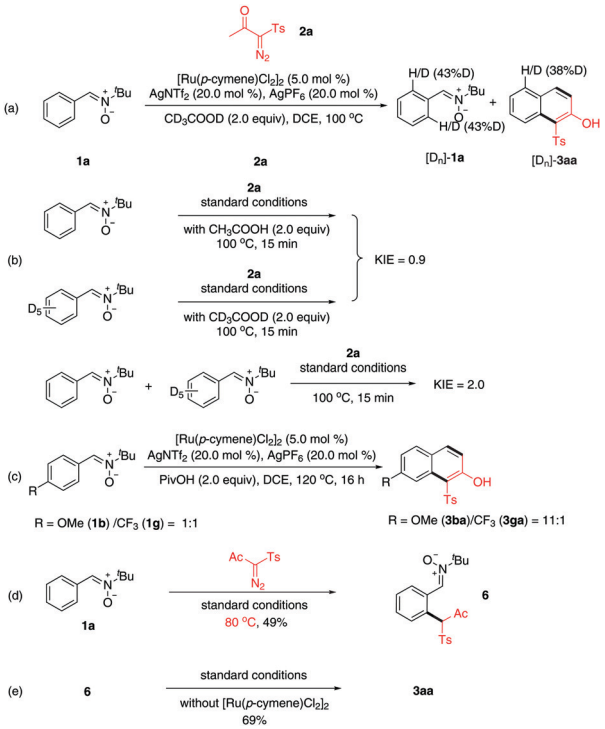


Scheme 3 The scope of α-diazocarbonyl compounds. Reaction conditions: nitrone **1a** (0.3 mmol), diazo compound **2** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%), $AgNTf_2$ (20.0 mol%), $AgPF_6$ (20.0 mol%), and PivOH (2.0 equiv.) in DCE (2.0 mL) at 120 °C for 16 h in a sealed tube under N_2. Isolated yield.

halogenation product **5** was obtained with excellent yield when treated with NBS (eqn (3)).[15]

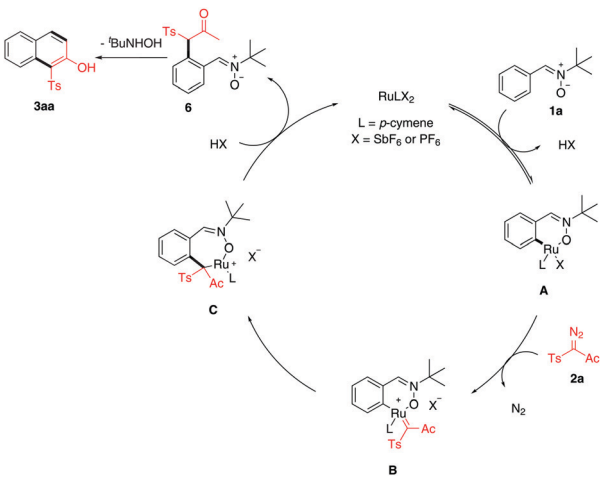


Experimental studies have been performed to probe the reaction mechanism. H/D exchange reactions have been carried out for aryl nitrone **1a** with CD_3COOD as a deuterium source in the presence of diazo **2a**. Significant levels of deuterium incorporation (43% and 38%) at the *ortho*-position of the recovered **1a** and product **3aa** were observed, indicating the reversibility of the C–H bond cleavage (Scheme 4a). To further probe the C–H activation event, KIE studies from parallel reactions using **1a** and **1a**-d_5 gave k_H/k_D = 0.9, and a k_H/k_D value of 2.0 was obtained under intermolecular competition conditions, indicating that the C–H bond cleavage is probably not turnover-limiting (Scheme 4b). Moreover, the intermolecular competition experiment between equimolar amounts of **1b** and **1g** was performed, and the electron-rich aryl nitrone reacted at a higher rate (Scheme 4c). Significantly, an alkylation intermediate **6** was isolated in 49% yield from a coupling reaction performed at 80 °C (Scheme 4d). Control experiments confirmed that the Ru(II) catalyst was not necessary for the subsequent cyclization (Scheme 4e).



Scheme 4 Mechanistic studies.

On the basis of the mechanistic experiments and previous reports,[12] a plausible catalytic cycle is proposed in Scheme 5. Cyclometalation of aryl nitrone **1a** affords a cyclometalated Ru(II) complex **A**. Subsequent diazo **2a** coordination and denitrogenation give a ruthenium carbene species **B**. Facile migratory insertion into the carbene then occurs to give a seven-membered ruthenacyclic intermediate **C**, which is protonolyzed to give the isolable alkylation intermediate **6** and regenerate the Ru(II) catalyst. Finally, intermediate **6** undergoes the intramolecular nucleophilic addition and subsequent elimination of *N*-(*tert*-butyl)-hydroxylamine to furnish product **3aa**. Given the isolation of intermediate **6**, it is likely that the subsequent cyclization process



Scheme 5 Proposed catalytic cycle.

is turnover-limiting, and this proposal is in agreement with our measured small value of KIE.

In summary, we have demonstrated Ru(II)-catalyzed intermolecular [3+3] annulation of nitrones with α-diazo sulfonyl ketones for the synthesis of 2-naphthols *via* a C–H activation pathway. Stable and easily available diazo compounds react as C3 synthons under redox-neutral conditions. The reactions are generally efficient and proceeded with high functional group compatibility. Further C–H functionalization–annulation systems and other novel transformations of α-diazo sulfonyl ketones are underway in our laboratory.

We acknowledge the financial support for this work from the National NSF of China (21525208) and the Shaanxi Normal University.

Conflicts of interest

There are no conflicts of interest to declare.

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