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COMMUNICATION

Access to 2-Naphthols via Ru(II)-Catalyzed C-H Annulation of Nitrones with α -Diazo Sulfonyl Ketones

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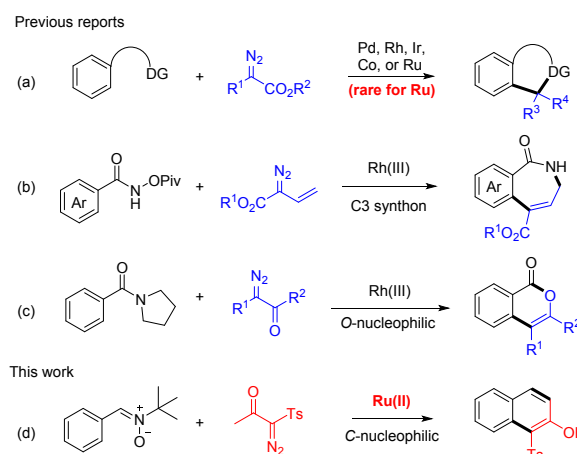
Efficient synthesis of 2-naphthols was realized by Ru(II)-catalyzed C-H activation of aryl nitrones and intermolecular [3+3] annulation with α -diazo sulfonyl ketones under redox-neutral conditions. Easily available α -diazo sulfonyl ketones act as a three-carbon component in the reaction

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 necessity of highly functionalized starting materials. Therefore, more efficient synthesis of 2-naphthols using readily available starting materials is under 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}-, Ru^{II}-catalysis.⁴ A series of elegantly 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 efficient synthesis of 2-naphthols (Scheme 1d). Of note, although synthesis of 1-naphthols has been well-studied by following C-H activation strategy,¹⁴ 2-naphthols have been rarely accessed via this method.^{2e}



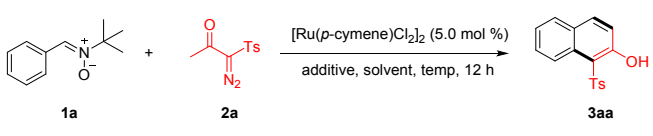
Scheme 1. Transition Metal-Catalyzed C-H Activation of Arenes with Diazo Compounds

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Table 1. Optimization of the Reaction Conditions^a

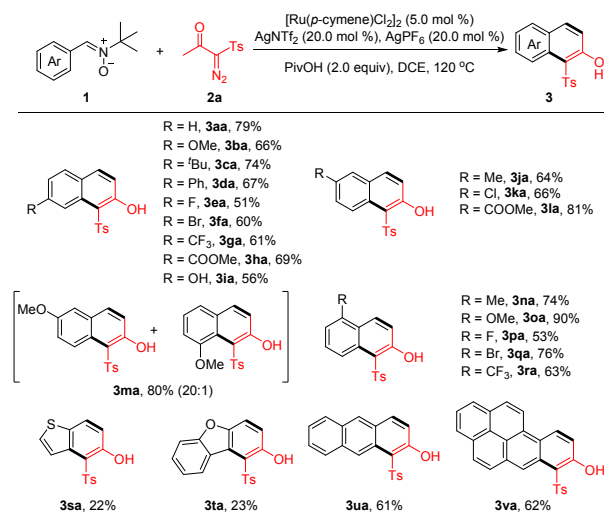
					
entry	additive	acid	solvent	T (°C)	yield (%) ^b
1	AgSbF ₆	MesCOOH	Ph-CF ₃	100	45
2	AgSbF ₆	PivOH	Ph-CF ₃	100	48
3	AgSbF ₆	AcOH	Ph-CF ₃	100	40
4	AgSbF ₆	PivOH	Ph-CF ₃	115	54
5	AgSbF ₆	PivOH	Ph-CF ₃	130	60
6	AgNTf ₂	PivOH	Ph-CF ₃	130	66
7	AgOAc	PivOH	Ph-CF ₃	130	62
8	AgOTf	PivOH	Ph-CF ₃	130	30
9	AgBF ₄	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*-cymenyl)₂Cl₂]₂ (5.0 mol %), additive (20.0 mol %), acid (2.0 equiv), solvent (2.0 mL), 16 h under N₂ 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*RhCl₂]₂ (4.0 mol %). ^f [Cp*IrCl₂]₂ (4.0 mol %). ^g [Cp*Co(CO)I₂] (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*-cymenyl)₂Cl₂]₂ as a catalyst in trifluorotoluene at 100 °C. The desired 2-naphthol **3aa** was obtained in 45% yield in the presence of AgSbF₆ 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). AgNTf₂

proved to be the optimal silver salt; switching to other silver salts such as AgOAc, AgOTf, AgBF₄ or AgPF₆ 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 using DCE as a solvent at 130 °C or 120 °C (entries 12-13). To our delight, switching the silver salt to an equimolar mixture of AgNTf₂ and AgPF₆ (DCE, 120 °C) gave rise to 79% isolated yield (entry 15). The Lewis acidic mixed silver salts AgNTf₂/AgPF₆ might facilitate intramolecular cyclization step. Moderate yields were obtained when [Cp*RhCl₂]₂ or [Cp*IrCl₂]₂ was used as a catalyst, while trace of product was observed when Cp*Co(CO)I₂ was used (entries 16-18).

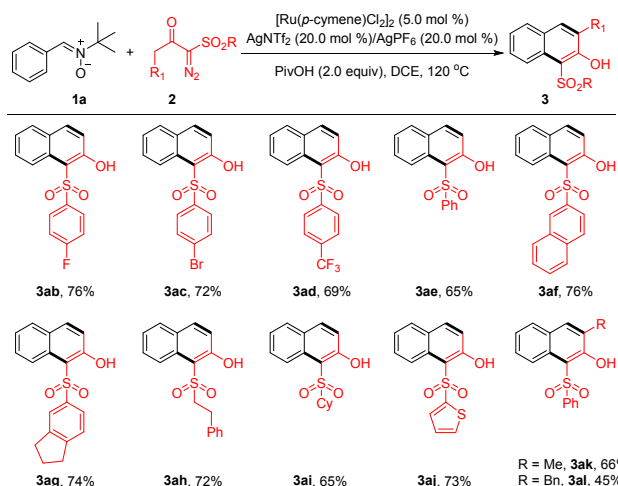
With the optimized reaction conditions in hand, the scope and generality of aryl nitrones in this process were next employed (Scheme 2). A range of aryl nitrones bearing electron-donating -withdrawing, and halogen substituents at the *para* position reacted smoothly with **2a**, affording the desired 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 (**3ia**). The reaction also worked well for *meta* methyl-, chloro-, and ester- substituted nitrones (**3ja**, **3ka**, and **3la**) in 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 enhanced efficiency, suggesting that the reaction was insensitive to 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.



Scheme 2. Scope of Arylnitrons. Reaction conditions: nitrone **1** (0.3 mmol), **2a** (0.2 mmol), [Ru(*p*-cymenyl)₂Cl₂]₂ (5.0 mol %), AgNTf₂ (20.0 mol %), AgPF₆ (20.0 mol %), and PivOH (2.0 equiv) in DCE (2.0 mL) at 120 °C for 16 h in a sealed tube under N₂. Isolated yield.

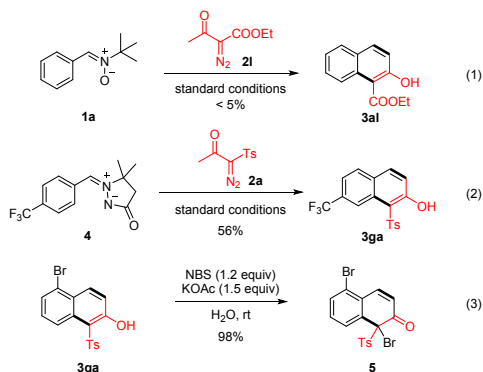
The coupling of aryl nitrone **1a** with various α -diazocarbonyl- α -sulfonyl compounds was next examined (Scheme 3). *para*-Substituted benzenesulfonyl α -diazos bearing halogen or CF₃ group coupled to afford the desired products **3ab-3ad** in good yields (69-76%). Meanwhile, the

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 steric effect at the alkyl position was tolerated.



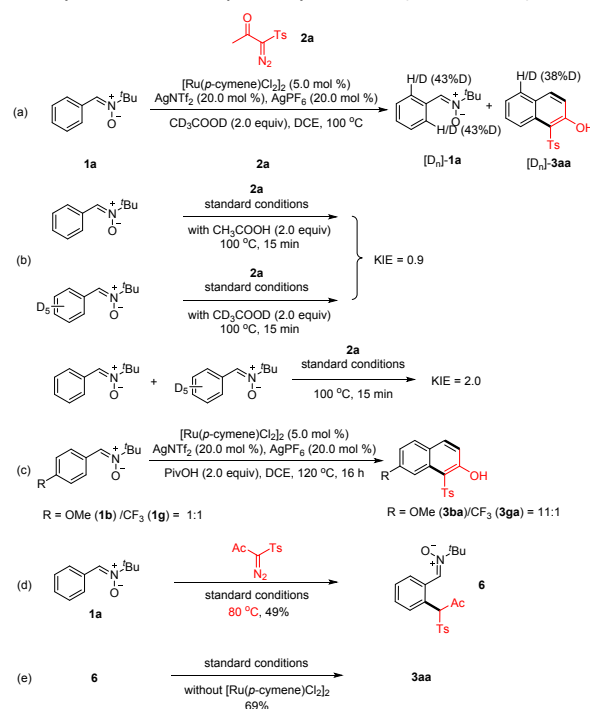
Scheme 3. The Scope of α -Diazocarbonyl Compounds. Reaction conditions: nitron **1a** (0.3 mmol), diazo compound **2** (0.2 mmol), [Ru(*p*-cymene) Cl_2] $_2$ (5.0 mol %), AgNTf $_2$ (20.0 mol %), AgPF $_6$ (20.0 mol %), and PivOH (2.0 equiv) in DCE (2.0 mL) at 120 °C for 16 h in a sealed tube under N $_2$. Isolated yield.

Additional experiments have been carried out to further define the scope and limitations of this reaction. Traces of product were observed using ethyl 2-diazo-3-oxobutanoate (**2l**) as coupling partner under the standard conditions (eq 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 (eq 2). To demonstrate the synthetic utility of this method, a derivatization reaction was carried out for a 2-naphthol product **3qa**, and a dearomative halogenation product **5** was obtained with excellent yield when treated with NBS (eq 3).¹⁵

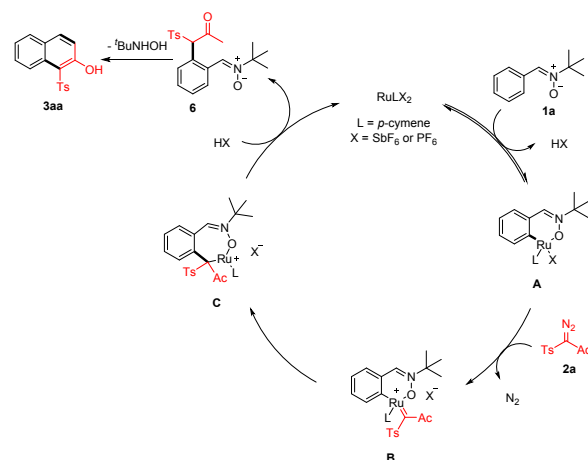


Experimental studies have been performed to probe the reaction mechanism. H/D exchange reactions have been carried out for aryl nitron **1a** with CD $_3$ COOD as a deuterium

source in the presence of diazo **2a**. Significant levels of deuterium incorporation (43% and 38%) at the *ortho*-position of the recovered **1a** and the product **3aa** were observed, indicating 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 value of $k_H/k_D = 2.0$ was obtained under intermolecular competition conditions, indicating that the C–H bond cleavage is probably not turnover-limiting (Scheme 4b). Moreover, intermolecular competition experiment between equimolar amounts of **1b** and **1g** was performed, and the electron-rich aryl nitron 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.



Scheme 5. Proposed Catalytic Cycle.

On the basis of the mechanistic experiments and previous reports,¹² a plausible catalytic cycle is proposed in Scheme 5. Cyclometalation of aryl nitron **1a** affords a cyclometalated Ru(II) complex **A**. Subsequent diazo **2a** coordination and denitrogenation gives 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 the product **3aa**. Given the isolation of intermediate **6**, it is likely that the subsequent cyclization process 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.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest to declare.

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