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Naphthol synthesis: annulation of nitrones with alkynes *via* rhodium(III)-catalyzed C–H activation†

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An efficient and redox-neutral naphthol synthesis has been realized *via* rhodium(III) catalyzed C–H activation of α-carbonyl nitrones and annulation with alkynes, where the nitrone group functioned as a traceless directing group.

Naphthols are an important structural motif in numerous pharmaceuticals and natural products (Fig. 1).[1] Consequently, the synthesis of naphthols has been an ongoing topic for decades. Traditional methods of constructing naphthols generally suffer from harsh conditions, low yield, and relatively low efficiency.[2] Thus, the development of efficient synthetic methodologies that allow the assembly of naphthols from readily available starting materials has attracted continuing interest. Transition metal-catalyzed synthesis of naphthols *via* hydroxylation of aryl halides has been well studied, providing mild and synthetically viable access to naphthols.[3] However, it is desirable to resort to the abundant, simpler arenes as substrates.

In the past decade, the versatility of the rhodium(III) catalyzed C–H activation and annulation strategy has been well documented and has provided mild, atom- and step-economical approaches to access complex molecules from simple arenes bearing a large array of directing groups.[4] This has been realized owing to sufficient interactions between a reactive Rh-C species and a reactive site for subsequent cyclization. While a great deal of effort has been devoted to the formation of various heterocycles *via* rhodium(III)-catalyzed C–H activation,[5] in which heteroatom directing groups, in part or as a whole, have been incorporated into the final product, construction of carbocyclic compounds still lags behind.[6–9]

We resort to rhodium-catalyzed approaches to naphthol synthesis (Scheme 1). Zhu recently described an oxidative synthesis of 2-formyl-1-naphthols *via* C–H activation of enaminones and coupling with alkynes (Scheme 1a).[7] Our group disclosed that certain arylnitrones could undergo C–H activation and coupling

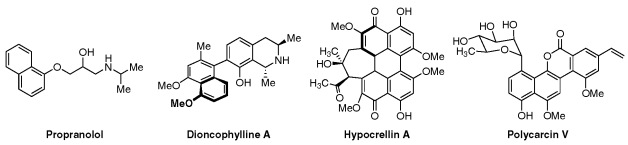

Fig. 1 Representative bioactive compounds with naphthol skeletons.

with cyclopropenones, providing 2,3-disubstituted 1-naphthols (Scheme 1b),[8] where the arylnitrone functions as a benzylidene synthon. However, cyclopropenones are not readily accessible, and the scope of the nitrone is also rather limited. We also realized naphthol synthesis *via* a C–H alkylation-Wittig reaction tandem between phenacyl triphenylphosphonium salts and diazo compounds,[9] where the diazo substrates are limited to acceptor, acceptor ones. On the other hand, we reported in 2013 the first catalytic C–H activation of benzaldehyde-derived nitrone and annulation with alkyne for indenone synthesis.[6b] We envisioned that coupling of alkyne with a phenylglyoxal-derived nitrone (**1a**, Table 1) that contains a carbonyl directing group and an EWG-activated imine may allow for 1-naphthol synthesis with elimination of a nitroso co-product. This calls for sufficient interactions between the nucleophilic Rh–C bond and the electrophilic imine group (Scheme 1c). However, challenges remain because ketone carbonyl is generally weak in directing the effect and its electrophilicity might induce undesired [3 + 2] annulation.[10]

We commenced our studies by examining the reaction parameters of the coupling of α-carbonyl nitrone **1a** with diphenylacetylene **2a** in the presence of a $[Cp^*RhCl_2]_2$ catalyst. To our delight, the desired product **3aa** was isolated in 20% yield in the presence of HOAc (entry 1). Replacing HOAc with HOPiv resulted in a higher yield (entry 2). Screening of solvents revealed DCE as the best choice (entries 3 and 4). Moving to $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as a catalyst, we were delighted to find that the yield improved to 57% (entry 6). Further investigation of the additives revealed that the reactive efficiency improved by introducing $Ni(OTf)_2$ (entries 7–9). It is likely that $Ni(OTf)_2$ acted as a mild Lewis acid that activated the nitrone toward nucleophilic attack by the Rh–vinyl bond. A higher yield of **3aa** was obtained when the reaction was

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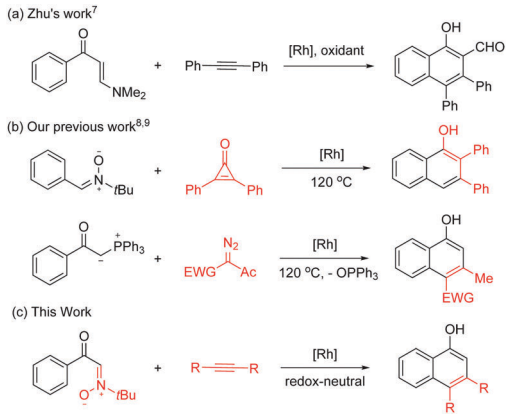
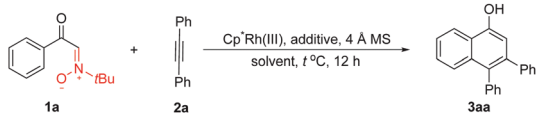


Scheme 1 Naphthol synthesis *via* C–H activation.

Table 1 Screening of the reaction conditions for the synthesis of naphthol[a]



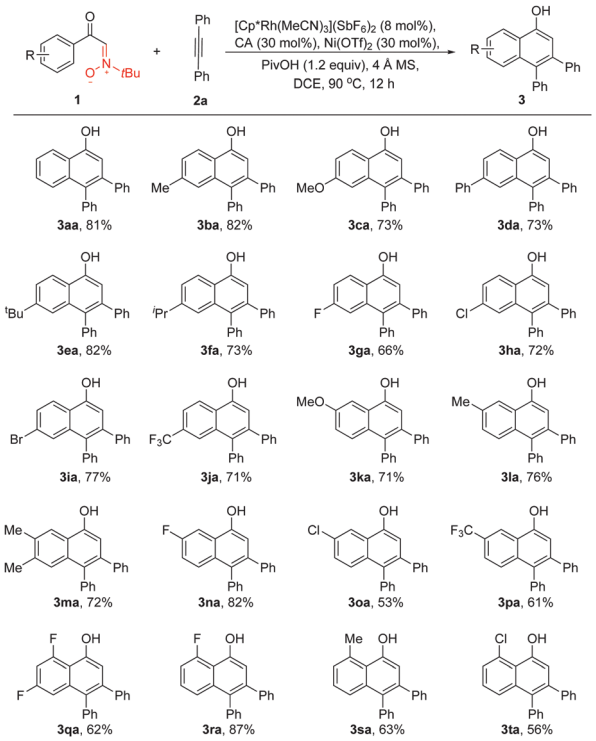
Entry	Catalyst (mol%)	Additive (mol%)	Acid (equiv.)	Solvent	Yield[b] (%)
1	C1 (4)	$AgSbF_6$ (16)	HOAc (1.2)	DCE	20
2	C1 (4)	$AgSbF_6$ (16)	HOPiv (1.2)	DCE	39
3	C1 (4)	$AgSbF_6$ (16)	HOPiv (1.2)	EtOAc	35
4	C1 (4)	$AgSbF_6$ (16)	HOPiv (1.2)	TFE	13
5	C1 (4)	$AgNTf_2$ (16)	HOPiv (1.2)	DCE	27
6	C2 (5)	—	HOPiv (1.2)	DCE	57
7	C2 (5)	$Ni(OTf)_2$ (30)	HOPiv (1.2)	DCE	63
8	C2 (5)	$Ni(OTf)_2$ (30)	HOPiv (1.2)	DCE	72
9[d]	C2 (5)	$Ni(OTf)_2$ (30)	HOPiv (1.2)	DCE	76
10[d]	**C2 (8)**	**$Ni(OTf)_2$ (30)**	**HOPiv (1.2) and CA[c] (0.3)**	**DCE**	**82**
11[d]	—	$Ni(OTf)_2$ (30)	HOPiv (1.2) and CA (0.3)	DCE	—
12[d,e]	C2 (8)	$Ni(OTf)_2$ (30)	HOPiv (1.2) and CA (0.3)	DCE	65

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.21 mmol), Rh(III) catalyst, additive, and 4 Å MS (100 mg) in a solvent (5 mL) at 80 °C. C1 = $[Cp^*RhCl_2]_2$; C2 = $[Cp^*Rh(MeCN)_3](SbF_6)_2$. [b] Isolated yield. [c] CA = citric acid. [d] At 90 °C. [e] Without 4 Å MS.

conducted at 90 °C (entry 9). Moreover, the yield improved to 82% when citric acid (CA) was further introduced as an acid additive to further facilitate the C–H activation process (entry 10). Finally, control experiments confirmed that the Rh(III) catalyst was necessary for this reaction (entry 11).

With the establishment of the optimal conditions, the reaction scope was then evaluated. A variety of nitrones underwent smooth coupling with **2a** (Scheme 2). Electron-withdrawing and -donating substituents at the aryl ring were tolerated and the naphthols **3ba–3ja** were isolated in moderate to good yields. The less sterically congested C–H bond was preferably functionalized for the meta-substituted nitrones with good to high yields (**3ka–3pa**). Notably, *ortho*-substituted nitrones also showed good reactivity despite the increased steric hindrance (**3qa–3ta**). Halogen groups are compatible with this reaction, which should provide handles for further functionalization.

Having explored the scope of the nitrone, we next examined the scope of alkynes (Scheme 3). Symmetrical diarylalkynes

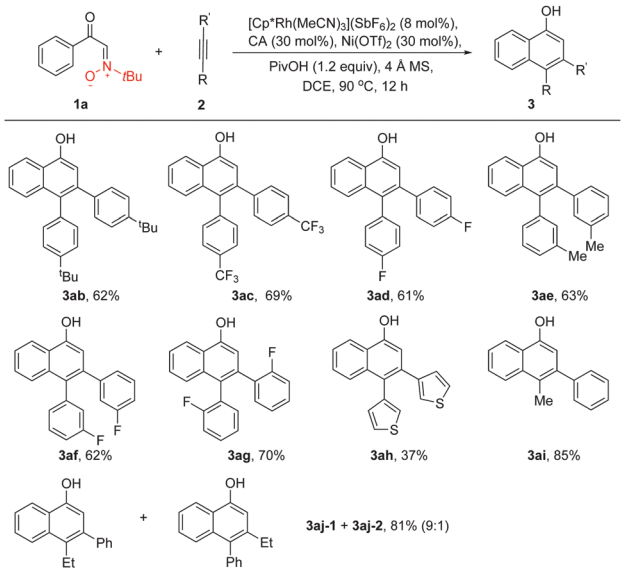


Scheme 2 Scope of nitrones in naphthol synthesis. [a]Reaction conditions: nitrone **1** (0.2 mmol), alkyne **2a** (0.21 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (8 mol%), $Ni(OTf)_2$ (30 mol%), citric acid (30 mol%), HOPiv (0.24 mmol) and 4 Å MS (100 mg) in DCE (5 mL) at 90 °C for 12 h under N_2. [b]Isolated yield.

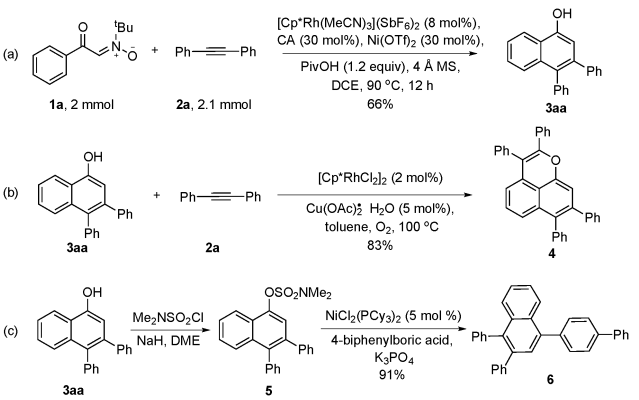
with electron-donating and -withdrawing substituents in the aryl ring all reacted smoothly under the optimal conditions. Furthermore, a sterically hindered alkyne was also found to be suitable for this transformation (**3ag**). A heteroaryl alkyne also coupled but with low efficiency under the standard conditions. High regioselectivity (>20 : 1) and reactivity were observed for prop-1-ynylbenzene (**3ai**), while a longer chain alkyne such as but-1-ynylbenzene exhibited high activity but with lower regioselectivity (**3aj1** and **3aj2**). In contrast, no reaction was observed when a terminal alkyne phenylacetylene or an ester functionalized alkyne (ethyl 3-phenylpropoiate) was used as a coupling partner under the standard conditions, indicative of the limitation in the electronic effect and in the type of alkyne.

To demonstrate the synthetic utility of this method, a larger-scale reaction of **1a** with **2a** has been performed, which afforded the naphthol **3aa** in moderate yield (Scheme 4a). Furthermore, the usefulness of an annulated product **3aa** was demonstrated in the following synthetic transformations. On the basis of a literature report,[11] an oxidative 4 + 2 coupling was achieved by rhodium-catalyzed oxidative annulation between **3aa** and alkyne **2a** (Scheme 4b). Naphthol **3aa** was also converted to sulfamate **5**, which then underwent a nickel-catalyzed cross-coupling reaction with 4-biphenylboric acid to afford **6** in 91% yield (Scheme 4c).[12]

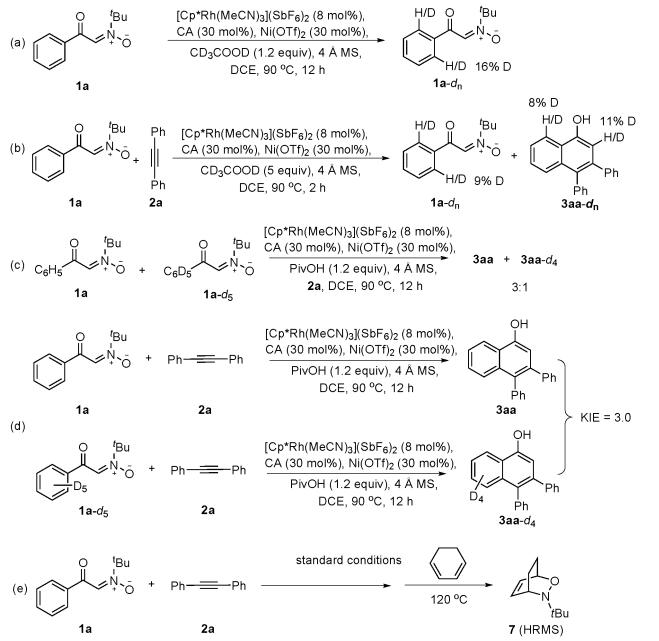
We next conducted preliminary mechanistic studies to gain insight into the reaction mechanism (Scheme 5). First, a H/D exchange experiment between **1a** and CD_3COOD was conducted. ^1H NMR analysis revealed partial deuteration (16% D) at both



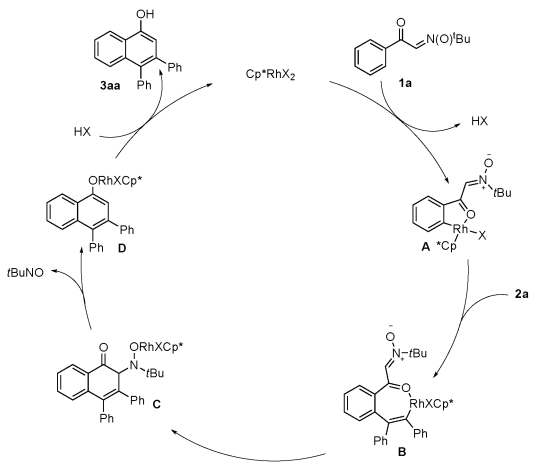
Scheme 3 Scope of nitrones in naphthol synthesis. [a]Reaction conditions: nitrone **1** (0.2 mmol), alkyne **2a** (0.21 mmol) $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (8 mol%), $Ni(OTf)_2$ (30 mol%), citric acid (30 mol%), HOPiv (0.24 mmol) and 4 Å MS (100 mg) in DCE (5 mL) at 90 °C for 12 h under N_2. [b]Isolated yield.



Scheme 4 Larger-scale synthesis and synthetic applications.



Scheme 5 Mechanistic studies.



Scheme 6 Proposed catalytic cycle.

ortho positions (Scheme 5a). H/D exchange in the presence of diphenylacetylene also led to H/D exchange in the recovered starting material and the product was also partially deuterated (Scheme 5b), indicating reversible C–H activation. Second, kinetic isotope effect (KIE) experiments have been conducted. KIE obtained from both parallel reactions (k_H/k_D = 3.0) and intermolecular competition (k_H/k_D = 3.0) using **1a** and **1a**-d_5 suggested that the cleavage of the C–H bond is likely involved in the turnover-limiting step (Scheme 5c and d). Finally, 1,3-cyclohexadiene was added as a diene to a reaction mixture of **1a** and **2a** to trap the nitroso co-product, and HRMS analysis suggested the formation of a [4 + 2] adduct **7**, which confirmed the formation of the *t*BuNO co-product (Scheme 5e).[8]

Based on the above experimental results and related rhodium(III)-catalyzed annulation of arenes and alkynes,[13] a plausible mechanism is proposed for this naphthol synthesis (Scheme 6).[14] Oxygen-directed C–H activation of nitrone **1a** gives a rhodacyclic intermediate **A**. Alkyne coordination and migratory insertion produced an alkenyl intermediate **B**. Then migratory insertion of the Rh–C(alkenyl) bond into the imine moiety of *N*-*tert*-butylnitrone gives a rhodium(III) aminoxide **C**, which is proposed to undergo β-carbon elimination to release *t*BuNO together with the formation of a rhodium(III) phenoxide **D**.[8] Subsequent protonolysis of **D** furnishes the naphthol **3aa** and closes the catalytic cycle.

In summary, we have realized Rh(III)-catalyzed C–H activation of α-carbonyl nitrones and annulation with alkynes, which provided a facile method to access 3,4-disubstituted naphthols. This catalytic system features the application of a weak, traceless directing group linked to an active imine site. This [4 + 2] annulation approach exhibited good functional group tolerability and regioselectivity, obviating the need for any oxidant.

Further investigations on the synthetic application of this transformation are in progress.

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Conflicts of interest

There are no conflicts of interest to declare.

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14 At this stage, we cannot rule out the possibility of carbon-coordination initiated cyclometallation of the nitrone, followed by α-elimination of the *t*BuNO co-product. This will lead to the formation of a rhodium α-oxo carbene species. See the ESI† for a detailed description of this alternative pathway.