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Divergent Access to 1-Naphthols and Isocoumarins via Rh(III)-Catalyzed C−H Activation Assisted by Phosphonium Ylide

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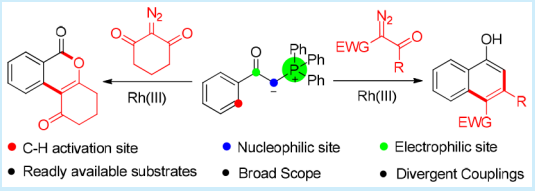
Supporting Information

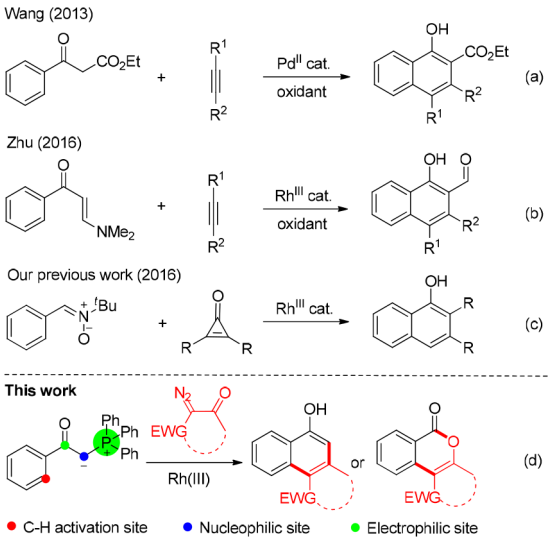
ABSTRACT: Rh-catalyzed C−H activation of phenacyl phosphoniums in coupling with α-diazocarbonyl compounds has been realized with the assistance of a mutifunctional phosphonium ylidic directing group, providing expedient accesses to 1-naphthols and isocoumarins. Switchable synthesis of 1-naphthols and isocoumarins was realized by substrate control, where these transformations were enabled by initial C−H activation and subsequent intramolecular Wittig reaction or nucleophilic C−O formation.



1-Naphthol scaffolds are an important motif for synthetic building blocks in natural product synthesis owing to their ubiquity in numerous biologically relevant compounds that display a broad spectrum of medicinal properties, such as antiviral activity[1] and antitumor and antibacterial activity,[2] among others.[3] As a result, numerous routes have been developed for 1-naphthol synthesis.[4] However, these methods typically suffered from drawbacks, such as harsh reaction conditions,[4b,g] employment of highly functionalized starting materials,[4c] multiple synthetic steps,[4d,f,h] and lack of substrate generality.[4i] Therefore, more efficient access to 1-naphthol using simple and easily available starting materials is highly desirable.

Recently, transition-metal-catalyzed C−H bond functionalization of arenes has been established as an increasingly important strategy for the construction of complex organic functional molecules.[5] This area further thrived with the high activity, selectivity, compatibility, and versatility of Cp*Rh(III) catalysts.[6] However, limited systems have been developed to access 1-naphthols via a C−H bond activation pathway (Scheme 1). In 2013, Wang and co-workers reported naphthol synthesis via palladium-catalyzed oxidative annulation of benzoylacetates with unactivated internal alkynes.[7] (Scheme 1a). Zhu's group recently reported a rhodium-catalyzed oxidative synthesis of highly functionalized 1-naphthols from enaminones and alkynes (Scheme 1b).[8] Our group recently reported a redox-neutral coupling of nitrones with cyclopropenones to furnish 1-naphthols, where the nitrone acted as an electrophilic and traceless directing group (DG, Scheme 1c).[9] These methods are still limited either to oxidative conditions or the use of preactivated, less readily available substrates. To address this limitation and in light of our previous research on Rh-catalyzed C−H activation of phenacyl ammoniums,[10] we designed simple and easily available phenacyl phosphonium salts as arenes (Scheme 1d). We reasoned that a phosphonium ylide DG should be readily

Scheme 1. Transition-Metal-Catalyzed Synthesis of 1-Naphthols



generated from this phosphonium salt upon deprotonation. Furthermore, the methylene is nucleophilic, but both the carbonyl and the phosphonium are electrophilic. Ideally, all of the functional groups of this DG can be utilized to deliver molecular diversity. Herein, we report diverse C−H activation of phenacyl phosphoniums, which allowed divergent synthesis of 1-naphthols and isocoumarins via a C−H activation pathway with intramolecular Wittig reaction and nucleophilic cyclization, respectively.

We initiated our studies by examining the reaction parameters of the coupling of phenacyl phosphonium salt **1**

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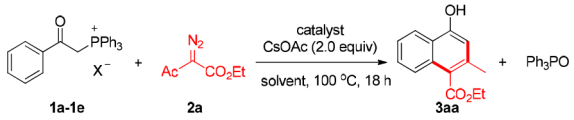
with ethyl α-diazoacetoacetate **2a** (Table 1). Several transition-metal catalysts were initially screened (entries 1–3), among

Table 1. Optimization Studies[a]



1a-1e 2a 3aa

entry	X	catalyst (mol %)	solvent	yield[b] (%)
1	OTf	$[IrCp^*Cl_2]_2$ (4)	MeCN	<10
2	OTf	$[Ru(p\text{-cymene})Cl_2]_2$ (4)	MeCN	<10
3	OTf	$[RhCp^*Cl_2]_2$ (4)	MeCN	11
4	OTf	$[RhCp^*Cl_2]_2$ (4)	EtOH	58
5	OTf	$[RhCp^*Cl_2]_2$ (4)	MeOH	55
6	OTf	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (20)	EtOH	77
7	**OTf**	**$[RhCp^*(MeCN)_3](SbF_6)_2$ (8)**	**EtOH**	**79**
8	Br	$[RhCp^*Cl_2]_2$ (4) /$AgSbF_6$ (20)	EtOH	21
9	SbF_6	$[RhCp^*Cl_2]_2$ (4) /$AgSbF_6$ (20)	EtOH	70
10	BF_4	$[RhCp^*Cl_2]_2$ (4) /$AgSbF_6$ (20)	EtOH	66
11	PF_6	$[RhCp^*Cl_2]_2$ (4) /$AgSbF_6$ (20)	EtOH	64

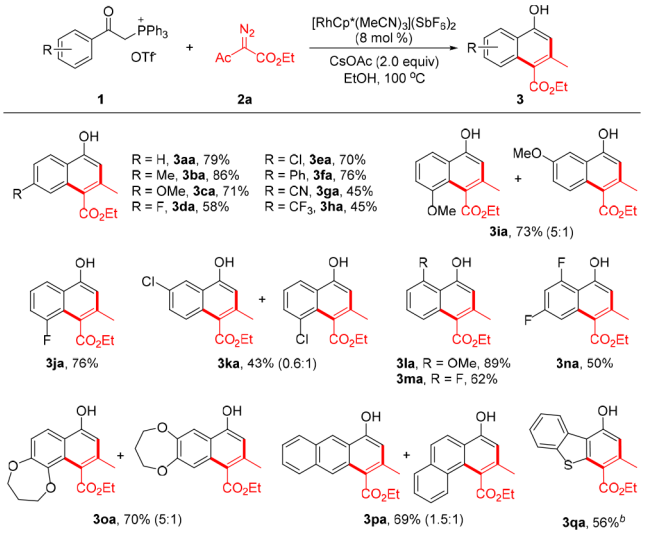
[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), catalyst, and base (2.0 equiv) in a solvent (2 mL) at 100 °C for 18 h. [b]Yields of isolated products.

which rhodium catalyst exhibited highest reactivity, and the expected 1-naphthol was generated likely via a C–H alkylation[11]–intramolecular Wittig reaction.[12] Ethanol was identified as the optimal solvent, and introduction of $AgSbF_6$ further improved the reaction efficiency (entry 6). The yield was reduced when other common anions were used (entries 8–11). Raising or lowering the reaction temperature all resulted in a slightly lower yield, and CsOAc proved to be the optimal base. Thus, the conditions in entry 7 were retained for subsequent studies, under which a Ph_3PO coproduct was also obtained (87% GC yield). We noted that Rh(III)-catalyzed C–H activation and annulation of substituted acetophenones have been reported, but the scope and patterns were limited.[13]

With the optimal conditions in hand, we then explored the scope of phenacyl phosphonium salts in the coupling with **2a** (Scheme 2). Phenacyl phosphonium salts bearing various electron-donating, -withdrawing, and halogen groups at the *para* position of the benzene ring all reacted smoothly with **2a** to furnish the corresponding naphthol products in 45–86% yields (**3aa–ha**). This carbocyclization also occurred smoothly when various *meta* substituents were added (**3ia–ka**, 43–76%), and the major regioisomeric product corresponds to C–H activation at the more hindered *ortho* position for *meta* substituents with a lone pair. In fact, this trend was maximized for a *meta* F-substituted substrate (**3ja**). Moreover, introduction of *ortho* OMe and F groups is also tolerated, indicative of tolerance of steric hindrance. Notably, disubstituted phosphonium salts were also viable, affording products in good yields (**3na–oa**, 50–70%). The arene ring was not limited to benzene, and a thiophene-based phosphonium also underwent smooth coupling (**3qa**, 120 °C).

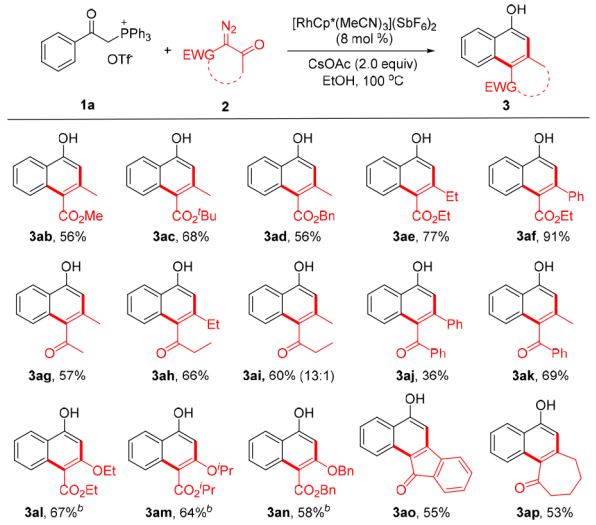
The generality of diazocarbonyl substrates was subsequently investigated. As shown in Scheme 3, the scope of acyclic α-diazocarbonyls, including α-diazo ketoesters (**3ab–af**), diketones (**3ag–ak**), and even diesters (**3al–an**), proved to be broad, and all of the corresponding naphthols were isolated in moderate to high yields. Of note, the coupling of diazocarbonyl compounds derived from unsymmetrically substituted β-

Scheme 2. Substrate Scope of Phenacyl Phosphoniums[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), $[RhCp^*(MeCN)_3](SbF_6)_2$ (8 mol %), CsOAc (2.0 equiv) in ethanol (2 mL) at 100 °C for 18 h. [b]120 °C.

Scheme 3. Substrate Scope of Diazocarbonyl Compounds[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $[RhCp^*(MeCN)_3](SbF_6)_2$ (8 mol %), CsOAc (2.0 equiv) in ethanol (2 mL) at 100 °C for 18 h. [b]With HOAc (2.0 equiv).

diketones generally exhibited high chemoselectivity in terms of the cyclization process (**3ai** and **3ak**). In addition, changing the diazocarbonyl compounds to those embedded in five- and seven-membered cyclic β-diketones only attenuated the yields (**3ao** and **3ap**).

A strinkingly different reaction pattern was observed when we applied 2-diazocyclohexane-1,3-dione as a coupling partner (Scheme 4). This reaction delivered an isocoumarin (**5aa**) in good yield as a result of C–C bond cleavage.[14] In this system, the stereoelectronic effects (ring size) of the diazocarbonyl compounds and the electrophilicity of the carbonyl[15] contributed to the observed C–O bond formation. The scope of this coupling system was briefly examined, and all of the products (**5aa–ea** and **5ab**) were isolated in moderate to good yields.

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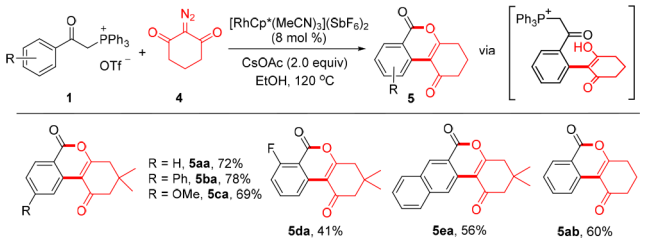
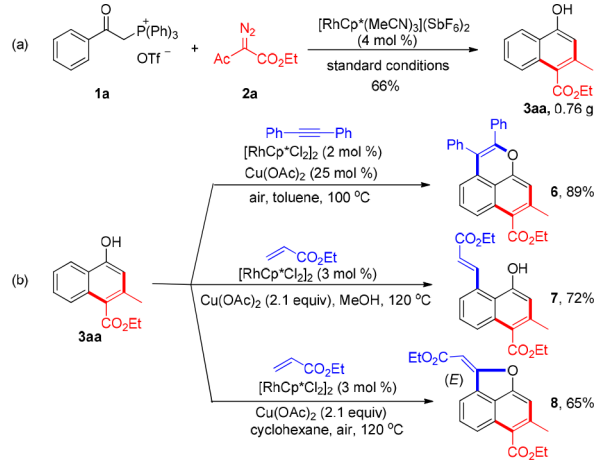
Scheme 4. Synthesis of Isocoumarins[a]



[a]Reaction conditions: **1** (0.2 mmol), diazocarbonyl compounds (0.24 mmol), $[RhCp^*(MeCN)_3](SbF_6)_2$ (8 mol %), and CsOAc (2.0 equiv) in EtOH (2 mL) at 120 °C for 18 h.

Synthetic applications of this protocol have been demonstrated (Scheme 5). Naphthol **3aa** was synthesized in 66% yield

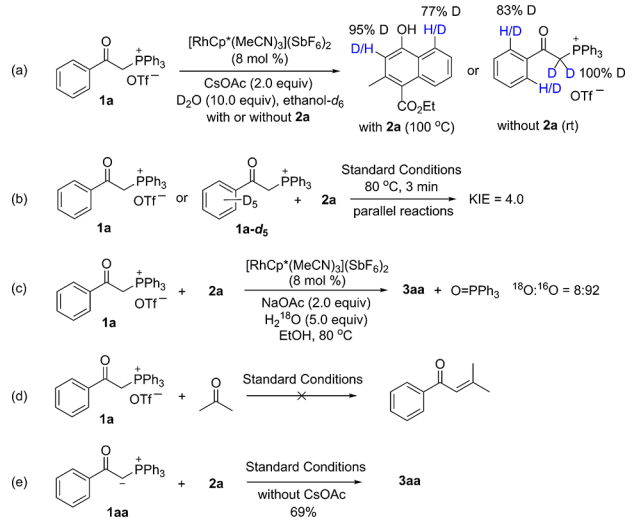
Scheme 5. Gram-Scale Synthesis and Derivatization Reactions of a Naphthol



on a gram scale even under reduced catalyst loading (Scheme 5a). Derivatization of naphthol **3aa** proceeded smoothly in several *peri* C−H activation systems. Thus, oxidative coupling of **3aa** with diphenylacetylene[16] delivered heterocycle **6**, which has found applications in solid-state fluorescence. Interestingly, solvent-dependent oxidative olefination[17] of **3aa** was attained (Scheme 5b). In MeOH, a *trans*-olefin **7** was generated. In contrast, a trisubstituted exocyclic (*E*)-olefin **8** was produced in cyclohexane via 2-fold oxidation.

A series of experiments have been conducted to elucidate the mechanism (Scheme 6). H/D exchange experiments were first performed for **1a** in ethanol-d_6. The methylene proton was acidic and was fully deuterated even in the absence of any catalyst or **2a**, but the *ortho* CH was deuterated (83% D) only in the presence of a Rh(III) catalyst and the base (Scheme 6a). In the presence of **2a**, H/D exchange was observed at both the 2- and 8-position of product **3aa**, suggesting reversibility of *ortho* C−H activation. The C−H activation is likely turnover-limiting as evidenced by a rather large value of k_H/k_D = 4.0 measured from parallel reactions (Scheme 6b). Reactions conducted in the presence of $H_2{}^{18}O$ or $CH_3C^{18}O_2Na$ produced O=PPh$_3$ with essentially no ^{18}O incorporation (Scheme 6c), which is consistent with an intramoelcular Wittig reaction. We attempted but failed to prepare the diazo-attached olefin species from **1a** and **2a** in order to probe the sequence of C−H activation and Wittig reaction. A control experiment was then

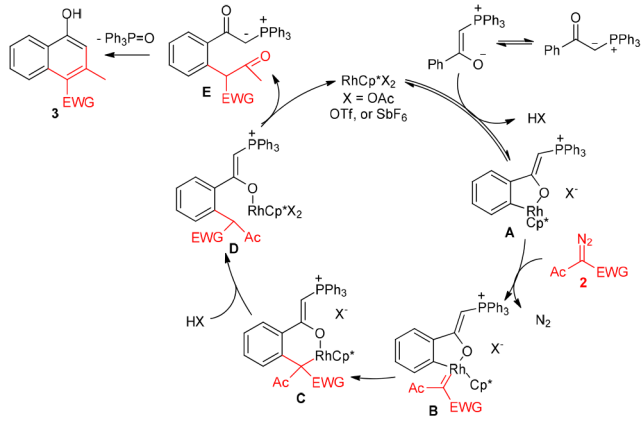
Scheme 6. Mechanistic Studies



performed for this purpose using acetone (Scheme 6d), but still no olefin or derivative was detected. This result suggests that initial Wittig olefination seems less likely. Further control experiments revealed that the corresponding phosphonium ylide of **1a** exhibited comparable activity (69%) in the absence of any base (Scheme 6e).

On the basis of our mechanistic studies and literature reports, a plausible catalytic cycle was extracted to depict the synthesis of 1-naphthols (Scheme 7). O- or C-coordination (shown for

Scheme 7. Proposed Mechanism for the Formation of 1-Naphthols



O-coordination only) of the ylidic form of **1a** and subsequent cyclometalation affords a rhodacyclic intermediate **A**.[18] Coordination of a diazocarbonyl substrate to **A** is followed by denitrogenation to generate a carbene species **B**, the Rh−aryl bond of which would undergo migratory insertion into the carbene to furnish a six-membered rhodacyclic intermediate **C**. Intermediate **D** was then formed via protonolysis of the Rh−alkyl bond in **C**. Ligand dissociation affords intermediate **E** with the regeneration of the active catalyst. The final annulated product **3** is produced upon intramolecular Wittig reaction together with formation of OPPh$_3$.

In summary, we have realized diversified C−H activation of phenacyl phosphoniums assisted by a multifunctional ylidic directing group. Two reaction patterns were realized in the coupling with α-diazocarbonyls. In most cases, naphthols were

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produced via a C−H alkylation−Wittig cyclization sequence. Some cyclic diazocarbonyls may couple to give isocoumarins with the phenacyl being an electrophilic directing group. These redox-neutral coupling systems feature broad substrate scope and easy availability of the starting materials. Our expedient and concise protocols may find applications in the synthesis of related complex scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01365.

General experimental procedures, characterization details, and ^{1}H, ^{13}C, and ^{19}F NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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