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Rh(III)-Catalyzed Enaminone-Directed Alkenyl C−H Activation for the Synthesis of Salicylaldehydes

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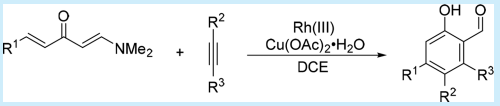
Supporting Information

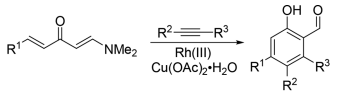
ABSTRACT: A Rh(III)-catalyzed enaminone-directed alkenyl C−H coupling with alkynes for the synthesis of salicylaldehyde derivatives is reported. This represents a unique example of benzene ring framework formation through a transition-metal-catalyzed, directed C−H activation strategy. The two incorporated reactive functionalities, aldehyde and hydroxy groups, provide convenient synthetic handles for further structural elaboration.



Transition-metal-catalyzed, directed intermolecular C−H functionalization has been developed as a powerful tool for organic synthesis.[1] This method has been particularly useful for the construction of diverse cyclic compounds, such as isoquinolines,[2] isoquinolones,[3] indoles,[4] chromenes,[5] cinnolines,[6] etc.[7] Typically, heteroatom-containing directing groups are integrated, in part or as a whole, into the newly formed heterocyclic frameworks. Synthetic access to pure carbocyclic compounds therefore constitutes a persistent challenge in the C−H activation field. We have recently demonstrated the use of enaminones as highly reactive, aromatic C−H activation directing synthons for coupling with alkynes and α-diazo-β-ketoesters and facile access to 1-hydroxy-2-naphthaldehyde derivatives, compounds containing both aldehyde and hydroxy groups.[8] Further extension of the enaminone reactivity profile to the coupling with 1,4,2-dioxazol-5-ones allows ready synthesis of quinolin-4(1*H*)-one derivatives.[9] We envisioned that switching from aromatic C−H activation to alkenyl C−H activation would provide a synthetic pathway to the construction of a benzene ring framework. Such a framework, to the best of our knowledge, has not been synthetically accessed via a transition-metal-catalyzed directed C−H activation method. Alkenyl C−H activation and functionalization are synthetically more demanding, and the aromatic C−H activation capability for a directing group does not automatically translate to its ability to activate the alkenyl C−H bond. Herein, we report the development of a Rh(III)-catalyzed enaminone-directed alkenyl C−H activation protocol for coupling with alkynes and synthesis of salicylaldehyde derivatives. Importantly, the two reactive functionalities, aldehyde and hydroxy groups, provide convenient synthetic handles for further structural manipulation.

Salicylaldehyde derivatives are an important class of organic compounds used extensively in academia and industry.[10] All previously reported salicylaldehyde synthesis methods start from the benzene ring framework and rely on functional group installation or transformation. Conventional methods for salicylaldehyde synthesis include: (1) Reimer−Tiemann reaction, requiring a substantial amount of NaOH and chloroform and with low yield (20−35%),[11] (2) formylation of phenol, involving several steps under severe conditions,[12] (3) direct oxidation of orthocresol, furnishing many byproducts,[13] (4) oxidation of saligenol, involving strong oxidants,[14] and (5) reduction of salicylic acid, requiring complicated and harsh conditions.[15] Ackermann's group has synthesized salicylaldehydes via C−H hydroxylation of benzaldehydes (Scheme 1), but the protocol demands the use of a complex-structured oxidant.[16] In contrast to the above strategies, the method reported herein enables the simultaneous construction of a benzene ring and installation of both aldehyde and hydroxy groups via a straightforward C−H activation pathway.

Scheme 1. Synthetic Access to Salicylaldehydes by Rh(III)-Catalyzed Enaminone-Directed C−H Activation



Synthetic features:
1) Synthesis of benzene ring framework via transition-metal-catalyzed directed C-H activation
2) Simultaneous incorporation of two functionalities (aldehyde and hydroxy groups)
3) Step-economic
4) Broad substrate scope
5) Demonstrated synthetic utility

We commenced our investigations by examining a model reaction between (1*E*,4*E*)-1-(dimethylamino)-5-phenylpenta-1,4-dien-3-one (**1a**) and prop-1-yn-1-yl benzene (**2a**) (Table 1). The initial screening of the reaction conditions in dichloroethane (DCE), with $[RhCp^*Cl_2]_2$ (5 mol %) and $AgSbF_6$ (20 mol %) as the catalyst precursor, indicates the required participation of an oxidant. Thus, the reaction does not proceed with the addition of 2 equiv of either NaOAc or HOAc (entries 1 and 2, Table 1). The participation of AgOAc as the oxidant enables the achievement of 26% yield for the synthesis of target salicylaldehyde derivative **3aa** after 12 h reaction at 80 °C (entry 3, Table 1). The switching to $Cu(OAc)_2{\cdot}H_2O$ provides an ideal

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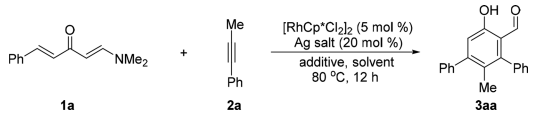
Table 1. Optimization of Reaction Conditions[a,b]



1a 2a 3aa

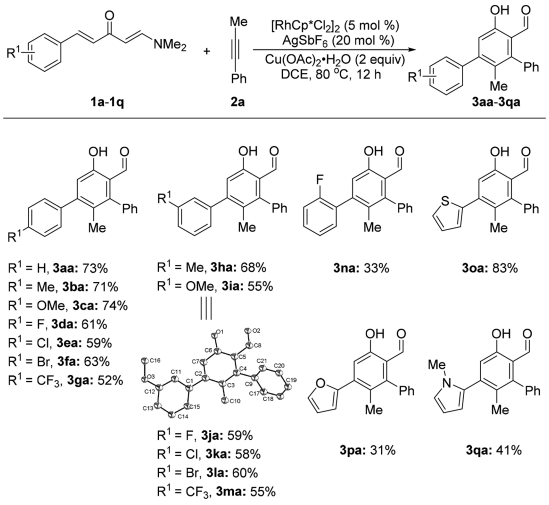
entry	additive (equiv)	Ag salt (mol %)	solvent	yield (%)
1	NaOAc (2)	$AgSbF_6$ (20)	DCE	trace
2	HOAc (2)	$AgSbF_6$ (20)	DCE	0
3	AgOAc (2)	$AgSbF_6$ (20)	DCE	26
4	**$Cu(OAc)_2·H_2O$ (2)**	**$AgSbF_6$ (20)**	**DCE**	**73**
5[c]	$Cu(OAc)_2·H_2O$ (2)	$AgSbF_6$ (20)	DCE	0
6	$Cu(OAc)_2·H_2O$ (2)	-	DCE	49
7	-	$AgSbF_6$ (20)	DCE	0
8	$Zn(OTf)_2$ (2)	$AgSbF_6$ (20)	DCE	0
9	$Cu(OAc)_2·H_2O$ (1)	$AgSbF_6$ (20)	DCE	62
10	$Cu(OAc)_2·H_2O$ (4)	$AgSbF_6$ (20)	DCE	69
11	$Cu(OAc)_2·H_2O$ (2)	$AgSbF_6$ (20)	TFE	trace
12	$Cu(OAc)_2·H_2O$ (2)	$AgSbF_6$ (20)	MeCN	trace
13	$Cu(OAc)_2·H_2O$ (2)	$AgSbF_6$ (20)	MeOH	trace
14	$Cu(OAc)_2·H_2O$ (2)	$AgSbF_6$ (20)	1,4-dioxane	trace
15	$Cu(OAc)_2·H_2O$ (2)	$AgSbF_6$ (20)	THF	47
16	$Cu(OAc)_2·H_2O$ (2)	$AgSbF_6$ (20)	HFIP	trace
17	$Cu(OAc)_2·H_2O$ (2)	AgOTf (20)	DCE	55
18	$Cu(OAc)_2·H_2O$ (2)	$AgBF_4$ (20)	DCE	61
19	$Cu(OAc)_2·H_2O$ (2)	AgO_2CCF_3 (20)	DCE	45

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), solvent (2 mL). [b]Isolated yields. [c]Without $[RhCp*Cl_2]_2$.

reaction condition, furnishing **3aa** in 73% yield (entry 4, Table 1). $Cu(OAc)_2$ is believed to serve as an additive for providing both the oxidant species, Cu(II), and the coordination ligand, OAc^-, for the catalysis. Rh(III) is indispensable, as no product is generated in the absence of $[RhCp*Cl_2]_2$ (entry 5, Table 1). $AgSbF_6$ is beneficial for the reaction, as without it, a lower yield (49%) is observed for **3aa** (entry 6, Table 1). No conversion to **3aa** is identified without $Cu(OAc)_2·H_2O$ (entry 7, Table 1) or with the change of $Cu(OAc)_2·H_2O$ to $Zn(OTf)_2$ (entry 8, Table 1), further supporting the necessity of using an oxidant. The quantity of $Cu(OAc)_2·H_2O$ was then explored. Deviation from 2 equiv negatively impacts the product yield (entries 9 and 10, Table 1), suggesting 2 equiv as the optimum quantity. Further screening of solvents (trifluoroethanol, or TFE; MeCN; MeOH; 1,4-dioxane; tetrahydrofuran, or THF; 1,1,1,3,3,3-hexafluoro-2-propanol, or HFIP) proves that no other solvent gives a better outcome than DCE (entries 11−16, Table 1). Similarly, the screening of Ag salts (AgOTf, $AgBF_4$, AgO_2CCF_3) confirms that $AgSbF_6$ is the best chloride abstracting reagent (entries 17−19, Table 1).

With the optimized conditions established, we then proceeded to the extensive evaluation of the synthetic scope. The substrate scope of enaminones (**1a−1q**) was first examined by reacting with **2a** (Scheme 2). Satisfactorily, a wide range of (1*E*,4*E*)-1-(dimethylamino)-5-phenylpenta-1,4-dien-3-one derivatives are compatible with the protocol. The reaction proceeds well for (1*E*,4*E*)-1-(dimethylamino)-5-phenylpenta-1,4-dien-3-ones bearing both electron-donating (Me, **1b**; OMe, **1c**) and electron-withdrawing (F, **1d**; Cl, **1e**; Br, **1f**; CF_3, **1g**) groups at the *para* position. In general, the electron-rich substrates give a better yield than the electron-poor substrates. Various *meta*-substituted substrates (Me, **1h**; OMe, **1i**; F, **1j**; Cl, **1k**; Br, **1l**; CF_3, **1m**) are also tolerated. However, in this case, the product yield for electron-rich substrates is not necessarily

Scheme 2. Substrate Scope for Enaminones[a,b]



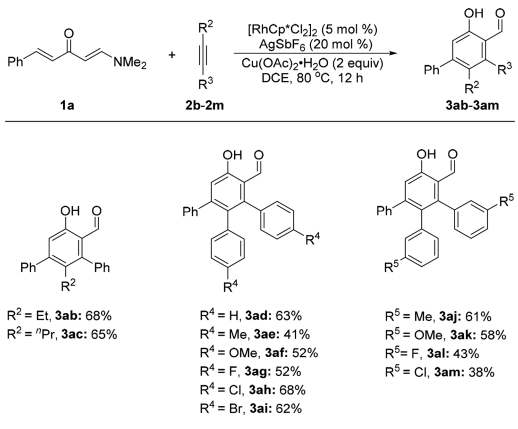
1a-1q 2a 3aa-3qa

[a]Reaction conditions: **1a−1q** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), and DCE (2 mL). [b]Isolated yields.

higher than that for electron-poor ones. Further, the *ortho* substitution (F, **1n**) is also compatible with the reaction. Importantly, the thienyl (**1o**), furanyl (**1p**), and pyrrolyl (**1q**) groups can also be accommodated, allowing the generation of as-expected target products. Preliminary experiments with (1*E*,4*E*)-1-cyclohexyl-5-(dimethylamino)penta-1,4-dien-3-one and (*E*)-1-(cyclohex-1-en-1-yl)-3-(dimethylamino)prop-2-en-1-one showed no reactivity.

We then proceeded to establish the substrate scope of alkynes by a reaction with **1a** (Scheme 3). The reaction occurs in a

Scheme 3. Substrate Scope for Alkynes[a,b]



1a 2b-2m 3ab-3am

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2b−2m** (0.3 mmol, 1.5 equiv), and DCE (2 mL). [b]Isolated yields.

regiospecific manner for a variety of unsymmetrically substituted phenyl/alkyl (Et, **2b**; ^{n}Pr, **2c**) alkynes. Also, diphenylacetylene (**2d**) and its derivatives can also be successfully employed in the reaction to afford respective target products. Both *para*- (Me, **2e**; OMe, **2f**; F, **2g**; Cl, **2h**; Br, **2i**) and *meta*-substituted (Me, **2j**; OMe, **2k**; F, **2l**; Cl, **2m**), electron-rich and electron-poor diphenylacetylenes can react smoothly. No reactivity is observed for alkyl/alkyl and ester/ester alkynes under the experimental conditions employed herein.

With the synthetic scope investigated, we next probed the mechanism of the reaction by H−D scrambling, competition,

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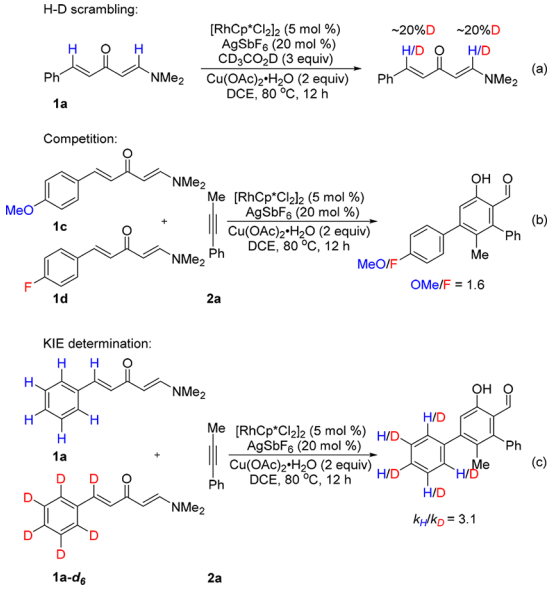
and kinetic isotope effect (KIE) experiments (Scheme 4). Treatment of **1a** under the standard reaction conditions with

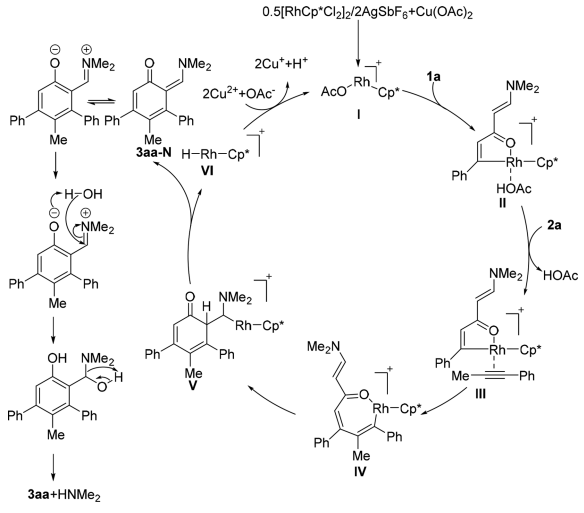
Scheme 4. Mechanistic Studies



CD_3CO_2D results in an approximately 20% D incorporation at the two alkene carbon atoms β to the ketone group (Scheme 4a), supporting ketone as the C−H activation directing group and formation of a five-membered rhodacycle after C−H activation.[8] The high H−D scrambling efficiency indicates that the C−H activation step is reversible for **1a**. The competition between an electron-rich and an electron-poor enaminone for reaction with **2a** (Scheme 4b) shows a higher reactivity for the electron-rich substrate, which is consistent with an electrophilic aromatic substitution C−H activation pathway. The reaction of **1a**/**1a**-d_6 and **2a** identified a high KIE value (k_H/k_D = 3.1) (Scheme 4c), suggesting that C−H activation is the rate-determining step.

Based on the literature[8] and the above mechanistic results, a plausible reaction pathway is proposed (Scheme 5), using **1a** and **2a** as the illustrative reactants: reaction of $[RhCp^*Cl_2]_2$/$4AgSbF_6$ with $Cu(OAc)_2$ to create rhodium acetate species **I**; coordination of the ketone group from **1a** and C−H activation

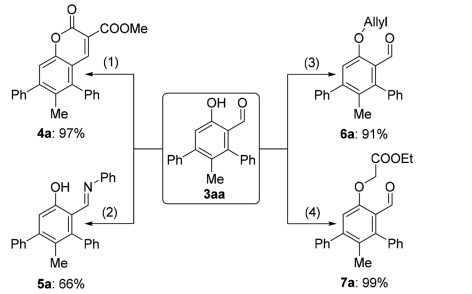
Scheme 5. Proposed Reaction Pathway



to generate rhodacycle complex **II**; further coordination of alkyne **2a** to yield **III**; migratory insertion of alkyne, migratory insertion of the alkene portion of the enaminone moiety, and β-hydride elimination provide intermediate species **IV**, **V**, and **VI** ($[Cp^*RhH]^+$) along with the formation of **3aa-N**; oxidation of $[Cp^*RhH]^+$ by $Cu(OAc)_2$ regenerates **I**; and nucleophilic attack of **3aa-N** by H_2O furnishes the final product **3aa**. The selectivity for 6-exo (insertion of alkene) rather than 5-exo (insertion of ketone) cyclization likely reflects the dominance of steric effect in this process.

The aldehyde and hydroxy groups contained in these salicylaldehyde derivatives suggest the ability to perform further synthetic manipulation. Several conversions utilizing **3aa** as the model reactant are illustrated here to demonstrate the powerful transformation capability enabled by our synthetic method (Scheme 6). In particular, one can use both aldehyde and

Scheme 6. Transformations of 3aa



Conditions: (1) **3aa** (0.1 mmol), dimethyl malonate (1.5 equiv), piperidine (5 mol %), MeCN, rt, 12 h
(2) **3aa** (0.1 mmol), $PhNH_2$ (1.5 equiv), MeOH, 60 °C, 6 h
(3) **3aa** (0.1 mmol), allylBr (1.5 equiv), K_2CO_3 (0.6 equiv), DMF, rt,12 h
(4) **3aa** (0.1 mmol), ethyl bromoacetate (1.5 equiv), K_2CO_3 (0.8 equiv), MeCN, reflux, 3 h

hydroxy groups to react with dimethyl malonate for the generation of cyclized product **4a**;[17] the aldehyde group can be used alone to react with the amino group for the formation of imine product **5a**; and the hydroxy group can serve as a nucleophile to react with bromo-containing molecules for the formation of ether linkages (**6a** and **7a**).[18]

In summary, we have developed herein a Rh(III)-catalyzed enaminone-directed alkenyl C−H activation method for coupling with alkynes and synthesis of salicylaldehydes. This represents a synthetically unique example of benzene ring framewok formation through a transition-metal-catalyzed, directed C−H activation strategy. The two reactive functionalities (aldehyde and hydroxy groups) generated along the way provide a powerful synthetic handle for further structural manipulation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01563.

Experimental procedures and product characterization (PDF)

Copies of the ^1H and ^{13}C NMR spectra of selected products (PDF)

Accession Codes

CCDC 1843803 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_

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request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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