Carbocyclization

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Enaminones as Synthons for a Directed C–H Functionalization: Rh^{III}-Catalyzed Synthesis of Naphthalenes

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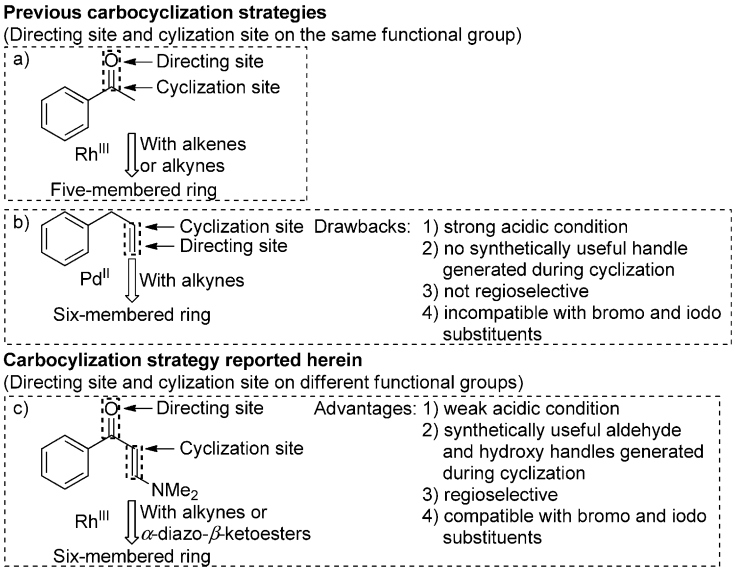
Abstract: *The use of enaminones as effective synthons for a directed C–H functionalization is reported. Proof-of-concept protocols have been developed for the Rh^{III}-catalyzed synthesis of naphthalenes, based on the coupling of enaminones with either alkynes or α-diazo-β-ketoesters. Two inherently reactive functionalities (hydroxy and aldehyde groups) are integrated into the newly formed cyclic framework and a broad range of substituents are tolerated, rendering target products readily available for further elaboration.*

Naphthalenes are an important class of organic compounds with applications in a wide range of academia and industrial sectors.[1] A plethora of conventional synthetic methods have been developed for accessing this type of highly useful polyaromatic structures, which include: Diels–Alder reactions, transition-metal-mediated cyclizations, ring rearrangements or expansions, and Lewis acid catalyzed cyclizations.[2] Despite progress, essentially all of the methods reported thus far rely on a laborious and tedious prearrangement of a complex set of functional groups.[3] The Lewis acid based intermolecular coupling protocols allow partial circumvention of the issue but come at the expense of limited substrate scope.[4]

Transition-metal-catalyzed, directed intermolecular C–H functionalization offers a powerful tool for the synthesis of cyclic scaffolds, which complements conventional methods.[5] Typical end products of these reactions are heterocycles, where heteroatom-containing directing groups, in part or as a whole, are incorporated into target frameworks.[6] The synthesis of carbocyclic compounds by this route is technically more challenging as it requires a dominant cyclization reactivity at a typically less reactive site. Therefore, a less strong directing group is resorted to for avoiding competing heteroatom cyclization pathways. The ketone group has been the primary focus of attention along this line of research because of its high electrophilic reactivity (Scheme 1 a). However, in spite of tremendous progress, only five-membered carbocycles have been obtained thus far.[7] To enable the construction of an alternative scaffold, the six-membered naphthalene ring structure, a weaker directing group, an alkene moiety, is positioned one carbon atom away from the phenyl ring to eliminate the five-membered-ring synthetic pathway (Scheme 1 b).[8] Using a weakly coordinating alkene group, however, translates to, inevitably, several major drawbacks associated with that Pd^{II}-based catalytic system: 1) required use of a strong acid for the generation of a highly electrophilic Pd^{II} species, 2) no synthetically useful functionalities integrated into the target framework during the ring-forming process, 3) poor regioselectivity associated with the alkyne coupling partner, and 4) incompatibility with synthetically useful handles such as bromo and iodo substituents.



Scheme 1. Schematic representation of different carbocyclization strategies.

For both of the above carbocyclization strategies, directing and cyclization site are located on the same functional group (ketone or alkene, respectively). We envisioned that a distinct reaction pathway should be possible when separating those two sites. A ketone group is typically a preferred site for coordination compared with an alkene group but the reactivity of an alkene group can override that of a ketone group under certain circumstances (e.g., organometallic migratory insertion, polarity matching). Herein, we report on the use of enaminones, which contain both ketone and

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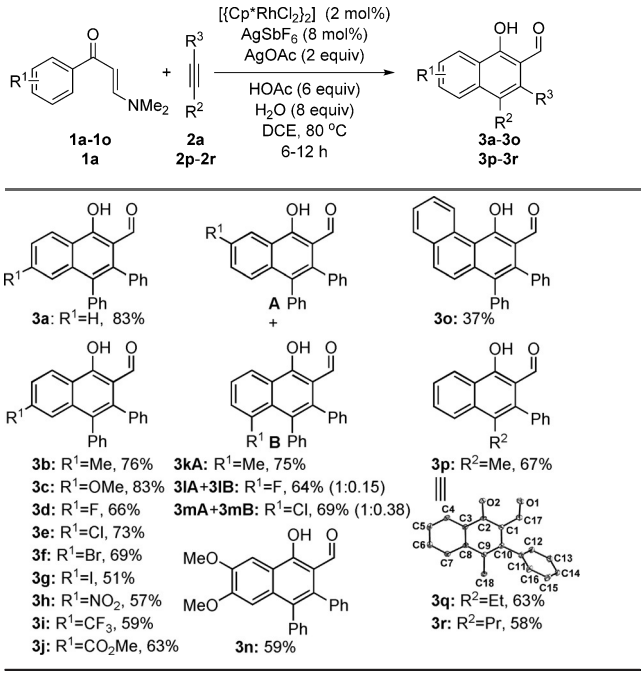
alkene groups, as effective synthons for the directed C–H functionalization (Scheme 1c). Proof-of-concept protocols for the synthesis of naphthalene derivatives have been developed based on the Rh^{III}-catalyzed coupling of enaminones with either alkynes or α-diazo-β-ketoesters. Enaminones, or enamines of 1,3-diketone or 3-ketoester compounds, represent a class of highly versatile synthetic intermediates because of their push–pull electronic structure.[9] This intriguing conjugated O=C–C=C–N system can exhibit reactivity as ambident nucleophile (enamine) and electrophile (enone).[10] Its broad synthetic utility is highlighted by the ability to construct a diversified set of cyclic scaffolds but nevertheless has never been demonstrated in the C–H functionalization context.[11] We used readily available aromatic enaminones (prepared from acetophenones and *N*,*N*-dimethylformamide dimethylacetal) for target transformations and importantly, the naphthalene derivatives obtained contain two oxygen-containing functional groups, aldehyde and hydroxy, that are amenable to further synthetic elaboration.

First, we examined the C–H functionalization/cyclization reaction between (*E*)-3-dimethylamino-1-phenylprop-2-en-1-one (**1a**) and diphenylacetylene (**2a**) using a variety of additives and solvents at 60 °C with [{Cp*$RhCl_2$}$_2$] (2 mol %)/$AgSbF_6$ (8 mol %) as the catalyst precursor (Table S1). With 2 equiv of either $Cu(OAc)_2$ or AgOAc, the target product 1-hydroxy-3,4-diphenyl-2-naphthaldehyde (**3a**) was formed in > 10 % yield. The combination of AgOAc and dichloroethane (DCE) gave the best result (25 % yield). Further screening of additives revealed that the addition of HOAc/H_2O (2.0 equiv each) promoted the yield to a promising 56 %. A further improvement in the yield (79 %) was possible by increasing the amount of HOAc (6.0 equiv) and H_2O (8.0 equiv). The yield could be boosted to 83 % with a slight adjustment of the reaction temperature to 80 °C.

Under optimized conditions, the scope of the enaminones was examined by using **2a** as the coupling partner (Table 1). Enaminones bearing an electron-rich substituent (**1b**, methyl; **1c**, methoxy) on the phenyl ring afforded the desired products in good yields (**3b**, 76 %; **3c**, 83 %). Substrates containing electron-deficient substituents (**1d**, fluoro; **1e**, chloro; **1f**, bromo; **1g**, iodo) were slightly less reactive, and the corresponding products **3d**–**3g** were isolated in 66, 73, 69, and 51 % yields, respectively. The compatibility with bromo and iodo substituents is an appealing feature differentiating the Rh catalysis system from the Pd system because oxidative addition of the polar carbon–bromo/carbon–iodo bond is a typical reactivity pattern observed for Pd. Importantly, our catalytic reaction worked even for substrates containing a highly electron-withdrawing group (**1h**, nitro; **1i**, trifluoromethyl; **1j**, methoxycarbonyl), and the corresponding products **3h**–**3j** were obtained in moderate yields (57, 59, and 63 %, respectively). For *meta*-substituted substrates (**1k**, methyl; **1l**, fluoro; **1m**, chloro), the preferred coupling site for the phenyl ring is the carbon atom *para* to the substituent (**3k**–**3m**), likely reflecting the operation of a steric effect. Among the substituents examined, the methyl group (**1k**) is the most bulky, thus offering the generation of a single product

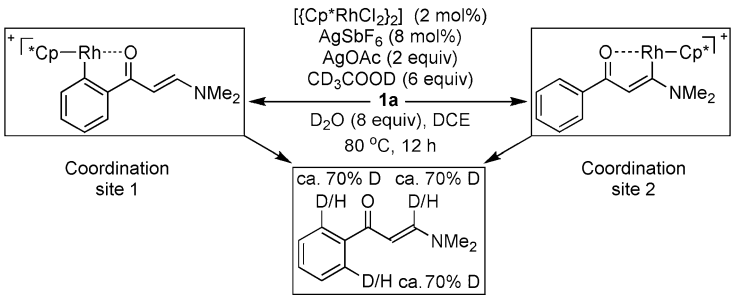
Table 1: Synthetic scope for the reaction between enaminones and alkynes.[a,b]



[a] Conditions: enaminone (0.5 mmol), alkyne (1.5 equiv), DCE (2.0 mL). [b] Yield of isolated product.

(**3kA**). The less sterically hindered fluoro (**1l**) and chloro (**1m**) groups cannot completely prevent the formation of *ortho*-coupled regioisomers (**3lB**, **3mB**), which accounted for a small percentage of the final products. The reaction can also be applied to multi-substituted (**1n**, dimethoxy) and polycyclic (**1o**, naphthyl ring) substrates, and the corresponding products (**3n**, **3o**) were acquired in 59 and 37 % yields, respectively. With the enaminone substrate scope examined, we next investigated the alkyne scope by using asymmetrically substituted alkynes. Most significantly, regioselectivity is excellent for such a type of substrate (phenyl/alkyl alkyne: **2p**, methyl; **2q**, ethyl; **2r**, propyl). Compound **3p** could be easily recrystallized and its single-crystal X-ray diffraction study provided unambiguous evidence for the formation of a naphthalene framework with pendant aldehyde and hydroxy groups.[12]

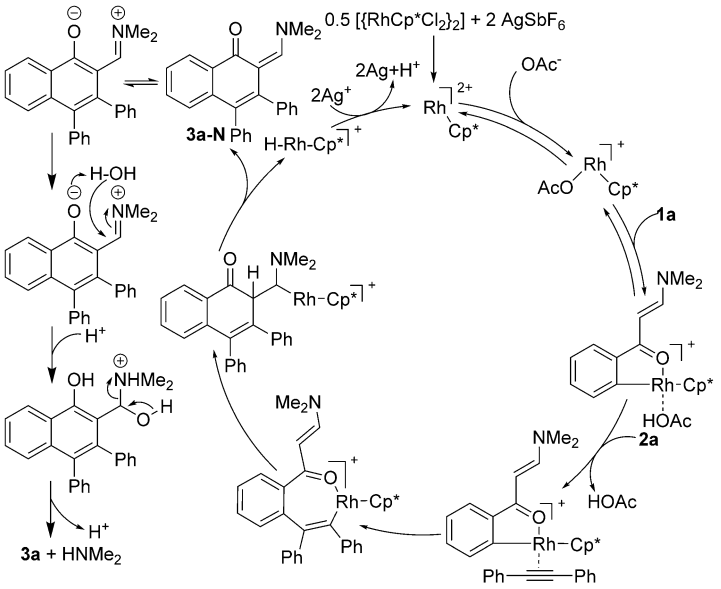
The reaction mechanism was investigated initially through a deuterium labeling study with **1a**. A key evidence for the



Scheme 2. Deuterium labeling study with **1a**.

ketone group as directing group came from the identification of three hydrogen/deuterium scrambling sites: the two *ortho* carbon atoms on the phenyl ring, and the alkene carbon atom next to the dimethylamino group (Scheme 2). Indeed, a π-coordination of the alkene group to Rh^{III} would allow C–H activation only at the two *ortho* carbon sites; whereas a coordination from the ketone oxygen atom would enable simultaneous C–H activation at all three sites, through the formation of two types of five-membered rhodacycles.

A large kinetic isotope effect (KIE) was observed ($k_H/k_D = 5.3$) in an experiment between **1a**/[D_5]-**1a** and **2a**, suggesting that C–H activation is involved in the turnover-limiting step. A competition experiment, reaction of electron-rich (**1c**) and electron-poor (**1d**) enaminones with **2a**, indicated a slightly higher reactivity for the electron-rich substrate, providing evidence for an electrophilic aromatic substitution (EAS) pathway. No reaction occurred in a control experiment performed with 1-phenylprop-2-en-1-one and **2a**, suggesting that the reaction outcome can be substantially influenced by even a remote substituent (most likely through electronic effects).



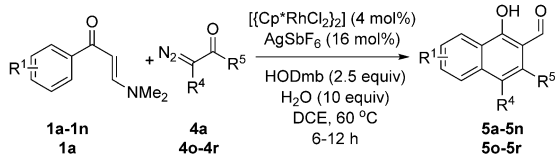
Scheme 3. Proposed mechanism for the reaction involving enaminones and alkynes.

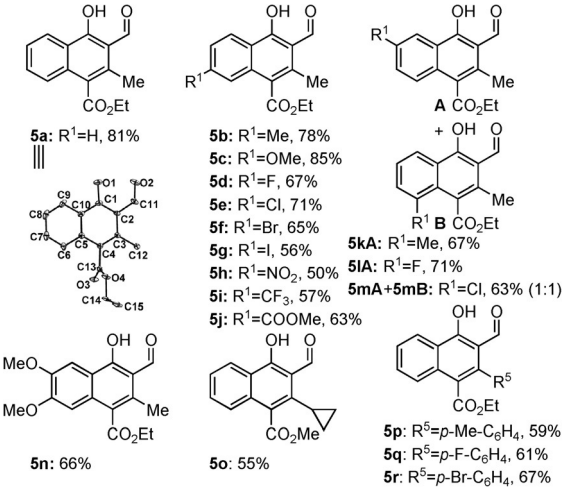
Based on these results, a plausible catalytic cycle is proposed in Scheme 3: reaction of [{Cp*$RhCl_2$}$_2$] and $AgSbF_6$ to produce a cationic $[Cp^*Rh]^{2+}$ species, coordination of OAc^- and the enaminone **1a**, turnover-limiting C–H activation, migratory insertion of the alkyne **2a**, further migratory insertion of the alkene, β-hydride elimination to release **3a-N** and $[Cp^*RhH]^+$, reoxidation of $[Cp^*RhH]^+$ to afford $[Cp^*Rh]^{2+}$ and H^+, nucleophilic attack of **3a-N** by H_2O to generate the final product **3a**. The proposal of a late-stage nucleophilic attack by H_2O, most likely after cyclization, is based on the fact that 1) the C–N bond remains intact after C–H activation (Scheme 2), 2) as a control, substitution (with a methyl group) at the alkene carbon atom next to the ketone group renders the enaminone prone to hydrolysis by H_2O, and 3) in the absence of H_2O, a product can still be formed (speculated to be **3a-N**) but is difficult to separate by silica gel chromatography.

With the satisfactory results obtained for alkyne substrates, we envisioned that α-diazo-β-ketoesters might equally well serve as competent coupling partners, considering the nucleophilic reactivity of alkene carbon atoms next to a ketone group and expected retention of the electrophilic ketone group from α-diazo-β-ketoesters after a typical Rh^{III} catalytic cycle. Indeed, a screening of reaction conditions under [{Cp*$RhCl_2$}$_2$] (2 mol%)/$AgSbF_6$ (8 mol%) catalysis in DCE, by using **1a** and ethyl 2-diazo-3-oxobutanoate (**4a**) as the coupling partners, confirmed a reaction with participation of an additive (Table S7). As expected, no oxidant was necessary. Among the additives, 2,2-dimethylbutyric acid (HODmb, 2 equiv)/H_2O (8 equiv) gave the best yield (46%) for **5a**. A change from DCE to other solvents negatively impacted the yield. An increase in the amount of catalytic species and additive proved to be helpful. Optimized reaction conditions include [{Cp*$RhCl_2$}$_2$] (4 mol%)/$AgSbF_6$ (16 mol%), HODmb (2.5 equiv), H_2O (10 equiv), DCE, 60 °C, under which **5a** could be obtained in 81% yield. Single-crystal X-ray analysis confirmed the structure assignment.[12]

Based on the optimized reaction conditions, the enaminone substrate scope was then investigated by using **4a** as the coupling partner (Table 2). Both electron-rich and electron-

Table 2: Synthetic scope for the reaction between enaminones and α-diazo-β-ketoesters.[a,b]

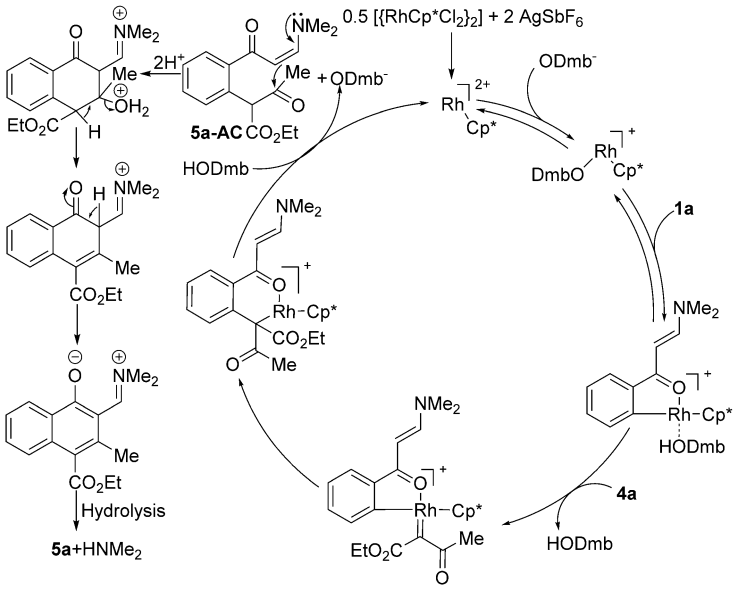




[a] Conditions: enaminone (0.5 mmol), α-diazo-β-ketoester (1.5 equiv), DCE (2.0 mL). [b] Yield of isolated product.

poor substituents on the phenyl ring were tolerated. In general, the electronic effect mirrors that from the alkyne coupling partner. Electron-rich substituents (**1b**, **1c**) gave better yields than electron-poor substituents (**1d**–**1j**). And again, the reaction could still proceed for substrates bearing very electron-deficient substituents (**1h**–**1j**), and the respective products were obtained in moderate yields. Compared to the alkyne case, the regioselectivity for *meta*-substituted substrates is better for the fluoro substituent (**1l**) but worse for the chloro substituent (**1m**), likely reflecting a mixed play of steric and electronic effects. A disubstituted substrate (**1n**) reacted equally well. An examination of the α-diazo-β-ketoester scope revealed compatibility with the cyclopropyl group (**4o**) as well as with a variety of substituents (**4p**, methyl; **4q**, fluoro; **4r**, bromo) on the phenyl ring (*para* to the ketone group).

Mechanistic experiments revealed a large KIE ($k_H/k_D = 6.1$ for the reaction between **1a**/[D_5]-**1a** and **4a**) and a small electronic effect (preferred reaction with **4a** for electron-rich **1c** over electron-deficient **1d**), again suggesting an EAS pathway for the turnover-limiting C–H activation step.

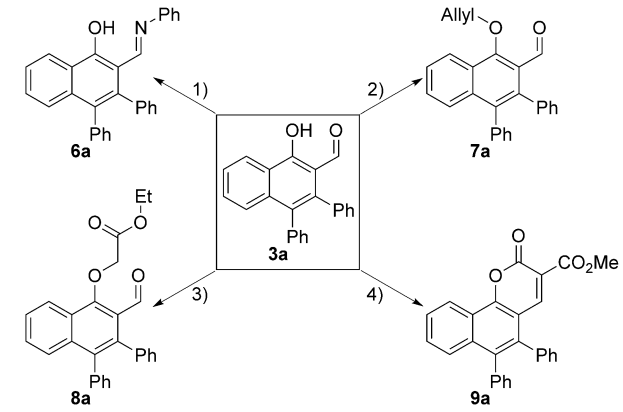


Scheme 4. Proposed mechanism for the reaction involving enaminones and α-diazo-β-ketoesters. The hydrolysis process is similar to that described in Scheme 3.

Based on the above results and literature precedents,[13] a plausible reaction mechanism is proposed in Scheme 4: generation of a cationic $[Cp^*Rh]^{2+}$ species for the C–H activation, formation of a Rh^{III}–carbene species, 1,1-migratory insertion and proto-demetalation to produce intermediate **5a-AC** and release of Rh^{III} for a new catalytic cycle, two consecutive nucleophilic attacks for the ring closure, and formation of the aldehyde.

The oxygen-containing functional groups of the formed naphthalene derivatives are amenable to further transformations. Briefly described herein are several conversions using **3a** as model reactant (Scheme 5). As expected, the aldehyde group reacted with an amino group (from aniline), affording an imine product (**6a**). And the hydroxy group provided a handle for the generation of ethers (**7a** and **8a**) through reaction with a bromo-containing molecule.[14] Significantly, participation of both aldehyde and hydroxy groups enabled the synthesis of another ring structure on the original naphthalene framework (**9a**).[15]

In summary, we have proposed an enaminone-directed C–H functionalization method and demonstrated its utility in the Rh^{III}-catalyzed synthesis of naphthalenes, through coupling with either alkynes or α-diazo-β-ketoesters. The reaction takes advantage of the C–H activation directing capability of ketone groups and the unique reactivity pattern associated with enaminones. Two inherently reactive functionalities (aldehyde and hydroxy) have been built into the naphthalene framework and a broad range of substitution patterns is tolerated, rendering target products readily available for further synthetic manipulation.



Conditions: 1) **3a** (0.5 mmol), $PhNH_2$ (1.2 equiv), MeOH, 60 °C, 6 h, 82%
2) **3a** (0.5 mmol), allylBr (1.2 equiv), K_2CO_3 (0.6 equiv), DMF, r.t., 12 h, 86%
3) **3a** (0.5 mmol), ethyl bromoacetate (1.5 equiv), K_2CO_3 (0.8 equiv), MeCN, reflux, 3 h, 91%
4) **3a** (0.5 mmol), dimethyl malonate (1.5 equiv), piperidine (5 mol%), MeCN, r.t., 12 h, 87%

Scheme 5. Transformations of **3a**.

Acknowledgements

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[12] CCDC 1479379 (**3p**) and 1479380 (**5a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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