Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Annulation of β-Enaminonitriles with Alkynes via Rh^{III}-Catalyzed C−H Activation: Direct Access to Highly Substituted 1-Naphthylamines and Naphtho[1,8-*bc*]pyridines

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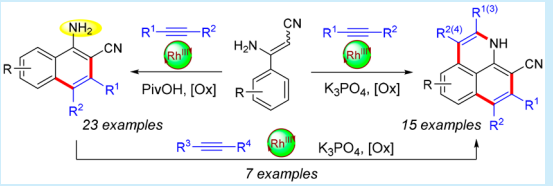
Supporting Information

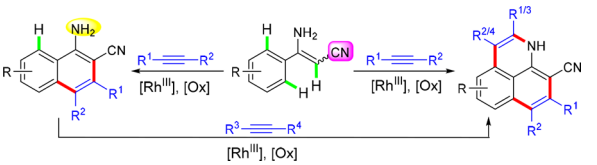
ABSTRACT: A Cp*Rh^{III}-catalyzed oxidative annulation of β-enaminonitriles with alkynes was reported to achieve selective synthesis of polysubstituted 1-naphthylamines and naphtho[1,8-*bc*]pyridines via multiple C−H activations. Assisted by a naphthylamine NH_2 group, 1-naphthylamines were also readily cyclized to produce naphtho[1,8-*bc*]pyridines. In addition, the obtained naphtho[1,8-*bc*]pyridine derivatives exhibit intense fluorescence in the solid state.



Over the past decade, transition-metal-catalyzed direct functionalization of inert C−H bonds has emerged to be an increasingly powerful tool for synthetic innovation.[1] In particular, Cp*Rh^{III} complexes have been established as highly active and versatile precatalysts in this field,[2] which has allowed the construction of various cyclic scaffolds in a more step-economical and waste-reducing manner. In this context, diverse approaches for heterocycle synthesis through Rh^{III}-catalyzed C−H activation and annulation strategies have been well-documented.[2,3] However, the formation of carbocyclic compounds[4] still lags behind. In particular, for six-membered carbocycles, whereas substituted fused arenes[5] and 1-naphthols[6] have been accessed by catalytic C−H functionalization, the preparation of 1-naphthylamine derivatives, to the best of our knowledge, remains unexplored. In continuation of our interest in transition-metal-catalyzed oxidative annulation reactions,[6a,7] we envisioned that the application of a cyclization methodology to construct substituted 1-naphthylamines would be highly interesting and attractive if simple and readily available enamide derivatives could be employed as reacting substrates.[8] Enamides have been frequently explored as valuable precursors in transition-metal-catalyzed C−H bond activation, but the typical end products are pyrroles and pyridines.[9] Thus, the introduction of a proper group to enamides might be a key point in manipulating the reaction pathway.

According to our previous observation on the significance of the nitrile group in the oxidative coupling of benzoylacetonitriles with alkynes, as well as the corresponding cyclization of *ortho*-substituted benzoylacetonitriles to 1-naphthol derivatives,[6a] β-enaminonitriles were chosen to verify our hypothesis. Indeed, 3-amino-3-arylacrylonitriles were suitable synthons for this transformation. We herein disclose our new development of oxidative annulation of β-enaminonitriles with alkynes under rhodium catalysis to selectively produce polysubstitued 1-naphthylamines and naphtho[1,8-*bc*]pyridines via multiple C−H activations (Scheme 1). The obtained 1-naphthylamines are also readily converted into naphtho[1,8-*bc*]pyridines via a naphthylamine NH_2 group directed C−H/N−H bond activation.[10] Note that the nitrile group is essential for carbocyclic 1-naphthylamine formations, as evidenced by the recent report that oxidative coupling of β-enamino esters with alkynes generated a six-membered N-containing heterocycle intermediate in the first cyclization process.[11] Importantly, the resulting naphthylamine and naphtho[1,8-*bc*]pyridine scaffolds are embedded in a large number of conjugated π-systems that exhibit important electrochemical and photochemical properties with potential applications as organic semiconductors and luminescence materials.[12]

Scheme 1. Rh(III)-Catalyzed Synthesis of Polysubstituted 1-Naphthylamines and Naphtho[1,8-*bc*]pyridines



Our initial attempt to synthesize a substituted 1-naphthylamine involved reaction of 3-amino-3-phenylacrylonitrile (**1a**) and diphenylacetylene (**2a**) as model substrates in the presence of $[Cp^*RhCl_2]_2$ catalysts. To our delight, the reaction did proceed to give the desired cyclized product **3a** in 26% isolated

Received: July 25, 2018

DOI: 10.1021/acs.orglett.8b02341
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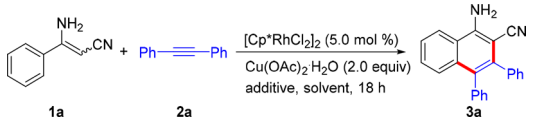
yield at 80 °C in DMF (Table 1, entry 1). The structure of **3a** was established by ^{1}H and ^{13}C NMR analysis as well as HRMS

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

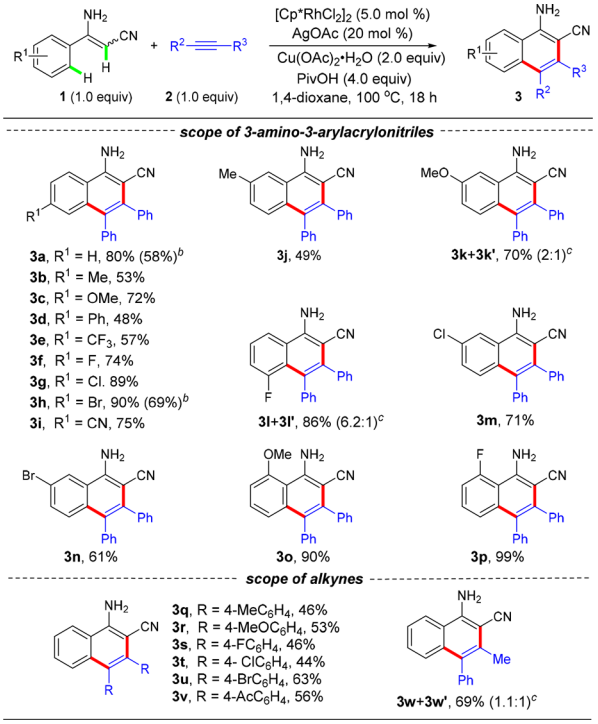
entry	additive (equiv)	solvent	temp (°C)	yield (%)[b]
1		DMF	80	26
2[c]		DMF	80	NR
3		MeCN	80	trace
4		DCE	80	trace
5		THF	80	52
6[d]		THF	80	44
7[e]		THF	80	23
8[f]		THF	80	NR
9		THF	60	trace
10		THF	100	57
11	PivOH (2.0)	THF	100	62
12	AgOAc (0.2)	THF	100	58
13	AgOAc (0.2) + PivOH (2.0)	THF	100	66
14	AgOAc (0.2) + PivOH (4.0)	THF	100	77
15	AgOAc (0.2) + PivOH (4.0)	dioxane	100	80

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv), additive (equiv), solvent (2.0 mL), Ar, temp, 18 h. [b]Isolated yield. [c]No [Rh] catalyst. [d]$Cu(OAc)_2$ was used instead of $Cu(OAc)_2{\cdot}H_2O$. [e]AgOAc was used instead of $Cu(OAc)_2{\cdot}H_2O$. [f]Ag_2CO_3 was used instead of $Cu(OAc)_2{\cdot}H_2O$. NR = no reaction.

spectrometry. As expected, no conversion was observed in the absence of rhodium catalyst (entry 2). Solvent screening revealed that THF was superior to DMF, MeCN, and DCE, leading to a higher yield (entries 1, 3–5). Among different oxidants evaluated, $Cu(OAc)_2{\cdot}H_2O$ was found to be optimal. Other oxidants including $Cu(OAc)_2$, AgOAc, and Ag_2CO_3 proved to be less effective or even ineffective (entries 6–8). The reaction efficiency was also sensitive to the reaction temperatures. Thus, the reaction was inactive when performed at 60 °C (entry 9), whereas higher reaction temperature (100 °C) gave a better result (entry 10). Various additives were then investigated on the benchmark reaction.[13] It was surprising to observe that although AgOAc (0.2 equiv) and PivOH (2.0 equiv) individually hardly promoted the reaction efficiency (entries 11 and 12), a combination of these two additives brought about notable progress in product yield (entry 13). Addition of 4.0 equiv of PivOH further enhanced the catalytic activity, and the yield of **3a** was increased to 80% in dioxane (entries 14 and 15).

With the promising optimal conditions, the reaction scope with respect to *β*-enaminonitrile was first explored (Scheme 2). A host of 3-amino-3-arylacrylonitriles could all be cyclized with good to excellent yields. Although various *para*-substituted substrates were coupled without difficulty (**3a**–**3i**), the desired cyclization was found to proceed more efficiently with halide groups (**3f**–**3h**). For substrates with *meta*-methyl, *meta*-chloro, or *meta*-bromo substituents, the most accessible aromatic C–H bond was preferentially activated (**3j**, **3m**, and **3n**). However, two regioisomers **3k** and **3k′** were obtained in a 2:1 ratio from a *meta*-methoxy-substituted substrate, indicating a considerable secondary directing group effect on the C–H bond activation.[14]

Scheme 2. Substrate Scope of Oxidative Annulation of 3-Amino-3-arylacrylonitriles to 1-Naphthylamines[a]



[a]Reactions in 0.2 mmol scale (0.1 M), isolated yield. [b]4.0 mmol scale reaction. [c]The structure of major regioisomer is shown.

This effect is more pronounced for the *meta*-fluoro substituent, thereby leading to the site selectivity that afforded the more sterically hindered compound **3l** as the major products. Interestingly, no steric influence at the *ortho* position was found as **3o** (90%) and **3p** (99%) were isolated in even higher yields.[15] We found that several functional groups, such as methoxy (**3c**, **3k**, and **3o**), trifluoromethyl (**3e**), fluoro (**3f**, **3l**, and **3p**), chloro (**3g** and **3m**), bromo (**3h** and **3n**), and nitrile (**3i**), remained intact under the present reaction conditions. Moreover, as shown for **3a** (58%) and **3h** (69%), scale-up reactions (4 mmol) provided moderate yield, thereby demonstrating the practicality of this method. Unfortunately, 1-naphthyl, 2-naphthyl, 2-thienyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl derived *β*-enaminonitriles exhibited very low or no reactivity under the current reaction conditions.

Next, we expanded the scope of this protocol to other alkyne substrates. As shown in Scheme 2, the present catalytic system could be extended effectively to a variety of symmetric diarylacetylenes containing methyl, methoxy, fluoro, chloro, bromo, and acetyl groups (**3q**–**3v**). Unsymmetrical aryl alkyl-disubstituted alkyne was also a suitable coupling partner, albeit with low regioselectivity. For example, prop-1-ynylbenzene gave rise to regioisomers **3w** and **3w′** in a 1.1:1 ratio. In contrast, dialkyl-substituted alkynes and terminal alkynes failed to work under the standard conditions, which is indicative of the limitation of the method.

To gain insight into the mechanism of this catalytic process, we next conducted preliminary mechanistic studies.[13] First, intermolecular competition experiments between **1c** and **1h** with **2a** showed electron-deficient substrates to be preferentially functionalized (Scheme S1-a), which suggests that the C–H activation step might not proceed in a simple electrophilic

DOI: 10.1021/acs.orglett.8b02341
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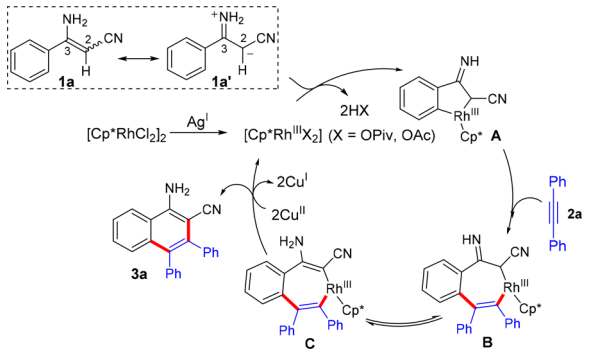
aromatic substitution process. Second, the H/D exchange experiment of **1a** revealed that the *ortho* C−H bond cyclometalated step is irreversible (Scheme S1-b). Finally, parallel intermolecular kinetic isotope effect experiments were studied between **1a** and **1a**-d_5, and a value of $k_H/k_D \approx 2.3$ was observed (Scheme S1-c), demonstrating that cleavage of the C−H bond is likely involved in the turnover-limiting step.[16]

On the basis of the above experimental results and the literature precedents,[6,7] a tentative reaction mechanism was proposed for this naphthylamine synthesis (Scheme 3). The

Scheme 3. Proposed Mechanism for Oxidative Annulation of 3-Amino-3-arylacrylonitriles to 1-Naphthylamines

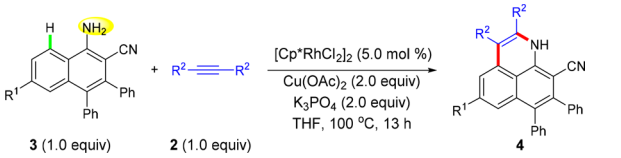


enamine resonance structure **1a**′ imparts the C(2) atom certain nucleophilic characteristics.[17] As a result, a five-membered rhodacylic intermediate **A** is formed initially through the reaction of *β*-enaminonitrile with the [Cp*Rh^{III}] species generated from $[Cp^*RhCl_2]_2$ and AgOAc, which involves an irreversible C-coordination and carboxylate-assisted cleavage of the *ortho* C(sp^2)−H bond.[18] Subsequently, coordination and migratory insertion of alkyne **2a** furnishes a seven-membered rhodacycle **B**. Tautomerization of **B** leads to the formation of intermedate **C**,[19] which then undergoes reductive elimination to afford the final product **3a** along with a Rh^I species. The Rh^I species is oxidized into the catalytically active Rh^{III} complex with the aid of copper oxidant.

With the satisfactory results obtained for the synthesis of polysubstituted 1-naphthylamine products, we anticipated that a further annulation with alkyne might take place under the assistance of the naphthylamine NH_2 group to yield tricyclic heteroaromatic compounds. Indeed, a screening of reaction conditions under rhodium(III) catalysis in THF, by using **3a** and **2a** as the coupling partners, confirmed a reaction with participation of $Cu(OAc)_2$ as an oxidant and K_3PO_4 as an additive. The corresponding naphtho[1,8-*bc*]pyridine **4a** was thus obtained in 93% isolated yield (Table 2, entry 1). Furthermore, substituted naphthylamines (**3g** and **3h**) and diarylacetylenes (**2b** and **2d**) reacted smoothly to provide the desired tricyclic products **4b**−**4e** (entries 2−5). This methodology could also be extended to dialkyl-substituted alkynes, as well, albeit in somewhat lower efficiency (entries 6 and 7).

In light of the results shown in Scheme 2 and Table 2, we speculated that the construction of naphtho[1,8-*bc*]pyridines **4** could be achieved in a tandem process by employing enaminonitrile **1** as starting substrates. As shown in Scheme 4, this was indeed the case; the cyclizations were readily carried out following a slightly modified Rh(III)-catalyzed conditions depicted in Table 2. To our satisfaction, all reactions gave the corresponding naphtho[1,8-*bc*]pyridine products (**4a**−**c**, **4h**−

Table 2. Substrate Scope of Oxidative Annulation of 1-Naphthylamines with Alkynes[a]

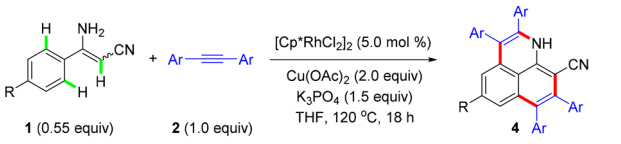


3 (1.0 equiv) 2 (1.0 equiv) 4

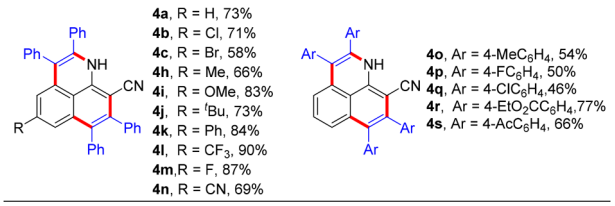
entry	3, R^1	2, R^2	4	yield (%)
1	**3a**, R^1 = H	**2a**, R^2 = Ph	**4a**	93
2	**3g**, R^1 = Cl	**2a**, R^2 = Ph	**4b**	63
3	**3h**, R^1 = Br	**2a**, R^2 = Ph	**4c**	68
4	**3a**, R^1 = H	**2b**, R^2 = 4-MeC_6H_4	**4d**	87
5	**3a**, R^1 = H	**2d**, R^2 = 4-FC_6H_4	**4e**	80
6	**3a**, R^1 = H	**2i**, R^2 = Et	**4f**	31
7	**3a**, R^1 = H	**2j**, R^2 = *n*-Pr	**4g**	55

[a]Reactions in 0.2 mmol scale (0.1 M), isolated yield.

Scheme 4. Substrate Scope of Oxidative Annulation of 3-Amino-3-arylacrylonitriles to Naphtho[1,8-*bc*]pyridines[a]



1 (0.55 equiv) 2 (1.0 equiv) 4



[a]Reactions in 0.15 mmol scale (0.075 M), isolated yield.

4s, Scheme 4) in moderate to high yields under the optimized reaction conditions.[20] Particularly noteworthy was that the naphtho[1,8-*bc*]pyridine derivatives **4** obtained above showed solid-state fluorescence in a range of 470−600 nm. In particular, compound **4a** was found to exhibit more intense luminescence (λ_{emis} = 534 nm).[13]

In summary, we have developed a general and selective construction of polysubstitued 1-naphthylamines and naphtho[1,8-*bc*]pyridines via rhodium(III)-catalyzed multiple C−H activation and cyclization reactions of *β*-enaminonitriles with internal alkynes. To the best of our knowledge, this is the first example of 1-naphthylamine synthesis via a catalytic C−H functionalization approach. Meanwhile, the obtained 1-naphthylamines can be transformed to naphtho[1,8-*bc*]pyridine derivatives through C−H/N−H bond activations by the direction of the naphthylamine NH_2 group. All of these catalytic approaches exhibit good functional group tolerance and broad substrate scope. Given the rapid assembly of otherwise hard to access skeletons, we anticipate that these protocols will facilitate the synthesis of related complex structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02341.

DOI: 10.1021/acs.orglett.8b02341
Org. Lett. XXXX, XXX, XXX−XXX

Full experimental procedures, additional experimental data, analytical data, and characterization of new compounds (^{1}H, ^{13}C, and ^{19}F NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21372121 and 21672108) for their generous financial support.

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DOI: 10.1021/acs.orglett.8b02341
Org. Lett. XXXX, XXX, XXX−XXX