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Oxadiazolone-Enabled Synthesis of Primary Azaaromatic Amines

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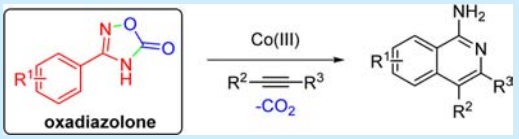
Supporting Information

ABSTRACT: Despite their tremendous synthetic and pharmaceutical utility, primary azaaromatic amines remain elusive for access based on a generally applicable C−H functionalization strategy. An oxadiazolone-enabled approach is reported for convenient entry into N-unsubstituted 1-aminoisoquinolines through Co(III)-catalyzed redox-neutral, step-, atom-, and purification-economic C−H functionalization with alkynes. A ^{15}N labeling experiment reveals the effectiveness of both oxadiazolone N atoms as directing sites. The installed primary amine can be harnessed as a synthetically useful handle for attachment of divergent appendages.



Heterocyclic compounds represent a ubiquitous class of organic structures with applications in a wide range of academia and industrial sectors.[1] Transition-metal-catalyzed C−H functionalization provides a synthetically efficient tool for the generation of such important molecular skeletons.[2] The high efficiency derives from the docking of the transition metal by the heteroatom-containing directing group in an appropriate orientation for the achievement of a high C−H activation reactivity. Simultaneous installation of a synthetically versatile functional group is important for the expansion of structural space,[3] but can be challenging to implement in the case of a strongly coordinating moiety, due to its capability of disrupting the docking process for target reaction course. Indeed, the accessible functional groups reported thus far are generally restricted to those weakly coordinating moieties that exhibit, as compared to the directing group, minimal competing docking capability.[4] Typically, these functional groups are located either at a distal site from the directing group or on the corresponding coupling partner.

We have recently initiated a research program aimed at the installation of a synthetically useful, albeit strongly coordinating, functional group during the heterocycle formation process. In particular, our initial target goal is to derivatize azaaromatic compounds with a primary amine, an arguably most important functional group that manifests a strikingly diverse set of utilities in synthetic and pharmaceutical chemistry.[5] In devising a versatile strategy for the preparation of primary azaaromatic amines, one can imagine three potentially viable synthetic scenarios: two structurally equivalent N atoms (either one acting as the directing N atom, for C−H activation and incorporation into the azaaromatic ring, with the other as an amino N atom, for the generation of primary amine) enabling the operation of a single reaction pathway; two structurally inequivalent N atoms (directing N atom and amino N atom serving respective roles) leading to the dominance of a preferred reaction pathway; two structurally inequivalent N atoms (either one acting as the directing N atom, with the other as amino N atom) allowing for the existence of two competing reaction pathways but leading to a synthetically identical target product (termed synthetically symmetric, because two N atoms are indistinguishable as far as synthetic target structure is concerned). In each of these synthetic scenarios, to achieve ideal step, atom, and purification economy, the masking group, generally required for eliminating undesired coordination orientation, should possess the following attributes: convenient installation during the substrate preparation process, efficient removal during the catalytic process, and extrusion in the form of a small gaseous molecular fragment (e.g., through a process initiated by the cleavage of a labile bond).

As a first demonstration of the synthesis of primary azaaromatic amines, the last scenario was examined based on the use of 1,2,4-oxadiazol-5(4*H*)-one (abbreviated as oxadiazolone herein). In using oxadiazolone as an effective synthon, we take into consideration the following factors (Scheme 1a): (1) the two N atoms for the azaaromatic ring and primary amine are structurally inequivalent but can be synthetically symmetric (*vide infra*), (2) the two N atoms are orchestrated into a single cyclic moiety to completely eliminate the C−H activation-incapable coordination orientation,[6] and (3) a sufficiently labile N−O bond exists as a trigger for the formation of a primary amine, with the simultaneous extrusion of a small molecular fragment.[7] In fact, oxadiazolone is a masked form for the parent structure, amidine,[8] an n-π conjugated heteroallylic system, and a versatile synthetic intermediate with a diverse range of applications. Oxadiazolone has demonstrated its synthetic utility as a handy precursor to amidine functionality (under hydrogenation condition)[9] but has never been recruited as a synthetic handle in the C−H functionalization context. We hypothesized that oxadiazolone featured a weak N−O bond, and after aza-cyclization, a variety of chemical events (e.g., organometallic oxidative addition process) could initiate a N−O bond cleavage/carbamate formation/decarboxylative reaction sequence for the

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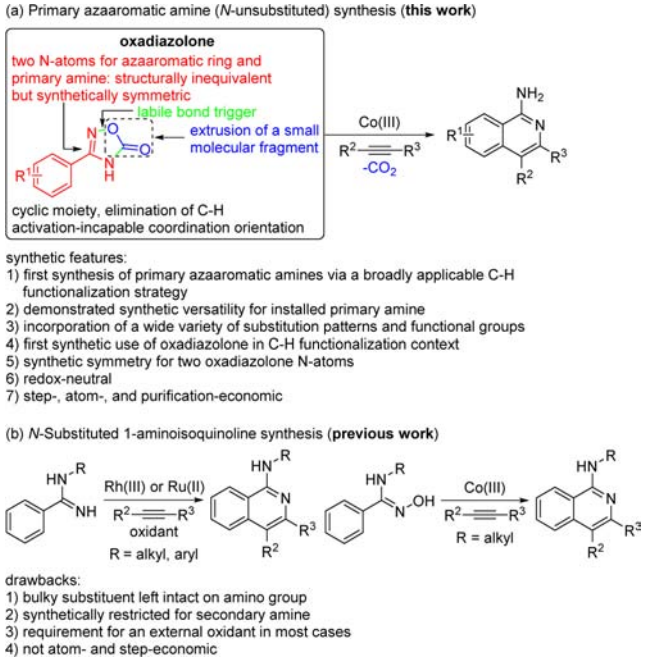
Scheme 1. Synthetic Strategies for the Preparation of Primary Azaaromatic Amines (*N*-Unsubstituted, Reported Herein), and *N*-Substituted 1-Aminoisoquinolines (Previous Work) through C−H Activation



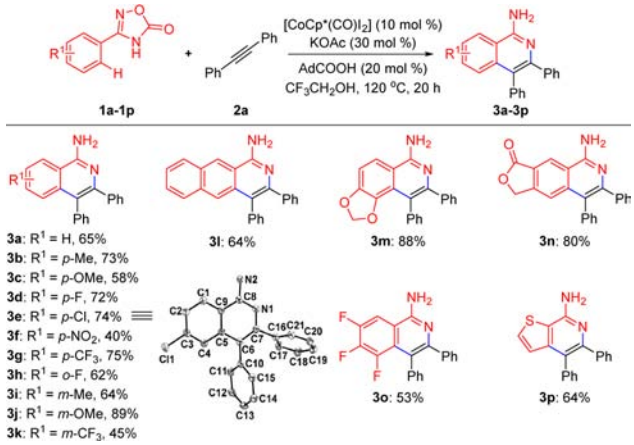
generation of a primary amine. Reaction development confirmed the synthetic utility of this important structural motif, and herein, we report on the oxadiazolone-enabled synthesis of primary azaaromatic amines.

Amidines bearing protecting groups on one or both of the N atoms have been previously employed for synthetic access to 1-aminoisoquinolines (Scheme 1b).[10,11] However, in the majority of reported protocols, the bulky group used for blocking the disfavored coordination orientation was left intact on the amino N atom.[10] Only a single isolated case[11] was briefly mentioned for the synthesis of a *N*-unsubstituted 1-aminoisoquinoline derivative through the capping of an imino N atom with a hydroxyl group, and no general applicability of the described transformation was demonstrated. In that amidoxime-directed reaction, a highly reactive cationic Rh(III) catalyst was resorted to for, presumably, overriding competing coordination modes/reaction pathways.[12] Taken together, despite their tremendous synthetic and pharmaceutical utility, primary azaaromatic amines remain elusive for access based on a broadly applicable C−H functionalization synthetic strategy. Indeed, forward reactivity analysis and pathway inference, for a directing group in our particular case, are critical for the increased chance of success in target reaction development. The oxadiazolone approach described herein provides convenient entry into *N*-unsubstituted 1-aminoisoquinolines through Co(III)-catalyzed C−H coupling with alkyne partners.

We commenced our studies by examining the reaction between 3-phenyl-1,2,4-oxadiazol-5(4*H*)-one (**1a**) and 1,2-diphenylacetylene (**2a**). Preliminary experiments identified [CoCp*(CO)I_2] as the ideal catalyst source and also suggested the necessity of using additives. The target 1-aminoisoquinoline derivative **3a** could be obtained in 51% yield in the presence of KOAc when reacting in CF_3CH_2OH at 120 °C for 20 h. A silver salt proved to be unnecessary for effecting the transformation. With the combination of an additional acidic additive, adamantyl carboxylic acid (AdCOOH), the yield could be boosted to 65%.

The acquisition of optimized reaction conditions allowed examination of the substrate scope of 3-aryl-1,2,4-oxadiazol-5(4*H*)-ones by employing **2a** as the coupling partner (Scheme 2). A variety of 3-aryl-1,2,4-oxadiazol-5(4*H*)-ones, bearing

Scheme 2. Substrate Scope for 3-Aryl-1,2,4-oxadiazol-5(4*H*)-ones[a,b]



[a]Reaction conditions: 3-aryl-1,2,4-oxadiazol-5(4*H*)-one (0.2 mmol), **2a** (0.24 mmol), [CoCp*(CO)I_2] (10 mol %), KOAc (30 mol %), AdCOOH (20 mol %), CF_3CH_2OH (2.0 mL). [b]Isolated yield.

electron-donating (**1b**, **1c**) and electron-withdrawing (**1d**−**1g**) groups at the *para* position of directing group, proved to be viable substrates for this process. The structure assignment for these products was further confirmed by a single-crystal X-ray analysis of **3e**. The transformation is also effective for an *ortho*-substituted substrate (**1h**). The regioselectivity for a *meta*-substituted substrate (**1i**−**1k**) is independent of electronic character of the substituent, allowing the smooth delivery of, likely through steric control, a single isomer. Di- and trisubstitution (**1l**−**1o**) pose no synthetic hurdle for the respective reaction. Interestingly, for substrate **1m**, C−H functionalization at the sterically more hindered site was observed.[10b] 3-(Thiophen-2-yl)-1,2,4-oxadiazol-5(4*H*)-one (**1p**) is also compatible with the developed protocol, furnishing a fused bicyclic heterocycle as the target product.

The optimized catalytic system was then used for establishing the substrate scope of alkynes by reacting with **1e** (Scheme 3). Satisfactorily, a variety of functional groups on diarylalkynes (**2b**−**2i**), irrespective of the electronic character (electron-donating or electron-withdrawing) and the location (*para*, *ortho*, or *meta*), were tolerated. A switch to di(thiophen-2-yl)acetylene (**2j**) does not cause apparent attenuation in the reactivity. Further, the reaction can accommodate alkynes bearing aryl/ester (**2k**) and aryl/ketone (**2l**) substituents. The regiospecificity is dictated by the steric effect. Substitution with alkyls (**2m**) also largely preserves the reactivity, and a slight adjustment of the reaction conditions can be beneficial for the reaction.

A key mechanistic insight into the catalytic process came from a ^{15}N labeling experiment. A reaction between **1a**-^{15}N (^{15}N labeling for carbonyl-neighboring N atom) and **2a** generated a mixture of **3a**-^{15}N-*R* (^{15}N located on the azaaromatic ring) and **3a**-^{15}N-*A* (^{15}N located on the primary amine) (**3a**-^{15}N-*R*: 39%; **3a**-^{15}N-*A*: 23%) (eq 1). This suggests the effectiveness of both N atoms in directing C−H activation for subsequent coupling/

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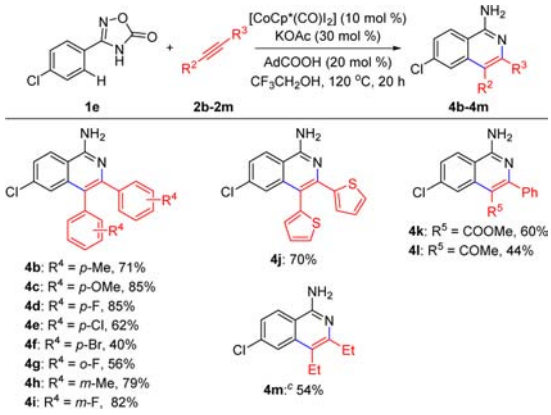
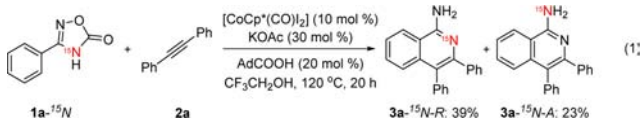
Scheme 3. Substrate Scope for Alkynes[a,b]



[a]Reaction conditions: **1e** (0.2 mmol), alkyne (0.24 mmol), [CoCp*-(CO)I_2] (10 mol %), KOAc (30 mol %), AdCOOH (20 mol %), CF_3CH_2OH (2.0 mL). [b]Isolated yield. [c]**1e** (0.2 mmol), **2m** (0.4 mmol), [CoCp*(CO)I_2] (15 mol %), KOAc (40 mol %), AdCOOH (30 mol %).



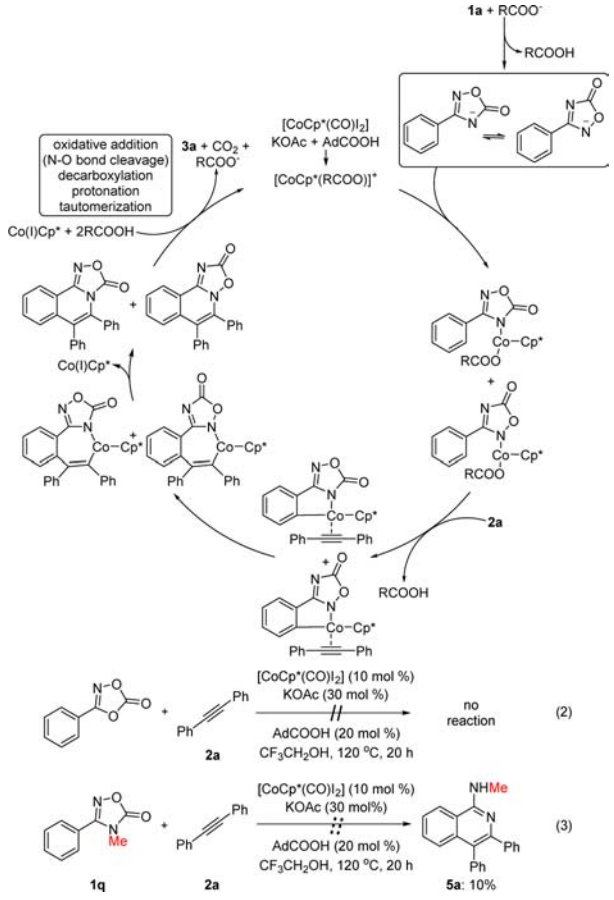
(1)

cyclization reaction. Based on the structural characteristic of the oxadiazolone group, the first step in the catalytic reaction sequence likely involves the following processes (Scheme 4): generation of a coordination-capable monoanionic N atom (either one on the oxadiazolone due to the resonance stabilization effect) through deprotonation, and coordination of a N atom to Co(III). Indeed, minimal reactivity was observed for two types of deprotonation-incapable species, a dioxazolone (eq 2) and a methyl-protected oxadiazolone (eq 3). Further mechanistic experimental results, the absence of H/D scrambling on the aryl ring and favored reaction for an electron-deficient oxadiazolone, suggest that C−H activation is irreversible and proceeds through a concerted metalation−deprotonation process. Following C−H activation, coordination of alkyne and 1,2-migratory insertion allows the generation of alkenylcobalt species for the subsequent reductive elimination process (C−N bond formation and release of Co(I) species). This is followed by oxidative addition of Co(I) species to N−O bond/N−Co(III) bond cleavage (demetalation as a result of protonation on O atom-neighboring N atom)/O−Co(III) bond cleavage/decarboxylative process/protonation of carbonyl-neighboring N atom/regeneration of Co(III) catalyst (stepwise or concerted). The target *N*-unsubstituted 1-aminoisoquinoline derivative is then generated by tautomerization.

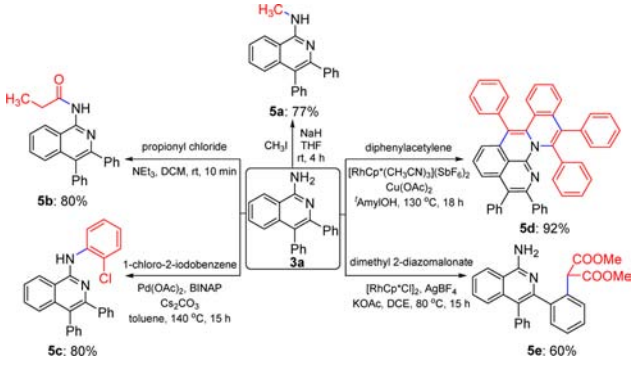
The synthetic utility of the reaction protocol developed herein is highlighted by the amenability of a primary amine to diverse functionalization (Scheme 5). A variety of halogenated compounds can serve as the electrophile for derivatization on the amino group (**5a**−**5c**). An extended fused ring system (**5d**) can also be generated through a Rh(III)-catalyzed double C−H activation and alkyne coupling pathway.[12] Further, one can elect to, with a primary amine intact, attach an appendage based on a heterocycle-directed C−H activation process (**5e**).

In summary, an oxadiazolone-enabled synthetic strategy has been developed for access of primary azaaromatic amines. Co(III)-catalyzed C−H functionalization with alkynes allows the generation of *N*-unsubstituted 1-aminoisoquinolines with a broad range of substitution patterns. The primary amine in 1-aminoisoquinoline products can be harnessed as a synthetically useful handle for attaching diverse appendages.

Scheme 4. Proposed Catalytic Mechanism



Scheme 5. Diversified Synthetic Transformations for 3a



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02814.

Experimental and synthetic details (PDF)
^{1}H and ^{13}C NMR data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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