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Co(III)-Catalyzed Synthesis of Quinazolines via C−H Activation of *N*-Sulfinylimines and Benzimidates

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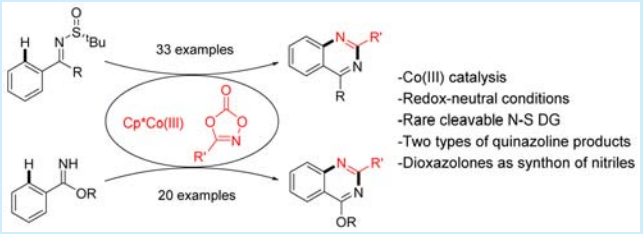
Supporting Information

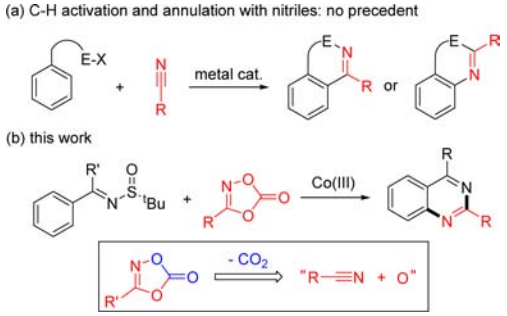
ABSTRACT: C−H activation of arenes has been established as an important strategy for heterocycle synthesis via annulations between arenes and unsaturated coupling partners. However, nitriles failed to act as such a coupling partner. Dioxazolones have been employed as a synthon of nitriles, and subsequent coupling with arenes such as *N*-sulfinylimines and benzimidates bearing a functionalizable directing group provided facile access to two classes of quinazolines under Co(III)-catalysis.



In the past decades, C−H bond functionalization of arenes has been extensively employed as a powerful strategy. The ubiquity of C−H bonds and the high atom- and step-economy of this strategy render it highly attractive in the synthesis of natural products and functional organic molecules, particularly heterocycles.[1] Direct C−H activation of arenes has mostly relied on rather costly second and third row transition metals.[1,2] High valent Rh(III) complexes have been widely employed as catalysts in the activation of a large array of arenes,[2] and the high activity is ascribed to the high propensity to activate C−H bonds, polarity of the M−C bond, and the Lewis acidity of the catalyst. Recently, earth abundant and environmentally benign first row transition metals have been increasingly employed as catalysts.[3] Given the higher Lewis acidity of the Co(III) congeners and enhanced metal−ligand corporation, efficient couplings between arenes and unsaturated coupling partners have been recently established as in the reports by Kanai,[4] Glorius,[5] Ackermann,[6] Ellman,[7] Daugulis,[8] Chang,[9] and others.[10]

In the context of C−H activation, late-transition-metal-catalyzed annulative couplings of arenes with various π-bond partners such as alkynes, alkenes, allenes, and carbene/nitrene precursors have been extensively explored.[1j,2a,k,5a,11] However, to the best of our knowledge, nitriles have not been applied for this purpose,[12] likely due to their inhibitive binding (σ-binding) and its failure to adopt the reactive π-coordination mode, although nitriles are well-known to undergo [2 + 2 + 2] cyclizations.[13] Thus, a synthon that is equivalent to nitriles needs to be identified. Very recently Chang[9c,14] and we[15] have independently achieved Co(III)- and Rh(III)-catalyzed, chelation-assisted activation of different types of C−H bonds in couplings with dioxazolones, leading to simple amidation without further reaction. We reasoned that dioxazolones may act as a synthetic equivalent of nitriles provided that the directing group (DG) of the arene is multifunctional and has sufficient interactions with the amidated intermediate. Thus, the design of a readily functionalizable or cleavable DG is a significant factor.[2b,16] Previously, such DGs are often based on cleavage of N−O, N−N, and other oxidizing bonds, and applications to Co(III)-catalyzed C−H activation are even more limited.[4e,6b] We now report the activation of arenes assisted by a rare functionalizable N−S bond[17] as a DG in the coupling with dioxazolones that function as a synthon of nitriles. This represents the first synthesis of quinazolines[18] via a C−H activation pathway. A number of quinazolines are known to exhibit important biological activities.[19] However, their syntheses are not trivial which required functionalized substrates and harsh conditions (Scheme 1).

Scheme 1. Coupling Using Dioxazolone As a Synthon of Nitrile



We embarked on our investigation with the optimization of the coupling between *N*-sulfinylimine **1a** and dioxazolone **2a** (see Table S1, Supporting Information (SI)). Rhodium(III) catalysts were initially employed, and both the amidation−cyclization product quinazoline **3aa** and the diamidation−cyclization product **3aaa** (eq 1) were obtained in comparable ratios under different conditions (entries 1−3). The identity of

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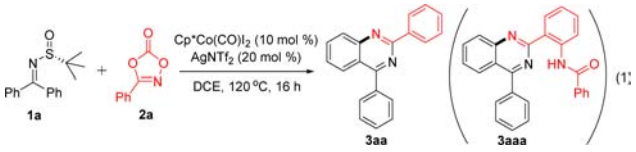
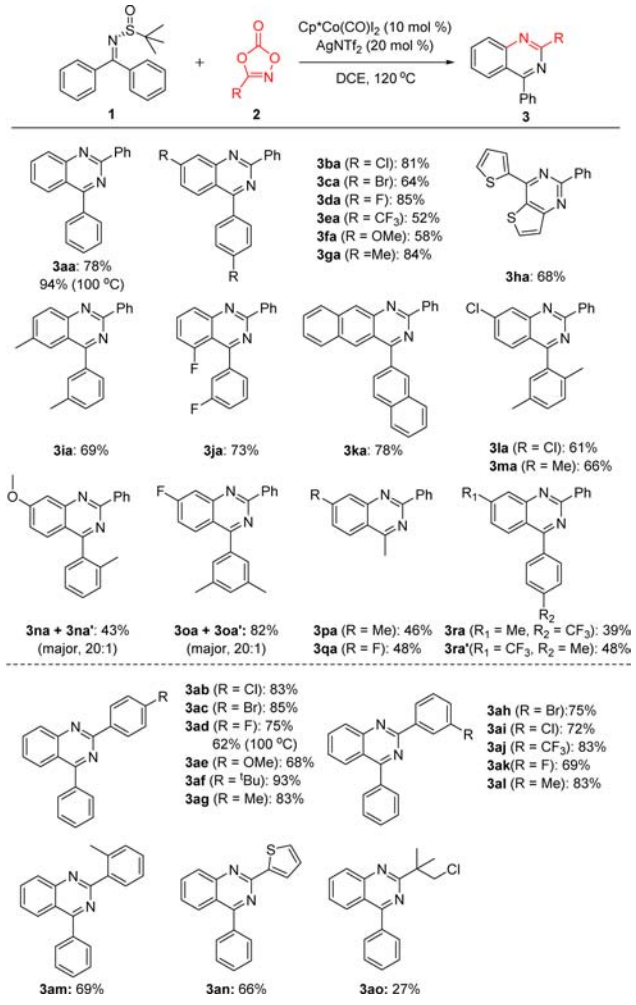


product **3aaa** has been secured by X-ray crystallography (CCDC 1433317). In addition, variable amounts of benzophenone were also obtained due to hydrolysis of **1a**. The same scenario applied to Ir(III) catalysis (entry 4). To our delight, switching the catalyst to the cobalt congener significantly improved the catalytic efficiency and selectivity, and only **3aa** was obtained (entry 5). Further optimization using CoCp*-$(CO)I_2$ improved the yield to 78%, and $AgNTf_2$ was identified as the optimal activator (entry 6). An excellent yield was realized when the reaction temperature was lowered to 100 °C (entry 9). In contrast, essentially no desired reaction occurred when benzoyl azide was used as an amidating reagent (entry 10). Moreover, shifting **1a** to the unfunctionalized benzophenone imine only afforded **3aa** in low yield due to significant hydrolysis (entry 11).

With the optimized conditions in hand, the scope and generality of this coupling were next examined (Scheme 2). It

Scheme 2. Synthesis of Quinazolines via C−H Activation of *N*-Sulfinylimines (see the SI for detailed reaction conditions)



was found that although 100 °C seems optimal for substrate **1a**, extension to other substituted *N*-sulfinylimines gave lower yields (see product **3ad**). Thus, all the coupling reactions were performed at 120 °C. *N*-Sulfinylimines derived from symmetrical benzophenones bearing *para* electron-donating and -withdrawing groups all coupled smoothly with **2a** in good to high yield (**3aa**−**3ga**). Notably, the arene substrate has been extended to a heterocycle, and a bis(2-thienyl)methanone-derived imine proved to be a viable substrate (**3ha**). Symmetrically *meta*-substituted imines were also efficient substrates, and the site selectivity varied with the *meta*-substituent. The C−H functionalization was directed to the less hindered site for relatively bulky *meta* groups (**3ia**, **3ka**), while C−H activation occurred at the kinetically more acidic *ortho* position when a *meta*-F was introduced (**3ka**). Site selectivity in the coupling of various nonsymmetrical imines was next explored in terms of both electronic and steric effects. The electronic bias between the *para*-CF_3 and $-CH_3$ groups seems insignificant because C−H activation was only slightly preferred at the electron-poor ring (39% yield of **3ra** versus 48% yield of **3ra′**). However, pronounced steric bias was observed. Thus, high site selectivity (≥20:1) has been consistently secured when an *ortho*- or *meta*-methyl was introduced as a blocking group, and the reaction took place at the less hindered ring (**3la**−**3oa**). The reaction was not limited to the benzophenone imine system. *N*-Sulfinylimines of acetophenone also reacted to afford the desired products (**3pa**, **3qa**), albeit with lower yields due to significant competitive hydrolysis of the imine. The scope of the amidating reagent was next explored. Introduction of various substituents into the *ortho*, *meta*, and *para* positions of the aryldioxazolone was fully tolerated, and the reaction efficiency was only marginally affected by the steric or electronic effects of these substituents (**3ab**−**3an**). In all cases consistently good to high yields have been obtained. The presence of halogen groups in the product should allow further chemical manipulation. Besides aryl-substituted dioxazolones, an alkyl-substituted one also reacted (**3ao**), but with significantly lower efficiency.

During our optimization studies (Table S1, entry 11), the observation of a small amount of quinazoline **3aa** using benzophenone imine suggested that a protic NH directing group might be possible. We reasoned that high efficiency was achievable if the imine is sufficiently stable and is less prone to hydrolysis. Thus, ethyl benzimidate (**4a**) was applied as a special aryl imine substrate. Indeed, the coupling of **4a** with **2a** under slightly modified, milder conditions afforded the desired 4-ethoxyquinazoline **5aa** in excellent yield (Scheme 3). A broad scope of substrates was next established. In line with the C−H activation of *N*-sulfinylimines, benzimidates bearing different *ortho*-, *meta*-, and *para*-substituents all coupled smoothly with high efficiency and selectivity (**5aa**−**5ha**), and the electronic and steric effects of the substituents had only marginal influence. The arene could be extended to a thiophene ring in good isolated yield. It was found that other alkyl esters (**5ja**, **5ka**) were also viable although the efficiency was somewhat lower. Examination of the scope of dioxazolones revealed that both alkyl and aryl substituents were well tolerated (**5ab**−**5aq**), and in this coupling system alkyl dioxazolones reacted with only slightly lower yields.

The synthetic utility of the quinazoline products has been previously reported. Treatment of **3aa** with TIPS-EBX under Rh(III) catalysis afforded the *ortho*-alkynylated product **6** in moderate yield (eq 2). The hydrolysis of **5an** in HCl/dioxane

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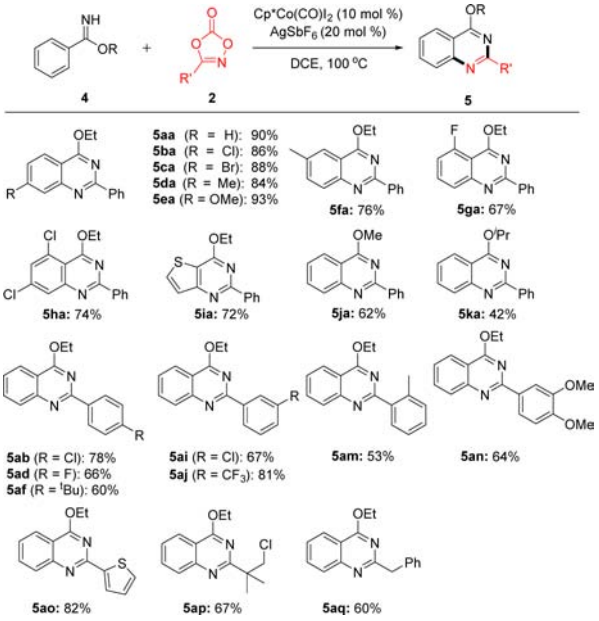
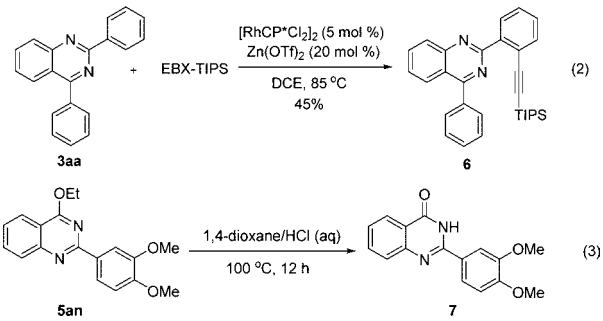
Scheme 3. Synthesis of Quinazolines via C−H Activation of Benzimidates (see the SI for detailed reaction conditions)

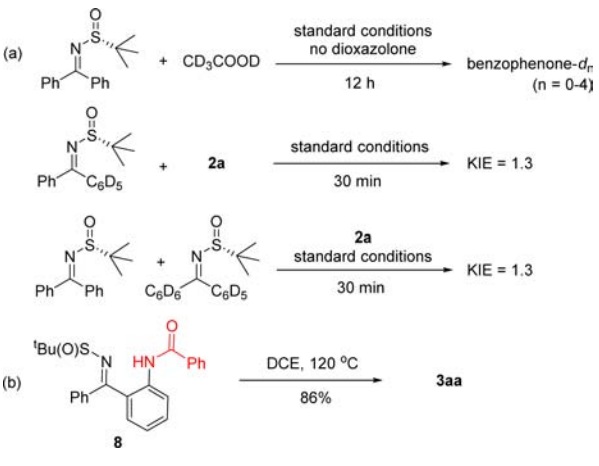




generated 4-quinazolinone **7** (eq 3), which can react with phosphoryl chloride and anilines to afford quinazoline compounds as a potent inhibitor of BCRP.[20]

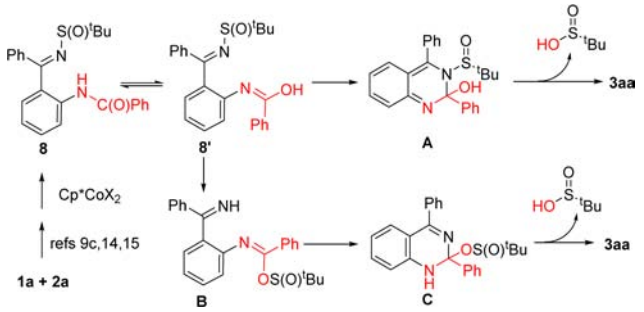
Experimental mechanistic studies have been briefly carried out (Scheme 4). To probe the C−H activation process, H/D exchange between imine **1a** and CD_3COOD has been performed. While only benzophenone was obtained as a result of hydrolysis, GC analyses revealed a mixture of protio and

Scheme 4. Preliminary Mechanistic Studies



duterio isotopologues (benzophenone-d_n (n = 0−4)), indicating relevancy of C−H activation (Scheme 5a). KIE was then

Scheme 5. Proposed Mechanism



measured to gain additional insight. Consistent values of KIE = 1.3 were obtained from both intramolecular competition using **1a**-d_5 and from intermolecular competitions using an equimolar mixture of **1a** and 1a-d_{10}. These small values suggest that C−H activation is not involved in the turnover-limiting step.[21] To probe the relevancy of initial C−H amidation, amide **8** was prepared. Stirring of **8** in DCE in the absence of any catalyst lead to isolation of product **3aa** in 87% yield (Scheme 5b), and this conversion even starts to be observed at 25 °C ($CDCl_3$).

The mechanism of the coupling of *N*-sulfinylimine **1a** with dioxazolone **2a** is given in Scheme 5. On the basis of our preliminary results and previous reports,[9c,14,15] the reaction likely involves initial Co(III)-catalyzed C−H activation en route to amidation to afford intermediate **8**. This amide intermediate is proposed to undergo 6-electron cyclization via the imidic acid tautomer (**8′**) to give a dearomatized intermediate **A**.[22] The product **3aa** is released upon elimination of a *tert*-butanesulfinic acid. Alternatively, **8′** may undergo intramolecular nucleophilic attack at the sulfinyl group to provide an ester **B**. Intramolecular nucleophilic addition of **B** gives **C**, and subsequent elimination of a *tert*-butanesulfinic acid furnishes the product. In either case, the postamidation processes are uncatalyzed.

In summary, we have realized the first synthesis of quinazolines via C−H activation of *N*-sulfinylimines and benzimidates in the coupling with dioxazolones. The reactions proceeded with high regio- and mono-/diselectivity, and two types of quinazolines have been synthesized starting from different arenes. In the case of *N*-sulfinylimines, the C−H activation was assisted by an autocleavable N−S bond, and the employment of *N*-sulfinylimine substrates seems to circumvent the poor reactivity and low stability of the corresponding NH ketoimines. On the other hand, the stability of benzimidates allowed direct construction of 4-alkoxyquinazolines. In these systems, the dioxazolone coupling partner acts as a synthon of (the oxidized form of) nitrile. These coupling reactions extended the concept of functionalizable DGs to cobalt catalysis. This new method offers a new rapid entry to quinazolines, and it is potentially useful for streamlining the synthesis of bioactive compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00227.

X-ray data for **3aaa** (CIF)

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General experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra of new compounds, and X-ray data for **3aaa**(PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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