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Amidines for Versatile Cobalt(III)-Catalyzed Synthesis of Isoquinolines through C−H Functionalization with Diazo Compounds

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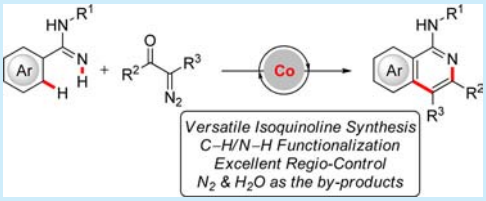
Supporting Information

ABSTRACT: A cobalt(III)-catalyzed C−H/N−H bond functionalization for the synthesis of 1-aminoisoquinolines from aryl amidines and diazo compounds has been developed. The reaction proceeds under mild reaction conditions, obviates the need for oxidants, produces only N_2 and H_2O as the byproducts, and features a broad substrate scope.



Functionalization of inert C−H bonds provides a strategy for improving the atom and step economy in organic synthesis.[1] Most of the achievements were accomplished with expensive second-row transition-metal catalysts, largely based on ruthenium, rhodium, and palladium complexes. In this context, the development of catalysts derived from the naturally abundant and cost-efficient 3d transition metal complexes,[2] particularly, the inexpensive cobalt catalysts, has received special attention due to their high activity in C−H bond activation.[3] In the recent past, major advances have being accomplished by high-valent cobalt catalysts, as reported by Matsunaga and Kanai,[4] Ackermann,[5] Glorius,[6] Daugulis,[7] Song,[8] and Chang,[9] among others.[10] Specially, the synthesis of diversely decorated, pharmacologically useful heterocycles, such as isoquinolines, quinolines, and indoles,[11] has received major attraction through cobalt(III)-catalyzed C−H activation. Despite these major advances, cobalt-catalyzed C−H functionalizations on aryl amidines have unfortunately thus far proven elusive.

Ubiquitous amidines[12] have thus far only been used for rhodium- and ruthenium-catalyzed C−H activation with internal alkynes for the synthesis of substituted 1-aminoisoquinolines, as was reported by Li,[13] as well as Ackermann and co-workers,[14] respectively. Beyond that, there is no other preparation of multisubstituted isoquinolines through transition metal-catalyzed cyclization by amidine assistance.[15] In this context, we became interested in exploring the first amidine-assisted cobalt(III)-catalyzed intermolecular annulation in an environmentally friendly way. Although isoquinoline syntheses and carbenoid insertions were mainly achieved with second-row transition-metal catalysts, the cobalt-catalyzed intermolecular aromatic C−H bond annulation on arylpyridines[6f] and imines[6b] with diazo compounds were only recently reported. However, transformations on more challenging aryl amidines with diazo compounds are thus far unprecedented. Herein, we report the first cobalt(III)-catalyzed C−H/N−H functionalization of amidines with carbonyl-containing diazo compounds to deliver the corresponding highly substituted isoquinolines under mild reaction conditions (Figure 1c).

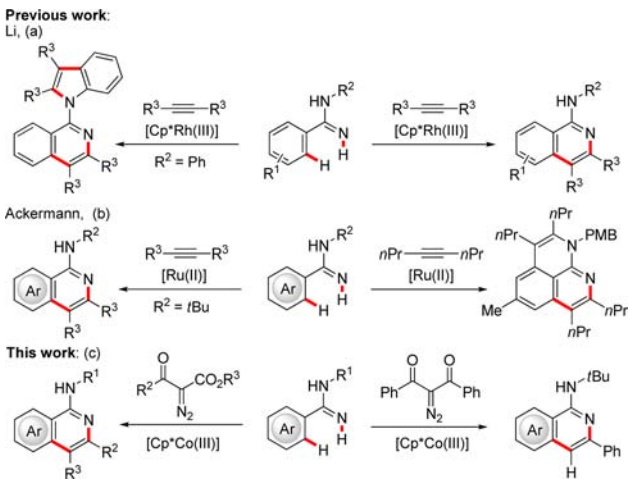


Figure 1. Annulation by aryl amidines to decorated isoquinolines via C−H functionalization.

We initiated our studies by testing different reaction conditions for the desired synthesis of aminoisoquinolines **3aa** (Table 1). Preliminary experiments demonstrated $Cp^*CoI_2(CO)$ as suitable metal complex, along with a combination of a $AgSbF_6$, and NaOAc or KOAc as the cocatalytic additives. While the desired product **3aa** was obtained in rather modest yields, there was no significant improvement with stoichiometric amounts of KOAc (Table 1, entries 1 and 2). Among a set of representative silver(I) salts and carboxylate salts, both $AgSbF_6$ and $AgPF_6$ combined with

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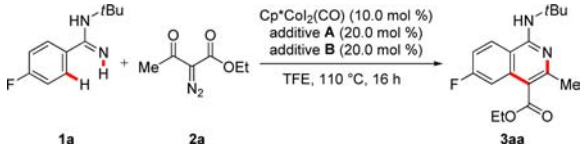
Table 1. Optimization of Cobalt(III)-Catalyzed C−H/N−H Functionalization with Benzamidine 1a[a]



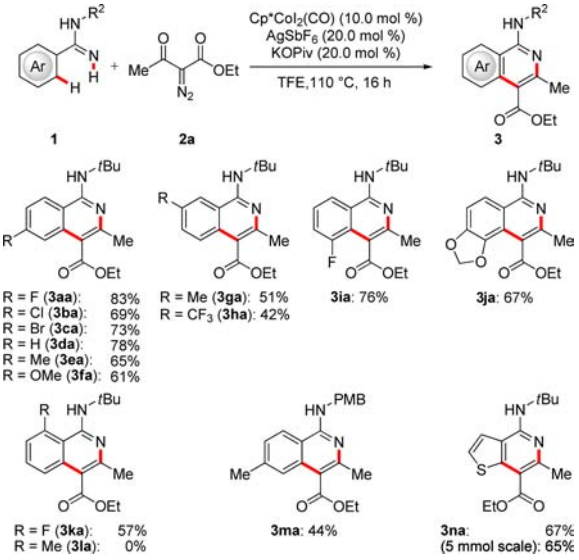
entry	[Co]	additive A	additive B	yield[b] (%)
1	$Cp^*CoI_2(CO)$	$AgSbF_6$	NaOAc	25
2	$Cp^*CoI_2(CO)$	$AgSbF_6$	KOAc	34 (36[c])
3	$Cp^*CoI_2(CO)$	$AgNTf_2$	KOAc	18
4	$Cp^*CoI_2(CO)$	$AgSbF_6$	AgOAc	38
5	$Cp^*CoI_2(CO)$	$AgSbF_6$	AgOPiv	67
6	$Cp^*CoI_2(CO)$	$AgPF_6$	AgOPiv	65
7	$Cp^*CoI_2(CO)$	$AgSbF_6$	PivOH	54
8	**$Cp^*CoI_2(CO)$**	**$AgSbF_6$**	**KOPiv**	**76 (83[d])**
9		$AgSbF_6$	KOPiv	0[d]
10	$Cp^*CoI_2(CO)$		KOPiv	0[d]
11	$Cp^*CoI_2(CO)$	$AgSbF_6$		25[d]
12	$CoBr_2$	$AgSbF_6$	KOPiv	0[d]
13	CoI_2	$AgSbF_6$	KOPiv	0[d]
14	$Co(acac)_2$	$AgSbF_6$	KOPiv	0[d]

[a]General reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), $Cp^*CoI_2(CO)$ (10.0 mol %), $AgSbF_6$ (20.0 mol %), KOPiv (20.0 mol %), undried solvent (2.0 mL), under Ar, 110 °C, 16 h. [b]Isolated yield. [c]KOAc (1.0 equiv). [d]Anhydrous TFE (TFE = trifluoroethanol).

AgOPiv gave good yields (entries 3−6), as was also observed when employing PivOH instead of AgOPiv, albeit in a slightly reduced yield (entry 7). However, we were pleased to find that the efficacy of the catalysis was remarkably improved when KOPiv was used as the carboxylate salt in TFE as the solvent, with a yield of 83% (entry 8). Moreover, omission of either of the catalyst's components or replacement of the [$Cp^*CoI_2(CO)$] by other typically used cobalt sources resulted in significantly reduced yield or completely inhibited the reaction (entries 9−14).

With the optimized cobalt(III) catalyst in hand, we tested its versatility in the C−H bond functionalization with amidines **1**. Notably, in the chelation-assisted direct synthesis of aminoisoquinolines **3**, valuable electrophilic functional groups, such as fluoro, chloro, or bromo substituents, were well tolerated by the cobalt catalyst when substituted benzamidines **1a−c** were utilized (Scheme 1). Electron-donating functional groups, such as methyl and methoxy *para*-substituted aryl amidines **1e**,**f** were also identified as viable substrates, furnishing the desired products in good yields. Intramolecular competition experiments with substrates bearing *meta*-methyl or *meta*-trifluoromethyl substituents were largely governed by steric interactions to deliver the products **3ga** and **3ha** at the less sterically hindered position. In contrast, the *meta*-substituted benzamidines **1i** and **1j** showed a considerable secondary directing group effect,[16] thus leading to a site-selective formation of sterically more hindered compounds **3ia** and **3ja** as the sole products. Substrate **1k** bearing an *ortho*-fluoro gave the desired product **3ka** in a slightly reduced yield. However, more sterically hindered *ortho*-methyl substituted amidine **1l** failed to deliver the desired product **3la**. Interestingly, the *p*-methoxybenzyl (PMB)-substituted benzamidine **1m** was successfully employed as well, albeit furnishing the product **3ma** in a rather modest yield. It is worth noting that thiophene derivative **1n** also proved to be a viable starting material, which gave the

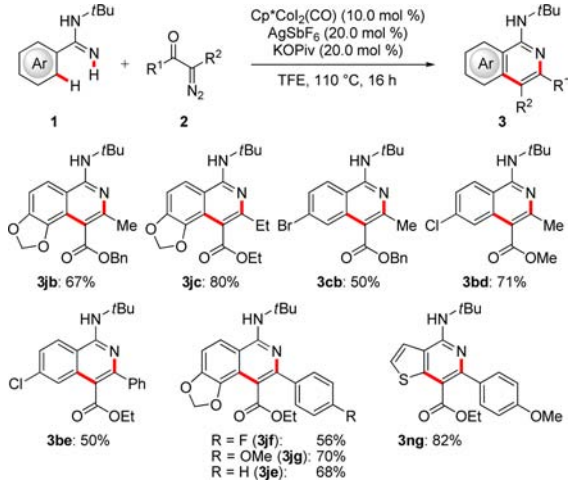
Scheme 1. Substrate Scope of Cobalt(III)-Catalyzed C−H/N−H Functionalization



annulated aza-benzothiophene **3na** through C−H/N−H functionalization process. In addition, this transformation can be easily scaled up with equal efficiency.

Thereafter, the versatility of the optimized catalytic system was probed in the annulation of differently decorated diazoesters **2** (Scheme 2). Among a set of substituted substrates

Scheme 2. Cobalt(III)-Catalyzed Synthesis of Aminoisoquinolines with Diazo Compounds 2



2, different substitutions were found to be tolerated under optimal conditions, and methyl, ethyl, or aryl groups afforded the corresponding aminoisoquinolines in modest to good yields (Scheme 2). Notably, thiophene derivative was also observed to give the desired product **3 ng** in 82% yield, while the cobalt-catalyzed 1-aminoisoquinoline synthesis from amidines and corresponding alkynes in the presence of internal oxidants did not deliver the desired products.

Interestingly, differently substituted amidines **1** furnished the unexpected products **4a−c** when the 2-diazo-1,3-diphenylpropane-1,3-dione (**2h**) was employed through a two-step reaction sequence consisting of the C−H/N−H functionalization and a decarbonylation (Scheme 3). It is noteworthy that these 4-

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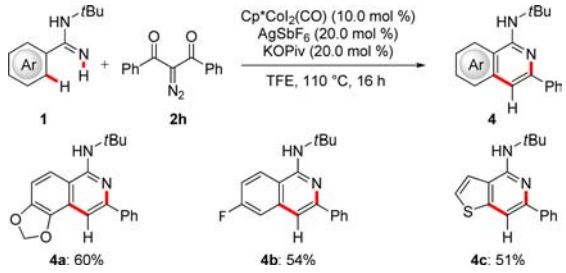
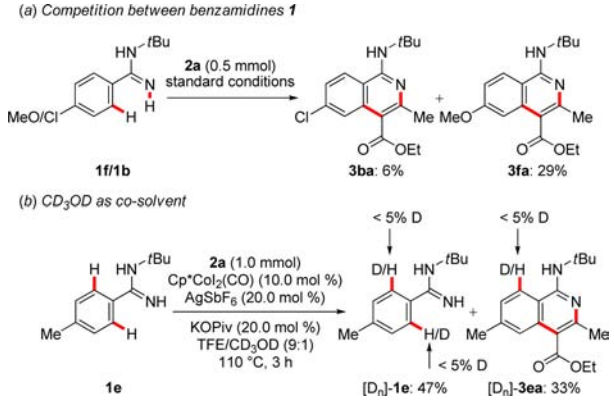
unsubstituted isoquinolines **4** are difficult to access by other metal-catalyzed C−H functionalizations with terminal alkynes.[13,14]

Scheme 3. Cobalt(III)-Catalyzed C−H Activation and Decarbonylation



Given the unique activity of the cobalt(III)-catalyzed C−H/N−H functionalization, we performed mechanistic studies to rationalize its mode of action. To this end, an intermolecular competition experiment between differently substituted substrates **1** highlighted that electron-rich benzamidine **1f** was preferentially converted as compared to electron-deficient substrate **1b** (Scheme 4a). This finding is in good agreement

Scheme 4. Mechanistic Studies: (a) Intermolecular Competition Experiment; (b) H/D Exchange Reaction

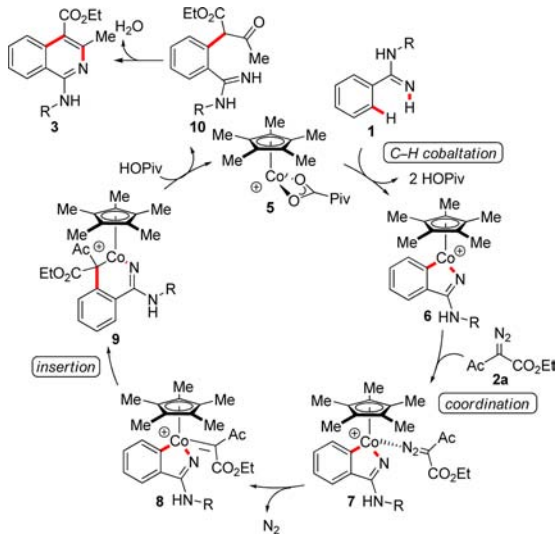


with the in situ generated cationic cobalt(III) complex operating by a base-assisted, intramolecular electrophilic substitution-type (BIES) activation mode.[5b,17] Furthermore, we did not observe any H/D exchange on both the product [D_n]-**3ea** and reisolated starting material [D_n]-**1e** when using isotopically labeled CD_3OD as the cosolvent (Scheme 4b).

Given our mechanistic studies and the literature precedence,[3a] we propose a plausible catalytic cycle which involves an irreversible C−H activation in amidines **1**, yielding the cyclometalated complex **6** through a base-assisted, intramolecular electrophilic substitution-type (BIES) activation mode[17] (Scheme 5). Subsequent coordination of diazo substrate **2a** produces the species **7**. The key intermediate **7** furnishes a cobalt−carbene **8** migratory insertion process along with a subsequent proto-demetalation step to yield compound **10**. The desired aminoisoquinoline **3** is obtained through an intramolecular nucleophilic attack of the amidine in intermediate **10**, followed by *β*-elimination of water to deliver the desired product **3**.

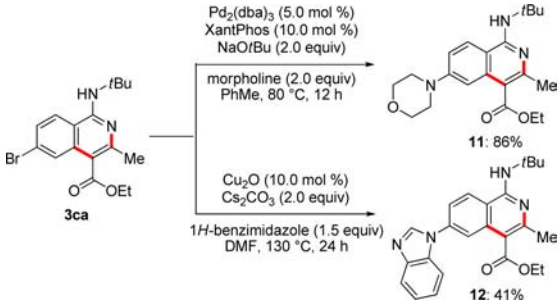
To demonstrate the synthetic utility of the products synthesized by our cobalt(III) catalysis, two derivatization

Scheme 5. Proposed Catalytic Cycle



reactions were performed through C−Br cleavage in isoquinoline **3ca** (Scheme 6). Palladium-catalyzed amination[18] delivered **11** in 86% yield, and *N*-arylation of 1*H*-benzimidazole with **3ca** furnished the corresponding product **12**.[19]

Scheme 6. Derivatization of Aminoisoquinolines 3



In summary, we have reported a novel cobalt(III)-catalyzed 1-aminoisoquinoline synthesis by C−H/N−H bond functionalization on easily accessible aryl amidines with diazo compounds. The in situ formed cationic cobalt(III) catalyst provided access to structurally diverse isoquinolines under the assistance of carboxylates **5**. The byproducts of N_2 and H_2O in the reaction make the process environmentally benign. Mechanistic studies provided strong support for an irreversible C−H bond activation. Further mechanistic studies are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01199.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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