Letter

Chelation-Assisted Rhodium-Catalyzed Direct Amidation with Amidobenziodoxolones: C(sp2)-H, C(sp3)-H and Late-Stage Functionalizations

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Chelation-Assisted Rhodium-Catalyzed Direct Amidation with Amidobenziodoxolones: C(sp^2)–H, C(sp^3)–H and Late-Stage Functionalizations

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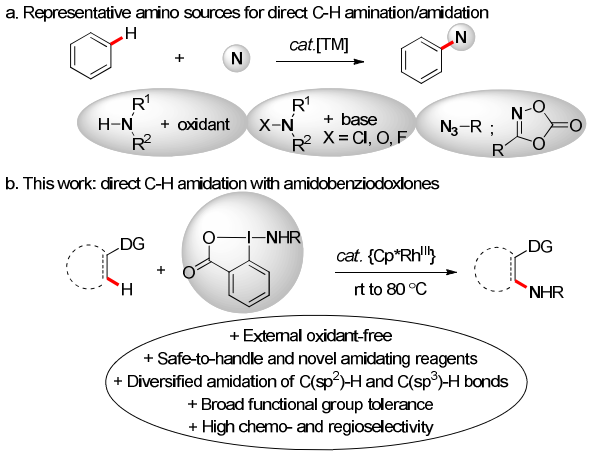
ABSTRACT: Air-stable and convenient amidobenziodoxolones as an amidating reagent were disclosed to enable direct amidation on a wide range of C(sp^2)–H bonds of (hetero)arenes and alkenes, as well as unactivated C(sp^3)–H bonds under Rh^{III} catalysis. The approach to access 49 examples of structurally diverse amides is featured by mild conditions, complete chemo- and regioselectivity, broad substrate scope (not limited to strongly heterocyclic coordinating groups), and tolerance of valuable functional substituents such as unprotected amine, hydroxyl groups. The synthetic applicability of this protocol is also demonstrated by late-stage functionalization of biologically important scaffolds.

KEYWORDS: *C–H amidation, rhodium, hypervalent iodine reagents, amide, directing group*

Direct catalytic C–H amination represents an efficient and straightforward approach to synthesize a myriad of nitrogen-containing compounds,[1] which are ubiquitous in the chemistry community as natural products and pharmaceuticals. To date, several types of amino precursors have been successfully employed in C–N bond-forming process (Scheme 1a). Distinguished with the oxidative (an external oxidant is required)[2] and innate C–H amination,[3,4] chelation-assisted C–H amination with the involvement of preactivated amino sources[5] and azides[6] predominated in terms of high selectivity and efficiency. Despite tremendous expansion regarding this field, the demand for expedient construction of diversified C–N bonds and safe manipulation calls for alternate new amino sources. Very recently, the research groups of Chang,[7a,b] Li,[7c] Jiao,[7d] Ackermann,[7e] and Glorius[7f] have developed dioxazolones of nitrene equivalents[8] as a powerful amidating reagent in robust C–H amidation reactions. In this respect, we wish to introduce a series of air-stable amidobenziodoxolones as a complementary amide source for efficient amidation of various C(sp^2)–H and C(sp^3)–H bonds.

Hypervalent iodine reagents[9] containing I–N bonds have been intensively studied in nitrogen-transfer reactions in the past decades, whereby amidation preferentially occurs at inherently electron-rich C–H bonds.[10] In particular, notable contributions include the metal-free oxidative amidation with a class of structurally defined trivalent iodine reagents bearing I–N single bonds, as elegantly devised by the research groups of Zhdankin,[11] Muñiz,[12] and Minakata.[13] However, the relatively low reactivity of such privileged reagents towards direct functionalization of inert C–H bonds resulted in their synthetic utility beyond electrophilic amination being challenging and largely unexplored. Recently, DeBoef reported a single example of Cu-mediated C–H amidation of 2-phenylpyridines with phthalimide-derived iodane, albeit with modest reactivity.[14] An alternative strategy is through in situ generation of iminoiodinanes by employing a combination of the parent amine with hypervalent iodine oxidants; nevertheless, it suffers from harsh conditions, low regioselectivity, or limited substrate scope.[2f,g,j,l,4a-c,g,h] On the basis of Sanford's pioneering work on *N*-assisted stoichiometric amidation with iminoiodinanes in a stepwise manner,[15] we anticipated that competent hypervalent iodine reagents might enable a general strategy for C–N bond formation *via* a C–H activation pathway. Inspired by the previous observation that {Cp^*Rh^{III}} catalyst could facilitate C–H alkynylation with trivalent iodine reagents,[16] here we describe an unparalleled Rh-catalyzed C–H amidation of broadly defined substrates bearing coordinating functional moieties by using amidobenziodoxolones as a novel amidating reagent. The transformation provides a rapid and practical route to monoamidation products with high chemo- and regioselectivity and functional group tolerance (Scheme 1b).

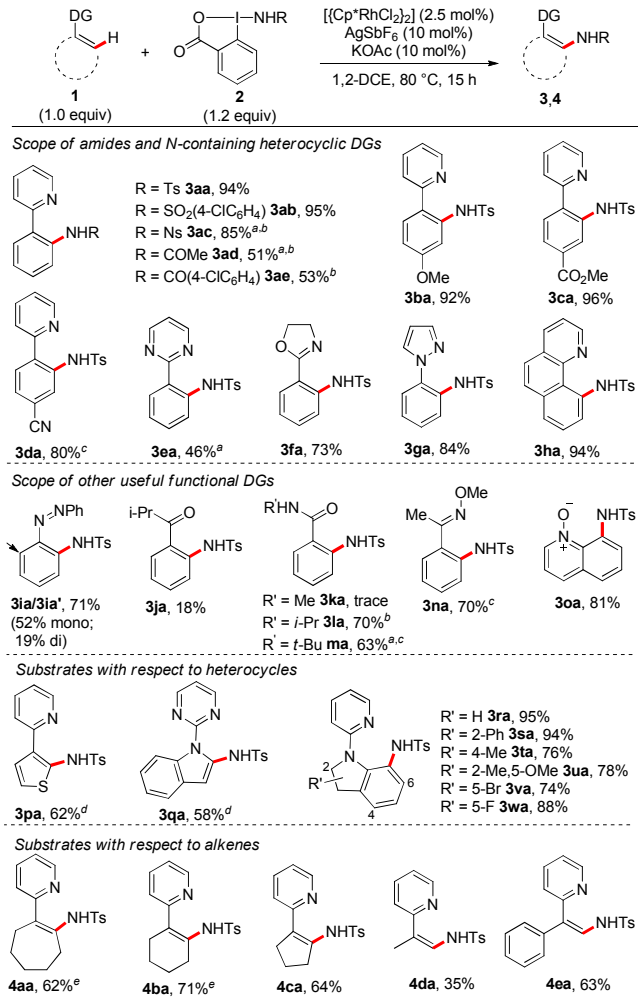


Scheme 1. Metal-catalyzed C–H amination/amidation

Our initial optimizations were undertaken with model substrate 2-phenylpyridine (**1a**) with Zhdankin's reagent[11a] (**2a**) as a convenient amide source catalyzed by a cationic Rh^{III} species. Careful examinations revealed that treatment of **1a** and 1.2 equiv of **2a** in the presence of [{Cp*$RhCl_2$}$_2$] (2.5 mol%), $AgSbF_6$ (10 mol%), KOAc (10 mol%) in 1,2-DCE at 80 °C for 15 h gave an optimal 94% yield of mono-amidated product **3aa** (Table S1, See Supporting Information). Other representative metal catalysts such as Ir^{III}, Ru^{II}, Co^{III} also displayed somewhat activity, but proved to be less effective. Importantly, in stark contrast to the previously reported strategies using in situ-generated iminoiodinanes,[2f,j,l,4a-c,g] this protocol does not require an excess amount of the substrate or high catalyst loading, thereby offering a potential opportunity for late-stage functionalization of complex molecules.

The reactivity of differently decorated amidobenziodoxolones (**2**) was subsequently evaluated in the amidation reaction with **1a** under this catalytic system (Scheme 2). The results indicated that this protocol was applicable to functionalized sulphonamides and simple amides. Then we turned our attention to assess the substrate scope and functional group compatibility for C(sp^2)–H amidation concerning **2a**. As depicted in the formation of *ortho*-amidated 2-phenylpyridine derivatives **3ba**–**3da**, both electron-donating and -withdrawing substituents were well tolerated at the *para* position of the phenyl moiety. While alteration of pyridine to additional heterocyclic coordinating groups, including pyrimidine (**3ea**), oxazole (**3fa**), and pyrazole (**3ga**), the amidation proceeded well to furnish the corresponding products in moderate to good yields. Furthermore, an excellent yield of **3ha** was obtained in the case of benzo[*h*]quinolone. The generality and limitation of this approach was further defined with several synthetically useful directing groups. The coupling reaction of azobenzene with **2a** took place to give mono- and diamidation products **3ia** and **3ia'** in 71% combined yield. Likewise, commonly used amides, ketoxime, and *N*-oxide were all found to facilitate *ortho*-selectivity efficiently (**3la**–**0a**), whereas the use of ketone led to inferior conversion (**3ja**). Exceptionally, subjecting heteroaromatic substrates to the standard conditions resulted in decomposition of the starting materials. We suspected that the acidic nature of the 2-iodobenzoic acid produced might be deleterious to heteroarenes. To our delight, introduction of MgO as the base additive, as suggested by Du Bois,[17] successfully rendered the transformation to afford the desired products in acceptable yields (**3pa** and **3qa**). Meanwhile, given the biologically relevant importance of indolines, a range of indoline derivatives with varied substitution patterns were employed and remarkably, valuable C-7 amidated indolines were produced in good to excellent yields (**3ra**–**wa**).

Of note, this catalytic protocol is not restricted to the (hetero)arene substrates, but also enables olefinic C–H amidation. Alkenes guided by strongly coordinating pyridinyl group underwent exclusively *Z*-selective C–H amidation. The transformation provides the unique access to a variety of unprecedented enamides **4aa**–**4ea** in 35–71% yields, which overrides the potentially competing allylic amination.[12a]

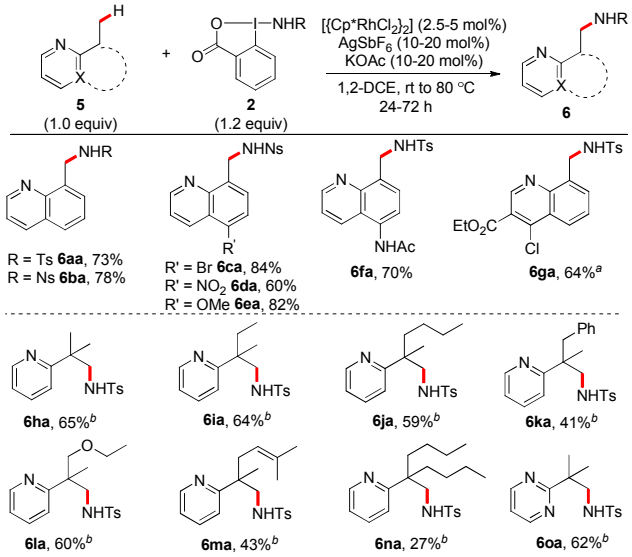


Scheme 2. Substrate scope of C(sp^2)–H amidation

Reaction conditions, unless otherwise noted: **1** (0.2 mmol), **2** (1.2 equiv), [{Cp*$RhCl_2$}$_2$] (2.5 mol%), $AgSbF_6$ (10 mol%), and KOAc (10 mol%) in 1,2-DCE (1.0 mL) at 80 °C for 15 h. Isolated yields are given. [a]At 100 °C. [b]For 24 h. [c][{Cp*$RhCl_2$}$_2$] (4.0 mol%), $AgSbF_6$ (16 mol%), and KOAc (16 mol%). [d]MgO (1.2 equiv) was added. [e]At rt. Ts = 4-toluenesulfonyl. Ns = 4-nitrobenzenesulfonyl.

The established protocol for direct C(sp²)–H amidation with amidobenziodoxlones intrigued us to consider the feasibility of applying our current catalytic system in the unactivated C(sp³)–H amidation (Scheme 3). To this end, substituted 8-methylquinolines[18] were tested in this reaction. Pleasingly, under the similar reaction conditions, a set of electronically modified 8-methylquinolines readily reacted at the benzylic position, despite the presence of the potentially chelating ester and amino moieties (**6aa–6ga**). It needs to be mentioned that the C–H amidation of electron-rich 8-methylquinolines is thus far difficult to be realized by utilizing azides as the amidating reagent.[18d]

Having achieved the successful amidation of benzylic C–H bond, we moved on to further expand the C(sp³)–H substrate scope to more unactivated 2-alkylpyridines.[19] Following slightly modified conditions (Table S2, see Supporting Information), the amide group was successfully installed at the primary C–H bond position assisted by an inherent pyridinyl group, furnishing monoamidation products **6ha–6na** at room temperature. Several tethered functional groups including phenyl, ethoxy, and alkene, were well-tolerated in the amidation event. Analogously, 2-alkylpyrimidine also proved to be a viable substrate (**6oa**).

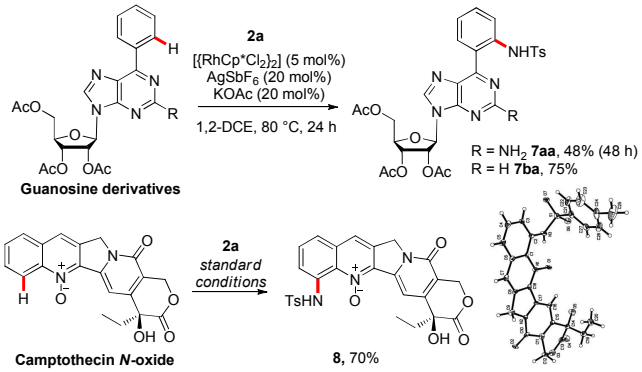


Scheme 3. Substrate scope of C(sp³)–H amidation

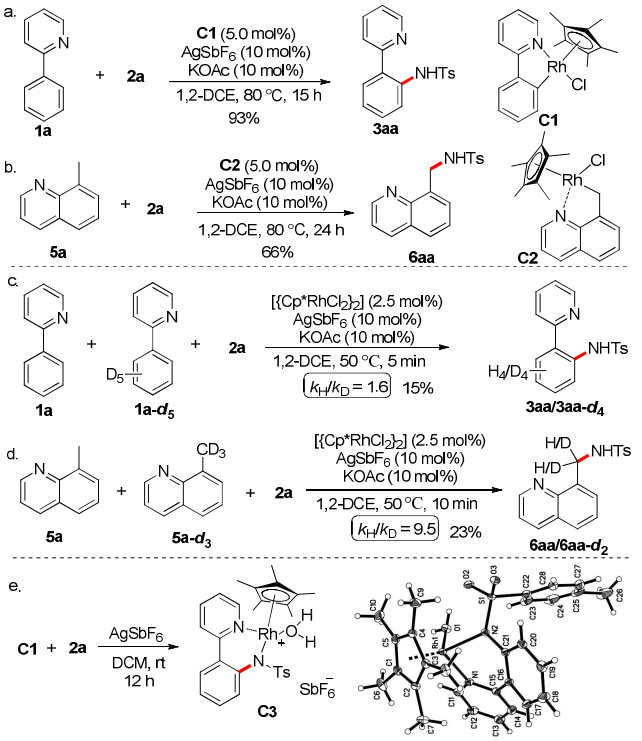
Reaction conditions, unless otherwise noted: **5** (0.2 mmol), **2** (1.2 equiv), [{Cp*RhCl₂}₂] (2.5 mol%), $AgSbF_6$ (10 mol%), and KOAc (10 mol%) in 1,2-DCE (1.0 mL) at 80 °C for 24 h. Isolated yields are given. [a]At 60 °C. [b]**5** (0.2 mmol), **2a** (1.2 equiv), [{Cp*RhCl₂}₂] (5.0 mol%), $AgSbF_6$ (20 mol%), and KOAc (20 mol%) in 1,2-DCE (1.0 mL) at rt for 72 h.

To showcase the applicability of the process, we performed the direct amidation of complex bioactive molecules bearing miscellaneous functional groups (Scheme 4). 6-Phenylpurinyl nucleosides, derived from guanosine, were monoamidated on the expected phenyl ring efficiently (**7aa** and **7ba**). Moreover, treatment with camptothecin *N*-oxide under the typical amidation conditions smoothly furnished the desired product **8** in 70% yield, as confirmed by X-ray crystallographic analysis. It should be pointed out that the unprotected amine and hydroxyl groups survived in this chemistry.

Finally, some preliminary mechanistic experiments were conducted to unravel the reaction mechanism. The observations that two well-defined rhodacyclic complexes **C1** and **C2** catalyzed the direct amidation instead of [{Cp*RhCl₂}₂], giving essentially the same yields of the corresponding products **3aa** and **6aa**, respectively, therefore indicate the potential intermediacy of a cyclometalated species during the process (Schemes 5a and 5b). In addition, the intermolecular kinetic isotope effects (KIE) of amidation with **2a** have been determined. For C(sp²)–H



Scheme 4. Late-stage C–H amidation



Scheme 5. Preliminary mechanistic experiments

amidation, a KIE value of 1.6 revealed that C–H cleavage might not be the rate-limiting step (Scheme 5c).[20] By contrast, a notable KIE for C(sp³)–H amidation suggests that C–H cleavage is plausibly involved in the turnover-limiting step (Scheme 5d). Interestingly, a rhodacyclic intermediate **C3**, which was previously obtained with tosyl azide by Chang,[21] was also successfully isolated (Scheme 5e).

As exemplified with C–H amidation of **1a**, a plausible mechanism for the catalytic system is proposed on the basis of the above mechanistic studies and additional control experiments (For details, see Supporting Information) as well as previous reports (Figire 1).[16,21] The amidation pathway may involve prior coordination of active rhodacycle **A** with **2a** to form Rh^{III} complex **B**. The structurally defined intermediate **C** can be accessed through two presumptive routes: (a) oxidative addition to afford putative Rh^{V} intermediate **D**, followed by reductive elimination to release 2-iodobenzoic acid; (b) insertion of Rh^{V}-nitrenoid species into Rh–C bond. It is also likely that dissociation of 2-iodobenzoic acid from **D** followed by reductive elimination leads to the same intermediate **E**. Protodemetallation of the resulting intermediate **C** delivers the product **3aa**, along with the regenerated {Cp*Rh^{III}} species.

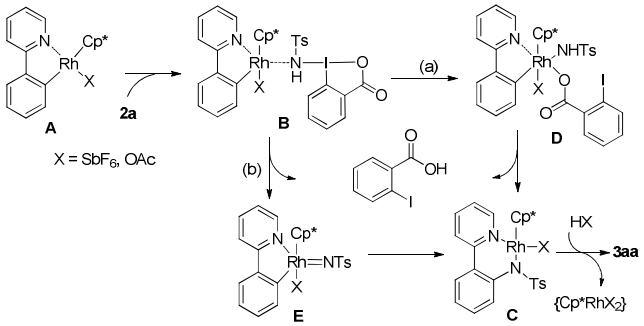


Figure 1. Simplified mechanistic proposal

In summary, a robust Rh-catalyzed C–H amidation using cyclic trivalent iodine reagents as a new amide source has been accomplished. The protocol is applicable to a broad spectrum of DG-containing substrates, including synthetically useful *N*-containing hetereocycles, azo, amide, ketoxime, and *N*-oxide. Specifically, the utility of these reagents allows direct amidation of both C(sp^2)–H and inert C(sp^3)–H bonds to yield monoamidation products by the release of environmentally benign 2-iodobenzoic acid. Considering the high amidation efficiency and functional group compatibility of the transformation, we envision that this newly developed method will pave a promising and complementary way for late-stage amidation of complex molecules in medicine and material related areas.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.0000000.

Experimental procedures and characterization data (PDF)
Crystallographic data for compounds **8** and **C3** (CIF)

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Notes

The authors declare no competing financial interest.

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