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Ir(III)-Catalyzed Carbenoid Functionalization of Benzamides: Synthesis of *N*-Methoxyisoquinolinediones and *N*-Methoxyisoquinolinones

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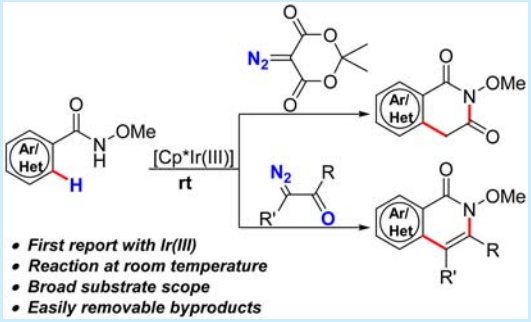
Supporting Information

ABSTRACT: A mild and efficient Ir(III)-catalyzed C−H carbenoid functionalization strategy has been developed to access *N*-methoxyisoquinolinediones and *N*-methoxyisoquinolinones. The reaction proceeds efficiently in high yield at room temperature over a broad range of substrates without requirement of any additional oxidants or a base.



Transition metal catalyzed C−H functionalization is an economic step and straightforward approach for the synthesis of *N*-heterocyclic compounds.[1] In this regard, the use of various coupling partners such as alkenes, alkynes, and allenes has been studied extensively. Over the past couple of years, diazo compounds have been successfully employed as versatile and efficient coupling partners in C−H activation/annulation reactions for the synthesis of various *N*-heterocyclic compounds.[2] The very first examples of Rh(III)-catalyzed C−H functionalization of arenes with diazomalonates was reported by Yu et al.[3] Following this, the amicability of diazocarbonyl compounds in Rh(III)-catalyzed C−H activation and annulation cascade has been aptly explored by several research groups to synthesize various *N*-heterocyclic compounds and/or heterocyclic *N*-oxides.[4] Very recently, Yi and co-workers have reported the synthesis of *N*-methoxyisoquinolinedione via the Rh(III)-catalyzed carbene insertion C−H annulation approach.[5]

In recent years, Cp*Ir(III) has been extensively used for constructing C−C and C−Het bonds via C−H activation.[6] However, only a handful of reports are available for C−H carbenoid functionalization using the Ir(III)-catalytic system, which were mostly limited to only the C−H alkylation reaction.[7] Thus, the development of a mild and efficient one-pot process for the synthesis of privileged *N*-heterocycles via the Ir(III)-catalyzed C−H carbenoid functionalization approach is of prime research interest. Recently, we have reported an Ir(III)-catalyzed C−H annulation of *N*-hydroxyoximes with α-diazocarbonyl compounds to give isoquinoline *N*-oxide.[8] Continuing our efforts to develop a mild and efficient Ir(III)-catalytic system for the synthesis of *N*-heterocyclic compounds via the C−H carbenoid functionalization strategy, we disclose here the broadly applicable Ir(III)-catalyzed C−H functionalization of benzamides with α-diazotized Meldrum's acid in the presence of air at rt to afford *N*-methoxyisoquinolinediones.[5] Interestingly, molecules having the isoquinolinedione moiety are known for their potent biological activity. Examples include aldose reductase (ALR2) inhibitors, antitumor activity against the human pancreatic carcinoma cell line, potent and selective inhibitors of cyclin-dependent kinase 4, and inhibitors of Lckkinase.[9] Furthermore, the same Ir(III)-catalytic system was applied for the synthesis of *N*-methoxyisoquinolinones.

At the outset of our studies, *N*-methoxybenzamide **1a** and 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (α-diazotized meldrum's acid) **2** were taken as model substrates for reaction optimization. After screening various reaction parameters, we were pleased to observe that the desired *N*-methoxyisoquinolinedione **3a** could be obtained in 90% yield using 2.0 mol % of $[IrCp^*Cl_2]_2$ and 8.0 mol % $AgNTf_2$ in 1,2-dichloroethane (1,2-DCE) at room temperature (see the Supporting Information for details). When the reaction time was reduced to 1 h, 60% of product **3a** was obtained (Table 1, entry 2). The reaction efficiency decreased to 68% when the catalyst loading was reduced to 1.0 mol % (Table 1, entry 3). Both the metal catalyst and silver additive were found to be essential for the reaction (Table 1, entries 4−5). A very poor yield was obtained, when $LiNTf_2$ was used in lieu of the silver species (Table 1, entry 6). Interestingly, commonly used Rh- and Ru-catalytic systems were found to be ineffective under the present conditions (Table 1, entries 7−8). Surprisingly, a reaction with other *N*-substituted benzamides such as *N*-(*tert*-butyl)benzamides, *N*-methylbenzamide, or *N*-hydroxybenzamide was found to be sluggish.

With the optimal conditions in hand, we next investigated the scope of substituted benzamides for the present reaction. For

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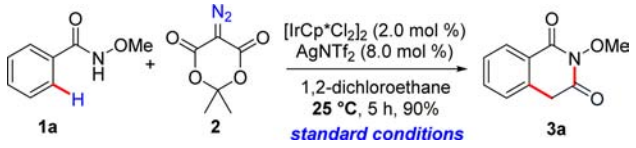
Table 1. Selected Observation during Reaction Optimization[a]

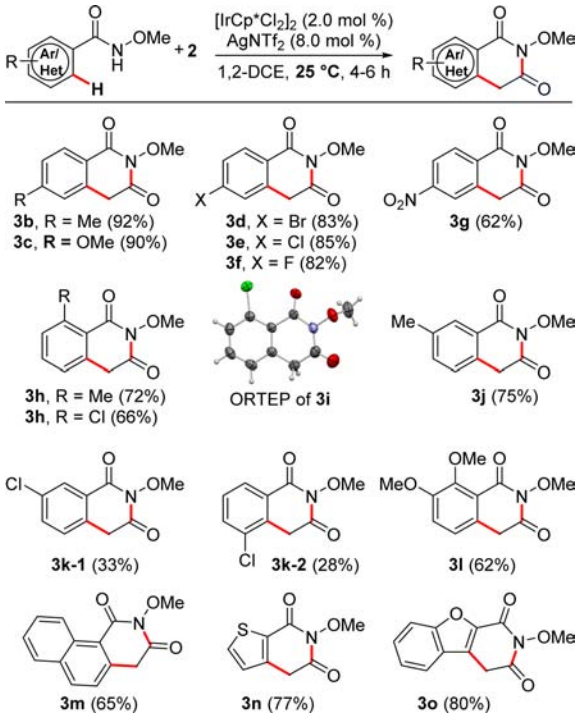


entry	deviation from standard conditions	3a (%)[b]
1	none	95 (90)
2	reaction time 1 h instead of 6 h	60
3	1.0 mol % of [Ir] instead of 2.0 mol %	68
4	no $[IrCp^*Cl_2]_2$	0
5	no $AgNTf_2$	12
6	$LiNTf_2$ instead of $AgNTf_2$	15
7	$[RhCp^*Cl_2]_2$ instead of $[IrCp^*Cl_2]_2$	<5
8	$[Ru(p\text{-Cymene})Cl_2]_2$ instead of [Ir]	<5

[a]Reaction conditions: **1a** (0.15 mmol) and **2** (1.1 equiv) in 1,2-dichloroethane (1,2-DCE) (1.0 mL). [b]Yields are based on ^1H NMR of crude reaction mixture (CH_2Br_2 as an internal standard); isolated yields are given in parentheses.

this, various substituted *N*-methoxybenzamides were treated with α-diazotized Meldrum's acid **2** to furnish the corresponding *N*-methoxyisoquinolinedione derivatives (Scheme 1). Overall,

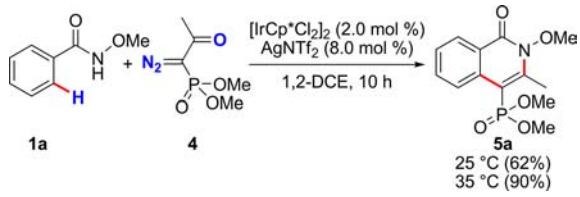
Scheme 1. Benzamide Substrate Scope[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (1.2 equiv) in 1,2-DCE (1 mL). Isolated yields are given.

the reaction proceeded smoothly at room temperature regardless of the position as well as electronic nature of the substituents on the aryl ring. Benzamides having both electron-donating **3b**–**3c** and electron-withdrawing **3d**–**3f** functionality at the *para*-position worked well and furnished the corresponding products in high yield. However, the benzamides bearing a strongly electron-withdrawing nitro group resulted in a slightly lower yield of **3g**. Similarly, benzamides with an *ortho*-substituent were found to be quite compatible and gave the desired product in

Scheme 2. *N*-Methoxyisoquinolinone Synthesis



good yields (**3h**, **3i**). Additionally, the structure of **3i** was confirmed by single crystal X-ray diffraction studies. It was observed that substitution at the *meta*-position plays a crucial role in controlling the regioselectivity of the present C–H annulation. For instance, when *m*-methylbenzamide was used for **3j**, C–H activation occurred predominantly at the less hindered position, whereas *m*-chloro benzamide gave the corresponding regioisomers **3k-1** and **3k-2** in a 1.2:1 ratio. Also, 2,3-dimethoxybenzamide **3l** and polyaromatic naphthalene benzamide **3m** were found to be compatible under the present reaction conditions. Furthermore, heterocyclic amide derived from thiophene **3n** and benzofuran **3o** underwent C–H annulations efficiently to furnish the corresponding products in high yield. However, the reaction was found to be sluggish when *N*-methoxymethacrylamide was used under the present Ir-catalytic conditions.

After successful exploration of the *N*-methoxyisoquinolinedione synthesis, we next focused on extending the present Ir(III)-catalytic system to synthesized isoquinolinones. Isoquinolinones and pyridinone structural units are widely present in many natural products. Some of their derivatives possess potential biological activity and are privileged scaffolds in medicinal chemistry.[10] Based on our previous report of Ir(III)-catalyzed isoquinoline *N*-oxide synthesis,[8] we envisioned the feasibility of C–H annulations of benzamide with previously used Ohira–Bestmann's diazo phosphonate **4** to give *N*-methoxyisoquinolinones. In this context, Wang and co-workers have documented an elegant method for the synthesis of isoquinolinone and pyridinones via Rh(III)-catalyzed C–H annulations of benzamide with the diazo compounds.[11]

As expected, treatment of *N*-methoxybenzamide **1a** with the diazocompound **4** under the present Ir(III)-catalytic conditions afforded the desired *N*-methoxyisoquinolinone **5a** in 62% yield. The product yield was increased up to 90% by running the reaction at 35 °C for 10 h (Scheme 2). With the adequate results in hand, the scope of various benzamides was investigated next. We were happy to observe that a wide range of benzamides containing both electron-donating and -withdrawing groups underwent C–H annulations smoothly to furnish the corresponding *N*-methoxyisoquinolinone derivatives **5a**–**5k** in good to very good yields (Scheme 3). Next, amides derived from naphthalene **5l**, benzofuran **5m**, and thiophene **5n** were found to be compatible with the present conditions. Furthermore, the reaction of *N*-methoxymethacrylamide under standard conditions gave the corresponding pyridinone **5o** in high yields. Then the scope of other α-diazocarbonyl compounds has been also investigated. In the case of the methyl 3-diazo-2,4-dioxopentanoate the product **5p** was obtained in moderate yield. Similarly, the cyclic α-diazocarbonyl compounds furnished the corresponding tetrahydrophenanthridinone derivatives **5q**, **5r** in good yields.

Next, a series of preliminary experiments were carried out in order to gain mechanistic insight into the present reaction (Scheme 4). The reversibility of the C–H activation step was determined by performing the reaction in the absence of **2** with

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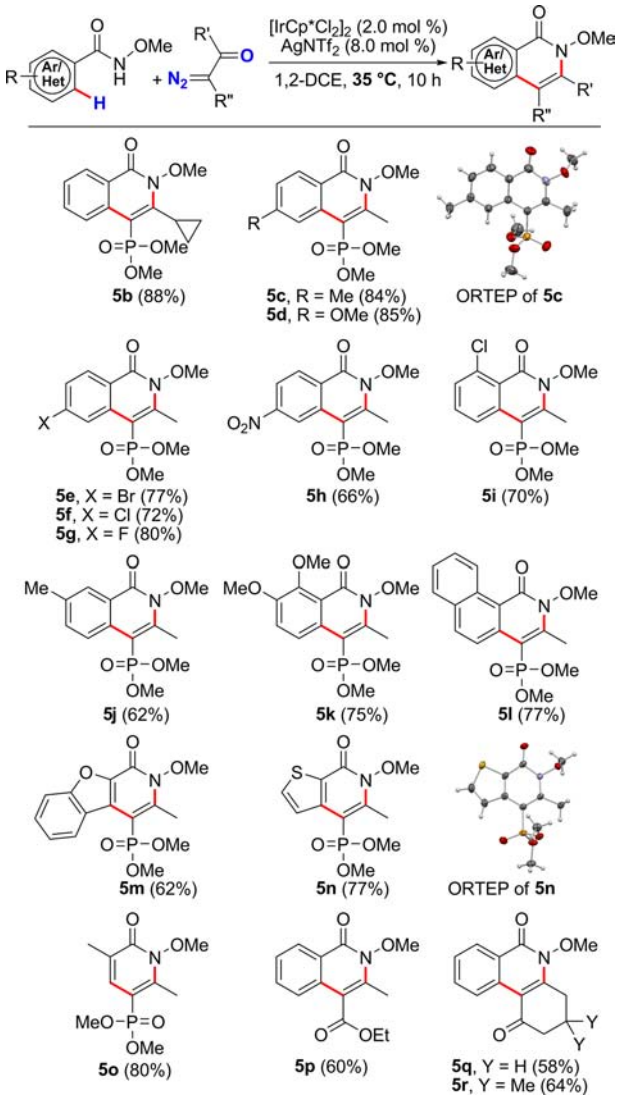
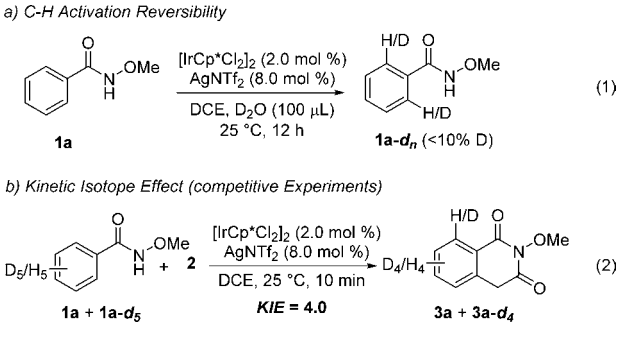
Scheme 3. Scope of *N*-Methoxyisoquinolinone Synthesis[a]



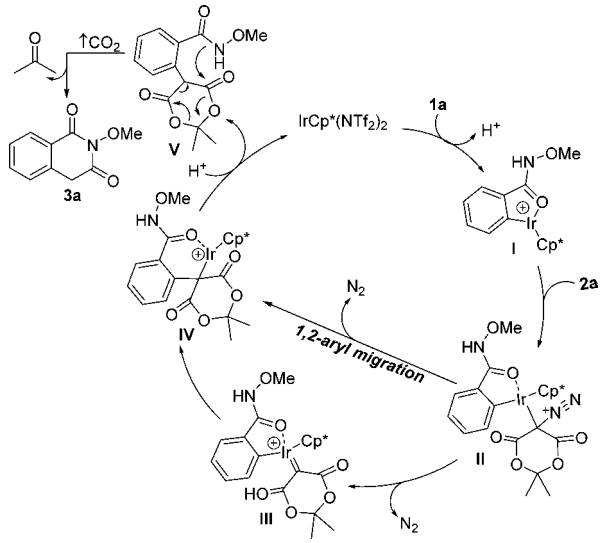
[a]Reaction conditions: **1** (0.15 mmol), diazo compound (1.2 equiv) in 1,2-DCE (1 mL). Isolated yields are given.

Scheme 4. Preliminary Mechanistic Investigation



DCE/D_2O (20:1) as solvent (Scheme 4, eq 1). Analysis of the ^1H NMR of the reaction after 12 h shows <10% deuterium incorporation at the *ortho* positions (Scheme 4, eq 1). This result indicates that the C−H bond activation is largely irreversible.[12] Next, a significant kinetic isotope effect (KIE) was observed from the intermolecular competition reaction ($K_H/K_D = 4.0$) (Scheme 4, eq 2). Together, these studies suggested that C−H bond cleavage is most likely the rate-determining step.[13]

Scheme 5. Proposed Catalytic Pathway



Based on the experimental results and precedent literature reports,[4,7b,8,14,15] a plausible catalytic pathway for *N*-methoxy isoquinolinedione formation is proposed in Scheme 5. First, a cationic [Cp*Ir(III)] species will react with benzamide through the key C−H bond cleavage step to form the five-membered iridacyclic intermediate **I** with the spontaneous loss of the *ortho* proton.[14] Coordination of the diazo compound with **I** will afford the diazonium species **II**, and then the release of N_2 will form the Ir-carbene species **III**. Subsequently migratory insertion of carbene to the Ir−C bond would form the six-membered iridacyclic intermediate **IV**. Alternatively, intermediate **IV** will form via intramolecular 1,2-migratory insertion of the aryl group. Next, protonation of **IV** delivers the alkylated intermediate **V** and regenerates the reactive [Cp*Ir(III)] species. Intermediate **V** then undergoes annulations via tandem addition, elimination, decarboxylation, and protonation to furnish the desired product **3**.[15] In the case of isoquinolinone synthesis, the catalytic cycle is identical up to the addition product, after which it undergoes dehydration similarly to a previous report of Rh(III)-catalysis.[12]

In conclusion, we have developed the first Ir(III)-catalyzed C−H carbenoid functionalization strategy to synthesize *N*-methoxyisoquinolinediones from *N*-methoxybenzamide and diazotized Meldrum's acid. The reaction proceeds efficiently at room temperature under atmospheric conditions and releases easily removable N_2, CO_2, and acetone as byproducts. Additionally, the Ir(III)-catalytic system was extended for the synthesis of phosphorylated *N*-methoxyisoquinolinone derivatives by using α-diazocarbonyl compounds instead of diazotized Meldrum's acid. Cleavage of the N−OMe bond will give the corresponding isoquinolinedione or isoquinolinone.[16] Further exploration of Ir-catalyzed *N*-heterocycles synthesis and detailed mechanistic investigations for the C−H carbenoid functionalization strategy are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedure, characterization of new compounds (^{1}H, ^{13}C NMR spectra) and X-ray crystallographic data (PDF)
X-ray data for **3i** (CIF)
X-ray data for **5n** (CIF)
X-ray data for **5c** (CIF)

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Notes

The authors declare no competing financial interest.

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