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Ir(III)-Catalyzed Synthesis of Isoquinoline *N*-Oxides from Aryloxime and α-Diazocarbonyl Compounds

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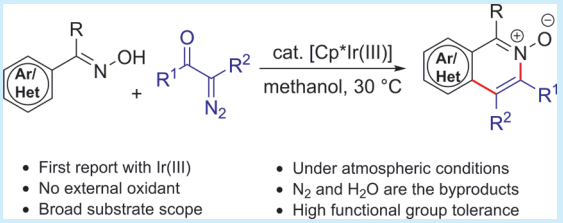
Supporting Information

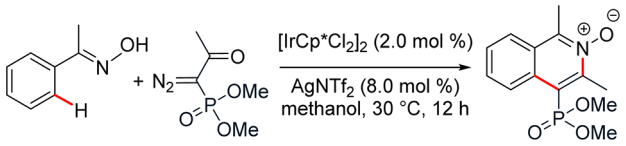
ABSTRACT: An efficient Ir(III)-catalyzed C−H activation and annulations of aryloxime with α-diazocarbonyl compounds has been developed for the synthesis of substituted isoquinoline *N*-oxides. The reaction proceeds under mild atmospheric conditions, without any external oxidants and releases N_2 and H_2O as the byproducts. In addition, synthetic applications of the *N*-oxide products have been established by performing further functionalization. An interesting dimeric iridacyclic complex allied through a bis-silver carboxylate bridge has been isolated that efficiently catalyzed the reaction.



The *N*-oxide of isoquinoline and pyridine derivatives represents an important structural unit found in various natural products,[1] pharmaceutical agents,[2] and chiral ligands.[3] Besides this, *N*-oxides are isolable synthons with widespread utility in the functionalization of heterocycles and the synthesis of natural products.[4] Traditional synthesis of *N*-oxides involves the direct oxidation of parent heterocycles with a stoichiometric amount of peroxides or peracids.[5] The major limitations of these methods are the prerequisite of a completely fabricated heterocyclic unit and the compatibility of the sensitive functional group present on the substrate. The use of transition-metal-catalyzed transformations had, to some extent, addressed the oxidation under mild conditions.[6] Recently, C−H activation approaches have taken precedence over traditional methods, especially in the context of the synthesis of isoquinoline(oxide) derivatives by the annulation of simple imines/oximes with easily accessible alkenes/alkynes.[7] The inaugural entry in this regard was documented by Huang et al. and involves the Pd-catalyzed annulations of aryloximes and diary acetylenes via an C−H activation approach leading to isoquinoline *N*-oxides.[8] However, the requirement of high temperature and a stoichiometric amount of acids and alkyne scope are the major limitations of this approach. Recently, the Glorius group reported an elegant example of a Rh(III)-catalyzed intermolecular annulation reaction using vinyl or aryloximes and diazo compounds for the synthesis of pyridine and isoquinoline *N*-oxides.[9a]

Although substantial progress has been made in this type of C−H functionalization, the scope is mainly limited to Rh(III) catalytic systems.[9,10] Consequently, finding alternative catalytic systems for the synthesis of (hetero)aryl-fused pyridine *N*-oxides and their derivatives with a divergent product scope is of leading research interest. To explore a new catalyst with a versatile reaction scope, our attention has been focused on the Cp*Ir(III) catalyst system because of its excellent performance in C−H bond functionalization.[11−13] Inspired by these results, we envisioned the feasibility of directed C−H activation and annulation of aryloxime and α-diazocarbonyl compounds under iridium catalytic systems. Herein, we report the first Ir(III)-catalyzed intermolecular C−H functionalization and annulations of aromatic oxime with α-diazocarbonyl compounds affording diversely substituted isoquinoline *N*-oxides that allows a considerable expansion of C−H activation and annulations approaches (Scheme 1). Additionally, the present reaction

Scheme 1. Isoquinoline *N*-Oxide Synthesis



conditions provide a straightforward approach to the preparation of phosphorylated heterocycles, which have numerous applications in organic synthesis and material science.

To initiate the study, acetophenone oxime **1a** and Ohira-Bestman's diazophosphonate **2a** were selected as model substrates to screen the reaction parameters. After performing a few optimization experiments, we were pleased to find that the reaction proceeded very well to give **3a** in 95% yield, using 2.0 mol % of the $[IrCp^*Cl_2]_2$ and 8.0 mol % of $AgNTf_2$ in methanol at 30 °C (Scheme 1). The effect of solvent is found to be very crucial for the reaction, and methanol is found to be the best solvent (see the Supporting Information for a detailed optimization table). Interestingly, under similar conditions, a

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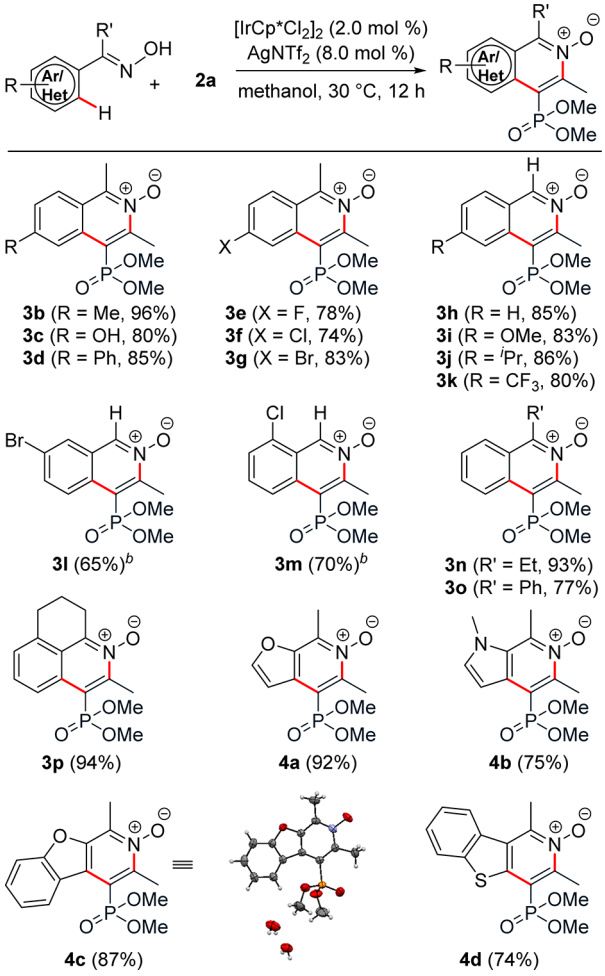
[Cp*Rh(III)] catalytic system was found to be less efficient (55% crude yield).

With the optimized reaction conditions in hand, we next examined the substrate scope of this transformation (Scheme 2).

Scheme 2. Substrate Scope of (Hetero)Aryl Oxime[a]



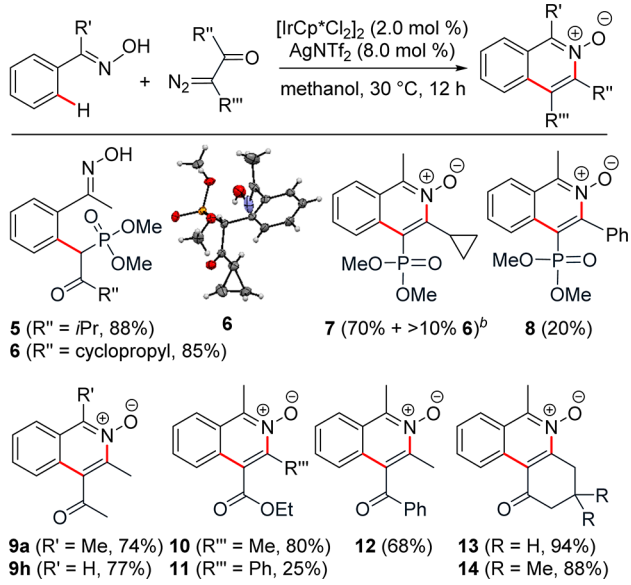
[a]Isolated yields are given. [b]Reaction carried out at 60 °C.

Substrates bearing both electron-donating groups (**3b**, **3c**) and electron-withdrawing groups (**3d**–**3g**) were compatible in this transformation and provided the corresponding *N*-oxide products in excellent yields. Next, the scope of the reaction was extended to benzaldehyde oxime derivatives. We were gratified to observe that not only benzaldehyde oxime **3h** but also substrates with electron-donating substituents **3i**–**3j** and electron-withdrawing substituents **3k**–**3m** were found to be compatible and provided the requisite *N*-oxide products in excellent yield. The reaction with substrates bearing substitution at *meta* (**3l**) and *ortho* (**3m**) positions were found to be sluggish under standard reaction conditions. However, the reaction yields could be increased to considerable amounts upon increasing the reaction temperature to 60 °C. Further, the effect of substitution on the methyl side of acetophenone oxime was studied. For instance, the reaction of oximes derived from acetophenone (**2n**), benzophenone (**2o**), and α-tetralone (**2p**) provided the cyclized products **3n**, **3o**, and **3p**, respectively, in excellent yields. However, reaction with vinyl and alkenyl oxime substrates was found to be very sluggish under the present conditions.

After successful conversion of aryloximes to isoquinoline *N*-oxide derivatives, we studied the feasibility of heteroaryloxime derivatives. We were pleased to see that the reaction of 1-(furan-2-yl)ethanone oxime with **2a** under standard reaction conditions gave the desired product **4a** in 92% yield (Scheme 2). Similarly, other heteroaromatic oximes derived from *N*-methylpyrrole (**4b**), benzofuran (**4c**), and benzothiophene (**4d**) were found to be compatible under these conditions. Additionally, the structure of **4c** was confirmed by X-ray crystallographic analysis.

With the established oxime scope in hand, we then explored the substituent effect on the diazo compound by changing the carbonyl substituent. Surprisingly, with treatment of dimethyl(1-diazo-3-methyl-2-oxobutyl)phosphonate, only the alkylated product **5** was observed in excellent yield, without further cyclization (Scheme 3). Likewise, the cyclopropyl-substituted

Scheme 3. Scope of α-Diazocarbonyl Compounds[a]



[a]Isolated yields are given. [b]Reaction carried out at 60 °C.

diazo compound gives exclusively the alkylated product **6** in high yield. The molecular structure of **6** was unambiguously established with the help of single-crystal X-ray structural analysis. At this stage, we hypothesized that maybe the higher energy barrier for the keto–enol isomerization is the reason for the isolation of the alkylated products and presumed that the increase in the reaction temperature is required to push the reaction to the final cyclized products. In fact, when the reaction was carried out at 60 °C, the cyclized *N*-oxide product **7** was obtained as the major product (70%) along with minor amount of alkylated products. This observation concludes that the overall reaction proceeds via alkylation followed by cyclization to give the isoquinoline *N*-oxide product. When phenyl-substituted diazo compound was used under standard conditions, only the cyclized product **8** was obtained in poor yield, maybe due to the steric bulkiness of the diazo compounds.

To further extend the generality of our reaction, the diazo compound without a phosphonate group was screened to afford various 4-substituted isoquinoline *N*-oxide (Scheme 3). The reaction of 3-diazopentane-2,4-dione occurred smoothly with both acetophenone oxime and benzaldehyde oxime to furnish desired *N*-oxide products **9a** and **9h**, respectively, in very good yield. Similarly, reaction of ethyl-2-diazo-3-oxobutanoate with **1a**

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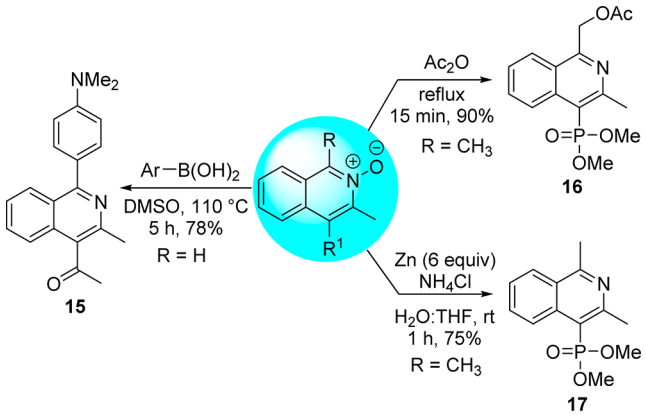
gave the desired product **10** in 80% yield. Sterically bulky ethyl-2-diazo-3-oxo-3-phenylpropanoate gave product **11** in poor yields. When the reaction was performed with sterically unsymmetrical 2-diazo-1-phenylbutane-1,3-dione, cyclization occurred exclusively with the less sterically hindered carbonyl group to give **12** in good yields. Similarly, cyclic diazocarbonyl compounds like 2-diazocyclohexane-1,3-dione and 2-diazo-5,5-dimethylcyclohexane-1,3-dione were found to be very efficient coupling partners to afford the corresponding tricyclic products **13** and **14** in excellent yield. However, 2-diazo-1-(piperidin-1-yl)butane-1,3-dione having an amide functionality was found to be an ineffective diazo source under the present conditions.

To shed light on the synthetic applicability of the *N*-oxide products, selected *N*-oxides were subjected to further functionalization (Scheme 4). For example, refluxing compound **9h** with

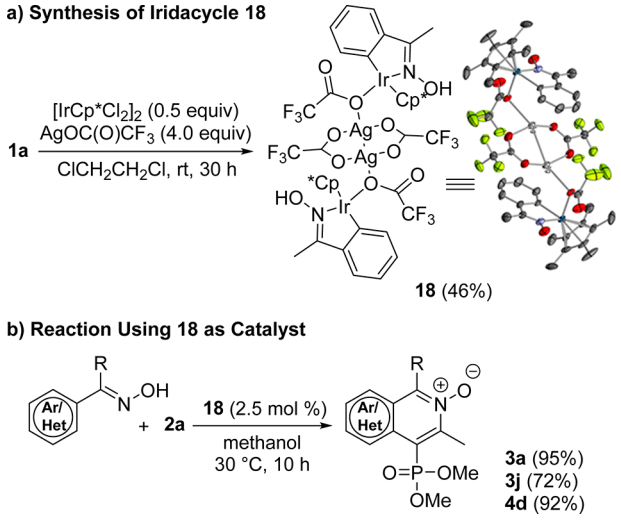
Scheme 4. Synthetic Application of *N*-Oxide Products



4-(dimethylamino)phenylboronic acid in DMSO gave the corresponding 1-arylated product **15** in good yield.[14] Selective acetoxylation of the C1-methyl of **3a** was achieved by refluxing with acetic anhydride to get product **16** in quantitative yield.[15] Further reduction of the N−O bond of **3a** using Zn and NH_4Cl gave the isoquinoline product **17** in good yields.[16]

To gain more mechanistic insight, we carried out several preliminary mechanistic experiments. A notable deuterium scrambling was observed when the reaction was performed in CD_3OD in the absence of diazo compound, indicating the reversibility of the C−H activation step. Performing the same reaction in the presence of **2a**, after 12 h of reaction, **3e** was isolated in 93%. Analysis of **3e** by ^1H NMR and ESI-MS showed no deuterium incorporation of the *ortho* proton (see the Supporting Information), suggesting the C−C bond formation to be significantly faster than the back reaction of the C−H activation step.[17] A relatively low value of primary kinetic isotope effects (KIE) was measured in parallel experiments (KIE = 1.43) and intramolecular competition reaction (KIE = 1.67). Although it is not convincing at the present stage, these KIE values indicate that the C−H bond cleavage may not be the rate-limiting stage.[12,18] After treatment of **2a** with $[IrCp^*Cl_2]_2$ and excess silver trifluoroacetate in 1,2-dichloroethane, a stable cyclometalated Ir(III) complex (**18**) was obtained, initially assumed to be monomeric Ir(III) complex.[19] The complex alone catalyzes the reaction without any Ag additives to give 95% of **3a**, which indicates the relevancy of C−H activation. X-ray crystallography analysis of the complex revealed that the complex contains two iridacycles connected through a dimeric silver bridge, as shown in Scheme 5a. To the best of our knowledge, this is the first isolation

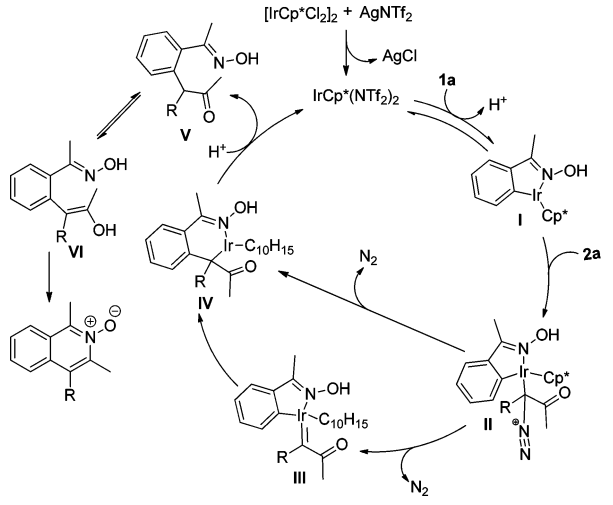
Scheme 5. Synthesis of Complex 18 and Its Catalytic Activity



of such types of bimetallic Ir complexes, which can catalyze the C−H activation very efficiently. Further, **18** was used as the catalyst for selected (hetero)aryloximes to furnish **3j** and **4d** in good to excellent yields (Scheme 5b).

Based on the above observed data and precedent literature reports,[9,13,20] a mechanistic pathway is proposed in Scheme 6.

Scheme 6. Proposed Catalytic Pathway



The first step is the generation of a cationic Ir(III) species from the $[IrCp^*Cl_2]_2$ with $AgNTf_2$ additive, which facilitates the key C−H bond activation to afford a five-membered iridacyclic intermediate **I**. The diazonium intermediate **II** may form by the coordination of the diazo compound with **I**. Generation of the carbene intermediate **III** is assumed to take place before the subsequent migratory insertion of carbene to the C−Ir bond, leading to **IV**.[20] Alternatively, intramolecular 1,2-migratory insertion of the aryl group would give **IV**.[13] Next, protonolysis of **IV** delivers the alkylated product **V**, which is supposed to be in equilibrium with the corresponding enol intermediate **VI**. Finally, intermediate **VI** undergoes dehydration either via 6π electrocyclization or nucleophilic cyclization to give the desired product.[9]

In summary, we have developed an Ir(III)-catalyzed mild and external oxidant-free approach for the synthesis of isoquinoline

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and heretoaromatic-fused pyridine *N*-oxide derivatives. In addition, the present protocol provides a straightforward approach for the synthesis of phosphorylated heterocycles, an important structural feature in organic synthesis and material chemistry. During the course of the mechanistic investigations, we isolated a rare dimer of bimetallic species containing two iridacyclic units, which catalyzes the reaction without any additives. Further studies on the dimeric Ir complex and studies to expand this methodology for the synthesis of pyridine *N*-oxide derivatives are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03462.

Experimental procedure,characterization of new compounds (^{1}H, ^{13}C NMR spectra) and X-ray crystallographic data (PDF)
X-ray data for **4c** (CIF)
X-ray data for **6** (CIF)
X-ray data for **18** (CIF)

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Notes

The authors declare no competing financial interest.

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