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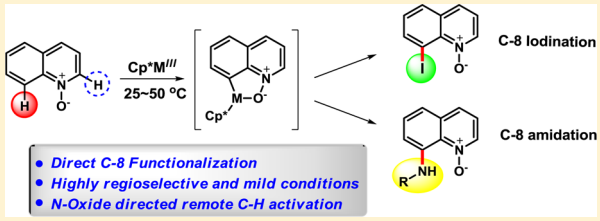
Regioselective Introduction of Heteroatoms at the C-8 Position of Quinoline *N*-Oxides: Remote C−H Activation Using *N*-Oxide as a Stepping Stone

Heejun Hwang,[†,‡,§] Jinwoo Kim,[†,‡,§] Jisu Jeong,[†,‡] and Sukbok Chang*[,‡,†]

[†]Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 305-701, Korea
[‡]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-701, Korea

Supporting Information

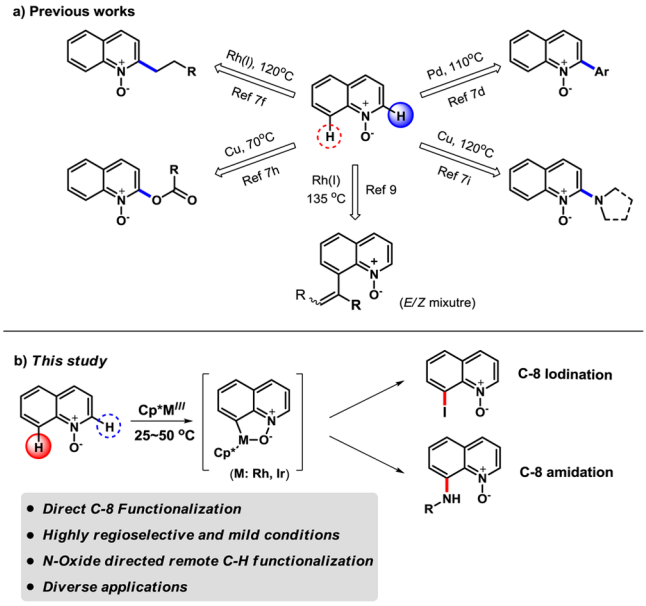
ABSTRACT: Reported herein is the metal-catalyzed regioselective C−H functionalization of quinoline *N*-oxides at the 8-position: direct iodination and amidation were developed using rhodium and iridium catalytic systems, respectively. Mechanistic study of the amidation revealed that the unique regioselectivity is achieved through the smooth formation of *N*-oxide-chelated iridacycle and that an acid additive plays a key role in the rate-determining protodemetalation step. While this approach of remote C−H activation using *N*-oxide as a directing group could readily be applied to a wide range of heterocyclic substrates under mild conditions with high functional group tolerance, an efficient synthesis of zinquin ester (a fluorescent zinc indicator) was demonstrated.



INTRODUCTION

Quinolines are an important structural motif found in numerous natural and synthetic compounds with broad applications in medicinal[1] and materials chemistry.[2] As a result, the development of synthetic procedures for the facile derivatization of quinolines has been actively investigated.[3] Although certain functional groups can be introduced into the quinoline skeleton, it often requires multiple steps or harsh conditions in most conventional approaches.[4] On the other hand, significant advances have been recently made in the direct C−H functionalization of readily available compounds.[5] This strategy has also been successfully applied for the direct C−C and C−X bond formation of quinolines[6] or their *N*-oxide derivatives,[7] wherein the latter can be readily interconverted to the former species. While a number of catalytic procedures have been reported for the C−H activation of quinolines, most of them allow functionalization at the C-2 position.[6d−f] Indeed, only a few cases are known to reveal the catalytic activation of quinolines at sites other than C-2, including our own[8a] and Sawamura's.[8b] Similarly, direct introduction of certain functional groups into quinoline *N*-oxides turned out to be facile, but again, only at the ortho position relative to the *N*-oxide moiety. In fact, quinoline *N*-oxides were employed for the alkylation,[7f,g] alkenylation,[7a,c] alkynylation,[7e] arylation,[7b,d] acetoxylation,[7h] and amidation[7i] all at the C-2 position under the corresponding catalytic conditions (Scheme 1a). In contrast, direct introduction of synthetically valuable functional groups at the 8-position has not been achieved except for a very recent example of the C-8 alkenylation of quinoline *N*-oxides using Rh(I) catalyst.[9] However, this reaction takes place at high temperatures, leading to an *E*/*Z* mixture of isomeric products.

Scheme 1. C−H Functionalization of Quinoline *N*-Oxides



This aspect is especially noteworthy in view of the fact that C-8 functionalized quinolines are widespread, having important utilities in diverse areas. In particular, as shown in Figure 1, notable biological activities are displayed by 8-aminoquinolines such as primaquine (commercialized antimalarial reagent),[1b]

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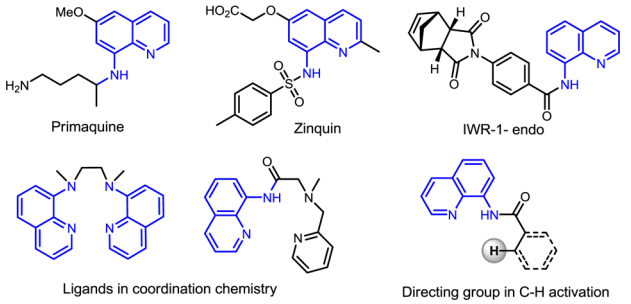


Figure 1. Utilities of 8-aminoquinoline derivatives.

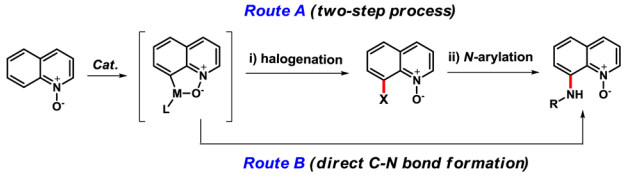
zinquin (fluorescent sensor for Zn(II)),[10] or IWR-1-endo (inhibitor of Wnt signaling and an axin stabilizer).[11] They are also effective ligands used in coordination chemistry.[12] In addition, 8-aminoquinolines are widely employed as effective bidentate chelates for the C−H functionalization of pendant sp^2 or sp^3 hydrocarbons.[13] While quinoline *N*-oxides are known to readily coordinate to various metal species such as Cu, Ni, Zn, Fe, Co, and Ti,[14] we hypothesized that the desired C-8 functionalization has been largely unsolved, presumably due to the difficulty in the selective formation of the corresponding metallacycles at that position.

These considerations led us to search for catalytic systems enabling efficient formation of metallacycles of quinoline *N*-oxides and smooth subsequent insertion of suitable functional groups. In this aspect, we have developed two catalytic procedures for the direct C-8 functionalizations of quinoline *N*-oxides: Rh-catalyzed iodination and Ir-catalyzed amidation under mild conditions (Scheme 1b).

RESULTS AND DISCUSSION

Regioselective Direct C−H Iodination of Quinoline *N*-Oxide. We originally envisioned two synthetic approaches to access to 8-aminoquinolines: (i) regioselective C−H halogenation of quinoline *N*-oxides and subsequent Buchwald−Hartwig *N*-arylation[15] (Scheme 2, route A), and (ii) direct

Scheme 2. Synthetic Routes to 8-Aminoquinoline *N*-Oxides

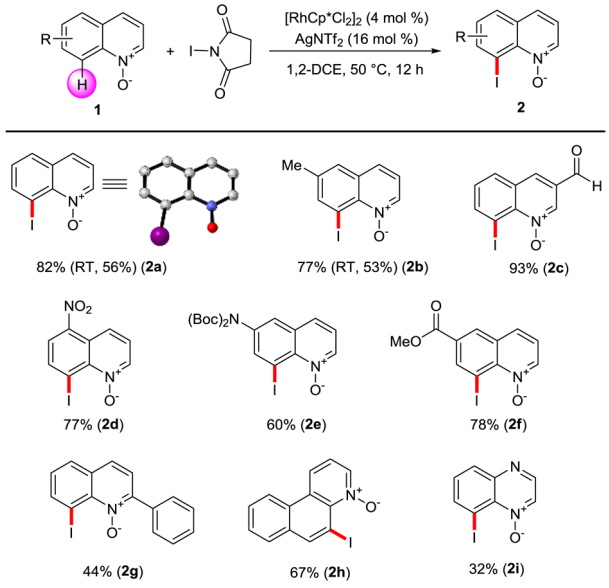


C−H amination at the same position (route B). Since the formation of five-membered metallacyclic intermediates by using *N*-oxide as a directing group was postulated to be essential for this remote C−H functionalization, we decided to use quinoline *N*-oxides as substrates for this purpose. The fact that quinolines and their *N*-oxides are readily interconverted under mild conditions[7d,16] led us to extensively investigate this strategy.

Although 8-haloquinolines can be used as starting materials for the *N*-arylation to afford 8-aminoquinolines, they are also highly versatile reactants for a variety of additional cross-coupling reactions.[17] Again, we need to emphasize that whereas elegant examples of ortho C−H halogenation of aromatics were revealed by Sanford,[18] Glorius,[19] and Ackermann,[20] regioselective direct C-8 halogenation of quinolines or their *N*-oxides has not been reported.

After exploring various reaction conditions (see the Supporting Information for details), we were pleased to find that a Rh(III) catalytic system facilitated the desired halogenation of quinoline *N*-oxides. While chlorination and bromination were not satisfactory (<20% yield), C-8 iodination of quinoline *N*-oxides was smooth under mild catalytic conditions when *N*-iodosuccinimide (NIS, 1.5 equiv) was used as a halogenating reagent, and the scope of this iodination reaction is presented in Table 1. Quinoline *N*-oxide (**1a**) was

Table 1. Selective C-8 Iodination of Quinoline *N*-Oxides[a]



[a]Reaction conditions: **1** (0.1 mmol), NIS (1.5 equiv), $[Cp^*RhCl_2]_2$ (4 mol %), $AgNTf_2$ (16 mol %) in 1,2-dichloroethane (1,2-DCE, 0.5 mL). Isolated product yields are given.

iodinated selectively at the C-8 position to afford the product **2a** in 82% yield at 50 °C using an in situ generated cationic Cp^*Rh^{III} catalyst, and the structure of **2a** was confirmed by an X-ray crystallographic analysis. The reaction proceeded even at room temperature, albeit with slightly lower efficiency (56% yield). 6-Methylquinoline *N*-oxide (**1b**) displayed a similar reactivity pattern leading to **2b**, without reaction at the potentially labile benzylic C−H bonds. While 3-formylquinoline *N*-oxide (**1c**) worked in excellent efficiency to furnish **2c**, functional group tolerance was found to be high, as demonstrated in the facile iodination leading to products **2d−f**. Interestingly, iodination of 2-phenylquinoline *N*-oxide (**1g**) was again regioselective at the C-8 position (**2g**), leaving the potentially reactive phenyl side chain intact. The same approach could be applied to other hetereocyclic substrates. For instance, benzo[*f*]quinoline *N*-oxide was smoothly iodinated exclusively at the C-5 position (**2h**). In addition, iodination of quinoxaline *N*-oxide (**1i**) was highly regioselective at the C-8 position without reacting at the C-5 position to afford **2i**, albeit in moderate yield.

As described above, since 8-halogenated quinolines (*N*-oxides) can easily be aminated according to the Buchwald−Hartwig protocol,[21] our developed iodination procedure is a highly valuable synthetic tool to access 8-aminoquinolines. Moreover, the fact that this catalytic reaction bears notable

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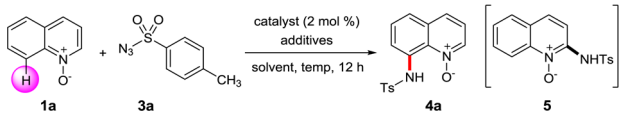
Table 2. Optimization of the Regioselective Amidation[a]



entry	catalyst system	additive	solvent	temp (°C)	yield (%)[b]
1	$[IrCp^*Cl_2]_2/AgNTf_2$		1,2-DCE	80	24
2	$[IrCp^*Cl_2]_2/AgNTf_2$	AcONa	1,2-DCE	80	43
3	$[IrCp^*Cl_2]_2/AgNTf_2$	AcOH	1,2-DCE	80	76
4	**$[IrCp^*Cl_2]_2/AgNTf_2$**	**AcOH**	**1,2-DCE**	**50**	**92**
5[c]	$[IrCp^*Cl_2]_2/AgNTf_2$	AcOH	1,2-DCE	25	87
6	$[IrCp^*Cl_2]_2/AgNTf_2$	AcOH	1,4-dioxane	50	20
7	$[IrCp^*Cl_2]_2/AgNTf_2$	AcOH	*t*-amylOH	50	19
8	$[IrCp^*Cl_2]_2/AgNTf_2$	CF_3CO_2H	1,2-DCE	50	23
9	$[IrCp^*Cl_2]_2/AgNTf_2$	CSA	1,2-DCE	50	18
10	$[IrCp^*Cl_2]_2/AgNTf_2$	PivOH	1,2-DCE	50	94
11	$[IrCp^*Cl_2]_2/AgNTf_2$	$PhCO_2H$	1,2-DCE	50	97
12	$[IrCp^*Cl_2]_2/AgSbF_6$	AcOH	1,2-DCE	50	82
13	$[RhCp^*Cl_2]_2/AgNTf_2$	AcOH	1,2-DCE	50	<1
14	$[Ru(p\text{-cymene})Cl_2]_2/AgNTf_2$	AcOH	1,2-DCE	50	<1
15	$Pd(OAc)_2$	AcOH	1,2-DCE	50	<1

[a]Reaction conditions: **1a** (0.2 mmol), **3a** (1.1 equiv), metal catalyst (2 mol %), Ag salt (8 mol %), and additive (30 mol %) in solvent (0.5 mL). [b]NMR yield (1,1,2,2-tetrachloroethane as an internal standard). [c]1 equiv of AcOH for 24 h.

features such as high regioselectivity, compatibility with diverse functional groups, and mild conditions allows us more opportunities for using 8-iodoquinolines or their *N*-oxides in additional synthetic transformations, representatively in metal-mediated cross-coupling reactions. Despite this attractive aspect of the iodination approach, we decided to investigate more extensively C−N bond formation of quinoline *N*-oxides, since it can directly introduce the amino group at the C-8 position; thereby we commenced our studies of the C-8 amidation of quinoline *N*-oxides.

Optimization of Direct C-8 Amidation of Quinoline *N*-Oxide. At the outset of our studies for the direct amidation of quinoline *N*-oxides, we examined optimal conditions in a model reaction of quinoline *N*-oxide (**1a**) with *p*-toluenesulfonyl azide (**3a**; Table 2). When our previously developed Ir catalytic conditions were applied,[22,23] only a low product yield was obtained at 80 °C (entry 1). The reaction efficiency was found to be improved by certain additives. While sodium acetate exhibited noticeable, but still unsatisfactory, effects (entry 2), acetic acid (0.3 equiv) gave a significant improvement (entry 3). We were pleased to see that the efficiency was further increased at lower temperature, giving rise to a 92% yield of **4a** at 50 °C using 2 mol % of iridium catalyst (entry 4). We need to emphasize that the reaction is *highly regioselective* in that *no isomeric product* (**5**) *was formed* under the present conditions. Interestingly, the amidation took place in high yield even at room temperature, albeit it required a higher loading of acetic acid (1 equiv) and prolonged reaction time (entry 5). Solvents other than 1,2-dichloroethane (1,2-DCE) were less effective (entries 6 and 7).

Strong acids such as trifluoroacetic acid and camphorsulfonic acid (CSA) did not exhibit a significant additive effect in comparison to acetic acid (entries 8 and 9). Although the addition of pivalic acid or benzoic acid resulted in slightly higher additive effects (entries 10 and 11), acetic acid was chosen for the subsequent studies because it is more convenient to use (e.g., stock solution) and easy to remove after the reaction. Silver salts, employed in this procedure for the in situ generation of cationic metal species, were also found to affect the reaction efficiency to some extent (entry 12). Other commonly used catalytic systems such as rhodium, ruthenium, and palladium were ineffective for this amidation (entries 13−15).

Reaction Scope of Direct C-8 Amidation of Quinoline *N*-Oxide. With the optimized conditions in hand, we next explored the substrate scope of quinoline *N*-oxides in reaction with 1.1 equiv of TsN_3 (Table 3). The position of alkyl substituents did not alter the reaction efficiency, as shown with methylated substrates (**4b−d**). The observation that substrates bearing a C-2 substituent underwent the amidation in high yield (**4c**) is noteworthy in that coordination of the iridium center to *N*-oxide is not sterically interrupted by the presence of a neighboring group (C-2). Halogenated quinoline *N*-oxides were amidated without difficulty, although the position of halides influenced the reaction efficiency to some extent (**4e−i**). Various functional groups commonly used in synthetic chemistry such as nitro (**4j**), esters (**4k,l**), acetal (**4m**), alkoxy (**4n**), silyloxy (**4o**), carbamate (**4p**), and aldehyde (**4q**) were all compatible with the present reaction conditions, thus significantly expanding the synthetic utility of the current amidation protocol.[24]

The scope of organic azides as the amide source was subsequently investigated in reactions with **1a** (Table 4). Alkanesulfonyl azides were highly facile for this selective C-8 amidation under the optimized conditions, leading to the desired products in high yields (**6a−c**). Benzenesulfonyl azides bearing substituents also reacted without difficulty (**6d,e**). Amidation of quinoline *N*-oxide also proceeded selectively with naphthalene-1-sulfonyl azide (**6f**). It was notable that acyl azides participated in the direct amidation under the current Ir catalytic system, giving rise to an acylamido product (**6g**), thus widening the scope of amide groups. However, aryl and alkyl azides did not react under the developed conditions.

The present strategy of utilizing *N*-oxide as a directing group for the remote C−H amidation was examined with polyaromatic heterocycles (Table 5). As anticipated, amidation

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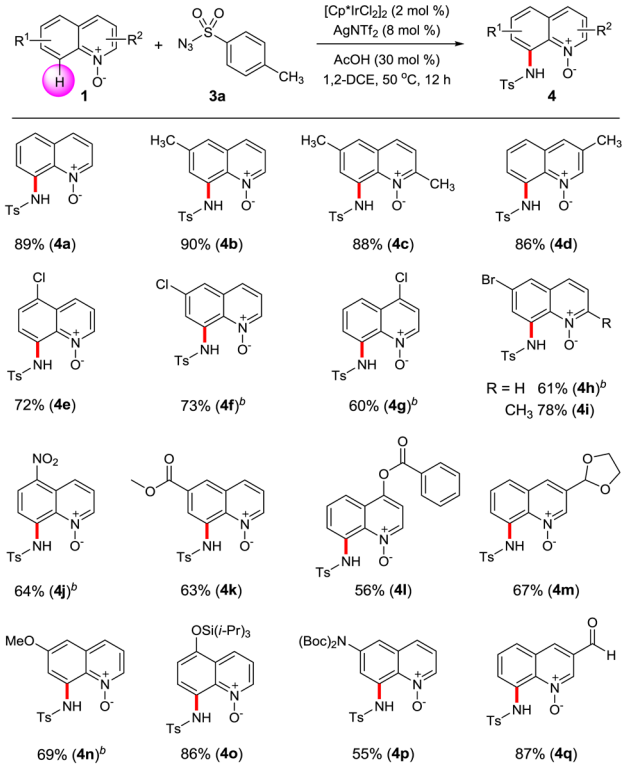
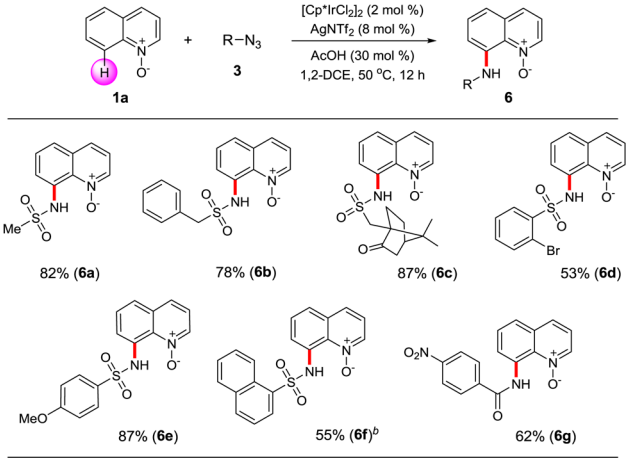
Table 3. Substrate Scope of Quinoline *N*-Oxides[a]



[a]Reaction conditions: **1** (0.2 mmol), **3a** (1.1 equiv), $[Cp^*IrCl_2]_2$ (2 mol %), $AgNTf_2$ (8 mol %), AcOH (30 mol %) in 1,2-DCE (0.5 mL). Isolated product yields are given. [b]AcOH (1.0 equiv) at 80 °C.

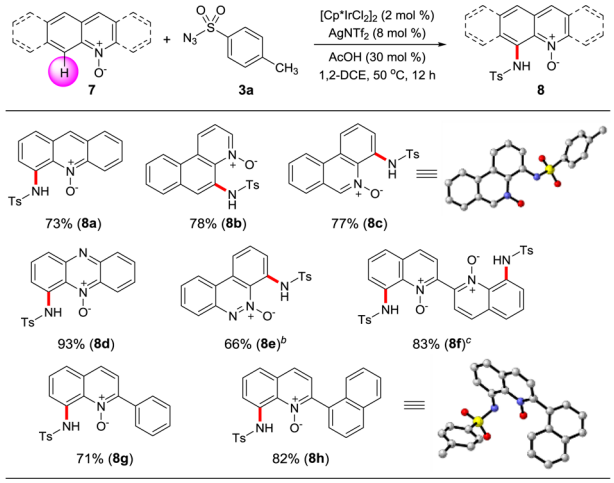
Table 4. Substrate Scope of Organic Azides[a]



[a]Reaction conditions: **1a** (0.2 mmol), **3** (1.1 equiv), $[Cp^*IrCl_2]_2$ (2 mol %), $AgNTf_2$ (8 mol %), AcOH (30 mol %) in 1,2-DCE (0.5 mL). Isolated product yields are given. [b]AcOH (1.0 equiv) at 80 °C.

of acridine *N*-oxide was facile to afford **8a** in good yield. Likewise, *N*-oxides of benzo[*f*]quinoline and phenanthridine were amidated exclusively at the desired position (**8b**,**c**), and the structure of the latter product was confirmed by an X-ray crystallographic analysis. Interestingly, the reaction of phenazine monoxide was highly regio- and chemoselective to furnish **8d** in excellent yield, and no amidation occurred at the *β*-position relative to the unoxidized nitrogen atom. Similarly, benzo[*c*]cinnoline monoxide was selectively amidated (**8e**).

Table 5. Substrate Scope of Polyaromatic Heterocycles[a]



[a]Reaction conditions: **7** (0.2 mmol), **3a** (1.1 equiv), $[Cp^*IrCl_2]_2$ (2 mol %), $AgNTf_2$ (8 mol %), AcOH (30 mol %) in 1,2-DCE (0.5 mL). Isolated product yields are given. [b]At 80 °C. [c]Reaction conditions: 2.2 equiv of **3a**, $[Cp^*IrCl_2]_2$ (4 mol %), $AgNTf_2$ (16 mol %), 80 °C, 24 h.

The current protocol could be successfully applied to a bis-*N*-oxide compound to lead to double amidation in good yield (**8f**) by using 2.2 equiv of azide.

Again, the amidation was selective at the C-8 position of quinoline *N*-oxides even in the presence of substituted phenyl or naphthyl pendants that bear potentially reactive C−H bonds (**8g**,**h**). It needs to be emphasized that the products obtained herein can serve as precursors of *β*-amino heterocycles which have enormous utilities in medicinal, coordination, and synthetic chemistry.[25]

Mechanistic Studies on the Present Reaction. To shed light on the mechanistic aspects of the present selective C−H amidation of quinoline *N*-oxides, we first performed an experiment to investigate kinetic isotope effects (KIE). Only small values of kinetic isotope effects (k_H/k_D = 1.1−1.2) were measured from parallel competition reactions between **1a** and **1a**-d_7, irrespective of the presence of acetic acid additive (Figure 2). This result implies that the C−H bond cleavage may not be involved in the rate-limiting step[26] and acid additives seem to play a crucial role in later catalytic stages (vide infra).

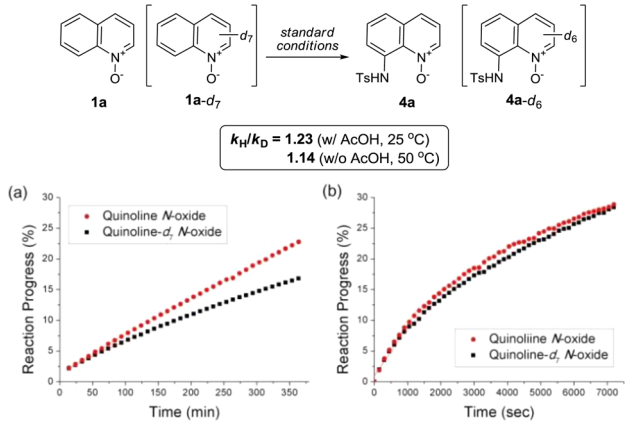


Figure 2. Comparison of C−H amidation profiles (a) in the presence of 30 mol % of AcOH and (b) in the absence of AcOH.

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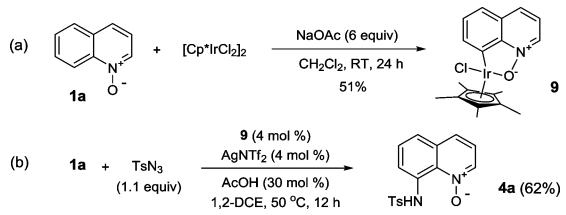
The iridacycle complex **9** was isolated upon treatment of **1a** with a catalyst precursor (Scheme 3a),[27] and its structure was

Scheme 3. Preliminary Mechanistic Studies



unambiguously determined by an X-ray crystallographic analysis (Figure 3). To the best of our knowledge, this

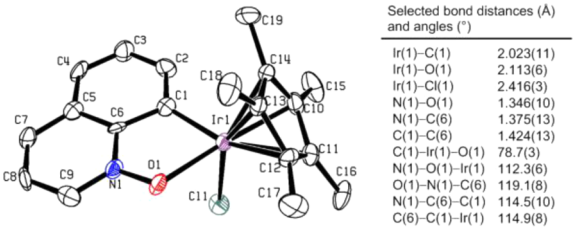
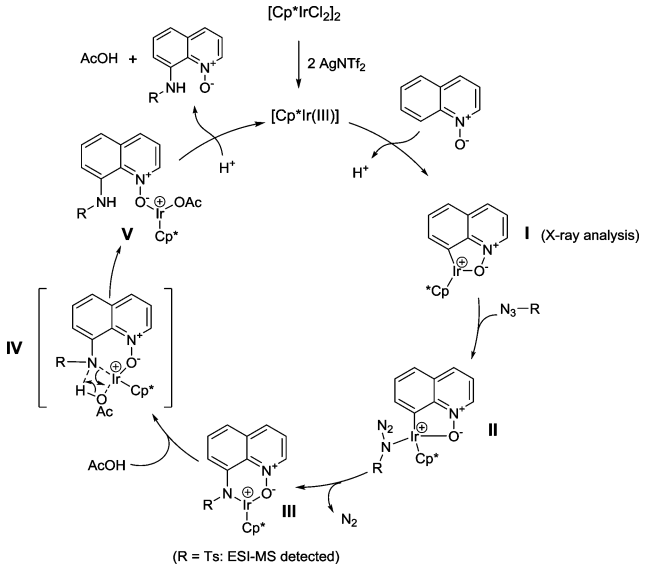


Figure 3. Crystal structure of **9** with 50% displacement ellipsoids.

represents the first example of a discrete iridacycle bound to *N*-oxide.[28] The isolated iridacycle **9** was found to catalyze an amidation reaction (Scheme 3b), suggesting that it could be involved as an intermediate in the catalytic cycle, although this is not unequivocal evidence, as this could be an off-cycle intermediate.

On the basis of the above experimental data and previous literature,[29] a mechanistic pathway is proposed in Scheme 4. The dimeric precursor $[IrCp^*Cl_2]_2$ is converted by a silver salt to a cationic species that undergoes the C−H bond cleavage of substrates, leading to the five-membered iridacycle **I**, a neutral analogue of which was isolated and characterized (Scheme 3a). Coordination of an azide to **I** will initiate a subsequent amido insertion to afford the Ir(III) amido species **III**, which was

Scheme 4. Proposed Reaction Pathway



detected by ESI-MS when R = Ts. At the final stage, it is proposed that protodemetalation of **III** will take place as a turnover-limiting step to afford the Ir-coordinated product **V**.

An observation that the reaction was sensitive to acid additives (Figure 4a) implies that the protodemetalation

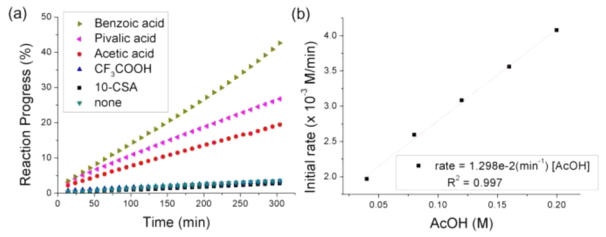
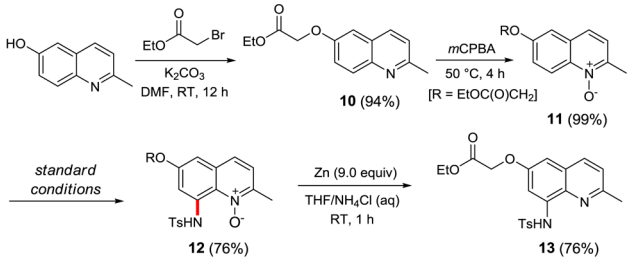


Figure 4. (a) Reaction profile in the Ir-catalyzed amidation of quinoline *N*-oxide (**1a**) with TsN_3 at 25 °C in the presence of various acid additives (10-CSA = 10-camphorsulfonic acid) (b) Plot of initial amidation rates versus [AcOH] showing the first-order dependence.

process can be facilitated by acid additives, which may influence the bond strength between the metal and inserted amido moieties.[30] In addition, the fact that initial amidation rates[31] were measured to have first-order dependence on the concentration of acetic acid (Figure 4b) also led us to postulate that the additive can facilitate this turnover-determining step, presumably passing through **IV** (Scheme 4).

Synthetic Application. The present protocol of direct C-8 amidation of quinoline *N*-oxides was successfully applied to a straightforward synthesis of zinquin ethyl ester (**13**), a derivative of important fluorescent sensors for Zn(II).[32] The requisite starting material (**11**) was prepared with excellent efficiency in two steps from commercially available 6-hydroxy-2-methylquinoline (Scheme 5). As anticipated, the main

Scheme 5. Synthesis of Zinquin Ethyl Ester



reaction of an ester-substituted quinoline *N*-oxide (**11**) proceeded with high selectivity under the standard conditions to furnish the desired product **12** in good yield. Deoxygenation of **12** was facile with the use of zinc reagent, leading to the desired product **13** in 54% overall yield (four steps).

CONCLUSION

In conclusion, we have for the first time succeeded in the direct introduction of heteroatomic groups at the C-8 position of quinoline *N*-oxides. Two catalytic systems were developed: Rh-catalyzed iodination and Ir-catalyzed amidation of quinoline *N*-oxides. Both reactions were highly regioselective, occurring at the C-8 position under mild conditions over a broad range of substrates with excellent functional group tolerance. In this approach, *N*-oxide was utilized as a stepping stone for the remote C−H functionalization. Mechanistic studies of the amidation reaction revealed an important role of acid additives

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promoting the rate-determining product-releasing step. As the utilities of the iodinated and amidated products accessible through the present study are enormous, the present protocol is anticipated to be an important synthetic tool.

■ ASSOCIATED CONTENT

Supporting Information

Text, tables, figures, and CIF files giving detailed experimental procedures and data for new compounds, including ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data for **2a**, **8c,h**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for S.C.: sbchang@kaist.ac.kr.

Author Contributions

[§]These authors contributed equally.

Notes

The authors declare no competing financial interest.

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