ACS Catalysis

Review

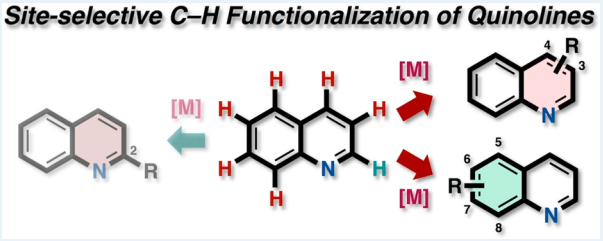
pubs.acs.org/acscatalysis

Transition-Metal-Catalyzed Site-Selective C−H Functionalization of Quinolines beyond C2 Selectivity

Tomohiro Iwai and Masaya Sawamura*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

ABSTRACT: Quinoline is an important scaffold in many natural products, biologically active compounds, and functional materials. The C−H functionalization of quinoline scaffolds by transition metal catalysis provides an efficient method for rapidly obtaining substituted quinolines. This review summarizes recently reported transition-metal-catalyzed site-selective C−H functionalization of quinolines, excluding C2 selective reactions. A review of direct functionalization of quinoline *N*-oxides at the C8 position also is provided.



KEYWORDS: *quinolines, quinoline N-oxides, C−H activation, transition metal catalysts, site-selectivity*

1. INTRODUCTION

Quinoline is a versatile and important heterocyclic system found in many natural products, pharmaceuticals, agrochemicals, functional materials, and ligands in transition metal catalysts (Figure 1).[1−3] Thus, the development of efficient methods for synthesizing substituted quinolines is important in organic synthesis; however, conventional methods of quinoline synthesis, such as condensation of amines and carbonyl compounds (e.g., Skraup, Döbner−Von Miller, Friedländer, Conrad−Limpach, and Combes syntheses), require harsh acidic conditions that limit substrate scope.[4]

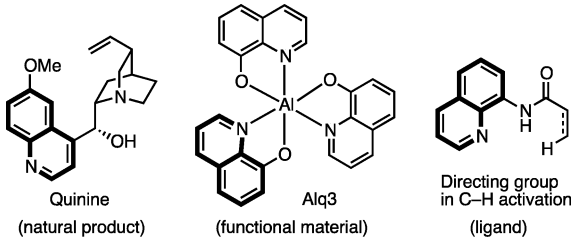


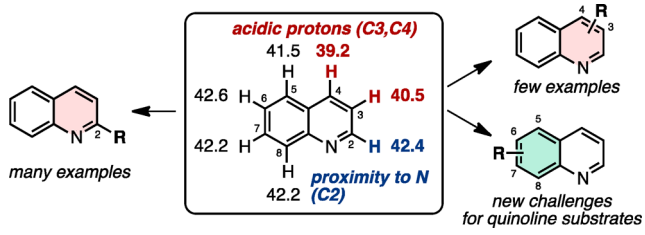
Figure 1. Representative compounds containing a quinoline scaffold.

Substitution reactions involving a preformed quinoline scaffold also are useful for preparing functionalized quinolines; however, electrophilic aromatic substitution reactions are not suitable for electron-deficient azaheteroarenes. In addition, their sp^2-hybridized nitrogen atoms often interact with electrophiles or Lewis acids, decreasing reactivity. Thus, quinolines preferentially undergo electrophilic substitution reactions at the carbocyclic ring rather than the heterocyclic ring. Metalation with organolithium or organomagnesium reagents through metal−halogen exchange or direct deprotonation, followed by trapping with electrophiles, causes problems with functional-group compatibility and unfavorable nucleophilic aromatic substitution.[5,6] Recent progress inspired by classical reactions of heteroarenes (e.g., Chichibabin[7,8] and Minisci[9,10] reactions) has resulted in the development of efficient methods for late-stage functionalization.

Recent transition-metal-catalyzed C−H activation/functionalization has received attention for organic synthesis that involves atom- and step-saving processes with high functional group compatibility. Thus, late-stage, site-selective C−H functionalization of a preformed quinoline scaffold is desirable for the straightforward synthesis of complex molecules with a quinoline scaffold. A number of C2 functionalization reactions of quinolines have been reported because of the intrinsic reactivity of the C=N bonds and the effects of nitrogen-to-metal coordination.[11] In contrast, only a few examples exist of catalytic systems producing C3 and C4 functionalization,[12] whereas their reaction sites in the quinoline ring have relatively acidic protons (Scheme 1).[13] However, synthesis of quinoline derivatives involves the challenge of controlling site selectivity on the carbocyclic ring (C5−C8 positions).

This Review focuses on transition-metal-catalyzed, site-selective C−H functionalization of quinolines outside of C2 selective reactions. The types of reactions can be classified as follows: C−H functionalization without a proximity effect

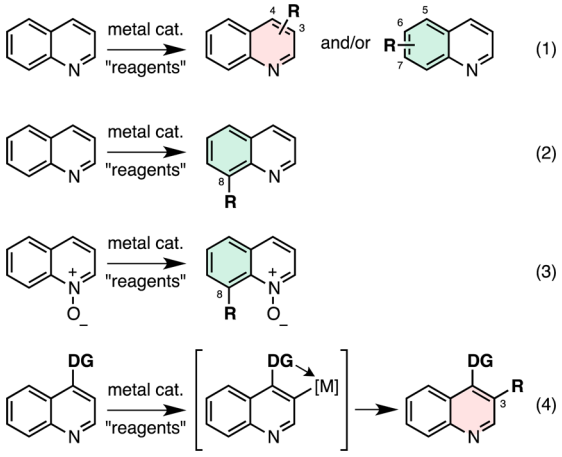
Scheme 1. Site-Selective C−H Functionalization of Quinoline and Its Calculated pK_a Values in DMSO[13,35]



Received: June 3, 2015
Revised: July 17, 2015
Published: July 21, 2015

DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031−5040

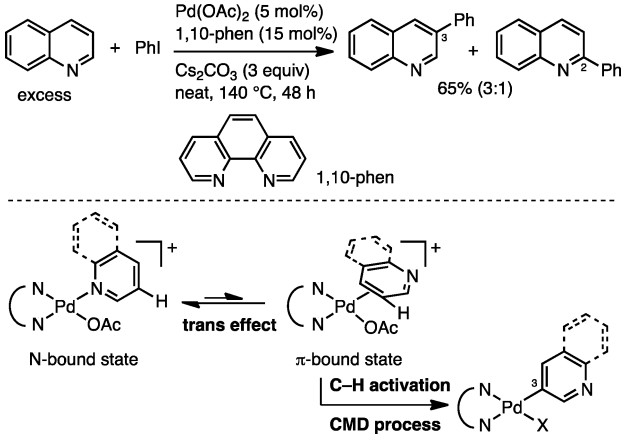
through heteroatom−metal coordination (eq 1), C8 functionalization of quinolines (eq 2) and their *N*-oxides (eq 3), and C−H functionalization with a directing effect of pendant groups in coordination with metals (eq 4).



2. SITE-SELECTIVE C−H FUNCTIONALIZATION OF QUINOLINES WITHOUT RELYING ON PROXIMITY DUE TO HETEROATOM−METAL COORDINATION (EQ 1)

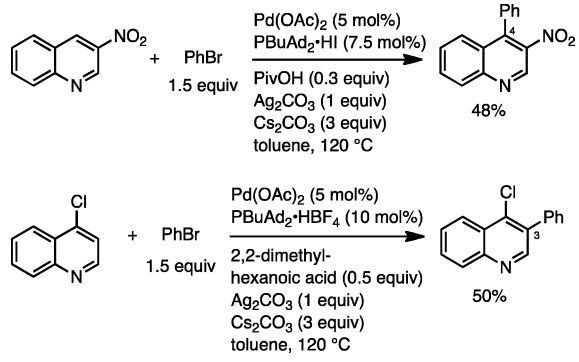
2-1. Coupling with C(sp^2)−X Electrophiles. Transition-metal-catalyzed C−H activation of (hetero)arenes, followed by coupling with C(sp^2)−X electrophiles (X = halides, OR, etc.), is a powerful method for generating carbon−carbon bonds. Yu et al.[14] and Sames et al.[15] independently reported the Pd-catalyzed oxidative arylation of azines at the C3 or C4 position. As shown in Scheme 2, arylation of quinoline with iodobenzene

Scheme 2. Palladium-Catalyzed C3 Arylation of Quinoline and Its Proposed Mechanism[14]



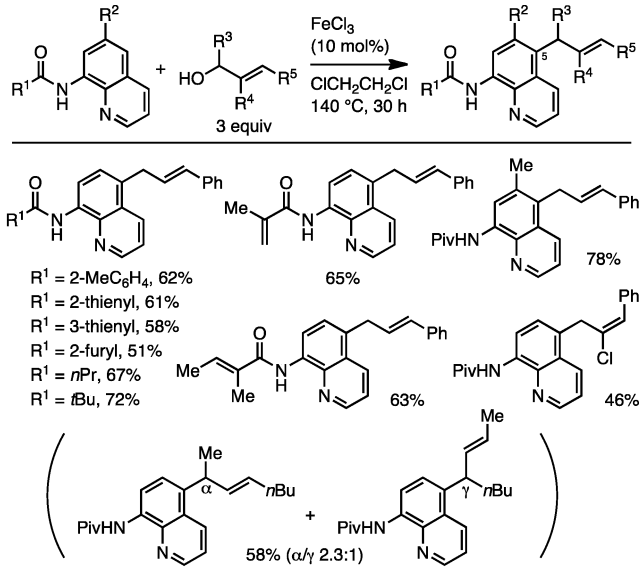
under conditions reported by Yu afforded 3-phenylquinoline over the C2 isomer in a ratio of 3:1; however, a large excess of azines was required for obtaining acceptable yields. The authors proposed that N,N-chelating ligands promoted dissociation of N-bound azine substrates from the Pd center due to the trans effect, allowing conversion to π-bound states. The η^2-azine-Pd complexes underwent C−H activation at the C3 position through a concerted metalation-deprotonation (CMD) mechanism.[16] Sames found that electron-withdrawing substituents on the azines increased site-selectivity at the C3 or C4 position (Scheme 3).[15]

Scheme 3. Palladium-Catalyzed C3 and C4 Arylation of Quinolines Containing Electron-Withdrawing Substituents[15]



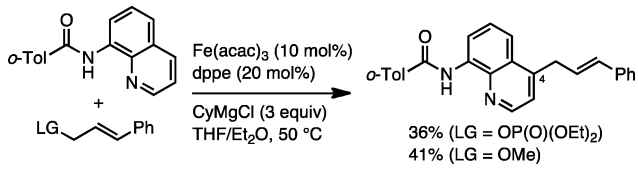
2-2. Allylation. The Fe-catalyzed C4 or C5 allylation of 8-aminoquinolines, which are often employed as bidentate directing groups in C−H activation/functionalization protocols,[17,18] was reported by Cong and Zeng.[19] Specifically, reactions between 8-aminoquinoline-bearing carboxyamides and allyl alcohols catalyzed by $FeCl_3$ (10 mol %) at 140 °C gave C5-allylation quinolines in useful yields (Scheme 4). In

Scheme 4. Iron-Catalyzed C5 Allylation of 8-Aminoquinolines[19]



contrast, C4-allylation products were obtained with a low-valent Fe catalyst system, which was generated using an excess of organomagnesium reagent (Scheme 5). These unique site-

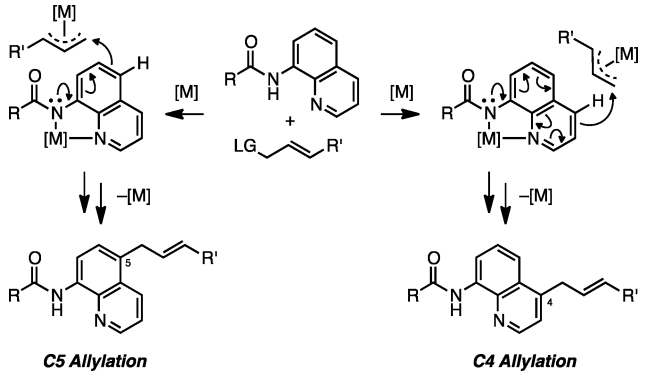
Scheme 5. Iron-Catalyzed C4 Allylation of 8-Aminoquinoline[19]



DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031−5040

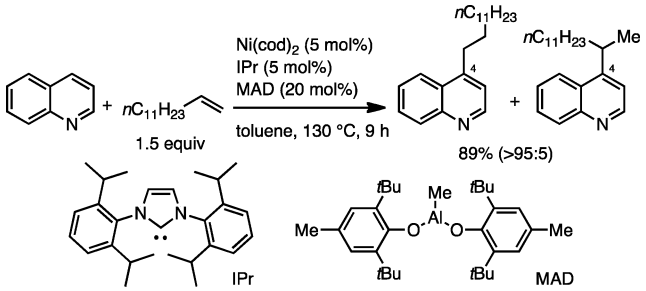
selective reactions occur through chelation-induced nucleophilic attack of the C4 or C5 quinoline carbon to the π-allyl species (Scheme 6). Similar C5 functionalization of 8-aminoquinoline derivatives using Cu catalysts also was reported by Ertem and Stahl (Section 2-8).[20]

Scheme 6. Proposed Mechanism for Fe-Catalyzed C4 and C5 Allylations of 8-Aminoquinolines[19]



2-3. Insertion of π-System. Insertion of π-systems, such as carbon−carbon and carbon−heteroatom unsaturated bonds, into metal−carbon bonds formed via C−H bond activation is a valuable strategy for preparing alkyl- and alkenyl-substituted compounds from readily accessible substrates. In 2008, Nakao and Hiyama reported the C2 alkenylation of pyridines with alkynes by Ni(0)−Lewis acid cooperative catalysis.[11a] This strategy was extended to the C4 alkylation of azines, including quinolines, with alkenes by the same group (Scheme 7).[21] The use of the sterically hindered N-heterocyclic carbene ligand (IPr) and Lewis acid (MAD) was crucial for C4 selectivity.

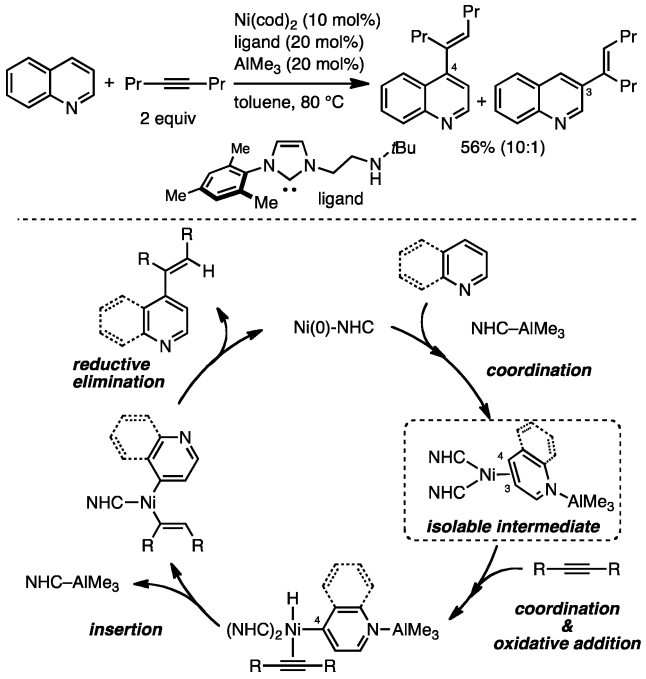
Scheme 7. C4 Alkylation of Quinoline with an Alkene by Ni−Al Cooperative Catalysis[21]



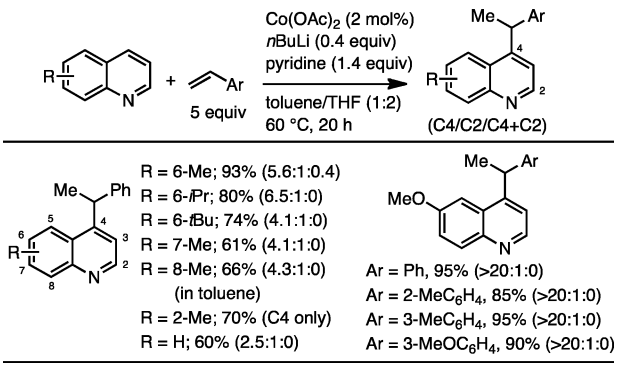
Ong also reported the C4 alkenylation of azines with alkynes through Ni−Al cooperative catalysis (Scheme 8).[22] A Ni(0)−NHC complex bound to the pyridine−$AlMe_3$ adduct at the C3−C4 positions was isolated and characterized by single-crystal X-ray diffraction. This result indicated that the catalytic cycle was initiated by π coordination of Al-bound azines toward the Ni center. Subsequent oxidative addition of the C−H bond at the C4 position, alkyne insertion, and reductive elimination provided the C4 alkenylated products and regenerated the Ni(0)−NHC species.

Matsunaga and Kanai reported that the Co-catalyzed C4 alkylation of quinolines with styrenes gave 4-alkylquinolines with branched selectivity (Scheme 9).[23] The catalyst system using $Co(OAc)_2$ in combination with *n*-BuLi and pyridine, which acted as reducing reagents to generate in situ active Co−H species, was optimized for quinoline substrates.[24] The sequence of hydrometalation, C4-selective nucleophilic addition, and rearomatization was proposed.

Scheme 8. C4 Alkenylation of Quinolines through Ni−Al Cooperative Catalysis[22]



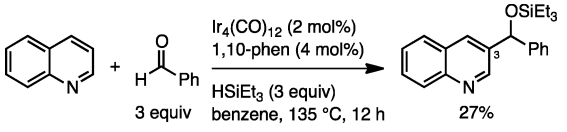
Scheme 9. Cobalt-Catalyzed C4 Alkylation of Quinolines[23]



Li and Shi reported Ir-catalyzed C3-selective nucleophilic addition of azines, including quinoline to aldehydes in the presence of $HSiEt_3$ (Scheme 10).[25] The authors proposed that a silyl iridium complex would be the active species in this reaction.

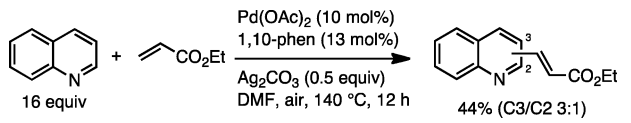
2-4. Heck-Type Alkenylation. Yu stated that the Pd-$(OAc)_2$/1,10-phenanthroline catalyst system allowed oxidative Heck-type alkenylation of quinoline to give 3-alkenylquinoline preferentially over the C2-alkenylated isomer (Scheme 11).[26] A reaction course similar to the Pd-catalyzed C3 arylation

Scheme 10. Iridium-Catalyzed C3 Addition of Quinoline to Benzaldehyde in the Presence of $HSiEt_3$[25]



DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031−5040

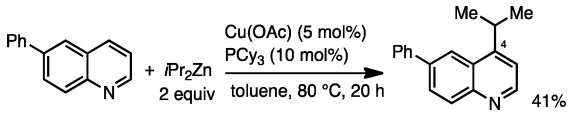
Scheme 11. Palladium-Catalyzed C3 Alkenylation of Quinolines[26]



reported by the same group (Scheme 2) was proposed to be initiated by ligand exchange of N-bound azine substrates to the π-bound state due to the strong trans effects of N,N-chelating ligands.[16]

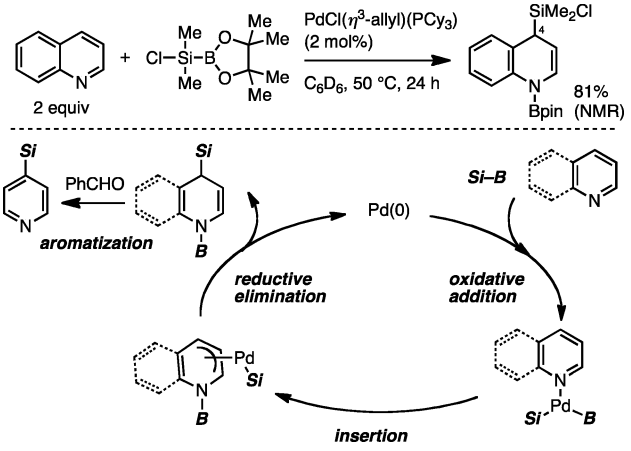
2-5. Substitution with an Alkylzinc Reagent. Addition of alkyl nucleophiles to azines, followed by oxidative aromatization, was a useful strategy for introducing alkyl substitutes on azaheteroarenes; however, the reaction sites of the direct substitution reaction are limited to the position α to the nitrogen atom due to the inherent reactivity based on the C=N bonds.[11c] Tobisu and Chatani found that the copper catalyst system Cu(OAc)/PCy_3 enabled C4 alkylation of 6-phenylquinoline with *i*-Pr_2Zn (Scheme 12).[27,28]

Scheme 12. Copper-Catalyzed C4 Alkylation of 6-Phenylquinoline with *i*Pr_2Zn[27]



2-6. Silylation. Ohmura and Suginome reported that the palladium catalyst system $[PdCl(\eta^3\text{-allyl})]_2/PCy_3$ enabled 1,4-silaboration of quinoline to give *N*-boryl-4-silyl-1,4-dihydroquinoline (Scheme 13).[29] The dihydropyridine derivatives

Scheme 13. Palladium-Catalyzed 1,4-Silaboration of Quinoline and Its Proposed Reaction Pathway[29]

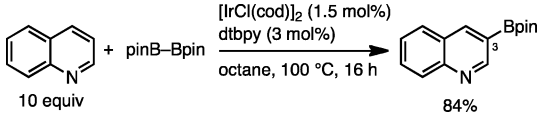


obtained through this catalysis were rearomatized by treatment with benzaldehyde; therefore, the overall process represents C4 silylation of azines. The proposed mechanism is shown in Scheme 13. The catalytic cycle was initiated by oxidative addition of silylborane to a Pd(0) complex. Insertion of the N-bound azines into the Pd–B bond, followed by reductive elimination, provided 1,4-adduct products and regenerated the Pd(0) species.

2-7. Borylation. (Hetero)arylboronic acid and derivatives are versatile intermediates in organic synthesis because of their air and moisture stability and broad functional-group compatibility. Transition-metal-catalyzed C–H borylation of (hetero)arenes is a straightforward method to prepare organoboron compounds.[30] Bipyridine-based iridium catalysts reported by Ishiyama, Miyaura, and Hartwig are widely used for this transformation.[31] The site-selectivity of this reaction generally was controlled by substrate steric factors: the less congested positions underwent borylation preferentially.

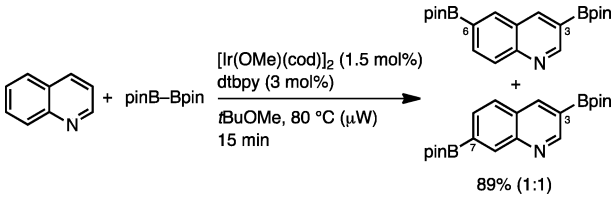
Miyaura and Ishiyama reported that borylation of quinoline (10 equiv) with bis(pinacolato)diboron in the presence of $[Ir(OMe)(cod)]_2$ (1.5 mol %) and 4,4′-di-*tert*-butylbipyridine (dtbpy) (3 mol %) in octane at 100 °C occurred at the C3 position (Scheme 14).[32,33] Marder and Steel found that

Scheme 14. Iridium-Catalyzed C3 Borylation of Quinoline[32]



microwave irradiation allowed a reduction in reaction time (80 °C, 15 min) for complete conversion of quinoline compared with the standard heating conditions (80 °C, 120 min), giving a mixture of 3,6- and 3,7-bisborylated quinolines (Scheme 15).[34]

Scheme 15. Microwave-Assisted Ir-Catalyzed C3 Borylation of Quinoline[34]

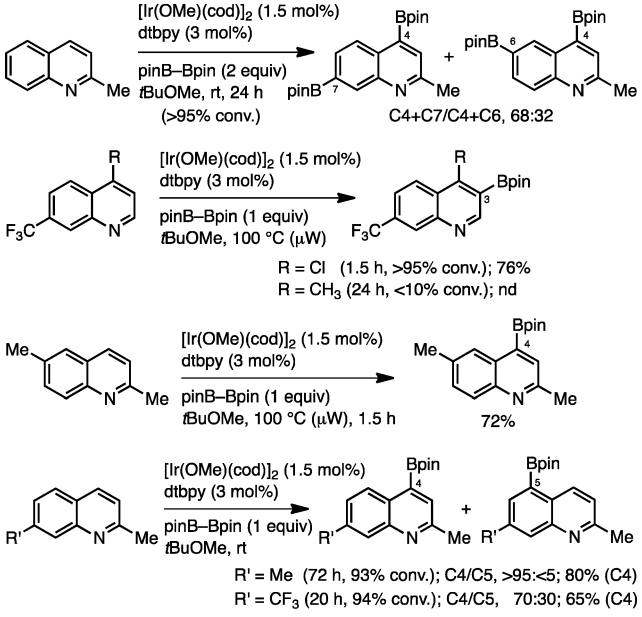


Marder and Steel presented practical guidelines for site-selectivity in C–H borylation of quinolines with the Ir-dtbpy catalyst.[35] Again, site selectivity of this reaction was dominated by steric factors, but an underlying electronic effect on selectivity also was observed under mild conditions. The C–H bonds of the azaheterocycle on the quinoline rings appeared to be more reactive than those of the carbocycle. Representative examples of the borylation are shown in Scheme 16. Double borylation of 2-methylquinolines with the excess diboron reagent gave a 68:32 mixture of 4,7- and 4,6-bisborylated products. 4-Chloro-7-trifluoromethylquinoline underwent borylation at the C3 position, whereas no efficient borylation took place for the 4-methyl analogue. Borylation of 2,6-dimethylquinoline occurred at the C4 position. Similarly, the C4 positions of 2,7-disubstituted quinolines, such as 2,7-dimethylquinoline and 2-methyl-7-trifluoromethylquinoline, underwent borylation preferentially. The authors suggested that ^1H and ^{13}C NMR chemical shifts of the quinoline substrates could predict the preferred reaction sites, which were deshielding (acidic) and sterically accessible C–H bonds. The DFT calculations of p*K*a values for the C–H bonds also supported these sites for the borylation (Scheme 1).

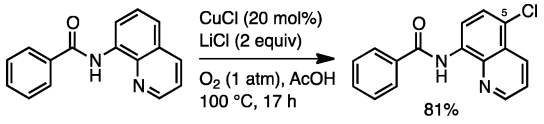
2-8. Chlorination. Ertem and Stahl reported the Cu-catalyzed oxidative C5 chlorination of 8-aminoquinolines under acidic conditions (Scheme 17).[20] On the basis of detailed experimental and computational studies, a single-electron-

DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031−5040

Scheme 16. C−H Borylation of Quinolines Catalyzed by the Ir-dtbpy System[35]



Scheme 17. Copper-Catalyzed C5 Chlorination of 8-Aminoquinoline[20]



transfer mechanism was proposed for the unique site selectivity similar to that seen in the Fe-catalyzed C4 or C5 allylation of 8-aminoquinolines (Scheme 4).[19]

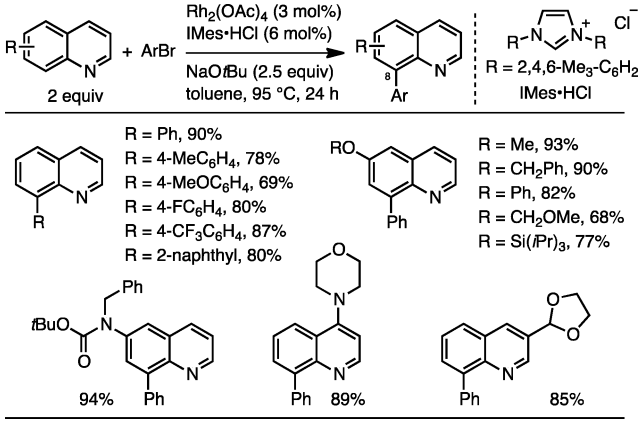
3. C−H FUNCTIONALIZATION AT THE C8 POSITION OF QUINOLINES (EQ 2)

Development of C−H functionalization at the C8 position of quinolines is important because of the broad utility of C8-substituted quinolines in medicinal chemistry and materials science.[1−3] However, only a few studies have been reported on the transition-metal-catalyzed C8 functionalization of quinolines without a dependence on exocyclic directing groups.

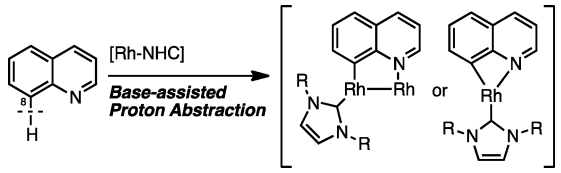
3-1. Coupling with C(sp^2)−X Electrophiles. Chang reported the C8 arylation of quinolines with bromoarenes catalyzed by Rh−NHC complexes (Scheme 18).[36] A wide variety of quinolines and aryl bromides participated in this transformation to give the corresponding C8 arylation products. The authors proposed a reaction pathway via base-assisted concerted proton abstraction and metalation by a bimetallic or monomeric Rh−NHC species (Scheme 19). This catalytic protocol complements Bergman and Elman's C2 arylation of azines with bromoarenes catalyzed by the electron-deficient Rh complex $[RhCl(CO)_2]_2$.[11b,d]

3-2. Borylation. The easy handling and diverse reactivity of the boronic acid derivatives 8-quinolinylboronates make them attractive intermediates for 8-substituted quinoline syntheses. Steel, Marder, and Sawamura reported a C8 borylation of quinolines with bis(pinacolato)diboron using an immobilized Ir catalyst system based on a silica-supported trialkylphosphine ligand Silica−SMAP (Scheme 20).[37] This heterogeneous

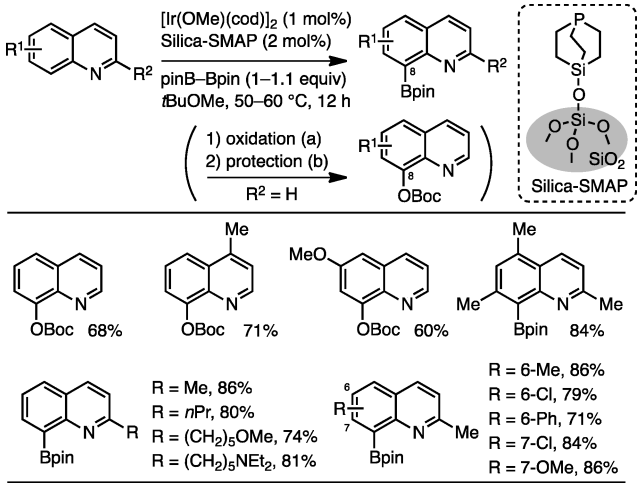
Scheme 18. C8 Arylation of Quinolines with Aryl Bromides Catalyzed by the Rh-NHC System[36]



Scheme 19. Proposed Reaction Pathway for Rh-Catalyzed C8 Arylation of Quinolines[36]



Scheme 20. C8 Borylation of Quinolines via Silica−SMAP−Ir Catalysis[37,a]



[a]Conditions: (a) $NaBO_3{\cdot}4H_2O$ (3 equiv) in THF/H_2O (1:1), rt. (b) $(Boc)_2O$ (2 equiv), DMAP (0.1 equiv) in THF, rt.

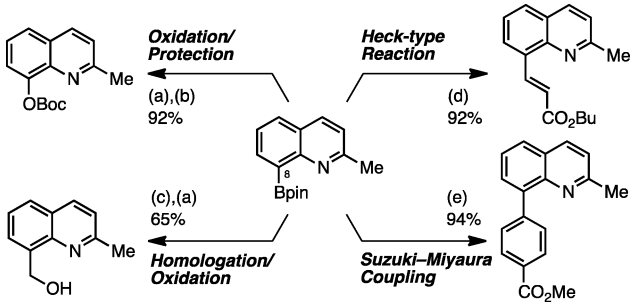
catalysis tolerated considerable steric hindrance around the reacting C−H bond to provide the sterically congested 8-quinolinylboronates. The authors suggested that the C8 selectivity was due to the Silica-SMAP ligand, which favored monoligation to metal centers. The reaction was initiated by coordination of the quinoline nitrogen atom to the Ir center, followed by C−H bond cleavage via a four-membered iridacyclic reaction pathway. This method complements the site selectivity of the bipyridine-based Ir catalyst systems (Schemes 14−16).[32,34,35]

The C8-borylated quinoline derivative obtained using the Silica-SMAP−Ir catalyst system can be used for various transformations, including oxidation, one-carbon-homologa-

DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031−5040

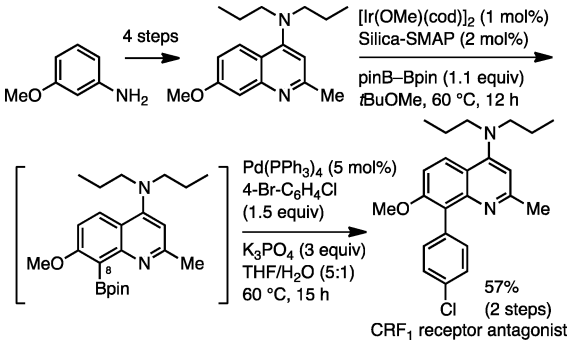
tion/oxidation, Rh-catalyzed Heck-type reaction, and Pd-catalyzed Suzuki−Miyaura coupling (Scheme 21). The synthesis of a corticotropin-releasing factor$_1$ (CRF$_1$) receptor antagonist based on a late-stage C−H borylation strategy was performed to demonstrate the utility of the C8 borylation (Scheme 22).

Scheme 21. Transformations of the C8-Borylated Quinoline Derivative[37a]



[a]Conditions: (a) $NaBO_3{\cdot}4H_2O$ (3 equiv) in THF/H_2O (1:1), rt, 3 h. (b) $(Boc)_2O$ (2 equiv), DMAP (0.1 equiv) in THF, rt, 1 h. (c) Bromochloromethane (2 equiv), *n*-BuLi in hexane (1.7 M, 1.7 equiv) in THF, −78 °C to rt, 1 h. (d) *n*-Butyl acrylate (5 equiv), $[Rh(OH)(cod)]_2$ (2.5 mol %) in 1,4 dioxane/H_2O (50:1), 90 °C, 16 h. (e) Methyl 4-bromobenzoate (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (3 equiv) in THF/H_2O (5:1), 60 °C, 12 h.

Scheme 22. Synthesis of a CRF$_1$ Receptor Antagonist Based on a Late-Stage C−H Borylation Strategy[37]

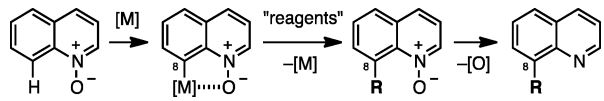


4. C8 FUNCTIONALIZATION OF QUINOLINE *N*-OXIDES (EQ 3)

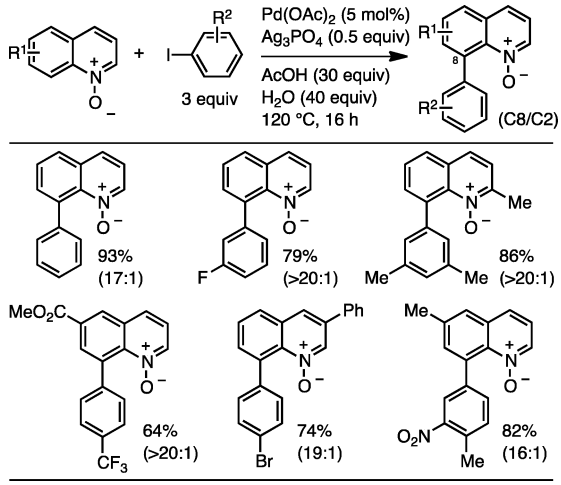
Pyridine *N*-oxides and related compounds are useful because of their synthetic utility and biological activity. A number of transition-metal-catalyzed ortho-C−H functionalizations of *N*-oxide compounds have been reported via coordination of the oxygen atoms with the metal centers.[38] Recent advances have made quinoline *N*-oxides suitable substrates for their C8 functionalizations. The *N*-oxide moiety worked as a directing group to form five-membered metallacyclic intermediates at the C8 position, which subsequently reacted with the appropriate reagents to give C8-substituted quinoline *N*-oxides (Scheme 23). Reduction of the N−O bonds provided the corresponding quinoline derivatives. Thus, the overall process represents the C8 functionalization of quinolines.

4-1. Coupling with iodoarenes. Larionov reported the Pd-catalyzed C8 arylation of quinoline *N*-oxides with iodoarenes under acidic aqueous conditions (Scheme 24).[39] Various functional groups were suitable on both quinoline *N*-oxides and on iodoarenes. Mechanistic studies based on experimental and computational observations showed that the use of $Pd(OAc)_2$ and aqueous AcOH was crucial for C8−H bond cleavage. This reaction complements the Pd-catalyzed C2 arylation of quinoline *N*-oxides reported by Fagnou's group with respect to regiochemistry.[40] Later, Larionov reported the Pd-catalyzed oxidative C8 homocoupling of quinoline *N*-oxides under conditions similar to those of the above C8 arylation but with AgOAc as an oxidant.[41]

Scheme 23. Metal-Catalyzed C8 Functionalization of Quinoline *N*-Oxides and Subsequent Reduction



Scheme 24. Palladium-Catalyzed C8 Arylation of Quinoline *N*-Oxides with Iodoarenes[39]



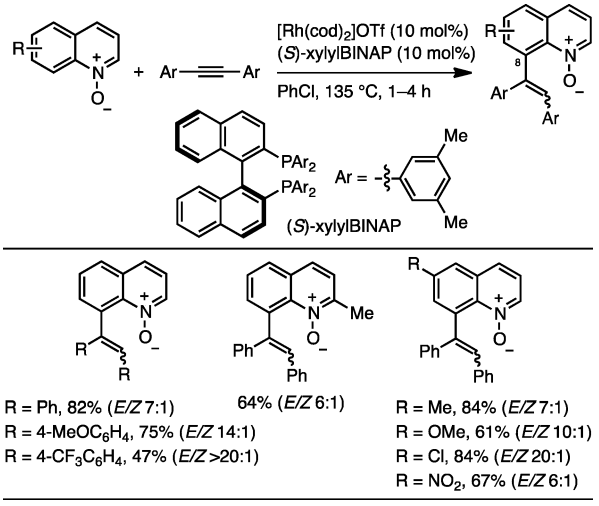
4-2. Insertion of Alkynes. Shibata and Matsuo reported that a cationic Rh(I)-xylylBINAP catalyst promoted C8 alkenylation of quinoline *N*-oxides with diarylalkynes (Scheme 25).[42] However, the alkenylated products underwent *E*/*Z* isomerization during the reaction. Mechanistic studies showed that this reaction involved reversible C−H bond cleavage of quinoline *N*-oxide at both the C2 and C8 positions. The alkenylated *N*-oxide compound was reduced by treatment with PCl_3, to give the corresponding quinoline derivative (Scheme 26).

Li (Scheme 27)[43] and Chang (Scheme 28)[44] independently reported the Rh-catalyzed reaction between quinoline *N*-oxides and internal alkynes to provide 2-(quinolin-8-yl)-ethanones through C−H activation of quinoline *N*-oxides at the C8 position, followed by alkyne insertion and intramolecular oxygen atom transfer. In this redox-neutral transformation, the *N*-oxide moiety acted not only as a directing group but also as an internal oxidant. Moreover, Li found that the use of $Zn(OTf)_2$ (20 mol %) improved the reactions with alkyl aryl acetylenes to give α-arylacetophenone derivatives with exclusive regioselectivity (Scheme 27).[43]

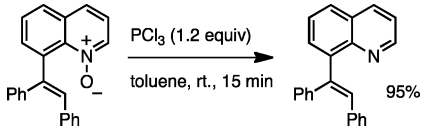
A reaction pathway proposed by Li and co-workers is shown in Scheme 29.[43] The first step was formation of five-membered rhodacycle **A** via C−H bond cleavage at the C8 position of the

DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031−5040

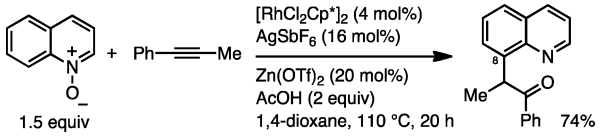
Scheme 25. Rhodium-Catalyzed C8 Alkenylation of Quinoline *N*-Oxides with Diarylalkynes[42]



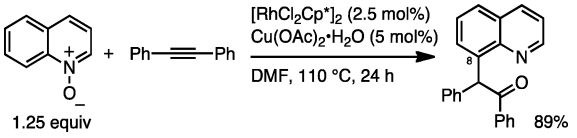
Scheme 26. Reduction of a Quinoline *N*-Oxide Derivative[42]



Scheme 27. Rhodium-Catalyzed Reaction between Quinoline *N*-Oxide and an Internal Alkyne, Reported by Li et al.[43]



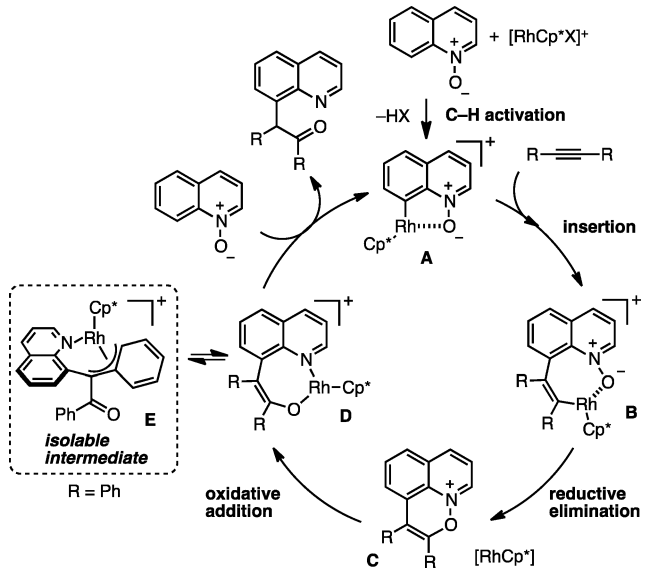
Scheme 28. Rhodium-Catalyzed Reaction between Quinoline *N*-Oxide and an Internal Alkyne, Reported by Chang et al.[44]



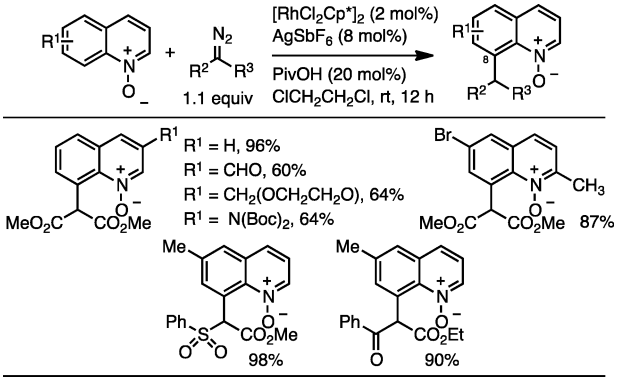
quinoline *N*-oxide. Insertion of the alkyne into the Rh−C bond followed by reductive elimination of a C−O bond generated cationic heterocyclic compound **C** along with a Rh(I) species. Oxidative addition of **C** to the Rh(I) center provided enolate **D**, which was tautomerized to isolable Rh(III)-η^3-benzyl complex **E**. Finally, the desired product was obtained through cyclometalation of the new incoming substrate, causing regeneration of the catalytically active rhodacycle **A**. Li and Lan later reported a computational study related to the mechanism shown in Scheme 29.[45]

4-3. Carbene Insertion and Alkynylation. Chang reported various types of C8 functionalization of quinoline *N*-oxides via formation of metallacyclic intermediates. For carbon−carbon bond formation, cationic Rh(III) catalyst systems enabled C8-alkylation and -alkynylation with diazo compounds and an alkynylated hypervalent iodine reagent (TIPS-EBX), respectively (Schemes 30 and 31).[46] These

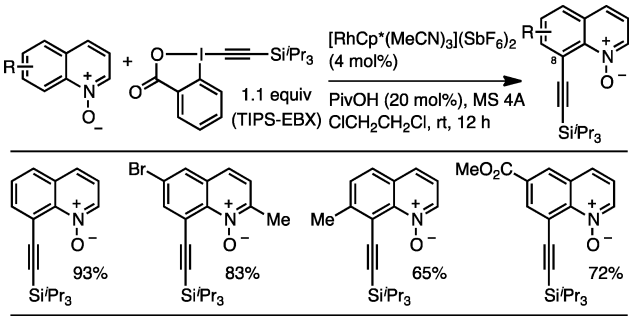
Scheme 29. Proposed Reaction Pathway of the Rh-Catalyzed Reaction between Quinoline *N*-Oxides and Internal Alkynes[44]



Scheme 30. Rhodium-Catalyzed C8 Alkylation of Quinoline *N*-Oxides with Diazo Compounds[46]



Scheme 31. Rhodium-Catalyzed C8 Alkynylation of Quinoline *N*-Oxides with TIPS-EBX[46]

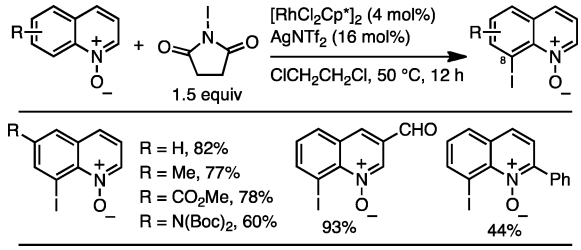


reactions proceeded at room temperature with high functional group compatibility. Kinetic isotope studies showed that the C−H bond cleavage was involved in the rate-determining step in both reactions (KIE > 2.7). Later, Chang reported the Ir(III)-catalyzed C8 arylation using aryldiazonium tetrafluoroborates, which served not only as an aryl reagent but also as an internal oxidant.[47]

DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031−5040

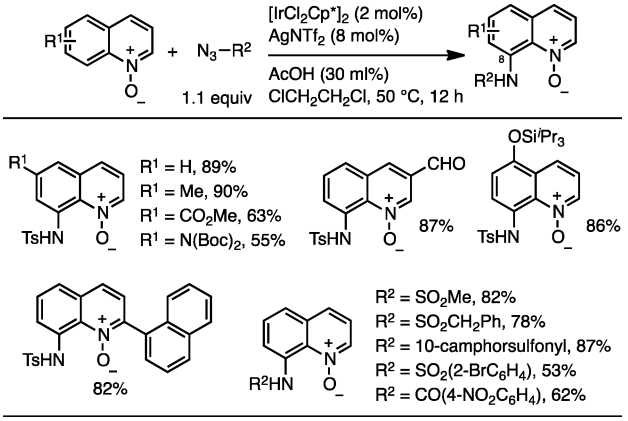
4-4. Formation of C–X (X = I, N) Bonds. Chang et al. extended the above strategy to carbon-heteroatom bond-forming reactions. Iodination with *N*-iodosuccinimide (Scheme 32) and amidation of quinoline *N*-oxides with sulfonyl azides

Scheme 32. Rhodium-Catalyzed C8 Iodination of Quinoline *N*-Oxides with *N*-Iodosccinimide[48]



(Scheme 33) were achieved with cationic Rh and Ir catalyst systems, respectively.[48] Both reactions proceeded with exclusive site selectivity under mild conditions.

Scheme 33. Iridium-Catalyzed C8 Amidation of Quinoline *N*-Oxides with Azides[48]



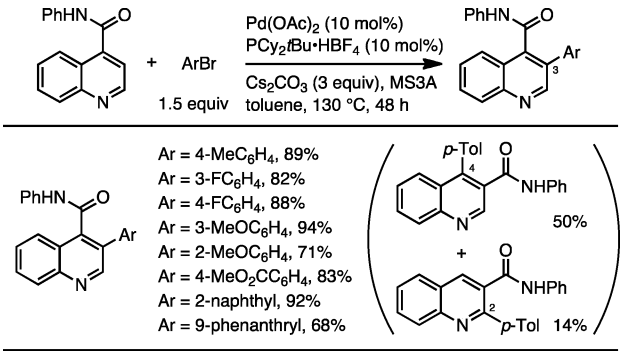
5. C–H FUNCTIONALIZATION OF QUINOLINES USING THE DIRECTING EFFECT OF METAL-COORDINATING PENDANT FUNCTIONAL GROUPS (EQ 4)

5-1. Coupling with C(sp²)–X Electrophiles. Yu reported the Pd-catalyzed amido-directed C3 or C4 arylation of quinolines with bromoarenes (Scheme 34).[49] Reactions of 4-carbamoylquinolines and aryl bromides in the presence of a $Pd(OAc)_2/PCy_2tBu{\cdot}HBF_4$ catalyst gave the corresponding 3-arylquinolines. In the reaction of 3-carbamoylquinoline, a mixture of C4- and C2-arylated products was obtained in favor of the C4 isomer.

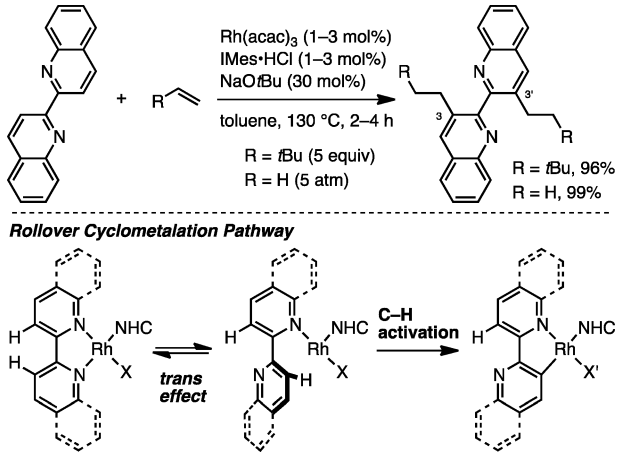
5-2. Insertion of Alkenes. Jung and Chang reported the Rh-catalyzed double hydroarylation of carbon–carbon unsaturated bonds with N,N-chelating molecules, such as 2,2′-biquinolines (Scheme 35).[50] Gaseous ethylene also was involved in this transformation. Experimental and theoretical studies showed that the strong trans effect of the NHC ligand weakened the N–Rh bond to facilitate a rollover cyclometalation pathway of N,N-chelating molecules.

5-3. C–H/C–H Coupling with Heteroarenes. Oxidative C–H/C–H coupling has become a straightforward strategy to

Scheme 34. Palladium-Catalyzed C3 Arylation of 4-Carbamoylquinolines[49]

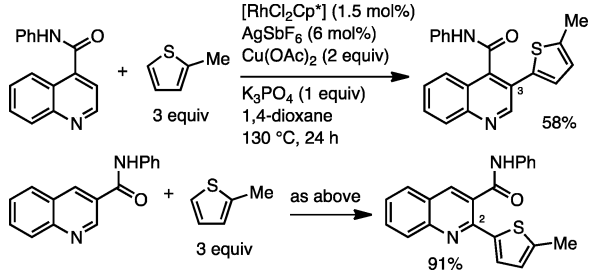


Scheme 35. Rhodium-Catalyzed Bis-hydroarylation of Alkenes[50]



synthesize (hetero)biaryl compounds from unmodified (hetero)arenes. Su reported the Rh(III)-catalyzed amide-directed dehydrogenative heteroarylation of azines, including quinolines. Reaction of 4-carbamoylquinoline and 2-methylthiophene afforded the corresponding C3-arylated quinoline through dual C–H bond cleavage (Scheme 36).[51] Likewise, 3-carbamoylquinoline provided the C2 arylation product in high yield.

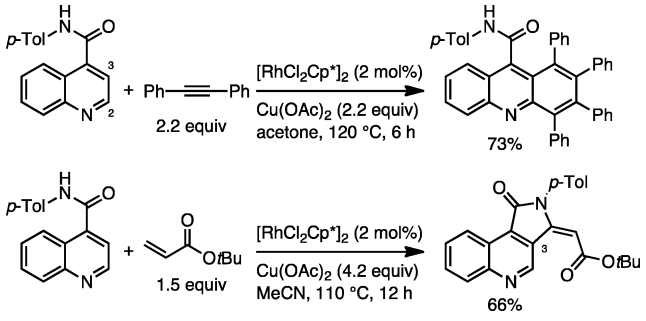
Scheme 36. Rhodium-Catalyzed C–H/C–H Coupling of 3- or 4-Carbamoylquinolines and 2-Methylthiophene[51]



5-4. Oxidative Coupling with π-Systems. Li stated that the Rh(III) complex $[RhCl_2Cp^*]_2$ allowed oxidative annulation of 4-carbamoylquinoline upon addition of 2 equiv of diphenylacetylene in the presence of $Cu(OAc)_2$ as an oxidant (Scheme 37).[52] 2-Fold C–H activation at both the C2 and C3 positions of the quinoline ring occurred to provide the

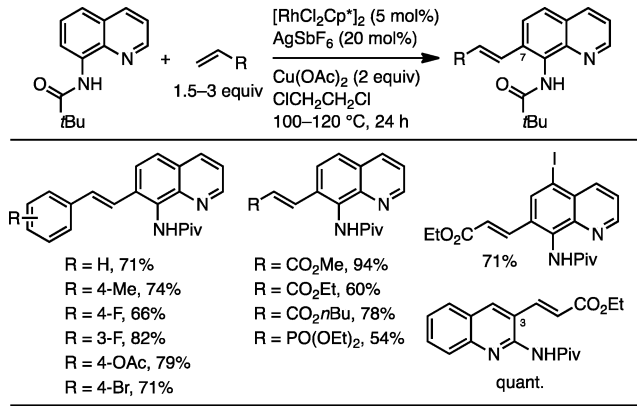
DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031–5040

Scheme 37. Rhodium-Catalyzed Oxidative Annulation of 4-Carbamoylquinoline with Alkyne or Acrylate[52,53]



corresponding acridine derivative. When acrylate was employed instead of alkyne, tricyclic compounds containing an exocyclic alkene moiety were obtained via C3 selective alkenylation, followed by oxidative amidation (Scheme 37).[53] Shi also reported oxidative C7 alkenylation of 8-aminoquinolines with styrenes or electron-poor alkenes in the presence of the cationic Rh(III) catalyst system (Scheme 38).[54] Reaction of 2-

Scheme 38. Rhodium-Catalyzed Oxidative C7 Alkenylation of 8-Aminoquinolines with Alkenes[54]



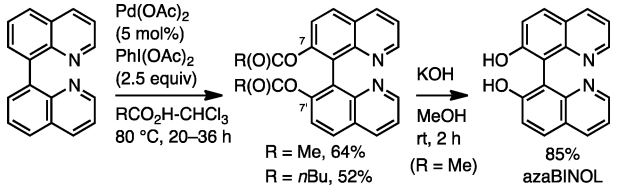
aminoquinoline derivatives gave the C3 alkenylated products exclusively. A quinoline-2-carboxyamide derivative also was a suitable substrate for the oxidative Rh(III)-catalyzed C3 alkenylation.[55]

5-5. Alkoxycarbonylation. Heteroatom-directed alkoxycarbonylation of C−H bonds through Pd catalysis is an attractive strategy for site-selective addition of oxygen functionalities to organic molecules.[56] Blakemore reported the efficient synthesis of 7,7′-dihydroxy-8,8′-biquinoline (azaBINOL) through Pd-catalyzed double C−H alkoxycarbonylation of 8,8′-biquinolines at both the C7 and C7′ positions followed by saponification (Scheme 39).[57]

6. SUMMARY AND OUTLOOK

This review summarizes the recent progress in transition-metal-catalyzed C−H functionalization of quinoline, which realized not only carbon−carbon bond formations but also carbon−heteroatom bond formations, such as C−B, C−Si, C−N, C−O, C−Cl, and C−I. Site-selectivity of the C−H bond at the C2 position of the quinoline ring was the main target of functionalization in the past because of intrinsic reactivity of the C=N bonds and proximity effects via nitrogen-to-metal coordination. However, more recent progress has made

Scheme 39. Synthesis of azaBINOL through Pd-Catalyzed Double C−H Alkoxycarbonylation of 8,8′-Biquinoline, Followed by Sponification[57]



selective C−H bond functionalization possible at different positions in the quinoline ring. In addition, quinoline *N*-oxide derivatives have become useful substrates for selective reactions at the C8 position. However, only a few studies on site-selective C−H functionalization reactions in the C5−C7 region in the carbocyclic portion of quinoline have been reported. Site-selectivity in these reactions relied on the directing effect of exocyclic metal-coordinating auxiliary groups. Improvement in quinoline functionalization methods will be facilitated by new reactions and strategies based on better understanding of the chemical properties of quinolines.

AUTHOR INFORMATION

Corresponding Author

*E-mail: sawamura@sci.hokudai.ac.jp.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported in part by CREST and ACT-C from JST, and a Grant-in-Aid for Young Scientists (B) (No. 25810056) from JSPS.

REFERENCES

(1) (a) Eicher, T.; Hauptmann, S.; Speicher, A. In *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, 2003; Vol. 6; pp 316−336. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166−187.

(2) McAteer, C. H.; Balasubramanian, M.; Murugan, R. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 7, pp 309−336.

(3) Chen, C. H.; Shi, J. *Coord. Chem. Rev.* **1998**, *171*, 161−174.

(4) (a) Manske, R. H. *Chem. Rev.* **1942**, *30*, 113−144. (b) Kouznetsov, V. V.; Mendez, L. Y.; Gomez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141−161. (c) Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. *RSC Adv.* **2014**, *4*, 24463−24476.

(5) (a) Gros, P. C.; Fort, Y. *Eur. J. Org. Chem.* **2002**, *2002*, 3375−3383. (b) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667−2722. (c) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376−393. (d) Gros, P. C.; Fort, Y. *Eur. J. Org. Chem.* **2009**, *2009*, 4199−4209. (e) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794−9824. (f) Klatt, T.; Markiewicz, J. T.; Sämann, C.; Knochel, P. *J. Org. Chem.* **2014**, *79*, 4253−4269.

(6) Mąkosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631−2666.

(7) Mcgill, C. K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988**, *44*, 1−79.

(8) (a) Fier, P. S.; Hartwig, J. F. *Science* **2013**, *342*, 956−960. (b) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 10139−10147.

(9) (a) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489−519. (b) Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocycl. Chem.* **1990**, *27*, 79−96. (c) Duncton, M. A. J. *MedChemComm* **2011**, *2*, 1135−1161.

DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031−5040

(10) (a) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194−13196. (b) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95−99. (c) O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122−12134.
(11) For selected examples, see: (a) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448−2449. (b) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926−14927. (c) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070−12071. (d) Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 7863−7868. (e) Guan, B.-T.; Hou, Z. *J. Am. Chem. Soc.* **2011**, *133*, 18086−18089. (f) Ren, X.; Wen, P.; Shi, X.; Wang, Y.; Li, J.; Yang, S.; Yan, H.; Huang, G. *Org. Lett.* **2013**, *15*, 5194−5197.
(12) For recent reviews, see: (a) Nakao, Y. *Synthesis* **2011**, *2011*, 3209−3219. (b) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20−40.
(13) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568−1576.
(14) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19090−19093.
(15) Guo, P.; Joo, J. M.; Rakshit, S.; Sames, D. *J. Am. Chem. Soc.* **2011**, *133*, 16338−16341.
(16) Engle, K. M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927−8955.
(17) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155.
(18) For a review, see: Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743.
(19) Cong, X.; Zeng, X. *Org. Lett.* **2014**, *16*, 3716−3719.
(20) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797−9804.
(21) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666−13668.
(22) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887−11889.
(23) Yamamoto, S.; Saga, Y.; Andou, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 401−405.
(24) Andou, T.; Saga, Y.; Komai, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3213−3216.
(25) Li, B.-J.; Shi, Z.-J. *Chem. Sci.* **2011**, *2*, 488−493.
(26) Ye, M.; Gao, G.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 6964−6967.
(27) Hyodo, I.; Tobisu, M.; Chatani, N. *Chem. - Asian J.* **2012**, *7*, 1357−1365.
(28) Knochel reported the BF_3-mediated C4 alkylation of azines using Grignard or organozinc reagents under transition-metal-free conditions: Chen, Q.; du Jourdin, X. M.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 4958−4961.
(29) Oshima, K.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 7324−7327.
(30) For recent reviews, see: (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890−931. (b) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992−2002. (c) Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229−3243.
(31) (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390−391. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056−3058.
(32) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649−5651.
(33) For selected recent works using heteroarenes as substrates, see: (a) Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287−4299. (b) Sadler, S. A.; Tajuddin, H.; Mkhalid, I. A. I.; Batsanov, A. S.; Albesa-Jove, D.; Cheung, M. S.; Maxwell, A. C.; Shukla, L.; Roberts, B.; Blakemore, D. C.; Lin, Z.; Marder, T. B.; Steel, P. G. *Org. Biomol. Chem.* **2014**, *12*, 7318−7327.
(34) Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586−3589.
(35) Tajuddin, H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A. S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.; Morris, J.; Lin, Z.; Marder, T. B.; Steel, P. G. *Chem. Sci.* **2012**, *3*, 3505−3515.
(36) Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 3780−3783.
(37) Konishi, S.; Kawamorita, S.; Iwai, T.; Steel, P. G.; Marder, T. B.; Sawamura, M. *Chem. - Asian J.* **2014**, *9*, 434−438.
(38) For a review of transition-metal-catalyzed C−H functionalization of *N*-oxide compounds at ortho positions, see: Yan, G.; Borah, A. J.; Yang, M. *Adv. Synth. Catal.* **2014**, *356*, 2375−2394.
(39) Stephens, D. E.; Lakey-Beitia, J.; Atesin, A. C.; Ateşin, T. A.; Chavez, G.; Arman, H. D.; Larionov, O. V. *ACS Catal.* **2015**, *5*, 167−175.
(40) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291−3306.
(41) Stephens, D. E.; Lakey-Beitia, J.; Chavez, G.; Ilie, C.; Arman, H. D.; Larionov, O. V. *Chem. Commun.* **2015**, *51*, 9507−9510.
(42) Shibata, T.; Matsuo, Y. *Adv. Synth. Catal.* **2014**, *356*, 1516−1520.
(43) Zhang, X.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 10794−10798.
(44) Sharma, U.; Park, Y.; Chang, S. *J. Org. Chem.* **2014**, *79*, 9899−9906.
(45) Li, Y.; Liu, S.; Qi, Z.; Qi, X.; Li, X.; Lan, Y. *Chem. - Eur. J.* **2015**, *21*, 10131−10137.
(46) Jeong, J.; Patel, P.; Hwang, H.; Chang, S. *Org. Lett.* **2014**, *16*, 4598−4601.
(47) Shin, K.; Park, S.-W.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 8584−8592.
(48) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 10770−10776.
(49) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275−1277.
(50) Kwak, J.; Ohk, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 17778−17788.
(51) Shang, Y.; Jie, X.; Zhao, H.; Hu, P.; Su, W. *Org. Lett.* **2014**, *16*, 416−419.
(52) Song, G.; Gong, X.; Li, X. *J. Org. Chem.* **2011**, *76*, 7583−7589.
(53) Wei, X.; Wang, F.; Song, G.; Du, Z.; Li, X. *Org. Biomol. Chem.* **2012**, *10*, 5521−5524.
(54) Zhou, J.; Li, B.; Hu, F.; Shi, B.-F. *Org. Lett.* **2013**, *15*, 3460−3463.
(55) Zhou, J.; Li, B.; Qian, Z.-C.; Shi, B.-F. *Adv. Synth. Catal.* **2014**, *356*, 1038−1046.
(56) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (b) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412−9423.
(57) Wang, C.; Flanigan, D. M.; Zakharov, L. N.; Blakemore, P. R. *Org. Lett.* **2011**, *13*, 4024−4027.

DOI: 10.1021/acscatal.5b01143
ACS Catal. 2015, 5, 5031−5040