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Nickel-Catalyzed Remote C4−H Arylation of 8-Aminoquinolines

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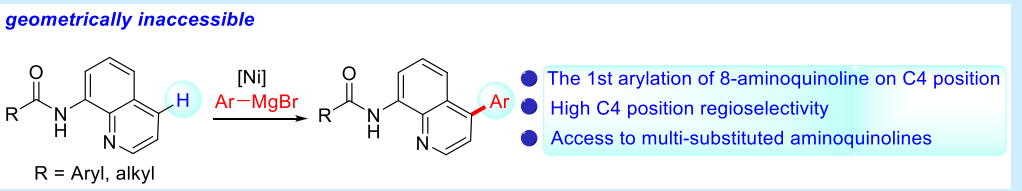
Supporting Information



ABSTRACT: A useful and convenient method for C−H bond arylation of 8-aminoquinoline motifs on the remote C4 position was developed. This method shows good functional group tolerance toward various Grignard reagents and aminoquinoline via a nickel catalysis, giving the desired arylated products in good yields. The present method affords an efficient access to construct multisubstituted aminoquinolines.

Given the importance and versatility of quinoline derivatives as bioactive natural products, medicines, functional materials (Figure 1),[1] and directing groups for C−H functionalization in transition-metal-catalyzed reactions,[2] developing highly efficient and environmentally benign protocols for the synthesis of various functionalized quinolines is highly desired. In the past several decades, tremendous progress has been made for the construction of quinoline motifs via cyclization of anilines derivatives[3] or cyclization of substituted alkynes[4] intermolecularly or intramolecularly.

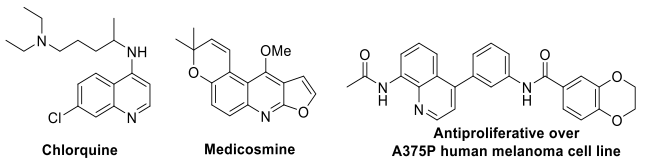
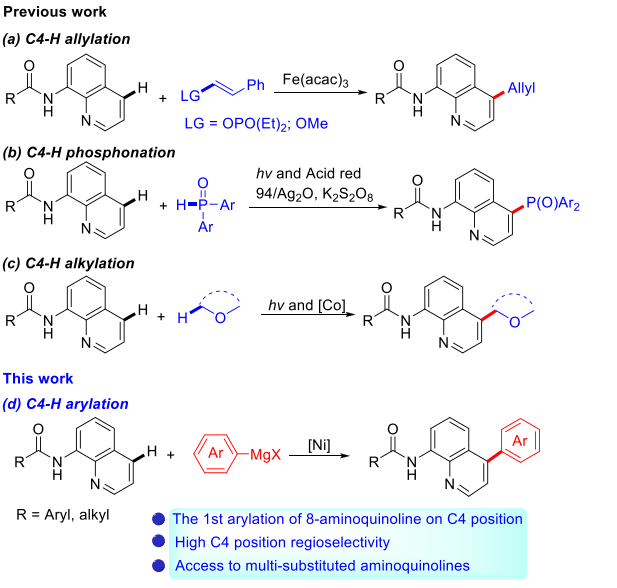


Figure 1. Representative biologically active compounds.

However, the above-mentioned methods suffer from drawbacks such as high prefunctionalized starting materials and low selectivity in some cases.[4d] An alternative synthetic method for functionalized quinolines is the site-selective modification of readily accessible quinoline frameworks via C−H functionalization. This method provides a quick access to functionalized quinolines. However, the regioselectivity has to be controlled. Many reactions for the C−H bond functionalization of the quinoline core are mainly on the position of C2,[5] C3,[6] C5,[7] and C8,[8] which are easily accessible. However, as for the functionalization of the important C4 position,[1d,e] which is relatively less electrophilic (more nucleophilic) among the 8-aminoquinioline core, progress is very slow.[9] In recent years, there are several reports concerning the functionalization on the C4 position of pyridine[10] or quinoline motif,[11] which provide some idea for the functionalization of 8-aminoquinoline. However, as for the remote C4−H functionalization of aminoquinolines, only three examples have been disclosed (Scheme 1).[9] In 2014, Zeng et al. reported the first two substrates of Fe-catalyzed remote C4−H allylation of 8-aminoquinolines (Scheme 1a).[9a] Wu et al. developed phosphonation of 8-aminoquinoline at C4 position via the combination of photocatalysis and transition metal catalysis

Scheme 1. C4−H Functionalization of 8-Aminoquinolines



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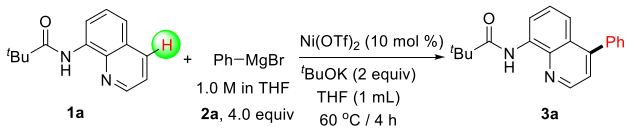
(Scheme 1b).[9b] Ranu et al. reported high efficient cobalt-catalyzed remote C4−H alkylation of 8-aminoquinoline with photocatalyst (Scheme 1c).[9c] As is known, the C−H bond arylation attracts immense attention among the various kinds of C−H functionalizations, which can greatly improve the complexity of the obtained substrates due to the obtained valuable biaryl structural motifs. However, the research of a method to build up C4-arylated aminoquinolines has never been disclosed.

Our group is very interested in the functionalization of aminoquinoline core[7d,12] and the cross-coupling reaction using Grignard reagents as important partner.[13] Herein, we reported the first nickel-catalyzed C4−H arylation of 8-aminoquinolines with aryl Grignard reagents (Scheme 1d). This method affords a useful and convenient access to construct multisubstituted aminoquinolines.

The cross-coupling between *N*-(quinolin-8-yl)pivalamide (**1a**) and phenylmagnesium bromide (**2a**) was examined as a model reaction (see Supporting Information). After optimization of reaction conditions, the C4 arylated product *N*-(4-phenylquinolin-8-yl)pivalamide (**3a**) was generated in 78% yield when $Ni(OTf)_2$ was used as catalyst in the presence of 2 equiv of ^{t}BuOK at 60 °C (Table 1, entry 1). If no nickle

Table 1. Optimization of the Reaction Conditions[a]



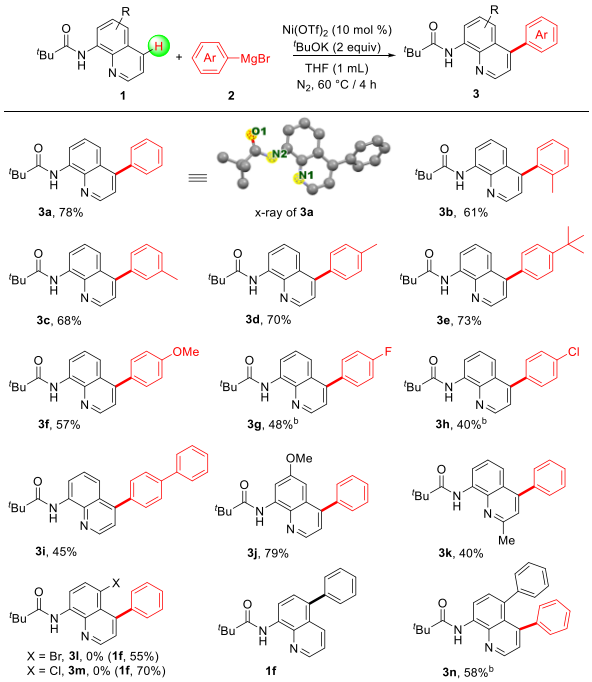
entry	variation from standard conditions	yield of **3a**[b] (%)
1	none	80 (78)
2	no $Ni(OTf)_2$	<1[c]
3	$Ni(COD)_2$ instead of $Ni(OTf)_2$	75
4	$NiCl_2$ instead of $Ni(OTf)_2$	66
5	no ^{t}BuOK	45
6	PhMgBr (3 equiv)	50

[a]Reaction conditions: *N*-(quinolin-8-yl)pivalamide (**1a**, 0.2 mmol), phenylmagnesium bromide (**2a**,1.0 M in THF, 4.0 equiv), solvent (1.0 mL), N_2 atmosphere. [b]GC Yield using *n*-dodecane as internal standard; the isolated yield was given in parentheses. [c]C2 arylated product (**3a′**) was obtained in 10%. The crude mixture contains a small amount of 1,2-dihydroquinoline derivative. After quenched by NH_4Cl (aq), it was oxidized to quinoline by adding 1 equiv of DDQ and stirring for 10 min at ambient temperature (procedures are similar hereinafter).

catalyst was used, **3a** was formed in less than 1% yield with C2 arylated product (**3a′**) generated in 10% yield (entry 2). When $Ni(COD)_2$ was used as catalyst under the standard condition instead of $Ni(OTf)_2$, the desired product **3a** was generated in 75% yield, indicating that the reactive species may be Ni(0). $NiCl_2$ can also catalyze this reaction, giving **3a** in 66% yield (entry 4). Without ^{t}BuOK, the reaction can be proceeded but in lower yield (entry 5). Lower the amount of Grignard reagent used in the reaction decreased the yield of **3a** (entry 6). The structure of **3a** was confirmed by single crystal X-ray analysis (figure in Scheme 2).

After having the optimized reaction conditions, we investigated the substrate scopes of Grignard reagents (Scheme 2). For various kinds of aryl Grignard reagents, the reaction proceeded smoothly to be arylated on C4 position selectively, yielding the desired products **3a−i** in good yields. Methyl

Scheme 2. Substrate Scope for Aryl Grignard Reagents[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (4.0 equiv), N_2, isolated yield. [b]Reaction conditions: 24 h.

groups attached to the phenyl Grignard reagents at different positions show no obvious steric hindrance, giving **3b−d** in middle to good yields (61−70%). When electron-donating group 4-Me, 4-^{t}Bu, or 4-OMe was attached to the para position, the corresponding **3d−f** were yielded in 57%−73% yield. Aryl Grignard reagents possessing electron-withdrawing substituents (4-F, 4-Cl) gave **3g,h** in modest yields. Biphenyl Grignard reagent gave **3i** in a slightly lower yield. The substituents on the quinoline core motifs were also investigated. When an aminoquinoline having a methoxy group on C6 position was employed, **3j** was generated in 79% yield. However, if a Br or Cl atom is attached to the C5 position, the desired products (**3l,m**) were not yielded, but C5 arylated product **1f** was obtained in 55%, 70%, respectively, indicating that the Kumada coupling is predominated. C5 arylated aminoquinoline can also tolerated to give **3n** in 58% yield, which shows no obvious steric hindrance to the C4 functionalization. Alkyl Grignard reagent such as butylmagnesium bromide and heteroaromatic Grignard reagent such as thiophen-2-ylmagnesium bromide failed to give the corresponding products (see Supporting Information).

As shown in Scheme 3, the reactions of phenylmagnesium bromide (**2a**) with various kinds of aminoquinolines were investigated. When replacing **1a** with 2,2-dimethyl-*N*-(quinolin-8-yl)butanamide, the corresponding product **4a** was yielded in 61% yield. For long-chain alkyl groups and cyclohexyl group, the arylation proceeded smoothly to give desired products **4b−d** in 65%−68% yield. It is noted that benzoyl aminoquinolines can also be tolerated in this system without the generation of *ortho* C−H bond arylated byproducts directed by 8-aminoquinoline group (**4e−j**).

In order to demonstrate the synthetic utility, the model reaction was enlarged to a gram scale, and 1.3 g **3a** was generated in 61% yield (Scheme 4). The amide group could be hydrolyzed under basic conditions to give C4-arylated

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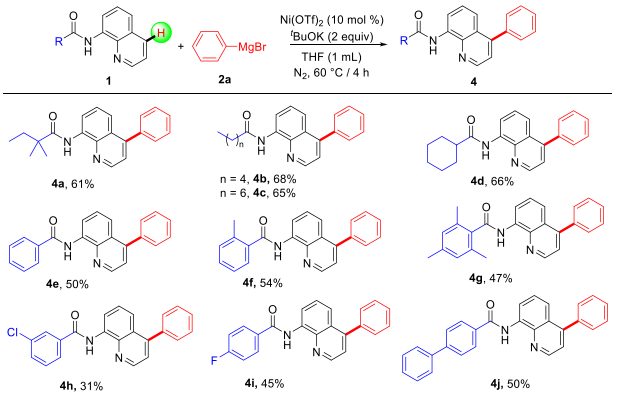
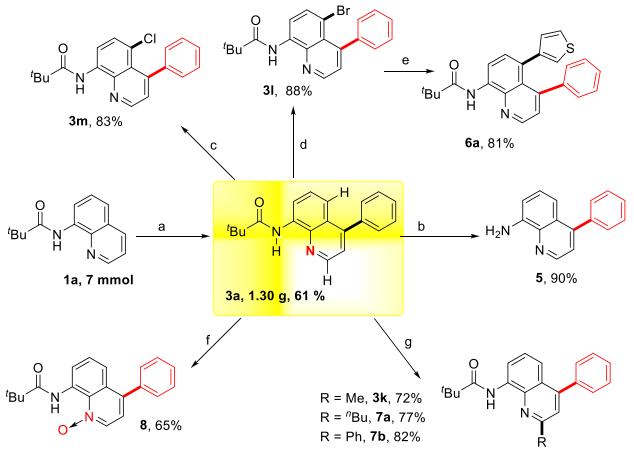
Scheme 3. Substrate Scope for Aminoquinolines[a]



[a]Reaction condition: **1** (0.2 mmol), **2a** (4.0 equiv), N_2, isolated yield.

Scheme 4. Synthetic Applications

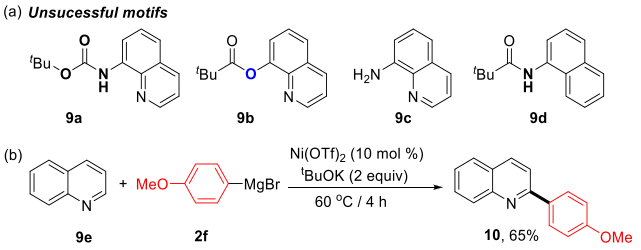


[a]Reaction conditions: $Ni(OTf)_2$ (10 mol %), **2a** (4 equiv), ^{t}BuOK (2 equiv), THF, 60 °C/12 h. [b]Reaction conditions: NaOH (10 equiv), EtOH, 100 °C/24 h. [c]Reaction conditions: NCS (1.1 equiv), DMF (2 mL), 50 °C/2 h, N_2. [d]Reaction conditions: NBS (1.1 equiv), DMF (2 mL), 50 °C/2 h, N_2. [e]Reaction conditions: 3-thiopheneboronic acid (2 equiv), Na_2CO_3 (2 equiv), $Pd(PPh_3)_4$ (10 mol %), DMSO, N_2, 140 °C/10 h. [f]Reaction conditions: m-CPBA (2 equiv), CH_2Cl_2, 25 °C/12 h, air. [g]Reaction conditions: R-Li (5 equiv), THF (2 mL), 0 °C/12 h, N_2. See Supporting Information for details.

quinoline-8-amine **5** in 90% yield. Furthermore, C5-position could selectively brominated and chlorinated to give **3l,m** in high yields according our previous report.[12b] It should be noted that these bromo- and cholor- products **3l,m** cannot be obtained by arylation of C5 bromo- or chloroquinolines (Scheme 2). With application of a Suzuki coupling reaction to this brominated compound,[12b] the thienyl group can be introduced at the C5 position to give **6a** in 81% yield. The C2 position was arylated and alkylated to give **3k**, **7a,b** in good yields by the reaction with organolithium reagents. *N*-oxide **8** was obtained by oxidation with *m*-CPBA.

To shed some light on the possible mechanism of the C4 arylation on 8-aminoquinlines, we performed several preliminary experiments as depicted in Scheme 5. When *tert*-butyl quinolin-8-ylcarbamate (**9a**), quinolin-8-yl pivalate (**9b**), or free amine quinolin-8-amine (**9c**) instead of **1a** was treated with phenylmagnesium bromide (**2a**) under the standard condition, no corresponding product was detected (Scheme 4a). The above-mentioned results indicate the important role

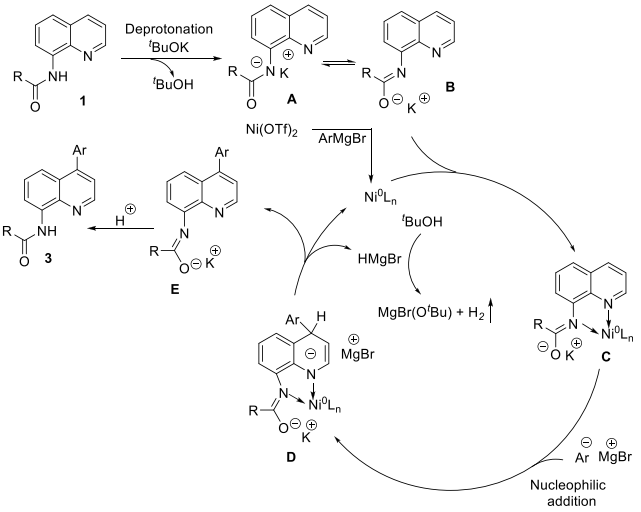
Scheme 5. Control Experiments



of the amide group at C8 position. *N*-(Naphthalen-1-yl)pivalamide (**9d**) was also not arylated. When unsubstituted quinoline (**9e**) was reacted with **2f**, only C2-arylted product **10** was obtained in 65% yield, as previous reported by Da et al.[14] In addition, by careful analysis of the atmosphere after reaction, a small amount of hydrogen was detected.

On the basis of the above results and literature,[10a] we propose here a possible pathway for the C4 arylation of 8-aminoquinoline derivatives (Scheme 6). Initially, deprotona-

Scheme 6. Possible Mechanism



tion of amide **1** by ^{t}BuOK followed by isomerization forms the intermediate **B**. Coordination of the Ni(0) species which was reduced by Grignard reagent from Ni(II) with aminoquinoline forms intermediate **C**. Then, nucleophilic addition of Grignard reagent generates intermediate **D**. The intermediate **D** then undergoes elimination and protonation to deliver the desired product **3** and generate Ni(0) species for the next catalytic cycle. A nickel insertion mechanism may also be possible (see Supporting Information).[10b,c,11b]

In summary, we demonstrated a useful and convenient nickel catalyzed protocol for C4-arylation of 8-aminoquinoline motifs. The reaction shows good tolerance toward various aryl Grignard reagents and aminoquinoline, giving the desired products in good yields. This method affords an efficient access to construct multisubstituted aminoquinolines.

■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures, characterization data, spectra copies of the ^{1}H, ^{13}C NMR for obtained products, and X-ray data of **3a** (PDF)

Accession Codes

CCDC 1842336 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Michael, J. P. Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep.* **2008**, *25*, 166−187. (b) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. Quinolines and structurally related heterocycles as antimalarials. *Eur. J. Med. Chem.* **2010**, *45*, 3245−3264. (c) Colomb, J.; Becker, G.; Fieux, S.; Zimmer, L.; Billard, T. Syntheses, radiolabelings, and in vitro evaluations of fluorinated PET radioligands of 5-HT6 serotoninergic receptors. *J. Med. Chem.* **2014**, *57*, 3884−3890. (d) O'Neill, P. M.; Bray, P. G.; Hawley, S. R.; Ward, S. A.; Park, B. K. 4-Aminoquinolines—Past, present, and future; A chemical perspective. *Pharmacol. Ther.* **1998**, *77*, 29−58. (e) Koh, E. J.; El-Gamal, M. I.; Oh, C. H.; Lee, S. H.; Sim, T.; Kim, G.; Choi, H. S.; Hong, J. H.; Lee, S. G.; Yoo, K. H. New diarylamides and diarylureas possessing 8-amino(acetamido)quinoline scaffold: synthesis, antiproliferative activities against melanoma cell lines, kinase inhibition, and in silico studies. *Eur. J. Med. Chem.* **2013**, *70*, 10−21. (f) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*, 3rd ed.; John Wiley & Sons, 2013. (g) Jentsch, N. G.; Hart, A. P.; Hume, J. D.; Sun, J.; McNeely, K. A.; Lama, C.; Pigza, J. A.; Donahue, M. G.; Kessl, J. J. Synthesis and Evaluation of Aryl Quinolines as HIV-1 Integrase Multimerization Inhibitors. *ACS Med. Chem. Lett.* **2018**, *9*, 1007−1012.

(2) 8-Aminoquinoline as directing group or ligands, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. Highly regioselective arylation of sp3 C-H bonds catalyzed by palladium acetate. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (b) Castro, L. C. M.; Chatani, N. Nickel Catalysts/N,N′-Bidentate Directing Groups: An Excellent Partnership in Directed C−H Activation Reactions. *Chem. Lett.* **2015**, *44*, 410−421. (c) Corbet, M.; De Campo, F. 8-Aminoquinoline: a powerful directing group in metal-catalyzed direct functionalization of C-H bonds. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896−9898. (d) Rouquet, G.; Chatani, N. Catalytic functionalization of C(sp2)-H and C(sp3)-H bonds by using bidentate directing groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743. (e) Wu, X.; Zhao, Y.; Ge, H. Nickel-catalyzed site-selective alkylation of unactivated C(sp3)-H bonds. *J. Am. Chem. Soc.* **2014**, *136*, 1789−1792. (f) Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. Synthesis of anthranilic acid derivatives through iron-catalyzed ortho amination of aromatic carboxamides with N-chloroamines. *J. Am. Chem. Soc.* **2014**, *136*, 646−649. (g) Pan, F.; Shen, P. X.; Zhang, L. S.; Wang, X.; Shi, Z. J. Direct arylation of primary and secondary sp3 C-H bonds with diarylhyperiodonium salts via Pd catalysis. *Org. Lett.* **2013**, *15*, 4758−4761. (h) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. Cupreines and cupreidines: an emerging class of bifunctional cinchona organocatalysts. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496−7504. (i) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. Transition metal-catalyzed C−H bond functionalizations by the use of diverse directing groups. *Org. Chem. Front.* **2015**, *2*, 1107−1295. (j) Liu, J.; Chen, G.; Tan, Z. Copper-Catalyzed or -Mediated C-H Bond Functionalizations Assisted by Bidentate Directing Groups. *Adv. Synth. Catal.* **2016**, *358*, 1174−1194. (k) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. Reusable directing groups [8-aminoquinoline, picolinamide, sulfoximine] in C(sp3)−H bond activation: present and future. *Tetrahedron* **2015**, *71*, 4450−4459.

(3) Construction of quinoline motifs via cyclization of anilines, see: (a) Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. Recent progress in the synthesis of quinolines. *Curr. Org. Chem.* **2005**, *9*, 141−161. (b) Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. Recent advances in the synthesis of quinolines: a review. *RSC Adv.* **2014**, *4*, 24463−24476. (c) Ramann, G. A.; Cowen, B. J. Recent Advances in Metal-Free Quinoline Synthesis. *Molecules* **2016**, *21*, 986−1008. (d) Shao, Y. D.; Dong, M. M.; Wang, Y. A.; Cheng, P. M.; Wang, T.; Cheng, D. J. Organocatalytic Atroposelective Friedlander Quinoline Heteroannulation. *Org. Lett.* **2019**, *21*, 4831−4836. (e) Gu, Z.-Y.; Zhu, T.-H.; Cao, J.-J.; Xu, X.-P.; Wang, S.-Y.; Ji, S.-J. Palladium-Catalyzed Cascade Reactions of Isocyanides with Enaminones: Synthesis of 4-Aminoquinoline Derivatives. *ACS Catal.* **2014**, *4*, 49−52. (f) Chen, P.; Nan, J.; Hu, Y.; Ma, Q.; Ma, Y. Ru(II)-Catalyzed/NH2-Assisted Selective Alkenyl C-H [5 + 1] Annulation of Alkenylanilines with Sulfoxonium Ylides to Quinolines. *Org. Lett.* **2019**, *21*, 4812−4815.

(4) Construction of quinoline motifs via cyclization of alkynes, see: (a) Wang, Y.; Chen, C.; Peng, J.; Li, M. Copper(II)-catalyzed three-component cascade annulation of diaryliodoniums, nitriles, and alkynes: a regioselective synthesis of multiply substituted quinolines. *Angew. Chem., Int. Ed.* **2013**, *52*, 5323−5327. (b) Rode, N. D.; Arcadi, A.; Di Nicola, A.; Marinelli, F.; Michelet, V. Gold-Catalyzed Cascade Reaction of beta-(2-Aminophenyl)-alpha,beta-ynones with Ynamides: A Sequential Route to Polysubstituted 2-Aminoquinolines. *Org. Lett.* **2018**, *20*, 5103−5106. (c) Jia, R.; Li, B.; Liang, R.; Zhang, X.; Fan, X. Tunable Synthesis of Indolo[3,2- c]quinolines or 3-(2-Aminophenyl)-quinolines via Aerobic/Anaerobic Dimerization of 2-Alkynylanilines. *Org. Lett.* **2019**, *21*, 4996−5001. (d) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. Palladium-catalysed hydroarylation and hydrovinylation of 3,3-dialkoxy-1-aryl-1-propynes. An approach to 3-aryl- and 3-vinylquinolines. *Tetrahedron* **1996**, *52*, 10225−10240.

(5) Modification of quinoline scaffolds on the C2 position, see: (a) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. Rh(I)-catalyzed direct arylation of pyridines and quinolines. *J. Am. Chem. Soc.* **2008**, *130*, 14926−14927. (b) Tobisu, M.; Hyodo, I.; Chatani, N. Nickel-catalyzed reaction of arylzinc reagents with N-aromatic heterocycles: a straightforward approach to C-H bond arylation of electron-deficient heteroaromatic compounds. *J. Am. Chem. Soc.* **2009**, *131*, 12070−12071.

(6) Modification of quinoline scaffolds on the C3 position, see: (a) Wasa, M.; Worrell, B. T.; Yu, J. Q. Pd0/PR3-Catalyzed Arylation of Nicotinic and Isonicotinic Acid Derivatives. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275−1277. (b) Sun, K.; Lv, Y.; Wang, J.; Sun, J.; Liu, L.; Jia, M.; Liu, X.; Li, Z.; Wang, X. Regioselective, Molecular Iodine-Mediated C3 Iodination of Quinolines. *Org. Lett.* **2015**, *17*, 4408−4411. (c) He, Y.; Wu, Z.; Ma, C.; Zhou, X.; Liu, X.; Wang, X.; Huang, G. Palladium-Catalyzed Selective C-H Activation: A Simple Method to Synthesize C-3 Site Arylated Quinoline Derivatives. *Adv. Synth.*

DOI: 10.1021/acs.orglett.9b02403
Org. Lett. XXXX, XXX, XXX−XXX

Catal. **2016**, *358*, 375−379. (d) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. Ligand-promoted C3-selective arylation of pyridines with Pd catalysts: gram-scale synthesis of (±)-preclamol. *J. Am. Chem. Soc.* **2011**, *133*, 19090−19093.

(7) Modification of quinoline scaffolds on the C5 position, see: (a) Iwai, T.; Sawamura, M. Transition-Metal-Catalyzed Site-Selective C−H Functionalization of Quinolines beyond C2 Selectivity. *ACS Catal.* **2015**, *5*, 5031−5040. (b) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. Divergence between organometallic and single-electron-transfer mechanisms in copper(II)-mediated aerobic C-H oxidation. *J. Am. Chem. Soc.* **2013**, *135*, 9797−9804. (c) Stephens, D. E.; Larionov, O. V. Recent Advances in the C-H-Functionalization of the Distal Positions in Pyridines and Quinolines. *Tetrahedron* **2015**, *71*, 8683−8716. (d) Zhu, L.; Cao, X.; Li, Y.; Liu, T.; Wang, X.; Qiu, R.; Yin, S. Recent Advances on the C-H Bond Functionalization on C(5) Position of 8-Aminoquinolines. *Youji Huaxue* **2017**, *37*, 1613−1628. (e) Khan, B.; Dutta, H. S.; Koley, D. Remote C−H Functionalization of 8-Aminoquinolinamides. *Asian J. Org. Chem.* **2018**, *7*, 1270−1297.

(8) Modification of quinoline scaffolds on the C8 position, see: (a) Boudet, N.; Lachs, J. R.; Knochel, P. Multiple regioselective functionalizations of quinolines via magnesiations. *Org. Lett.* **2007**, *9*, 5525−5528. (b) Kwak, J.; Kim, M.; Chang, S. Rh(NHC)-Catalyzed Direct and Selective Arylation of Quinolines at the 8-Position. *J. Am. Chem. Soc.* **2011**, *133*, 3780−3783.

(9) Modification of 8-aminoquinoline scaffolds on the C4 position, see: (a) Cong, X.; Zeng, X. Iron-Catalyzed, Chelation-Induced Remote C−H Allylation of Quinolines via 8-Amido Assistance. *Org. Lett.* **2014**, *16*, 3716−3719. (b) Qiao, H. J.; Sun, S. Y.; Zhang, Y.; Zhu, H. M.; Yu, X. M.; Yang, F.; Wu, Y. S.; Li, Z. X.; Wu, Y. J. Merging photoredox catalysis with transition metal catalysis: site-selective C4 or C5-H phosphonation of 8-aminoquinoline amides. *Org. Chem. Front.* **2017**, *4*, 1981−1986. (c) Ghosh, T.; Maity, P.; Ranu, B. C. Cobalt-Catalyzed Remote C-4 Functionalization of 8-Aminoquinoline Amides with Ethers via C-H Activation under Visible-Light Irradiation. Access to alpha-Heteroarylated Ether Derivatives. *Org. Lett.* **2018**, *20*, 1011−1014.

(10) Functionalization on the C4 position of pyridine, see: (a) Chen, Q.; du Jourdin, X. M.; Knochel, P. Transition-Metal-Free BF3-Mediated Regioselective Direct Alkylation and Arylation of Functionalized Pyridines Using Grignard or Organozinc Reagents. *J. Am. Chem. Soc.* **2013**, *135*, 4958−4961. (b) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. Bimetallic nickel aluminun mediated Para-selective alkenylation of pyridine: direct observation of η^2, η^1-pyridine Ni (0)− Al (III) intermediates prior to C−H bond activation. *J. Am. Chem. Soc.* **2010**, *132*, 11887−11889. (c) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. Selective C-4 alkylation of pyridine by nickel/Lewis acid catalysis. *J. Am. Chem. Soc.* **2010**, *132*, 13666−13668. (d) Guo, P.; Joo, J. M.; Rakshit, S.; Sames, D. C-H arylation of pyridines: high regioselectivity as a consequence of the electronic character of C-H bonds and heteroarene ring. *J. Am. Chem. Soc.* **2011**, *133*, 16338−16341.

(11) Functionalization on the C4 position of quinoline, see: (a) Nagase, M.; Kuninobu, Y.; Kanai, M. 4-Position-Selective C-H Perfluoroalkylation and Perfluoroarylation of Six-Membered Heteroaromatic Compounds. *J. Am. Chem. Soc.* **2016**, *138*, 6103−6106. (b) Yamamoto, S.; Saga, Y.; Andou, T.; Matsunaga, S.; Kanai, M. Cobalt-Catalyzed C-4 Selective Alkylation of Quinolines. *Adv. Synth. Catal.* **2014**, *356*, 401−405. (c) Liu, W. B.; Yang, X. B.; Zhou, Z. Z.; Li, C. J. Simple and Clean Photo-induced Methylation of Heteroarenes with MeOH. *Chem.* **2017**, *2*, 688−702.

(12) (a) Wang, X.; Xie, P.; Qiu, R.; Zhu, L.; Liu, T.; Li, Y.; Iwasaki, T.; Au, C. T.; Xu, X.; Xia, Y.; Yin, S. F.; Kambe, N. *Nickel-catalysed direct alkylation of thiophenes via double C(sp(3))-H/C(sp(2))-H bond cleavage: the importance of KH_2PO_4.* *Chem. Commun.* **2017**, *53*, 8316−8319. (b) Li, Y.; Zhu, L.; Cao, X.; Au, C.-T.; Qiu, R.; Yin, S.-F. Metal-free C5-H Bromination of Quinolines for One-pot C-X (X = C, O, S) Bond Formations. *Adv. Synth. Catal.* **2017**, *359*, 2864−2873. (c) Zhu, L.; Qiu, R.; Cao, X.; Xiao, S.; Xu, X.; Au, C. T.; Yin, S. F. Copper-Mediated Remote C-H Bond Chalcogenation of Quinolines on the C5 Position. *Org. Lett.* **2015**, *17*, 5528−5531. (d) Wang, X.; Qiu, R.; Yan, C.; Reddy, V. P.; Zhu, L.; Xu, X.; Yin, S. F. Nickel-catalyzed direct thiolation of C(sp(3))-H bonds in aliphatic amides. *Org. Lett.* **2015**, *17*, 1970−1973. (e) Wang, X.; Zhu, L.; Chen, S.; Xu, X.; Au, C. T.; Qiu, R. Nickel-Catalyzed Direct C (sp(3))-H Arylation of Aliphatic Amides with Thiophenes. *Org. Lett.* **2015**, *17*, 5228−5231. (f) Tang, Z.; Liu, Z.; Tong, Z.; Xu, Z.; Au, C. T.; Qiu, R.; Kambe, N. Cu-Catalyzed Cross-Dehydrogenative Coupling of Heteroaryl C-(sp(2))-H and Tertiary C(sp(3))-H Bonds for the Construction of All-Carbon Triaryl Quaternary Centers. *Org. Lett.* **2019**, *21*, 5152−5156.

(13) (a) Kambe, N.; Iwasaki, T.; Terao, J. Pd-catalyzed cross-coupling reactions of alkyl halides. *Chem. Soc. Rev.* **2011**, *40*, 4937−4947. (b) Iwasaki, T.; Kambe, N. Ni-catalyzed C−C couplings using alkyl electrophiles. *Top. Curr. Chem.* **2017**, 1−36. (c) Iwasaki, T.; Kambe, N. 3.07 Coupling Reactions Between sp3-Carbon Centers. In *Comprehensive Organic Synthesis II*; Elsevier, 2014; pp 337−391. (d) Iwasaki, T.; Min, X.; Fukuoka, A.; Zhu, L.; Qiu, R.; Yang, T.; Ehara, M.; Sudalai, A.; Kambe, N. Ni-Catalyzed Dimerization and Hydroperfluoroarylation of 1,3-Dienes. *J. Org. Chem.* **2018**, *83*, 9267−9277. (e) Zhu, L.; Le, L.; Yan, M.; Au, C. T.; Qiu, R.; Kambe, N. Carbon-Carbon Bond Formation of Trifluoroacetyl Amides with Grignard Reagents via C(O)-CF3 Bond Cleavage. *J. Org. Chem.* **2019**, *84*, 5635−5644.

(14) Functionalization on the C2 position of quinoline, see: Zhuo, F. F.; Xie, W. W.; Yang, Y. X.; Zhang, L.; Wang, P.; Yuan, R.; Da, C. S. TMEDA-assisted effective direct ortho arylation of electron-deficient N-heteroarenes with aromatic Grignard reagents. *J. Org. Chem.* **2013**, *78*, 3243−3249.

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