Nickel-Catalyzed Site-Selective C3-H Functionalization of Quinolines with Electrophilic Reagents at Room Temperature

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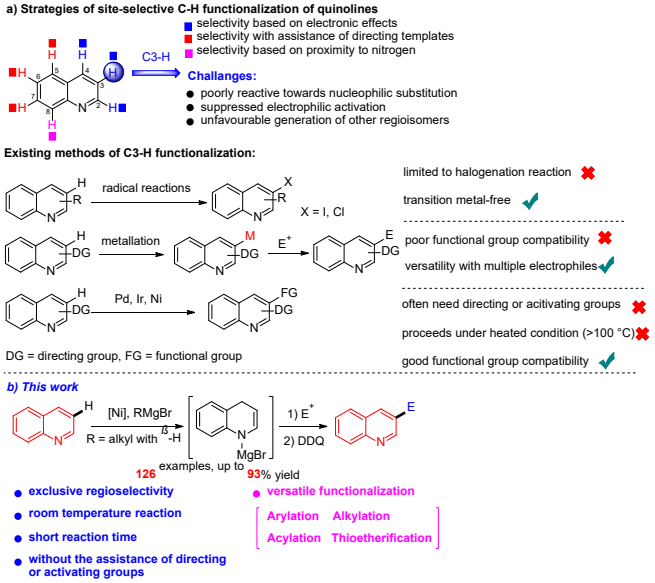
ABSTRACT: Herein, we disclose a mild and versatile nickel-catalyzed method for exclusive C3-selective thioetherification, alkylation, arylation, acylation, and phosphorylation of quinolines with a variety of electrophiles. Unactivated quinolines can be functionalized without directing groups at room temperature. Control experiments indicated that quinolines underwent 1,4-addition with nickel hydride species generated from *β*-H elimination of alkyl nickel intermediates to produce 1,4-dihydroquinolines, which further went through subsequent nucleophilic attack to external electrophiles and oxidative aromatization to generate C3-H functionalized products.

1. Introduction

Quinolines are prevalent in numerous natural products,[1] pharmaceuticals[2] and ligands[3], thus tireless endeavors have been made on the synthesis of this important scaffold.[4] Among various synthetic methods towards substituted quinolines, C-H functionalization of preformed quinolines possesses most step- and atom-economical properties.

Due to the existence of multiple C-H bonds, increasing site-selectivity of C-H functionalization of quinolines is a central issue.[5] Various strategies have been developed to realize site-selective C-H functionalization of quinolines including exploiting electronic effects, proximity effects and directing templates. Methods of activating C-H bonds of other aza-arenes including pyridine[6] in site-selective manner also provide valuable guidance. Because of the intrinsically electrophilic character of C2-H[7] and C4-H[8], they were generally functionalized via the nucleophilic metalation process. C8-H can be selectively functionalized by utilizing the proximity of C8-H to Lewis basic nitrogen which help to direct the catalyst.[9] For the site-selective functionalization of remote benzocyclic C5-C7 positions with much more challenges, reversibly-binding directing templates were ingeniously utilized to position the catalyst proximate to the target remote C–H bond via a macrocyclophanic pre-transition state.[10] Furthermore, achieving C3–H selectivity is particularly challenging as such an activation typically proceeds via an electrophilic activation pathway, while the reactivity of this process is further suppressed by electron-deficient property of pyridine ring and detrimental interaction between sp^2-hybridized nitrogen atom and electrophiles (Scheme 1a). At the expense of step economy or substrates scope, C3 selectivity can be realized by using directing groups or attaching electron-withdrawing / -donating substituent groups. Only few examples were reported to realize site-selective C3-H functionalization of unactivated quinolines without the assistance of directing groups,[8b, 11] but these reactions mostly proceed under heated conditions and generate other regioisomers as minor isomers.

Scheme 1. The challenges and strategies of C3-H functionalization of quinolines



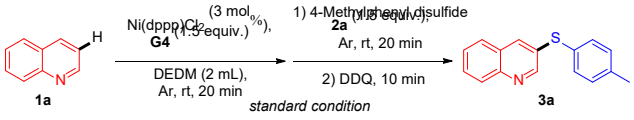
Inspired by conventional deprotonative metalation of azines[12], it is an ideal method to largely differentiate C3 from other positions on the nucleophilicity to achieve exclusive C3 functionalization with a variety of electrophiles. 1,4-Dihydroquinolines/1,4-dihydropyridines are much more nucleophilic than quinolines/pyridines and have nucleophilic property only at β positions of nitrogen atoms.[13] It is hypothesized that transformation of quinolines to 1,4-DHQs followed by the nucleophilic attack to external electrophiles and oxidative aromatization could realize the exclusive C3 selectivity.

Here, we disclose a mild and versatile nickel-catalyzed method for C3-H thioetherification, alkylation, arylation, acylation, and phosphorylation with a variety of electrophiles (Scheme 1b). The exclusive C3 selectivity can be realized within one hour at room temperature. Control experiments indicated that quinolines underwent 1,4-addition with nickel hydride species generated from β-H elimination of alkyl nickel intermediates to produce 1,4-DHQs.

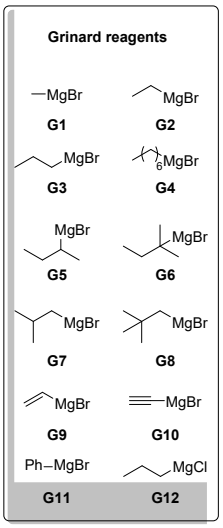
2. Results and Discussion

2.1. Selective C3-H Thioetherification of Quinolines and Other Related Aza-arenes. The reaction with quinoline **1a** and 4-methylphenyl disulfide **2a** as the electrophilic coupling partners was examined by employing different Ni catalysts and Grignard reagents. Under standard conditions shown in Table 1, the combination of Ni(dppp)Cl2 and n-heptylmagnesium bromide G4 led

Table 1. Optimization of the reaction conditions.[a]



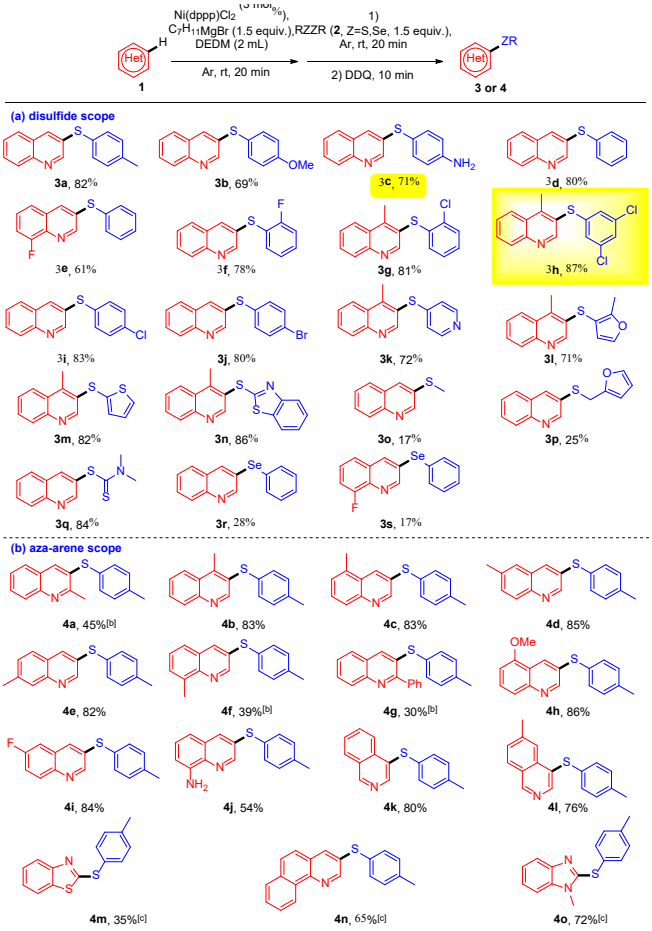
Entry	Deviation from standard condition	Yield (%)[b] of **3a**
1	none	87
2	$NiCl_2$ instead of Ni(dppp)Cl	74
3	$NiBr_2$ instead of Ni(dppp)Cl	52
4	NiF_2 instead of Ni(dppp)Cl	17
5	Ni(acac)2 instead of Ni(dppp)Cl	62
6	Ni(OAc)2 instead of Ni(dppp)Cl	60
7	Ni(OTf)2 instead of Ni(dppp)Cl	82
8	without $Ni(dppp)Cl_2$	0
9	**G1** instead of **G4**	0
10	**G2** instead of **G4**	79
11	**G3** instead of **G4**	85
12	**G5** instead of **G4**	13
13	**G6** instead of **G4**	5
14	**G7** instead of **G4**	82
15	**G8** instead of **G4**	0
16	**G9** instead of **G4**	3
17	**G10** instead of **G4**	0
18	**G11** instead of **G4**	0
19	**G12** instead of **G4**	78
20	without **G4**	0



[a] Reaction conditions: **1a** (0.4 mmol), Nickel catalyst (0.012 mmol, 3.0 mol%), Grignard reagent (0.6 mmol, 1.5 equiv.), and dimethyldiglycol (DEDM) (2.0 mL) at room temperature for 20 minutes, then before the addition of DDQ (0.4 mmol, 1.0 equiv.), **2a** (0.6 mmol, 1.5 equiv.) was added and stirred for 20 minutes, Ar atmosphere. [b] Yield of **3a** was determined by GC analysis using n-dodecane as an internal standard.

to an 87% yield of the desired product 3a (entry 1), while other Ni salts had worse catalytic effect (entries 2-7). In addition, when no Ni catalyst was used, the target product 3a could not be generated (entry 8). Besides, a series of Grignard reagents G1-G12 were investigated with Ni(dppp)Cl2 selected as the catalyst. When methylmagnesium bromide G1 was used, 3a could not be detected (entry 9), while ethylmagnesium bromide G2 led to a 79% yield of 3a (entry 10), indicating that the existence of Grignard reagents' β-H is essential. To verify this hypothesis, G3, G7 and G8 were compared under the same reaction condition. As expected, G3 led to a higher yield than G7 (entries 11, 14), and G8 failed to achieve the functionalization of quinoline (entry 15). In addition, the secondary and tertiary alkyl Grignard reagents G5 and G6 were also examined, and the yield of 3a significantly declined with the increase of steric effect of alkyl group (entries 12, 13). Besides, unsaturated Grignard reagents with vinyl, ethynyl or phenyl led to a poor yield of 3a or even failed to functionalize quinoline 1a (entries 16-18). Alkylmagnesium chlorine G12 also promoted the reaction, albeit less efficiently (entry 19). When no Grignard reagent was added, the thioetherification process could not happen (entry 20).

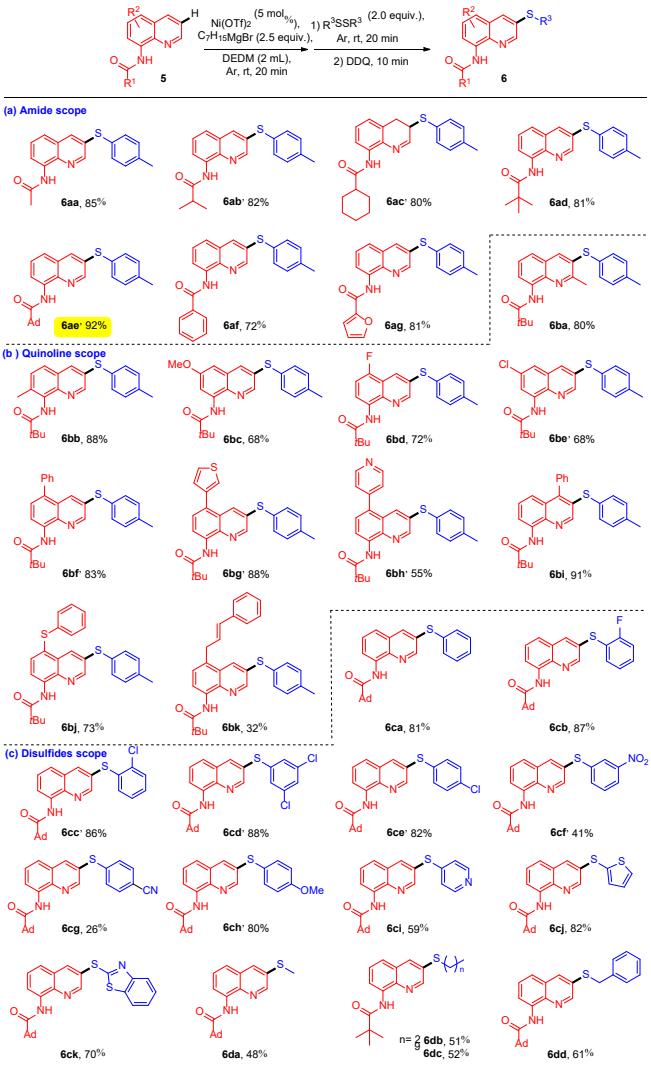
Scheme 2. Scope for the C-H thioetherification of aza-arenes with disulfides.[a]



[a] Reaction conditions: **1** (0.4 mmol), Ni(dppp)Cl_2 (0.012 mmol, 3.0 mol%), **G4** (0.6 mmol, 1.5 equiv.), and DEDM (2.0 mL) at room temperature for 20 minutes, then before the addition of DDQ (0.4 mmol, 1.0 equiv.), **2** (0.6 mmol, 1.5 equiv.) was added and stirred for 20 minutes, Ar atmosphere. Isolated yields. [b] Ni(OTf)$_2$ (0.02 mmol, 5.0 mol%), stirring at 60 °C for 1 h before adding disulfide instead. [c] Ni(OTf)$_2$ (0.02 mmol, 5.0 mol%), stirring for 6 hours at room temperature before adding disulfides instead.

With the acquired optimized reaction conditions, the scope of disulfides was first examined. As shown in Scheme 2, diphenyl disulfides performed well in good to excellent yields (**3a-3j**), the product yields varied slightly according to electronic properties of substituents attached to the phenyl ring of diaryl disulfides. Besides, the diphenyl disulfides with chlorine group at the *o*-, *m*-, or *p*-position led to similar yields of C3-H thioetherification products (**3g-3i**), which were all more than 80% even in the presence of the Grignard reagent. Notably, heteroaryl disulfides containing nitrogen, oxygen or sulfur atom were also effective coupling partners with reasonable yields (**3k-3n**). Fortunately, this approach could also be applied to alkyl disulfides and compared to **2o** and **2p**, disulfides with the sulfur atom connected to unsaturated carbon atom performed better (**3q**). Despite the low yields, when disulfides were displaced by diselenides, selenoetherification could also be achieved (**3r**, **3s**).

Scheme 3. Scope for the C-H thioetherification of 8-amidoquinolines with disulfides.[a]



[a] Reaction conditions: **5** (0.4 mmol), Ni(OTf)$_2$ (0.02 mmol, 5.0 mol%), **G4** (1.0 mmol, 2.5 equiv.), and dimethyldiglycol (DEDM) (2.0 mL) at room temperature for 20 minutes, then before the addition of DDQ (0.4 mmol, 1.0 equiv.), disulfide (0.8 mmol, 2.0 equiv.) was added and stirred for 20 minutes. Ar atmosphere. Isolated yields.

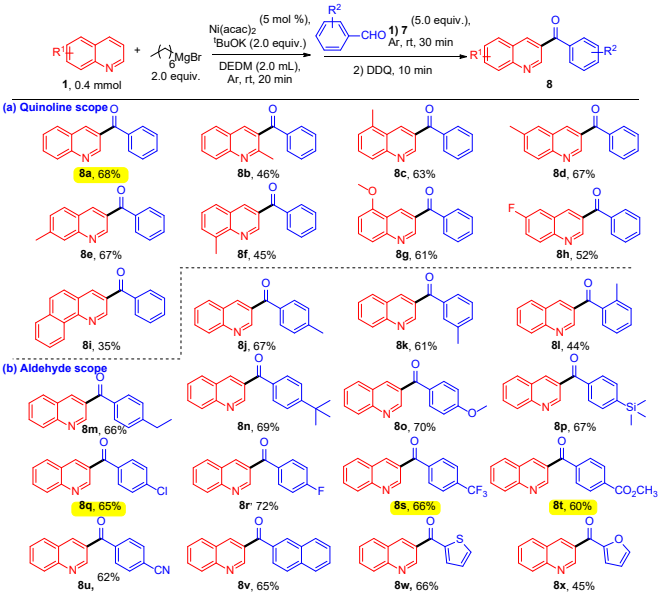
Then, the scope of heteroarenes was investigated with *p*-tolyldisulfide as the coupling partner (Scheme 2b). Quinolines with methyl at the C4-C7 position were all well tolerated (**4b-4e**), while when C2-H or C8-H was substituted, the yields decreased significantly (**4a**, **4f**, **4g**), probably due to steric effects which respectively hindered the electrophilic attack of disulfides and the coordination of nickel catalyst with the nitrogen atom. Quinolines carrying a methoxyl or fluorine group both demonstrated ideal reaction efficiency (**4h**, **4i**). The amino group with active hydrogen atoms was also compatible with the reaction (**4j**). Significantly, cross-coupling reactions between *p*-tolyldisulfide and other benzofused heteroarenes, including isoquinoline, 7,8-benzoquinoline, benzimidazole and benzothiazole also proceeded in a regioselective way (**4k-4o**).

Taking into consideration that the 8-aminoquinoline scaffold exists extensively in pharmacologically active molecules[14] and the modest reaction effect of 8-aminoquinoline with disulfides, the amino group was protected by forming amido

bond and then the substrate scope of C-H thioetherification was further investigated after optimizing the reaction conditions (Scheme S2). As we can see in Scheme 3a, various amide groups (**6aa-6ag**) were all tolerated, and good to excellent yields (72-93%) were achieved. The protocol tolerated multiple functional groups such as methyl (**6aa-6bk**), methoxyl (**6bc**, **6ch**), halides (**6bd**, **6be**, **6cb-6ce**), nitryl (**6cf**) and cyano (**6cg**) no matter whether they were connected to the quinoline ring or the phenyl ring of disulfides (Scheme 3b). Notably, chlorine group could also be retained with the existence of the Grignard reagent (**6be**, **6cc-6ce**). Besides, aryl (**6bf-6bi**) and thio group (**6bj**) on the quinoline ring were well tolerated, while allyl (**6bk**) led to an unsatisfactory yield (32%). In addition, heteroaryl disulfides (**6ci-6ck**) were also examined with the yields up to 82%. To our delight, alkyl disulfides (**6da-6dd**) could also act as the coupling partners with moderate yields of corresponding products (Scheme 3c).

2.2. Selective C3-H Acylation of Quinolines with Aryl Aldehydes. After examining the reactivity of disulfides, we further investigated the electrophilic aldehyde to verify our hypothesis that quinolines can be functionalized with different electrophiles (Scheme 4). With optimized reaction conditions in hand (Scheme S3), the scope of quinolines was examined first (Scheme 4a). The acylation reaction of quinolines with benzaldehyde proceeded smoothly to yield **8a** (71%). When methyl was attached to different position of quinoline (**8b-8f**), C2- or C8-methyl substituted quinoline clearly led to poorer yields probably because the steric effect hindered the coordination of nickel catalyst with quinolines. The methoxy group led to a 9% higher yield than the fluorine group (**8g**, **8h**). Despite the non-ideal yield, the C3-H acylation of 7,8-benzoquinoline could also be realized (**8i**). As for the aldehyde scope (Scheme 4b), various electron-donating groups (**8j-8o**) (methyl, ethyl, tertiary butyl, methoxy) and electron-withdrawing groups (**8q-8u**) (fluorine, chlorine, trifluoromethyl, ester and cyano group) were examined and the corresponding acylation products were formed in moderate to good yields. It is worth noting that trimethylsilyl unit which could be further transformed to other functional groups was also tolerated (**8p**). Other aromatic aldehyde with naphthyl, thienyl or furyl ring could also undergo the cross-coupling reaction in moderate yields (**8v-8x**).

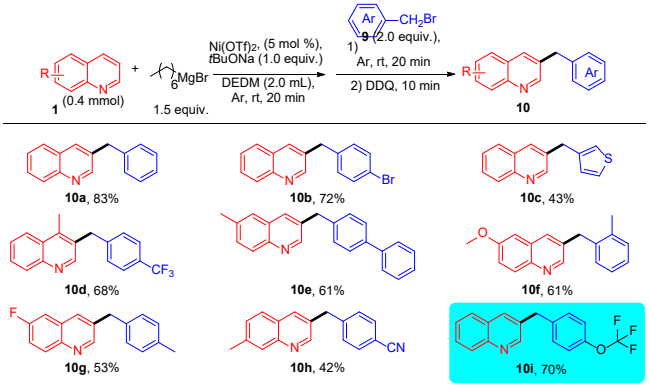
Schem 4. Scope for the C3-H acylation of quinolines with aryl aldehydes.[a]



[a] Reaction conditions: **1** (0.4 mmol), $Ni(acac)_2$ (0.02 mmol, 5.0 mol%), **G4** (0.8 mmol, 2.0 equiv.), *t*BuOK (0.8 mmol, 2.0 equiv.) and dimethyldiglycol (DEDM) (2.0 mL) at room temperature for 20 minutes, then before the addition of DDQ (0.4 mmol, 1.0 equiv.),**7** (2.0 mmol, 5.0 equiv.) was added and stirred for 30 minutes, Ar atmosphere. Isolated yields.

2.3. Selective C3-H Benzylation of Quinolines with Benzyl Bromides.

Scheme 5. Scope for the C3-H benzylation of quinolines with benzyl bromides.[a]



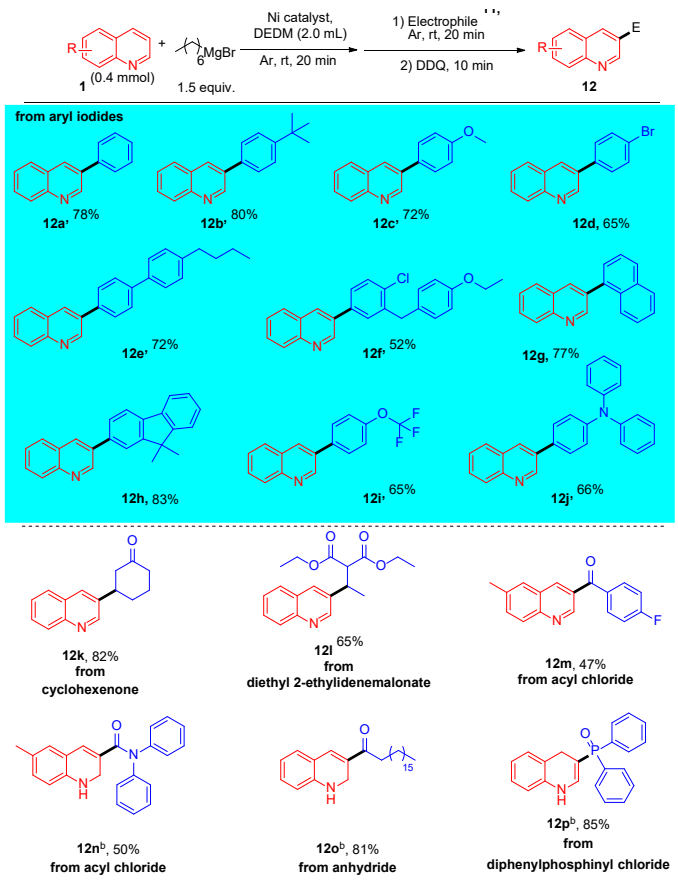
[a] Reaction conditions: **1** (0.4 mmol), $Ni(OTf)_2$ (0.02 mmol, 5.0 mol%), **G4** (0.6 mmol, 1.5 equiv.), *t*BuONa (0.4 mmol, 1.0 equiv.) and DEDM (2.0 mL) at room temperature for 20 minutes. then before the addition of DDQ (0.4 mmol, 1.0 equiv.), **9** (0.8 mmol, 2.0 equiv.) was added and stirred for 20 minutes, Ar atmosphere. Isolated yields.

After making a few adjustments to the reaction conditions, this catalytic method could also be well applied to the cross-coupling of quinolines with benzyl bromides (Scheme 5). When non-substituted quinoline and benzyl bromide were selected as the starting materials, the target product (**10a**) was obtained in an 83% yield. The benzylation product (**10b**) was selectively formed in a good yield with 4-bromobenzyl bromide as the substrate. 3-Bromomethylthiophene was also compatible with

the methylenation process (**10c**). Besides, the cross-coupling reaction proceeded smoothly between quinoline with methyl, methoxyl or fluorine and benzyl bromide with methyl, phenyl, trifluoromethyl or cyano group, the corresponding products (**10d-10h**) were formed in moderate to good yields.

2.4. Selective C-H Functionalization of Quinolines with Other Electrophiles.

Scheme 6. Scope for the C3-H functionalization of quinolines with aryl iodides and other electrophiles.[a]

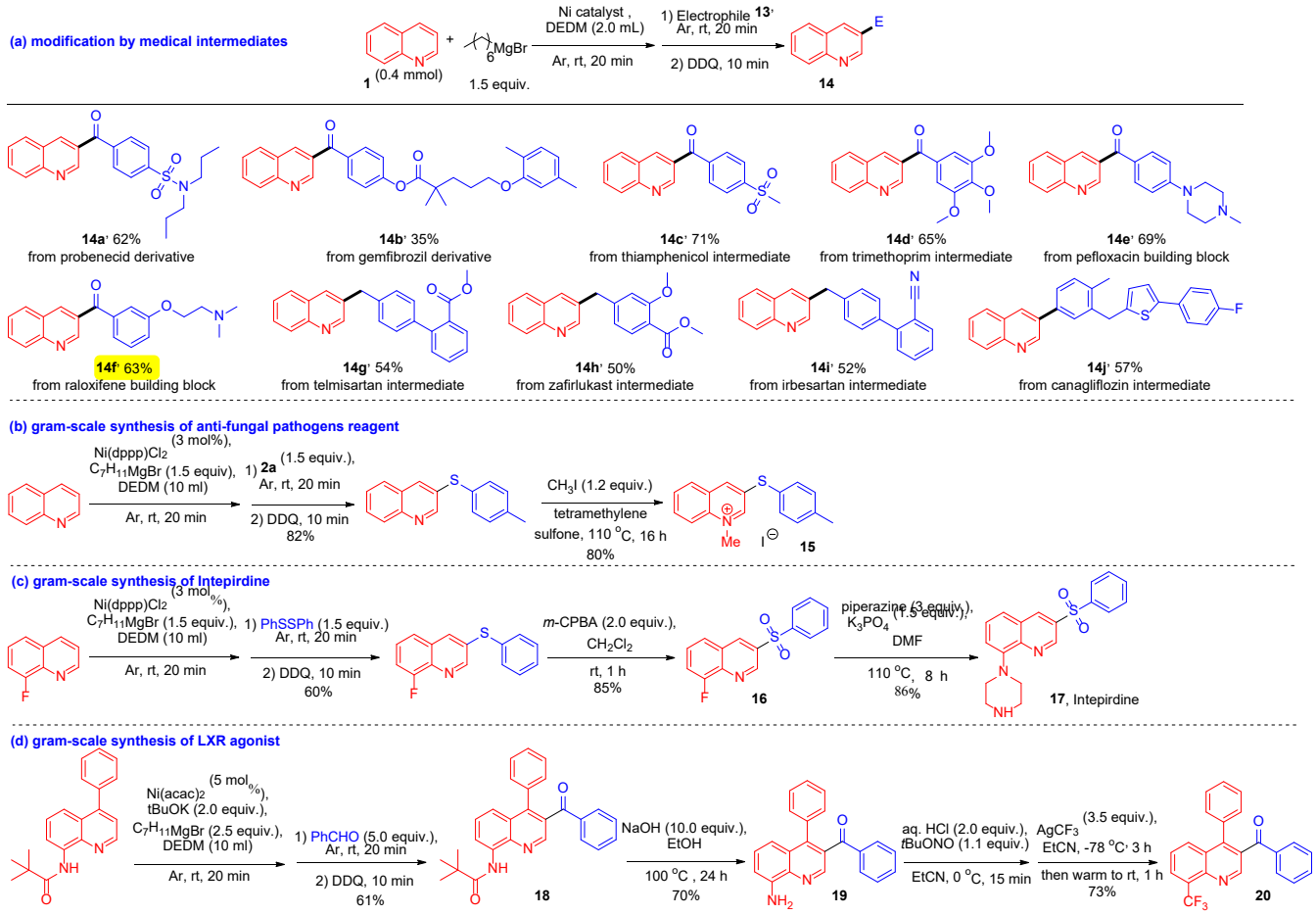


[a] Reaction conditions: **1** (0.4 mmol), Nickel catalyst (0.02 mmol, 5.0 mol%), **G4** (0.6 mmol, 1.5 equiv.), and dimethyldiglycol (DEDM) (2.0 mL) at room temperature for 20 minutes, then before the addition of DDQ (0.4 mmol, 1.0 equiv.), **11** was added and stirred for 20 minutes, Ar atmosphere. Isolated yields. [b] Without the addition of DDQ instead.

Then we tried to utilize this method to synthesize C3-arylated quinolines with aryl iodides (Scheme 6). Firstly, we selected 1a and 11a as the coupling partners, we found that when the reaction time after the addition of aryl iodides was extended from 30 minutes to 2 hours, the yield increased obviously to 78%. With the optimized reaction conditions on hand, we continued to examine the substrate scope. When tert-butyl, methoxy, or phenyl was attached to the phenyl ring of iodobenzene, the yields slightly changed (**12a-12c**, **12e**). Besides, bromide and chloride can be remained (12d,12f). While trifluoromethoxy and diphenylamino groups led to drease of yields (**12i**, **12g**). Other aryl iodides including 2-iodo-9,9-dimethyl-9H-fluorene and 1-iodonaphthalene can also serve as the coupling reagents (**12g**, **12h**). The versatility of this method was further verified by the construction of C-C bonds with iodobenzene, cyclohexenone, diethyl 2-ethylidenemalonate, 4-fluorobenzoyl chloride, diphenylcarbamic chloride, and stearic anhydride as electrophiles. Besides, considering the wide applications of arylphosphorus compounds,[15] we also tried and realized the construction of C-P bond by the cross-coupling reaction between quinoline and diphenylphosphinyl chloride. The above cross-coupling reactions proceeded smoothly to produce **12k-12n** in 47% to 85% isolated yields (Scheme 6). It is worth noting that dihydroquinoline compounds **12o-12p** were obtained without exposure to the oxidizing agent DDQ. However, we have not found efficient methods to further aromatize them in acceptable yields.

2.5. Synthetic Application. To prove the practicability of the above reaction system, a series of drug intermediates and derivatives[16] **13a-13j** were selected as coupling reagents, and three biologically active molecules were synthesized in gram scale (Scheme 7). At first, anti-gout drug probenecid and anti-hyperlipidaemia drug gemfibrozil were transformed to aldehydes, through reduction and esterification with 4-hydroxybenzaldehyde, which then coupled with quinoline to generate the corresponding acylation products **14a** and **14b**. Besides, four other aldehyde compounds serving as intermediates or building blocks of pharmaceutical molecules reacted smoothly with quinoline to generate the corresponding target products **14c-14f** in 65%-71% yields. In addition, quinoline was further modified by drug intermediates containing the moiety of benzyl bromide or iodobenzene and the functionalized products **14g-14j** were formed in moderate yields. Then, the method was applied to gram-scale synthesis of anti-fungal pathogens reagent **15**,[17] the potential Alzheimer's disease drug Intepirdine **17**[18] and the LXR (Liver X Receptor) agonist **20**[19]. It is worth noting that compared to the reported examples of synthesizing intepirdine[20] which used much more expensive starting materials 8-fluoro-3-iodoquinoline or 8-chloro-3-iodoquinoline, cheap 8-fluoroquinoline was selected in our synthetic route.

Scheme 7. Modification and synthetic application.



2.6. Mechanistic Study on the C3-H Functionalization of Quinolines. We first performed the reactions with quinoline **1a** and bis(4-tolyl)disulfide **2a** as the coupling partners, the process was monitored with the results plotted in Figure 1. The yield of **3a** reached 60% in only one minute, which rose smoothly to 88% in 20 minutes. To further gain an insight into the reaction mechanism, a series of control experiments were further conducted (Scheme 8). Firstly, kinetic isotope effect (KIE) experiments were performed (Scheme 8a). The reactions with quinoline or deuterated quinoline as substrates were stirred for 5 – 25 minutes at 0 ℃ after the addition of the disulfides, then DDQ was added and the yields of target products were determined by crude ^{1}H NMR using mesitylene as the internal standard. The obtained average yields for two trials were plotted and the KIE value was calculated to be 2.86, indicating that the C-H bond cleavage of quinoline is the rate-determining step. Then, the replacement of disulfide with benzenethiol failed to give **3a** (Scheme 8b). In addition, when *n*-propylmagnesium bromide **G3** was replaced by **G8** without *β*-H, the yield of target product dropped to 0% from 78%, which indicated the essentiality of *β*-H of Grignard reagents (Scheme 8c).

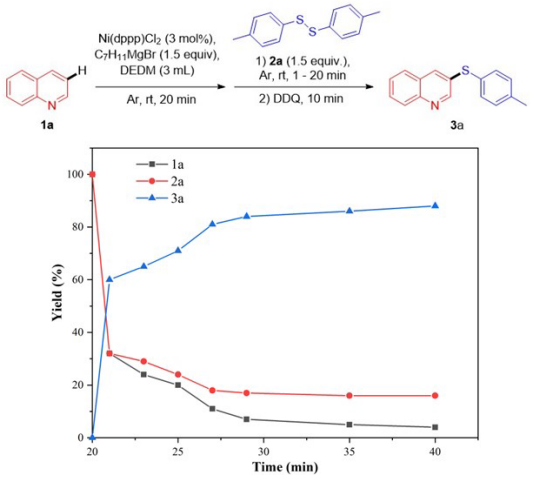
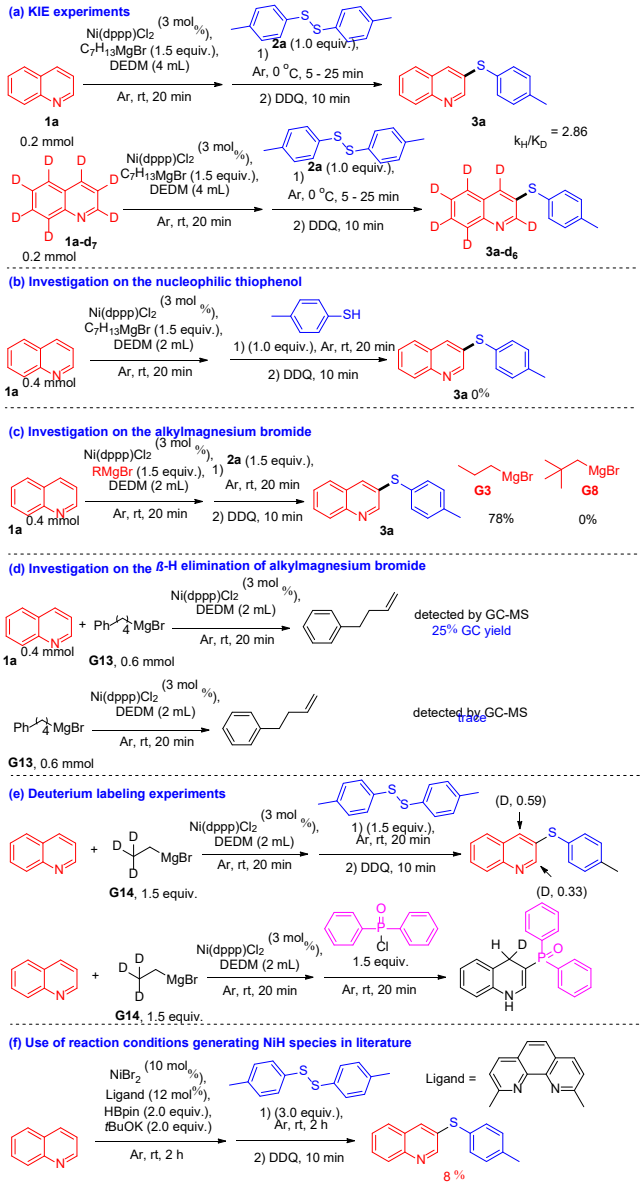


Figure 1. Time course plots of the reaction of quinoline **1a** with bis(4-tolyl)disulfide **2a**. Reaction conditions: **1a** (0.4 mmol), Nickel catalyst (0.012 mmol, 3.0 mol%), *n*-heptylmagnesium bromide (0.6 mmol, 1.5 equiv.), and dimethyldiglycol (DEDM) (2.0 mL) at room temperature for 20 minutes, then before the addition of DDQ (0.4 mmol, 1.0 equiv.), **2a** (0.6 mmol, 1.5 equiv.) was added and stirred for 1-20 minutes, Ar atmosphere., and GC yields using dodecane as an internal standard.

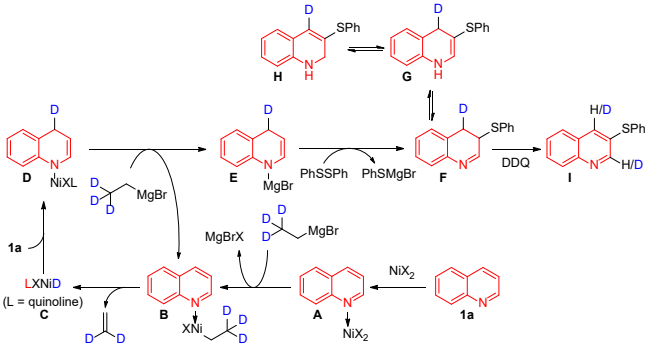
Scheme 8. Investigation of reaction mechanism.



Besides, when freshly made Grignard reagent **G13** was used, 4-phenyl-1-butene was detected with the GC yield of 25%, which further confirmed the process of *β*-H elimination (Scheme 8d). However, almost no alkene was detected in the absence of quinoline, indicating the coordination of quinoline was involved in the process of *β*-H elimination. Then fully *β*-H deuterated ethylmagnesium bromide was subjected to the standard reaction conditions to trace *β*-H, C2-H and C4-H of the target product were both deuterated (Scheme 8e). When diphenylphosphinyl chloride was used as the electrophile, the phosphated product without oxidative aromatization was isolated successfully and deuterium was found only at C4 position, suggesting that a proton transfer process was involved in the step of oxidative aromatization. Based on the above findings and literature, we speculated that the nickel hydride species were generated from *β*-H elimination of alkyl nickel intermediates[21] and then quinolines underwent 1,4-addition with nickel hydride species to produce 1,4-DHQs. To confirm whether the process was promoted by NiH species, we followed the procedure of a reported work[22] in which NiH species was generated in situ and then added the disulfide **2a** into the reaction mixture. Consequently, the C3-H functionalized product was obtained as expected (Scheme 8f).

Therefore, according to the above findings and relevant literature,[11d, 12b, 21-23] a NiH-catalyzed mechanism was proposed as follows (Scheme 9): Initially, coordination of quinoline **1a** with the Ni(II) catalyst gave the complex **A**, followed by the transmetallization with the Grignard reagent to generate alkyl nickel species **B**. Then the intermediate **B** underwent *β*-H elimination to give **C**, whose deuterium atom further transferred to another molecule of quinoline **1a** through 1,4-addition to form **D**. The intermediate **D** further went through transmetallization with ethylmagnesium bromide to renew **B** and produce **E**, which underwent nucleophilic attack to disulfide to generate 3,4-dihydroquinoline species **F** and its tautomers (**G** and **H**). Finally, oxidative aromatization happened and the target product **I** was formed.

Scheme 9. Proposed mechanism



3. Conclusion

We developed a Ni-catalyzed method realizing exclusive C3-H functionalization of quinolines with multiple electrophiles including disulfide, aldehyde, benzyl bromide, aryl iodide, cyclohexenone, diethyl 2-ethylidenemalonate, acyl chloride, phosphinic chloride, and anhydride. The functionalization process could proceed without the assistance of directing groups at room temperature. Control experiments indicated that quinolines underwent 1,4-addition with nickel hydride species generated from *β*-H elimination of alkyl nickel intermediates to produce 1,4-DHQs, which further went through subsequent nucleophilic addition to external electrophiles and oxidative aromatization and generated C3-H functionalized products. The practicability of this method was proved by using a series of drug intermediates or derivatives as coupling reagents and synthesizing three biologically active molecules.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information (PDF) contains general information, synthetic procedures, optimization details, control experiments, X-ray crystallographic data, and NMR copies of all compounds.
This material is available free of charge via the Internet at http://pubs.acs.org.

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