Photocatalysis

Light-Promoted Nickel Catalysis: Etherification of Aryl Electrophiles with Alcohols Catalyzed by a Ni^II-Aryl Complex

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Abstract: *A highly effective C−O coupling reaction of (hetero)aryl electrophiles with primary and secondary alcohols is reported. Catalyzed by a Ni^II-aryl complex under long-wave UV (390–395 nm) irradiation in the presence of a soluble amine base without any additional photosensitizer, the reaction enables the etherification of aryl bromides and aryl chlorides as well as sulfonates with a wide range of primary and secondary aliphatic alcohols, affording synthetically important ethers. Intramolecular C−O coupling is also possible. The reaction appears to proceed via a Ni^I–Ni^III catalytic cycle.*

Alkyl aryl ethers are versatile structural components and are widely found in natural products, agrochemicals, and pharmaceuticals.[1] Effective approaches, such as the Williamson ether synthesis,[2] the Mitsunobu reaction,[3] and nucleophilic aromatic substitution,[4] have contributed to the easy synthesis of alkyl aryl ethers. However, owing to the abundance of various electrophiles and alcohols, it would be useful to be able to synthesize such ethers through metal-catalyzed cross-coupling of these two types of starting materials.[5–7] Pioneering work based on palladium,[6] copper,[7] and nickel[8] catalysis has been carried out, with the former two metals being most widely used for etherification at the present time. However, all of these C−O coupling reactions necessitate the use of strong inorganic bases or metal alkoxides, which brings solubility and compatibility issues and related operational challenges. In the closely related C−N coupling, these issues have already caught attention and have been elegantly addressed with amine bases recently by Buchwald and co-workers.[9] Likewise, using mild, soluble amines as bases for the coupling of alcohols with aryl electrophiles, especially inexpensive and abundant (hetero)aryl chlorides,[10] would provide a practical solution to the long-standing challenge in the synthesis of alkyl aryl ethers. An inexpensive metal catalyst could make the method more attractive.

Ni complexes are prone to undergoing oxidative addition with C_{sp^2}−Cl bonds,[11] which could make them able, economic catalysts for the C−O cross-coupling of (hetero)aryl chlorides with alcohols. Recently, two successful strategies for Ni catalyzed C−O couplings of aryl electrophiles with alcohols have in fact been developed.[8] By using a Ni^II complex bearing a bulky, electron-rich diphosphine ligand as precatalyst, aryl electrophiles were coupled with alcohols to afford aromatic ethers under thermal conditions (Scheme 1 A).[8a] However, highly basic metal alkoxides were required, which are moisture-sensitive and incompatible with base-sensitive functional groups.[8a] The merger of photoredox and nickel catalysis has provided another strategy, where the oxidation state of the nickel catalyst is modulated by the excited photosensitizer (Scheme 1 B).[8b] Although this dual-catalytic method affords an important alternative for the synthesis of alkyl aryl ethers, the scope is limited to the use of (hetero)aryl bromides, and expensive iridium photocatalysts and insoluble inorganic bases are needed.

Recently, we reported a hydroxylation reaction of aryl halides with water enabled by the merger of organophotoredox and nickel catalysis with mildly basic *N,N*-diisopropylethylamine as a base.[12] Our study showed that only organic amines can promote the reaction, with traditional strong bases such as NaO^tBu and inorganic bases being ineffective. In a continuation of our work, we report herein a highly effective C−O coupling reaction of aryl electrophiles with alcohols catalyzed by the dual action of a Ni^II-aryl complex

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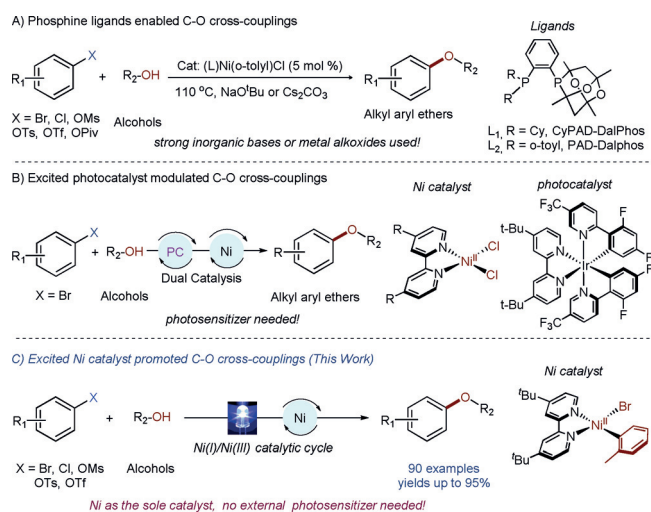
Scheme 1. Nickel-catalyzed C−O coupling of aryl electrophiles with alcohols.

and light, with an organic amine as a base and without the use of any external photosensitizers[13] (Scheme 1 C).

In our initial study, we discovered that the isolable, air-stable Ni[II]-aryl halide complexes **A–D**[14] could catalyze the cross-coupling reaction of *p*-acetylchloro benzene **1** with *n*-butanol **2** (Table 1, entries 1–4) under irradiation with long-wave UV light (390–395 nm, purple LEDs) in the absence of any external photosensitizers.[15] Notably, light was found to play a crucial role in the reaction; only long-wave UV light could afford high product yields. Whilst irradiation using other light also promoted the reaction, it was much less effective (Table 1, entries 5–8). Moreover, only a trace amount of product was obtained when the reaction was run at 120 °C in the absence of light (Table 1, entry 9), thus revealing the critical role of the long-wave UV light. The choice of base also significantly affects the success of the reaction, and to our delight, the cheap amine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) outperformed all other bases tested.[15] In addition, the presence of oxygen dramatically decreased the reaction efficiency (Table 1, entry 10). Further optimization demonstrated that a combination of complex **A** and DBU in toluene was the best with respect to reaction yield.[15] Under such conditions, the desired product **3** was obtained in 92% isolated yield following reaction at 80 °C for 12 h with irradiation with long-wave UV light under argon. Further control experiments revealed that the reaction did not proceed in the absence of nickel catalyst, light, or base (Table 1, entries 11–13).

To investigate the scope of this new method, a variety of aryl electrophiles and alcohols were tested. First, a wide range of aryl chlorides were explored. As summarized in Scheme 2,

Table 1: Reaction development and optimization.[a]
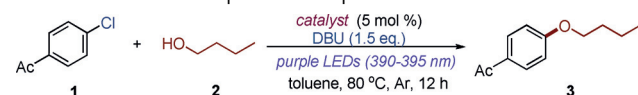
Entry	Deviation from the standard conditions	Yield [%][b]
1	catalyst **A**	97, 92[c]
2	catalyst **B**	94
3	catalyst **C**	91
4	catalyst **D**	95
5	catalyst **A**, blue LEDs (460–465 nm)	34
6	catalyst **A**, white LEDs	20
7	catalyst **A**, green LEDs (530–535 nm)	14
8	catalyst **A**, UV (365–370 nm)	52
9	catalyst **A**, no light, heating to 120 °C	trace
10	catalyst **A**, air instead of Ar	48
11	no nickel catalyst	0
12	catalyst **A**, no light	0
13	catalyst **A**, no base	0
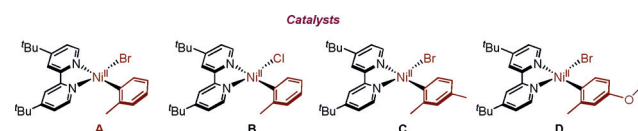
Catalysts

[a] **1** (0.5 mmol), **2** (2.0 mmol, 4.0 equiv), catalyst (5.0 mol%), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 0.75 mmol), toluene (1 mL). For details, see the Supporting Information. [b] Yields determined by ^{1}H NMR. [c] Yield of isolated product.
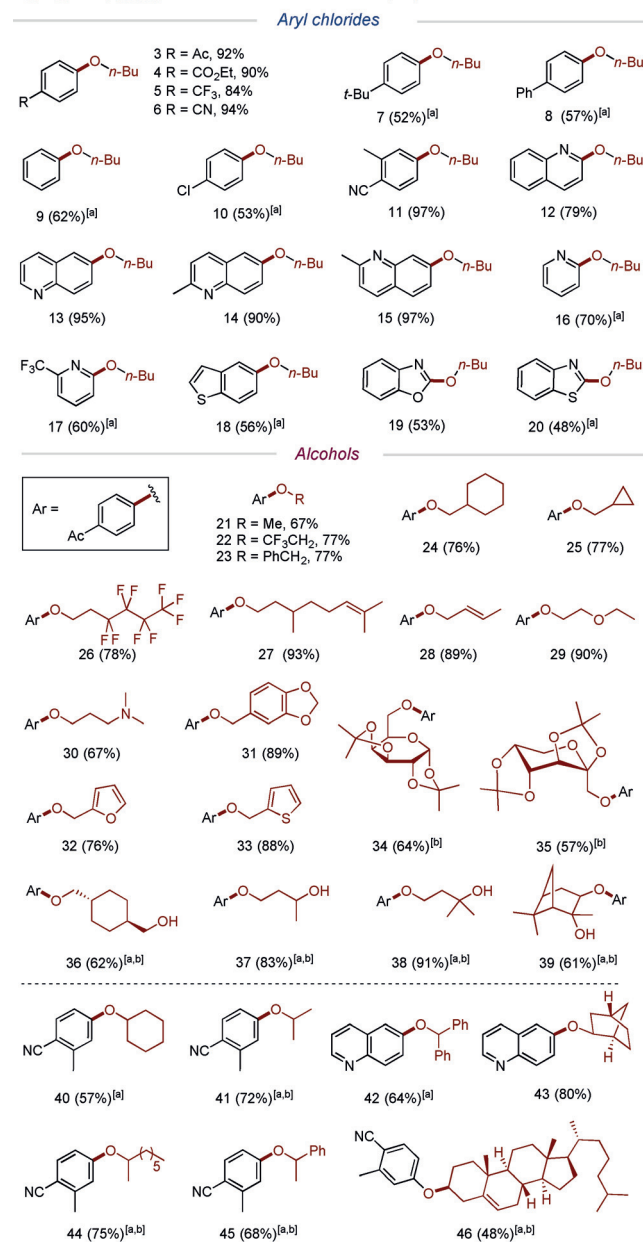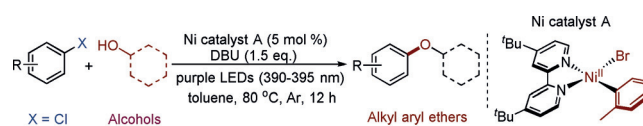
Scheme 2. Etherification of aryl chlorides. Yields of isolated product are given. For details, see the Supporting Information. [a] Ni catalyst **A** (15 mol%). [b] 24 h.

electron-deficient aryl chlorides containing ketone (**3**), ester (**4**), trifluoromethyl (**5**), and cyano (**6**) groups show higher efficiency in coupling with *n*-butanol. It is noted that functionalities such as ester and cyano groups may not be compatible with the conventional strongly-basic conditions. Indeed, owing to the use of strong bases, transesterification in copper catalysis[7f] and the formation of impurities in palladium catalysis due to the cyano group[16] have been reported. In contrast, all tested ester- and cyano-containing electro-

philes were suitable for this new method, thus demonstrating the advantage of using organic amines as base. More importantly, the challenging electron-neutral aryl chlorides also worked well, albeit at a higher catalytic loading (15 mol %; **7–9**). However, this was achieved at a lower reaction temperature compared to the thermal reaction catalyzed by copper[7f] and nickel[8a] systems. Unfortunately, electron-rich aryl chlorides such as 4-chloroanisole were found inactive under the current conditions. Notably, for aryl chloride bearing a chloro substituent, the mono-etherified product (**10**) was dominant, thus providing the possibility for subsequent transformation. Of further interest is that a range of (hetero)aryl chlorides were compatible, delivering the desired products containing quinolines (**12–15**), pyridine (**16**, **17**), benzothiophene (**18**), benzoxazole (**19**), and benzothiazole (**20**), which are important building blocks in drug molecules, with good to excellent yields.

As shown in Scheme 2, various alcohols can be used. The simple, abundant methanol afforded **21** in good yield, thereby opening a route to anisole derivatives.[6i] Primary aliphatic alcohols bearing benzylic and branched structures (**23–25**) as well as pendant trifluoroethanol (**22**), per-fluorobutylethanol (**26**), alkenyl (**27**, **28**), amino (**30**), furan-2-yl (**32**), and thiophen-2-yl (**33**) groups were also good coupling substrates. It is worth noting that the catalyst was not poisoned by the coordinative amino and thiophen moieties. To our delight, the carbohydrate alcohols derived from D-galactopyranose (**34**) and fructose (**35**) also worked well. Diols could also be employed (**36–39**). We note that the mono-substituted products were dominant, thus showing sterically less cumbersome alcohols to be more reactive (**37–39**). Although secondary alcohols were typically less reactive for the coupling with acetylchloro benzene **1**, a higher catalytic loading (15 mol %) and longer reaction time (24 h) afforded the etherified products in good yields (**40–46**).

Next, we explored the scope and limitations with respect to aryl bromides for this C−O coupling reaction. As shown in Scheme 3, aryl bromides with a variety of functional groups reacted efficiently with two equivalents of the alcohol, delivering the desired products with good to excellent yields (**47–57**). Notably, for aryl bromides bearing both a chloro and bromo substituent, the corresponding mono-substituted products were obtained with good yields (**49**, **50**). Disubstituted aryl bromides bearing either electron-donating or electron-withdrawing groups were all applicable, affording the desired products in high yields (**53–57**). A wide range of (hetero)aryl bromides were also compatible. Thus, etherified heteroarenes containing quinoline, carbazole, benzothiophene and indole were obtained with good to excellent yields (**58–60**, **13**, **18**). However, aryl bromides bearing methoxy, carboxylic acid, amide, or *ortho*-substituents gave poor yields or showed no activity under the standard conditions.[15]

Various types of alcohols were next explored. As in the case of aryl chlorides, the coupling reactions exhibited high efficiency and functional-group compatibility (**61–79**). To further demonstrate the application of this new etherification method, intramolecular C−O bond formation[8c,17] was studied (**80–90**). As shown in Scheme 3, a series of important five- and six-membered-ring products were obtained with high yields.
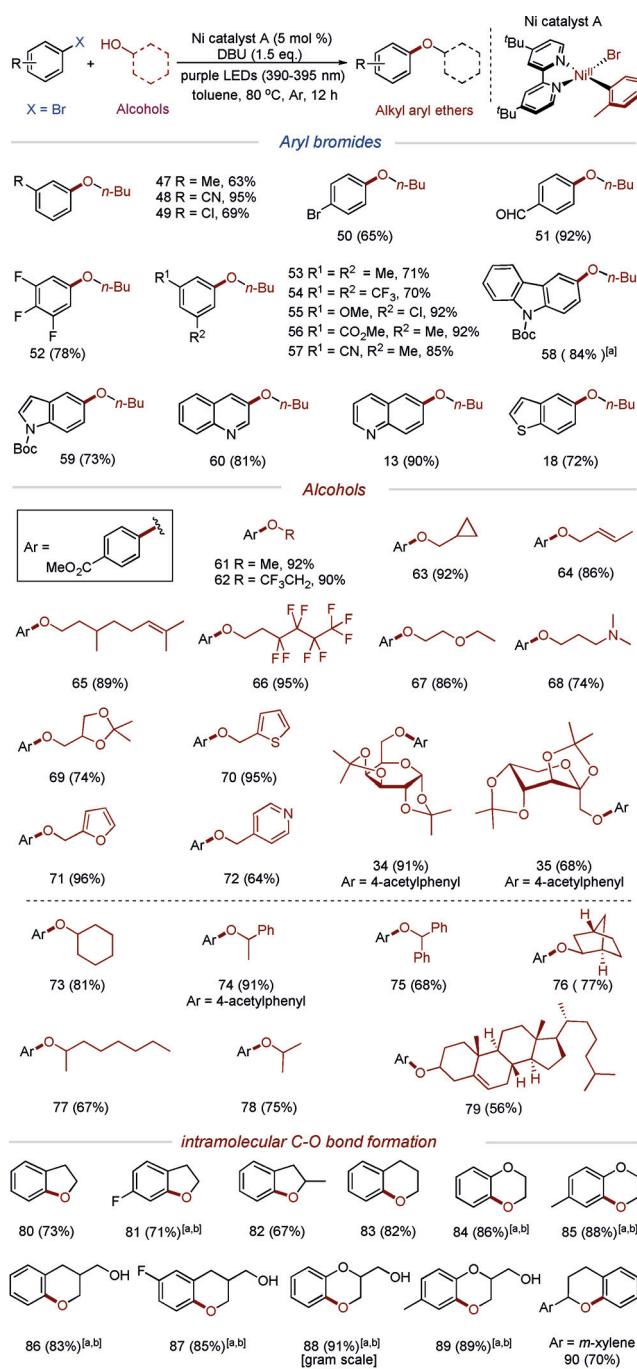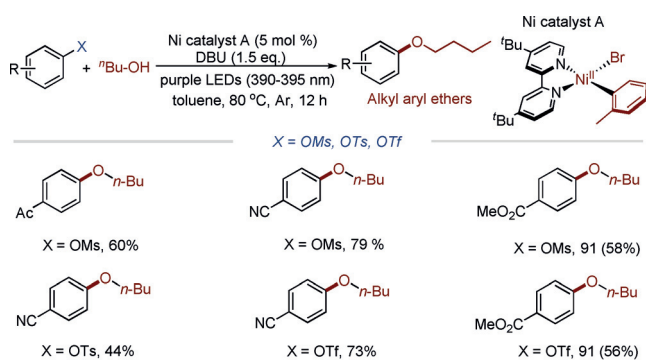

Scheme 3. Etherification of aryl bromides with 2 equivalents of alcohols. Yields of isolated product are given. For details, see the Supporting Information. [a] Ni catalyst **A** (10 mol %). [b] 24 h.

Furthermore, compound **88** could be prepared on a gram scale, which showcases the significant potential of this method for the practical synthesis of complex molecules.[18]

Finally, the scope with respect to electrophiles was expanded to sulfonates. As shown in Scheme 4, mesylates, tosylates, and triflates were all viable in the coupling with *n*-butanol, affording the ethers with good yields.

The detailed mechanism of the etherification remains to be delineated. Recent in-depth studies of the photophysics

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Scheme 4. Etherification of aryl sulfonates. Yields of isolated product are given. For details, see the Supporting Information.

and photochemistry of complex **B** by Doyle and co-workers[14a,d] indicated that complex **A** may itself act as a photocatalyst, promoting the reaction via a Ni[I]–Ni[III] cycle. The results from our preliminary experiments appear to be in line with this. As shown in Scheme 5, when complex **A** was irradiated at 390–395 nm for 1 h without substrates, significant amounts of arenes were observed, thus indicating concomitant formation of Ni[I] (Scheme 5A).[14d] When the in situ prepared Ni[0] complex Ni(dtbbpy)(cod)[19] was used as the catalyst under the standard conditions, the reaction proceeded with high yields; however, when the light was omitted, the desired product was not observed (Scheme 5B), thus highlighting that light is required to enable the C–O coupling, regardless of whether the pre-catalyst is Ni[II] or Ni[0].[15]

Next, the Ni[II] complex **A** was irradiated under long-wave UV light for 30 min in the absence of substrates and then the irradiation was stopped. Following introducing the substrates and carrying out the reaction in the dark for 12 h, the corresponding product was obtained with a low yield of 35%.
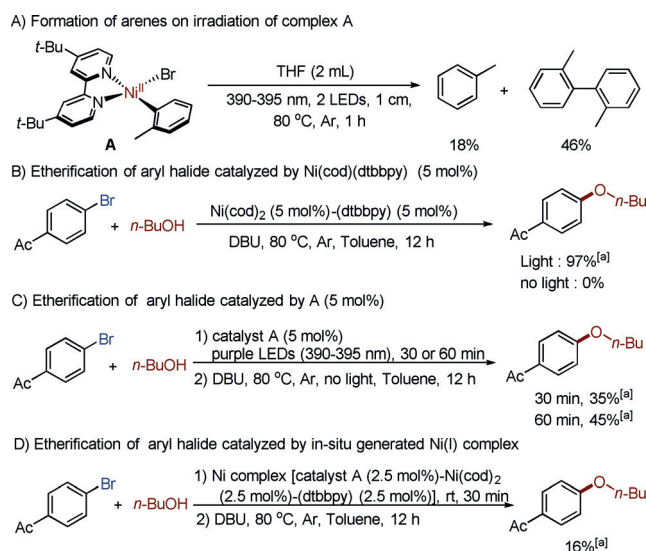
Scheme 5. Reactions aimed to probe the reaction mechanism.
[a] Yields determined by ^{1}H NMR. For details, see the Supporting Information. THF = tetrahydrofuran.

A somewhat higher yield was seen when the initial irradiation was extended to 60 min (Scheme 5C). Electron paramagnetic resonance (EPR) analysis of the irradiated **A** (in the absence of substrates) revealed a signal with $g_{\parallel} = 2.25$ and $g_{\perp} = 2.07$ (SI, Figure 8),[15] which indicates the formation of a d^9 Ni[I] species.[19,20] Moreover, when the Ni[I] complex, prepared in situ through the comproportionation of catalyst **A** and Ni(dtbbpy)(cod) by following the procedure of Nocera and co-workers,[19] was used as catalyst, the desired product was obtained only in 16% yield under thermal conditions (Scheme 5D). The EPR signal of the resulting Ni species is similar to that of the irradiated Ni[II] catalyst **A** (Figure S9 in the Supporting Information).[15]

The observations above suggest that the etherification in question involves Ni[I] species and light is required throughout to achieve high product yields. On the basis of these results and the studies of Doyle, Scholes, and Nocera et al,[14,19] a simplified mechanistic pathway is tentatively suggested for the etherification under question (Scheme 6). Irradiation of **A** at 390–395 nm would excite the Ni[II] complex to a ^{3}MLCT state[21] that probably decays to a long-lived ^{3}d-d state, which could then undergo homolysis of the nickel−carbon bond to generate Ni[I] and aryl radicals.[14d] The former could then react with the aryl halide to generate a Ni[III]-Ar intermediate, which would undergo facile reductive elimination upon ligand exchange with the alcohol (presumably facilitated by DBU),[22] affording the coupled ether product while regenerating the Ni[I]. Continuous irradiation is necessary. This is probably due to the formation of off-cycle catalytically inactive Ni[II] from the comproportionation of Ni[III] and Ni[I],[19a] which requires irradiation to convert back to the active Ni[I].[23,24]
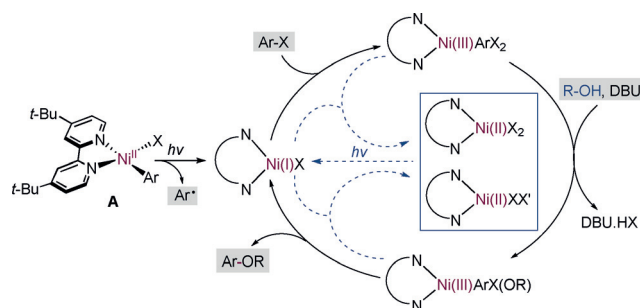
Scheme 6. A tentative mechanism for the etherification under light-promoted nickel catalysis (X = halide, X′ = Ar or OR; see Ref. [24]).

In summary, we have developed a highly effective light-promoted C–O coupling reaction, which uses an air-stable Ni[II]-aryl halide complex as a catalyst and DBU as a base, with no need for any other photosensitizer. The method features a very wide substrate scope, allowing primary and secondary aliphatic alcohols to couple with a wide range of (hetero)aryl electrophiles with diverse functional groups, including the more readily available but more challenging (hetero)aryl chlorides. Our preliminary study appears to suggest that the catalysis proceeds via a Ni[I]–Ni[III] cycle; however, there are still questions that remain to be answered.[24]

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