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# Ni-Catalyzed C($sp^2$)–H alkylation of *N*-quinolylbenzamides using alkylsilyl peroxides as structurally diverse alkyl sources†

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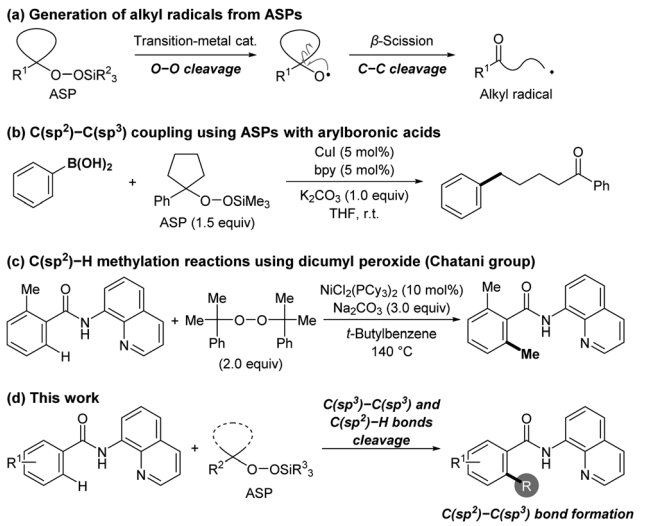
**A Ni-catalyzed direct C–H alkylation of *N*-quinolylbenzamides using alkylsilyl peroxides as alkyl-radical precursors is described. The reaction forms a new C($sp^3$)–C($sp^2$) bond *via* the selective cleavage of both C($sp^3$)–C($sp^3$) and C($sp^2$)–H bonds. This transformation shows a high functional-group tolerance and, due to the structural diversity of alkylsilyl peroxides, a wide range of alkyl chains including functional groups and complex structures can be introduced at the *ortho*-position of readily available *N*-quinolylbenzamide derivatives. Mechanistic studies suggest that the reaction involves a radical mechanism.**

The cleavage of the most abundant chemical bonds in a molecule represents one of the most attractive yet challenging transformations in modern organic chemistry. As the majority of most organic molecules consist of carbon–carbon (C–C) and carbon–hydrogen (C–H) bonds, synthetic methodologies involving the selective cleavage of these bonds allow greatly simplified synthetic routes to access complex molecules.[1] Accordingly, tremendous effort has been devoted to the development of efficient methods for the cleavage of C–C and C–H bonds.[2,3] Among these methods, chemical reactions that involve radical species enable diverse functionalization of organic molecules *via* homolytic bond cleavage.[2d,3e] Indeed, we have reported a series of efficient methods for the generation and subsequent functionalization of alkyl radicals *via* the cleavage of C($sp^3$)–C($sp^3$) bonds in alkylsilyl peroxides (ASPs) (Scheme 1a).[4,5] ASPs are bench-stable organic peroxide derivatives that can be readily prepared from various tertiary alcohols or alkenes.[6] Thus, they can be considered structurally diverse precursors for alkyl radicals.[7] Using this method, we have recently developed a Cu-catalyzed cross-coupling reaction between the alkyl radical generated *in situ* from an ASP and an arylboronic acid, which afforded a variety of alkylarenes (Scheme 1b).[5f] While this process allows using arylboronic acids that can bear various functional groups, the preparation of these boronic acids, some of which are relatively unstable, is limited to some extent.[8] To expand the synthetic utility of our chemistry, the development of a novel coupling strategy using more readily available arenes and ASPs is required.

Transition-metal catalysis assisted by directing groups is a powerful strategy for the regioselective cleavage of strong C–H bonds.[9] While these transformations have been achieved using several transition-metal catalysts, particular interest has been focused on nickel-based catalysts, given their low cost and high abundance. These reactions have been intensively researched




Scheme 1 Various reactions using organic peroxides as the alkyl-radical precursor.

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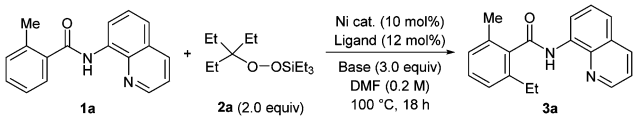
as has the discovery of various alkyl sources.[10] In 2008, the Li group reported dicumyl peroxide as a methyl source for the Pd-catalyzed aryl C($sp^2$)–H methylation.[11] Later, the Chatani group achieved the Ni-catalyzed *ortho*-C–H methylation of *N*-quinolylbenzamide using the same methyl source (Scheme 1c).[10h] This report is the first example of the use of an organic peroxide as an alkyl radical precursor in a Ni-catalyzed C($sp^2$)–H alkylation. However, the lack of structural diversity in the organic peroxides has hampered their wider use as alkyl sources beyond being methylating agents in C($sp^2$)–H alkylation reactions. Therefore, we were interested in the possibility of designing Ni-catalyzed C($sp^2$)–H alkylation reactions where ASPs are used as versatile alkyl radical precursors (Scheme 1d). This transformation can be expected to proceed *via* the selective cleavage of C($sp^3$)–C($sp^3$) and C($sp^2$)–H bonds to form a new C($sp^3$)–C($sp^2$) bond. Thus, we envisaged that a range of functionalized alkyl groups could be introduced at the *ortho*-position of the benzamide derivatives.

Initially, we optimized the reaction conditions of the Ni-catalyzed C($sp^2$)–H ethylation starting from benzamide **1a** and ASP **2a** (Table 1). When the reaction was performed in DMF at 100 °C for 18 h using 1.0 equiv. of **1a** and 2.0 equiv. of **2a** with $NiCl_2(PCy_3)_2$ as the catalyst and $Na_2CO_3$ as the base, the desired *ortho*-ethylated product (**3a**) was obtained in 20% NMR yield (entry 1). An investigation of different Ni catalysts revealed that the use of $Ni(OAc)_2{\cdot}4H_2O$ slightly improved the product yield (entries 2 and 3). We then examined a variety of bases and ligands to further improve the yield of **3a** (entries 4–8). The use of $Et_3N$ as the base and 2-pyridone as the ligand was found to be optimal, affording **3a** in 80% isolated yield.[12] Finally, when the reaction was conducted at lower temperature (80 °C), the yield of **3a** decreased (entry 9).

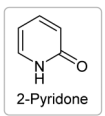
With the optimized reaction conditions in hand, we subsequently examined the substrate scope with respect to the amide **1** using ASP **2a** as the ethylating agent (Table 2). The reactions of *meta*-methyl-, methoxy-, and trifluoromethyl-substituted benzamides proceeded at the less hindered of the *ortho*-C–H bonds, and **3b–3d** were obtained in good yield (72–73%). *ortho*-Alkynyl-substituted benzamide and 2-naphthalenecarboxamide were also well tolerated under these reaction conditions to furnish the corresponding products **3e** and **3f** in 79% and 71% yield, respectively. Although the reaction could be applied to α,β-unsaturated amides, the yield of the final product **3g** was merely moderate (52%). Fortunately, we found that the addition of 1.0 equiv. of LiBr improved the yield of **3g** to 75%.[13] We then examined substrates which have two equivalent *ortho*-C–H bonds as potential reaction sites. While the reactions of *para*-substituted benzamides resulted in mixtures of mono- and di-ethylated products, the use of an excess of **2a** (4.0 equiv.) and 1.0 equiv. of LiBr predominantly afforded the di-ethylated products **3h** and **3i** in 71% and 73% yield, respectively. However, the reaction of a *meta*-fluoro-substituted benzamide under these adapted conditions gave both a small amount of the mono-ethylated product **3j′** (at the 6-position, 8%) and the di-ethylated product **3j** (44%).

To synthesize benzamides with a variety of functionalized alkyl moieties, ASPs with different structures were used in the C($sp^2$)–H alkylation of benzamide **1a** (Table 3). When cyclic ASPs were used, LiBr significantly affected the yield. In the absence of LiBr only a trace amount of the alkylated product **3k** was obtained from the reaction of benzamide **1a** with the six-membered cyclic ASP **2b**, while the addition of LiBr significantly

Table 1 Optimization of the reaction conditions[a]

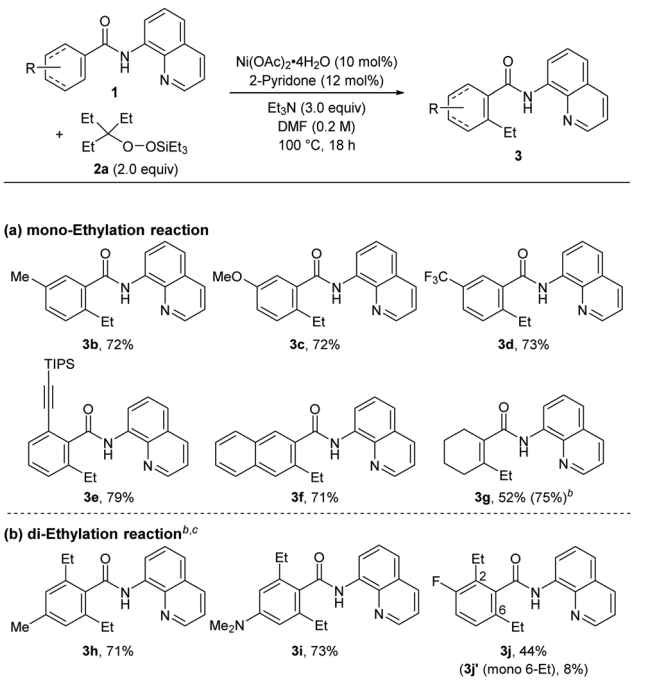



| Entry | Ni catalyst | Ligand | Base | **1a**[b] (%) | **3a**[b] (%) |
|---|---|---|---|---|---|
| 1 | $NiCl_2(PCy_3)_2$ | — | $Na_2CO_3$ | 66 | 20 |
| 2 | $NiBr_2$ | — | $Na_2CO_3$ | 86 | 11 |
| 3 | $Ni(OAc)_2{\cdot}4H_2O$ | — | $Na_2CO_3$ | 40 | 30 |
| 4 | $Ni(OAc)_2{\cdot}4H_2O$ | — | NaOAc | 61 | 10 |
| 5 | $Ni(OAc)_2{\cdot}4H_2O$ | — | $Li_2CO_3$ | 26 | 64 |
| 6 | $Ni(OAc)_2{\cdot}4H_2O$ | — | $CaCO_3$ | 14 | 80 |
| 7 | $Ni(OAc)_2{\cdot}4H_2O$ | 2-Pyridone | $CaCO_3$ | 10 | 88 |
| 8 | $Ni(OAc)_2{\cdot}4H_2O$ | 2-Pyridone | $Et_3N$ | 03 | 90 (80[c]) |
| 9[d] | $Ni(OAc)_2{\cdot}4H_2O$ | 2-Pyridone | $Et_3N$ | 34 | 53 |




[a] Reactions were performed on a 0.2 mmol scale in DMF (1.0 mL) under a $N_2$ atmosphere. [b] Yields were determined by $^1H$ NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield. [d] Reaction was performed at 80 °C.

Table 2 Substrate scope of the amide component[a]




[a] Reactions were performed on a 0.2 mmol scale in DMF (1.0 mL) under a $N_2$ atmosphere. [b] LiBr (1.0 equiv.) was added. [c] ASP (4.0 equiv.) were used.

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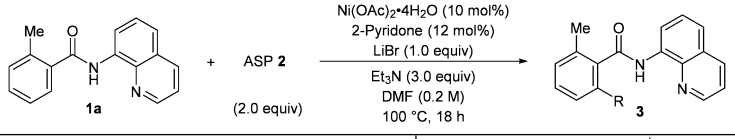
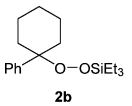
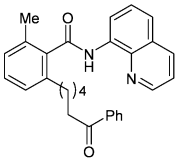
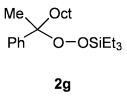
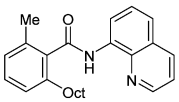
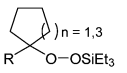
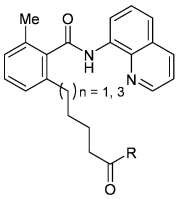
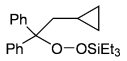
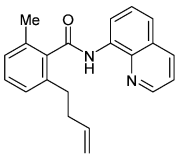
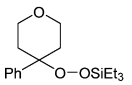
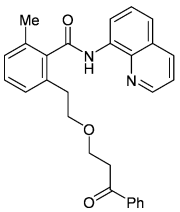
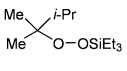
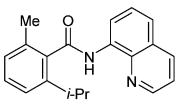
Table 3 Substrate scope of the ASP component[a]



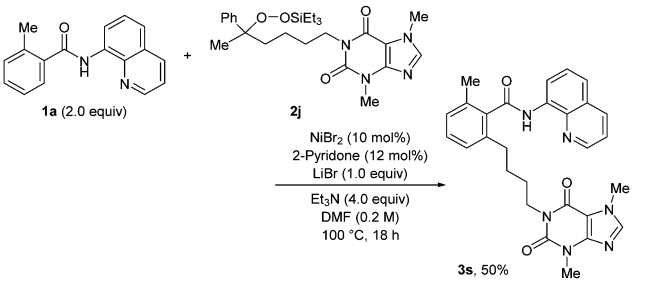

| ASP 2 | Product 3 | ASP 2 | Product 3 |
|---|---|---|---|
|  **2b** |  **3k**, 85% (8%)[b] |  **2g** |  **3p**, 58% |
|  **2c** (n = 1, R = Et)<br>**2d** (n = 1, R = Ph)<br>**2e** (n = 3, R = Ph) |  **3l** (n = 1, R = Et), 84%<br>**3m** (n = 1, R = Ph), 81%<br>**3n** (n = 3, R = Ph), 88% |  **2h** |  **3q**, 54% |
|  **2f** |  **3o**, 24%[c] |  **2i** |  **3r**, N.D.[d] |

[a] Reactions were performed on a 0.2 mmol scale in DMF (1.0 mL) under a $N_2$ atmosphere. [b] Reaction was performed without LiBr. [c] An additional 2.0 equiv. of ASP were added after the reaction was performed for 9 h. [d] Performed at 80 °C.

improved the yield of **3k** (85%). The use of five- or seven-membered cyclic ASPs **2c–2e** also furnished the corresponding products (**3l–3n**) in high yield (81–88%). The reaction with **2f**, a compound bearing a cyclic ether moiety, afforded **3o**, albeit in low yield (24%). We also attempted reactions using acyclic ASPs other than **2a**. The use of ASP **2g** with methyl-, octyl-, and phenyl substituents on the carbinyl moiety selectively afforded the octyl-substituted benzamide **3p** in 58% yield. When using ASP **2h**, which contains a cyclopropylmethyl moiety, homoallylated **3q** was obtained in 54% yield *via* a radical ring-opening process. In contrast to the successful introduction of primary alkyl groups to **1a**, the alkylated benzamide **3r** resulting from the transfer of a secondary alkyl group from ASP **2i** was not observed. This may be due to the steric hindrance of the isopropyl radical, which inhibits the Ni-catalyzed coupling process.[10b]

To demonstrate the utility of our method for the functionalization of bioactive molecules, the reaction was conducted using ASP **2j**, which is derived from pentoxifylline, *i.e.*, a drug commonly used to treat peripheral artery diseases. To our delight, benzamide **3s**, which contains a nitrogen-rich xanthine core, was obtained in 50% isolated yield (Scheme 2). In their entirety, the obtained results suggest that ASPs are among the best precursors for highly functionalized alkyl radicals in Ni-catalyzed C($sp^2$)–H alkylation reactions.

To better understand the underlying reaction mechanism, we conducted several control experiments. First, we performed a competition experiment using a 1 : 1 mixture of **1c** and **1d** in




Scheme 2 Access to benzamide bearing a nitrogen-rich xanthine core.

the presence of ASP **2a** (Scheme 3a), which resulted in the preferential conversion of **1d**, *i.e.*, the substrate with an electron-withdrawing group. This tendency can also be seen in previous reports for the related C–H activation methods.[10,14] Second, we added an excess of tetrachloromethane ($CCl_4$), *i.e.*, a chlorine-atom donor, to the reaction of **1a** with **2d** (Scheme 3b).[5h,15] As a result, the formation of **3m** was completely inhibited, and 5-chloro-1-phenylpentan-1-one (**4**) was obtained instead (62% yield based on **2d**). It is reasonable to assume that **4** is formed *via* the abstraction of a chlorine atom from $CCl_4$ by alkyl radical **5**, which is generated *in situ via* the cleavage of the C–C bond in **2d**. This result, together with the observation that the reaction using **2h** afforded **3q**, suggests that alkyl radical intermediates are involved in this Ni-catalyzed *ortho*-C–H alkylation reaction.[16]

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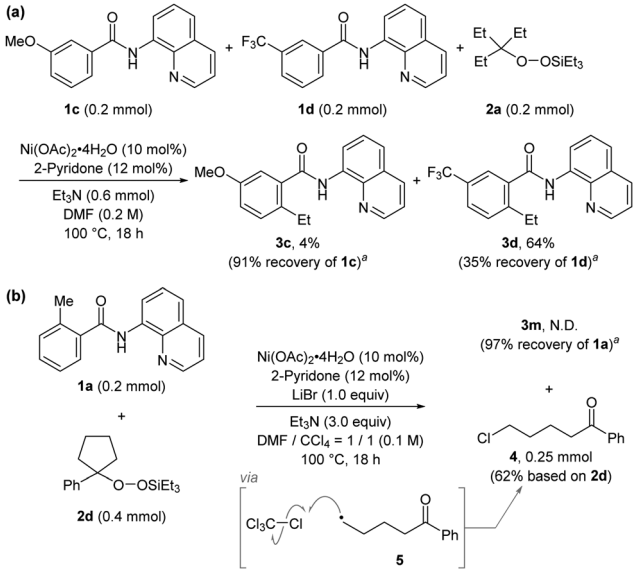


Scheme 3 (a) A competition experiment. (b) A radical trapping experiment. [a] $^1$H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard.

In summary, we have developed a Ni-catalyzed C($sp^2$)–H alkylation of *N*-quinolylbenzamide using alkylsilyl peroxides as versatile alkyl radical sources. The reaction proceeds *via* the cleavage of both C($sp^3$)–C($sp^3$) and C($sp^2$)–H bonds and affords a wide range of *ortho*-alkylated *N*-quinolylbenzamide with highly functionalized and complex structures. Mechanistic studies suggest that the reaction involves a radical mechanism.

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## Conflicts of interest

There are no conflicts to declare.

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