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Nickel-Catalyzed Aromatic C–H Alkylation with Secondary or Tertiary Alkyl–Bromine Bonds for the Construction of Indolones

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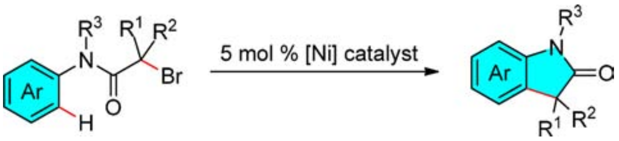
ABSTRACT

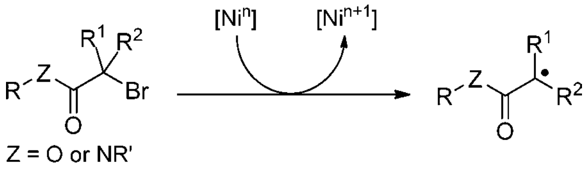


A nickel-catalyzed aromatic C–H alkylation with tertiary or secondary alkyl–Br bonds for the construction of indolones was demonstrated. Various functional groups were well tolerated. Moreover, the challenging secondary alkyl bromides were well introduced in this transformation. Radical trapping and photocatalysis conditions exhibited that it is most likely to be a radical process for this aromatic C–H alkylation.

Transition-metal-catalyzed C–H functionalization has become a hot topic in recent years.[1] Many efforts have been devoted to replace C–M by using C–H as nucleophiles in the area of transition-metal-catalyzed cross-couplings between nucleophiles and electrophiles. Until now, the mainly applied electrophiles have been aryl halides and aryl pseudo halides.[2] Another group of electrophiles, alkyl halides, have been utilized less to cross-couple with aromatic C–H bonds in which primary alkyl halides were mainly applied.[3] Only isolated examples have been demonstrated in the cross coupling of secondary or tertiary alkyl halides with aromatic C–H bonds.[4] This may be mainly due to the sluggish oxidative addition of secondary or tertiary alkyl halides and also the facile β-hydride elimination of the related alkyl–metal species generated via a general oxidative addition pathway.

Compared with alkyl–metal species, the alkyl radicals do not tend to undergo β-hydride elimination. Moreover, it is also possible for aromatic C–H activation via a radical addition process. Consequently, the aromatic C–H alkylation via a radical process has a high likelihood of success for both secondary and tertiary alkyl halides, which has always been challenging.

Scheme 1. Interaction between α-Carbonyl Alkyl Bromide and Nickel Species



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(1) (a) Yu, J.-Q.; Ackermann, L.; Shi, Z. *C–H Activation*; Springer: Heidelberg, 2010; (b) Lyons, T.; Sanford, M. *Chem. Rev.* **2010**, *110*, 1147. (c) Giri, R.; Shi, B.-F.; Engle, K.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.

(2) (a) Alberico, D.; Scott, M.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (c) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

(3) (a) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (b) Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495.

(4) (a) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485. (b) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877. (c) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616. (d) Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. *Org. Lett.* **2012**, *14*, 1748. (e) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045.

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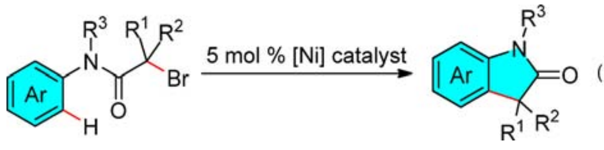
Recently, we have demonstrated a Heck-type alkenylation of α-carbonyl alkyl halides in the presence of a nickel catalyst.[5] The α-carbonyl alkyl radical was believed to be generated via the SET reduction of α-carbonyl alkyl bromides in the presence of a low valent nickel species (Scheme 1). We envisioned that this α-carbonyl alkyl radical might effect intramolecular radical addition to the aromatic rings (when R is an aromatic group, Scheme 1) to realize aromatic C−H alkylation.[6] Herein, we demonstrated a nickel-catalyzed aromatic C−H alkylation with secondary or tertiary alkyl−Br bonds for the construction of indolones (eq 1).[7]



(1)

With the above idea in mind, the following reactions were first tested (Scheme 2). When an aryl α-bromoester **1a** was applied as substrate under the conditions of 5 mol % of Ni(PPh$_3$)$_4$/6 mol % of dppp, 2 equiv of K$_3$PO$_4$, in toluene at 100 °C for 24 h, no product **2a** was detected. When **1b**, in which the O-atom was replaced by an NH group, was tested, no product **2b** was detected either. To our delight, when **1c** (Z = NMe) was applied, the corresponding C−H alkylation product **2c** was obtained in an 86% isolated yield. These results indicated that the Z group has a significant influence on the reactivity of the aromatic rings for the C−H alkylation process.[8]

Scheme 2. Reactions of Aryl α-Bromoester and Amides

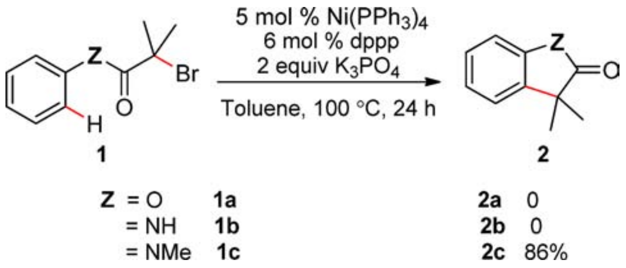
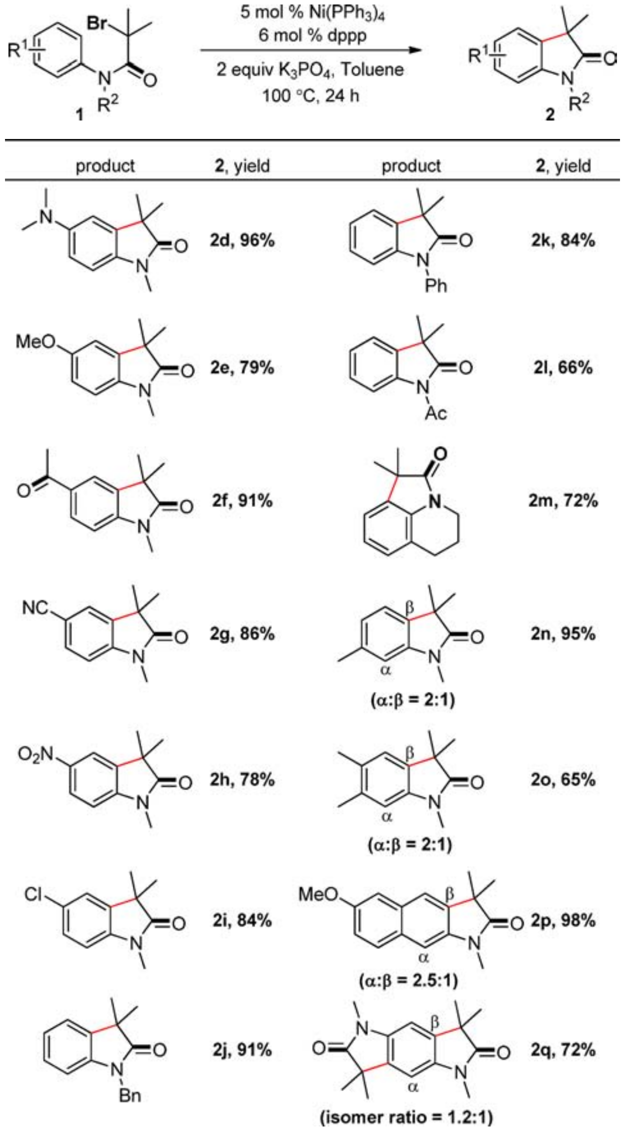


Table 1. Nickel-Catalyzed Aromatic C−H Alkylation with Tertiary Alkyl−Br Bonds[a]



[a] Reactions were carried out with **1** (0.5 mmol), Ni(PPh$_3$)$_4$ (0.025 mmol), dppp (0.030 mmol), and K$_3$PO$_4$ (1.0 mmol) in toluene (2 mL) at 100 °C for 24 h. Yields shown were of isolated products.

Then, other aryl α-bromoamides were further tested for this aromatic C−H alkylation process with tertiary alkyl−Br bonds following the same reaction conditions (Table 1). Various substituents on the aromatic rings were well tolerated. Electron-donating groups such as *p*-NMe$_2$- and *p*-OMe-containing substrates afforded the corresponding products **2d** and **2e** in good to excellent yields, respectively. Electron-withdrawing groups *p*-Acyl (**2f**), *p*-CN (**2g**), and *p*-NO$_2$ (**2h**) were also well tolerated. The aromatic C−Cl bond was remained untouched, and the corresponding cyclization product **3i** was obtained in an isolated yield of 84%. When a *N*-benzyl-containing substrate was applied, the selective C−H alkylation on the *N*-Ph ring to form the corresponding indolone **2j** was observed, and no C−H alkylation on the *N*-benzyl ring was detected. Furthermore, the R^2 group was changed to be a phenyl group (**2k**) or an electron-deficient acyl group (**2l**).

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[5] Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638.

[6] Selected examples on Ni-catalyzed C−H alkylation, see: (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (b) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 775. (c) Hu, X. *Chimia* **2012**, *66*, 154. (d) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061.

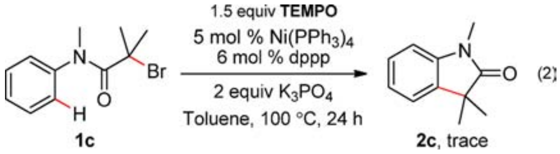
[7] Three previous reports on C−H alkylation with tertiary alkyl−Br bonds have been demonstrated. For the reactions using excess nickel powder or light irradiation, see: (a) Nishio, T.; Asai, H.; Miyazaki, T. *Helv. Chim. Acta* **2000**, *83*, 1475. (b) Nishio, T.; Iseki, K.; Araki, N.; Miyazaki, T. *Helv. Chim. Acta* **2005**, *88*, 35. For the reaction with 1,3-dicabonyl tertiary alkyl−Br bonds, see (c) Xuhui, J.; Yan, L.; Pingjing, J.; Weifei, L.; Wei, Y. *Org. Biomol. Chem.* **2012**, *10*, 498.

[8] (a) Peng, H.; Yuan, Z.; Wang, H.-y.; Guo, Y.-l.; Liu, G. *Chem. Sci.* **2013**, *4*, 3172. (b) Mu, X.; Wu, T.; Wang, H.-y.; Guo, Y.-l.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878. (c) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972.

The corresponding products **2k** and **2l** were obtained in moderate to good yields. An *ortho*-substituted aromatic ring has one reactive site, and the corresponding C−H alkylation product **3m** was obtained in 72% yield. When *meta*-substituent-containing substrates were utilized, two different reactive sites (α, β) were available for the cyclization. Two isomers were obtained in a total yield of 95% (**2n**) and 65% (**2o**), respectively. The ratio of the two isomers is 2:1 (α/β). Similarly, when β-naphthyl amide was applied, both isomers of the cyclization on the α and β positions were obtained, in which the α-position alkylation isomer was dominant (**2p**). The total yield was 98%. When 1,4-diaminobenzene-derived diamide was subjected to this transformation, the corresponding dicyclization product **2q** was obtained in a good yield.

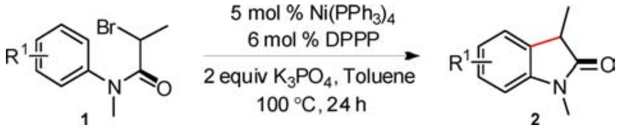
Compared to the tertiary alkyl radical, the secondary alkyl radical is less stable, which makes this aromatic C−H alkylation with secondary alkyl−Br bonds more challenging. To the best of our knowledge, only one compound was successfully reported to achieve the aromatic C−H alkylation with a secondary alkyl−X bond for the construction of the corresponding indolones.[9] Thus, substrates with secondary alkyl−Br were further tested in this aromatic C−H alkylation process. To our delight, the cyclization proceeded well to generate the corresponding indolones (Table 2, **2r**−**x**). Electron-neutral (**2r**), electron-rich (**2s**, **2t**), and electron-deficient (**2u**) aromatic rings could all be alkylated to generate the cyclization products. Furthermore, aromatic carbon halide bonds were well tolerated (**2v**, **2w**, **2x**). In particular, the tolerance of the C−Br (**2w**) and C−I (**2x**) bonds allows further transformation to introduce the indolone unit into complex molecules.

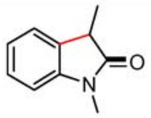
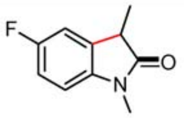
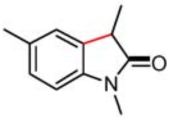
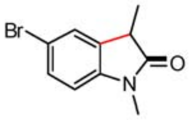
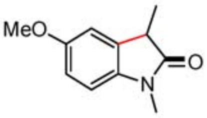
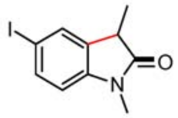
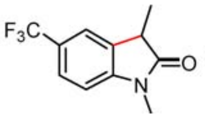
As stated above, this transformation is most likely to proceed via a radical process. To establish this possibility further, a radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) was added in the reaction of **1c** under the standard conditions (eq 2). As a result, only a trace amount of the desired product was observed, indicating that it is likely to be a radical process.



1c → **2c**, trace (2)

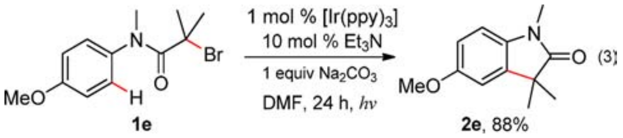
Table 2. Nickel-Catalyzed Aromatic C−H Alkylation with Secondary Alkyl−Br Bonds[a]



product	**2**, yield	product	**2**, yield
	**2r, 66%**		**2v, 56%**
	**2s, 45%**		**2w, 55%**
	**2t, 59%**		**2x, 67%**
	**2u, 44%**		

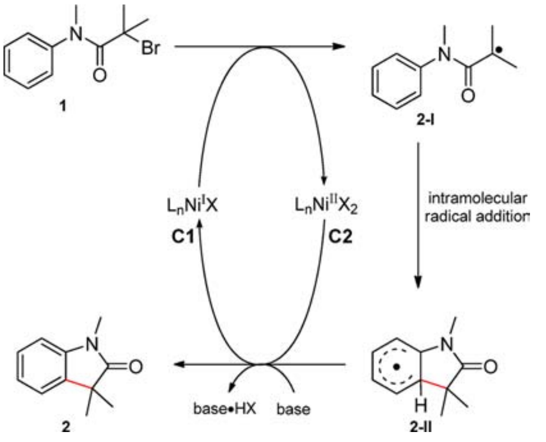
[a] Reactions were carried out with **1** (0.5 mmol), $Ni(PPh_3)_4$ (0.025 mmol), dppp (0.030 mmol), and K_3PO_4 (1.0 mmol) in toluene (2 mL) at 100 °C for 24 h. Yields shown were of isolated products.

Furthermore, it is well-known that visible light-promote organic transformation usually proceeds via a radical process.[10] We have previously shown that the iridium complex $Ir(bpy)_3$ could activate α-carbonyl alkyl bromide via a radical process in the presence of visible light.[11] To establish the SET process for this transformation further, the reaction conditions of the photocatalysis were applied for the cyclization of substrate **1e** (eq 3). The corresponding C−H alkylation product **2e** was obtained in 88% yield. This promising result further indicates the radical process of this nickel-catalyzed C−H alkylation.



1e → **2e**, 88% (3)

Scheme 3. Proposed Mechanism



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(9) Only ref 7a provided one secondaryl alkyl chloride with good yield. Secondary alkyl bromides have also been tested in both ref 7b and 7c, while the desired indolone synthesis was not successfully achieved.

(10) (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(11) Liu, Q.; Yi, H.; Liu, J.; Yang, Y.; Zhang, X.; Zeng, Z.; Lei, A. *Chem.—Eur. J.* **2013**, *19*, 5120.

Moreover, it has been suggested that Ni^0 reacts with alkyl halides via a single-electron-transfer process to generate a Ni^I species, which could further react with alkyl halide to generate alkyl radical and a Ni^{II} species.[5,12] Here, a mechanism involving Ni^I/Ni^{II} catalytic cycle was believed to proceed (Scheme 3). First, the active Ni^I species **C1** was generated by the reaction of alkyl halide **1** with $Ni(PPh_3)_4$. The catalytic cycle starts from the further reaction of **C1** with alkyl halide **1** via a SET process. The radical species **2-I** and a Ni^{II} species **C2** are generated. Then, the intramolecular radical addition of the carbon radical to the aromatic ring affords intermediate **2-II**, which is further oxidized by the Ni^{II} species **C2** to afford the final product **2**. Meanwhile, **C2** was reduced to regenerate the active Ni^I species **C1**.

In summary, we have demonstrated a nickel catalyzed aromatic C−H alkylation with tertiary or secondary alkyl−Br bonds for the construction of indolones. Various functional groups were well tolerated. In particular, the challenging secondary alkyl bromides were well introduced in this transformation. Radical trapping and photocatalysis conditions showed that this aromatic C−H alkylation is most likely a radical process.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(12) (a) Heimbach, P. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 648. (b) Porri, L.; Gallazzi, M. C.; Vitulli, G. *Chem. Commun.* **1967**, 228. (c) Otsuka, S.; Nakamura, A.; Yoshida, T.; Naruto, M.; Ataka, K. *J. Am. Chem. Soc.* **1973**, *95*, 3180.