Nickel-Catalyzed Selective Oxidative Radical Cross-Coupling: An Effective Strategy for Inert Csp³−H Functionalization

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S *Supporting Information*

ABSTRACT: An effective strategy for inert Csp³−H functionalization through nickel-catalyzed selective radical cross-couplings was demonstrated. Density functional theory calculations were conducted and strongly supported the radical cross-coupling pathway assisted by nickel catalyst, which was further confirmed by radical-trapping experiments. Different arylborates including arylboronic acids, arylboronic acid esters and 2,4,6-triarylboroxin were all good coupling partners, generating the corresponding Csp³−H arylation products in good yields.
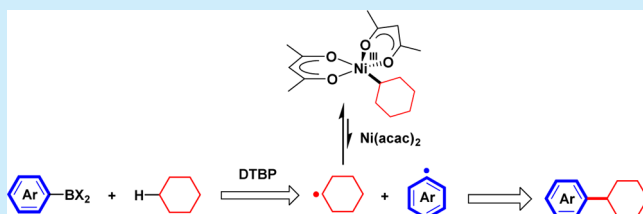
C−H functionalization has emerged as a powerful synthetic method during the past several decades[1] and has also been widely employed in the syntheses of various pharmaceuticals and biologically active molecules,[2] due to its environmental sustainability and its lack of need for prefunctionalization. Direct Csp³−H functionalization is highly attractive, but it has been rarely developed,[3] attributing to the relatively inert properties of Csp³−H bonds. Previous reports on direct functionalization of heteroatom adjacent Csp³−H bonds were relatively common,[4] probably owing to the activation effect of heteroatoms to the adjacent Csp³−H bonds. However, it is still a challenging task to achieve direct functionalization of inert Csp³−H bonds, especially simple alkanes. Until now, only isolated examples on oxidative inert Csp³−H functionalization have been demonstrated.[5] Oxidative arylation of simple alkanes has also been very rare.[6]

Recently, radical oxidative coupling reactions have gone through an extremely rapid development in organic synthesis,[7] in which different radical species were generally involved in bond formations. However, selective bond formations between two radical species were rarely developed, probably due to the competition of unavoidable radical homocoupling reactions. Normally, radical cross-coupling could selectively occur between a persistent radical and a transient radical.[8] However, most radicals in chemical transformations are transient radicals, and therefore, it is difficult to achieve selective cross-coupling.[9] One effective strategy is to tranform one of the transient radicals into a persistent radical. During the past several decades, transition metal catalysts have been demonstrated to interact with radicals through redox bond formation, coordination or atom transfer, etc.[10] Notably, some of these transformations were reversible, which could slowly release one radical to cross-couple with the other, thus providing a novel and efficient strategy for selective radical cross-coupling

reactions. Considering the great significance and challenge of inert Csp³−H functionalization, we communicate herein an effective strategy for inert Csp³−H functionalization through selective radical cross-coupling assisted by nickel catalyst (Scheme 1).

Scheme 1. Effective Strategy for Inert Csp³−H Functionalization through Selective Radical Cross-Coupling Assisted by Nickel Catalyst
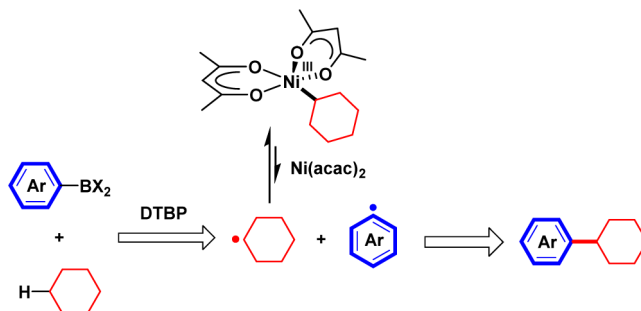
In our initial study, phenylboronic acid (**1a**) and cyclohexane (**2a**) were chosen as the coupling partners, since both of them could generate the corresponding phenyl radical and cyclohexyl radical respectively in the presence of transition metal catalyst and oxidant.[3g−i,k−m,p,11] Then, with the assistance and stabilization of nickel catalyst, selective radical cross-coupling between phenyl radical and cyclohexyl radical could deliver the desired Csp³−H functionalized product. With this assumption in mind, we started to conduct detailed investigation of this

reaction. After a considerable test of different reaction parameters, we obtained the desired product **3a** in 73% GC yield in the presence of Ni(acac)$_2$ as the catalyst, Ph$_3$P and dppb (1,4-bis(diphenylphosphino)butane) as the ligand, K$_3$PO$_4$ as the base, DTBP (di-*tert*-butyl peroxide) as the oxidant at 130 °C for 10 h (for detailed condition optimizations, see Supporting Information).

In order to clarify the probable nickel-assisted radical cross-coupling pathway of this reaction, relative radical stabilities were investigated using density functional theory (DFT) calculation employing the method B3LYP.[12] Initially, as shown in Figure 1a,b, either cyclohexane **2a** or phenylboronic

Figure 2. Geometry of complex **13**. The numbers in parentheses are respective Mulliken spin densities on each atom.

suggests that most spin is located on the nickel atom. Consequently, the homocoupling of cyclohexyl radical **6** could be avoided with the aid of Ni(acac)$_2$ catalyst, and the cross-coupling product is preferred, which provides strong support for nickel-assisted radical cross-coupling pathway.

Further radical-trapping experiments support the radical process of this reaction (Scheme 2). When equivalent amount
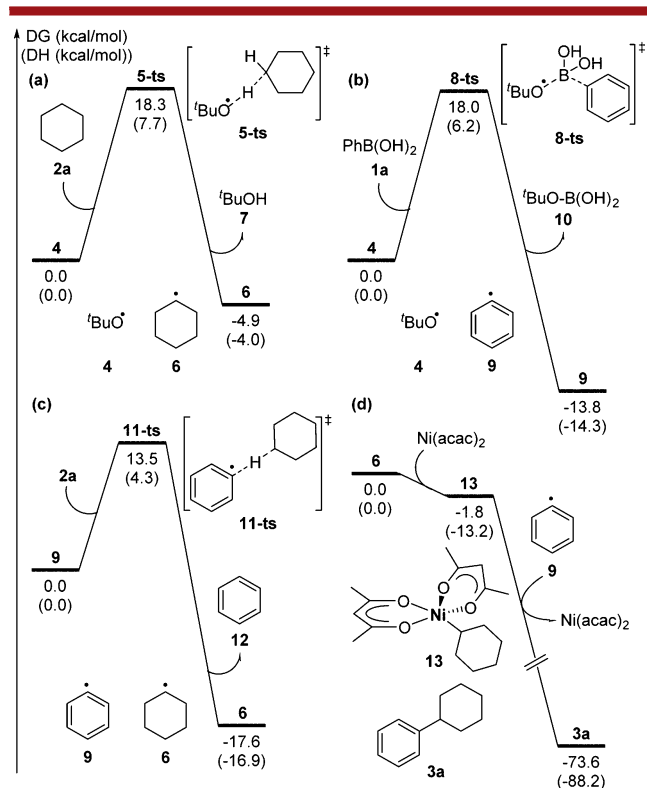

Figure 1. Free energy profile for the following: (a) The generation of cyclohexyl radical **6**. (b) The generation of phenyl radical **9**. (c) Radical substitution between radical **9** and cyclohexane **2a**. (d) The generation of product **3a** in the presence of Ni(acac)$_2$.

Scheme 2. Radical-Trapping Experiments

acid **1a** could react with *tert*-butoxyl radical **4**, leading to the generation of corresponding cyclohexyl radical **6** or phenyl radical **9** via transition state **5-ts** or **8-ts**. The activation energies of these two reactions are 18.3 and 18.0 kcal/mol, respectively, which is nearly the same. However, the radical substitution between radical **9** and cyclohexane **2a** shown in Figure 1c reveals the huge difference between relative radical stabilities of radicals **9** and **6**. Through transition state **11-ts** with a barrier of 13.5 kcal/mol, radical **6** could be generated with 31.1 kcal/mol exothermic, which indicates that radical **6** is more stable than radical **9** by 17.6 kcal/mol. Therefore, as the most stable radical, cyclohexyl radical **6** is supposed to be the main radical species under these reaction conditions. Moreover, in the presence of Ni(acac)$_2$ catalyst, radical **6** could be further stabilized by 1.8 kcal/mol through the generation of a nickel(III) complex **13** (Figure 1d), and subsequent cross coupling irreversibly affords the desired product **3a** with 71.8 kcal/mol exothermic. Besides, the Mulliken spin density of complex **13** shown in Figure 2
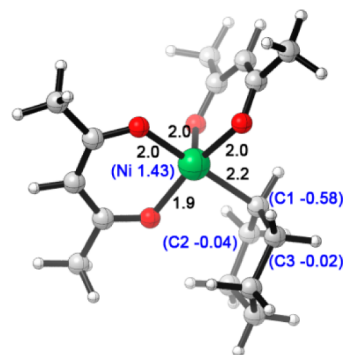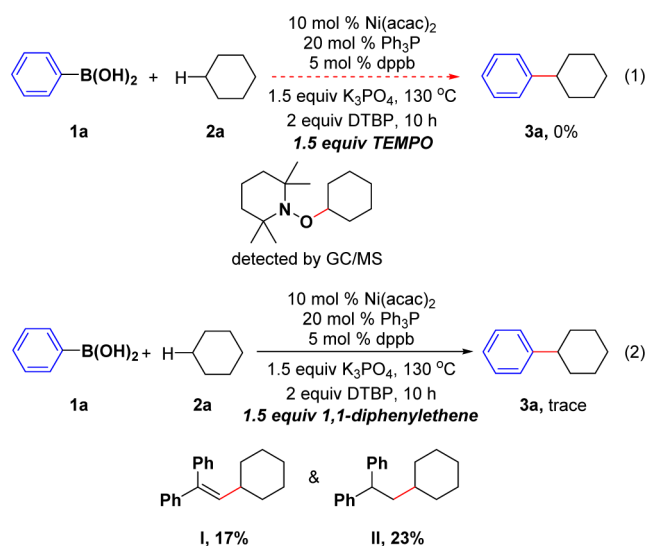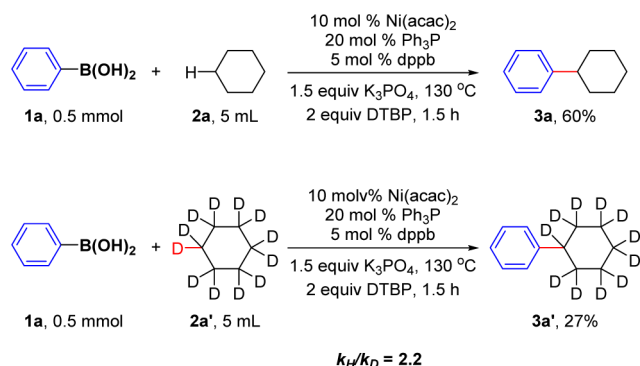
of TEMPO was added into the reaction system, the reaction was totally shut down, along with the formation of trapping product of cyclohexyl radical detected by GC−MS analysis (Scheme 2, eq 1, see Supporting Information for more details). Moreover, when 1,1-diphenylethene was employed as the radical-trapping reagent, the main reaction was greatly inhibited, only trace amount of the target product was obtained. Notably, cyclohexyl radical was also successfully trapped by 1,1-diphenylethene, generating the corresponding trapping products in 17% and 23% NMR yields, respectively (Scheme 2, eq 2, see Supporting Information for more details). These results strongly support that cyclohexyl radical is the most stable radical in the whole reaction.
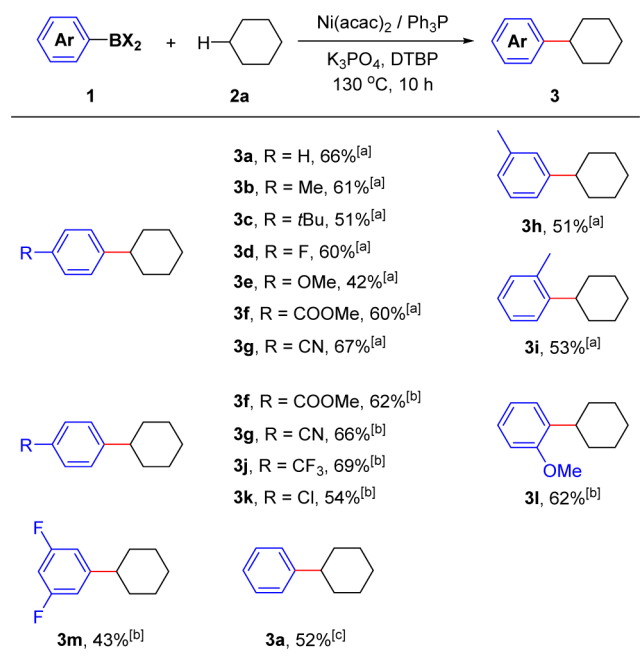
Moreover, two parallel reactions were carried out with cyclohexane and cyclohexane-d_{12} as the substrates respectively to determine the kinetic isotopic effect (KIE) (Scheme 3). As a result, a $k_H/k_D = 2.2$ was obtained (see Supporting Information for details). We further did an intermolecular KIE experiment.

Scheme 3. Kinetic Isotopic Effect (KIE) Experiment

Ph—B(OH)₂ (**1a**, 0.5 mmol) + H—cyclohexane (**2a**, 5 mL)

10 mol % Ni(acac)₂
20 mol % Ph₃P
5 mol % dppb
1.5 equiv K₃PO₄, 130 °C
2 equiv DTBP, 1.5 h

→ phenylcyclohexane (**3a**, 60%)

Ph—B(OH)₂ (**1a**, 0.5 mmol) + D-cyclohexane-d (**2a'**, 5 mL)

10 molv% Ni(acac)₂
20 mol % Ph₃P
5 mol % dppb
1.5 equiv K₃PO₄, 130 °C
2 equiv DTBP, 1.5 h

→ phenylcyclohexane-d (**3a'**, 27%)

$k_H/k_D = 2.2$

This time, a significant KIE value of $k_H/k_D = 5.7$ was observed (see Supporting Information for details). These experiments indicated that the C–H cleavage of cyclohexane was probably involved in the rate-determining step.

Furthermore, considerable efforts have been made to test the substrate generality of this reaction under the optimized reaction conditions. Notably, different arylborates such as arylboronic acids, arylboronic acid neopentylglycol esters and even 2,4,6-triphenylboroxin could cross-couple smoothly with cyclohexane to afford the corresponding products in good yields (Scheme 4). First, different arylboronic acids were tested. Notably, this reaction has a good compatibility of different groups on aryl rings. Phenylboronic acids with p-Me and p-tBu
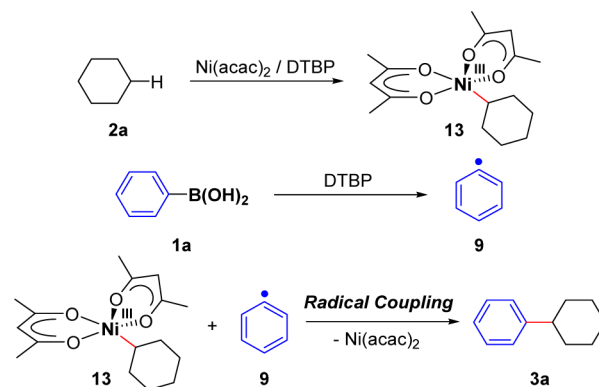
substituents could be well tolerated, affording the corresponding oxidative alkylation products in good yields (**3b** and **3c**). And also, halogenated phenylboronic acids such as p-F-PhB(OH)₂ could cross-couple smoothly with cyclohexane in good yield (**3d**). However, phenylboronic acids with electron-rich substituents such as OMe generated the desired oxidative alkylation product in a slightly lower yield (**3e**). While phenylboronic acids with electron-poor substituents such as COOMe and CN groups were good coupling partners (**3f** and **3g**). In addition, *ortho*- and *meta*-substituted arylboronic acids could also be well tolerated, generating the desired Csp³–H functionalized products in moderate yields (**3h** and **3i**). Second, we tried to test the reactivity of different arylboronic acid esters, during which we found that arylboronic acid neopentylglycol esters were good coupling partners. Notably, these types of reactions could proceed smoothly in the presence of dppb as the sole ligand, in which electron-rich (**3l**), electron-poor (**3f**, **3g** and **3j**) and halogen substituents (**3k** and **3m**) could all be well tolerated, delivering the corresponding products in good yields. Finally, 52% yield of the desired arylation product could be obtained with 2,4,6-triphenylboroxin as the arylborate. It should be noted that reactions of other simple alkanes are not efficient enough. The reaction of (4-(methoxycarbonyl)-phenyl)boronic acid with cyclopentane only afforded 30% yield of the desired product. And with *n*-hexane as the substrate, only 19% yield of the desired products were obtained with a poor selectivity (see Supporting Information for details).

According to the above research and previous reports, we proposed a plausible pathway for this reaction.[13] As depicted in Scheme 5, the most stable cyclohexyl radical is preferred to be

Scheme 4. Substrate Scope for Nickel-Catalyzed Selective Radical Cross-Coupling Reactions[a]

Ar—BX₂ (**1**) + H—cyclohexane (**2a**)

Ni(acac)₂ / Ph₃P
K₃PO₄, DTBP
130 °C, 10 h

→ Ar—cyclohexane (**3**)

3a, R = H, 66%[a]
3b, R = Me, 61%[a]
3c, R = tBu, 51%[a]
3d, R = F, 60%[a]
3e, R = OMe, 42%[a]
3f, R = COOMe, 60%[a]
3g, R = CN, 67%[a]

3h, 51%[a]

3f, R = COOMe, 62%[b]
3g, R = CN, 66%[b]
3j, R = CF₃, 69%[b]
3k, R = Cl, 54%[b]

3i, 53%[a]

3l, 62%[b]

3m, 43%[b]

3a, 52%[c]

[a]Reaction conditions: [a] Arylboronic acids were used as the substrates. **1** (0.5 mmol), **2a** (5.0 mL), Ni(acac)₂ (10 mol %), Ph₃P (20 mol %), dppb (5 mol %), K₃PO₄ (0.75 mmol), DTBP (1.0 mmol), 130 °C, 10 h. [b] Arylboronic acid neopentylglycol esters were used as the substrates. **1** (0.5 mmol), **2a** (5.0 mL), Ni(acac)₂ (10 mol %), dppb (10 mol %), K₃PO₄ (0.75 mmol), DTBP (1.0 mmol), 130 °C, 10 h. [c] 2,4,6-Triphenylboroxin was used as the substrate. **1** (0.17 mmol), **2a** (5.0 mL), Ni(acac)₂ (10 mol %), Ph₃P (20 mol %), dppb (5 mol %), K₃PO₄ (0.75 mmol), DTBP (1.0 mmol), 130 °C, 10 h.

Scheme 5. Plausible Reaction Mechanism

cyclohexane (**2a**)

Ni(acac)₂ / DTBP → nickel(III) complex (**13**)

Ph—B(OH)₂ (**1a**)

DTBP → phenyl radical (**9**)

13 + **9**

Radical Coupling
– Ni(acac)₂

→ phenylcyclohexane (**3a**)

formed through the radical substitution under the standard reaction condition, followed by coordination toward the nickel catalyst to afford a nickel(III) complex **13**. Subsequent generated phenyl radical **9** could react with **13** to give the desired radical cross-coupling product **3a**.

In summary, we have demonstrated an effective strategy for inert Csp³–H functionalization through nickel-catalyzed selective radical cross-couplings. DFT calculations have been conducted and strongly supported the radical cross-coupling pathway assisted by nickel catalyst, which were further confirmed by radical-trapping experiments. Different arylborates including arylboronic acids, arylboronic acid esters and 2,4,6-triarylboroxin were all shown to be good coupling partners with cyclohexane. This reaction provides an effective protocol for inert Csp³–H functionalization via selective radical cross-couplings. Further studies on substrate scope and more

detailed mechanism are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experiment details and spectral data for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(13) For the plausible mechanism, there is another possibility that Ni(acac)$_2$ might conduct transmetalation with arylboronic acid to generate an aryl-Ni(II) complex, which further reacted with cyclohexyl radical to form a Ni(III) complex. Final reductive elimination of Ni(III) complex delivered the desired product. We also conducted DFT calculation to prove it. However, according to our calculation results, this possibility could be excluded, see Figure S1 in the Supporting Information for details.