

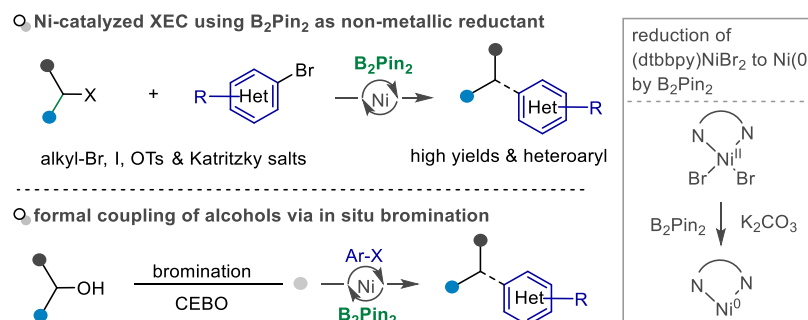
# Bis(pinacolato)diboron-Enabled Ni-Catalyzed Reductive Coupling of Alkyl with Aryl/Vinyl Electrophiles

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## Abstract

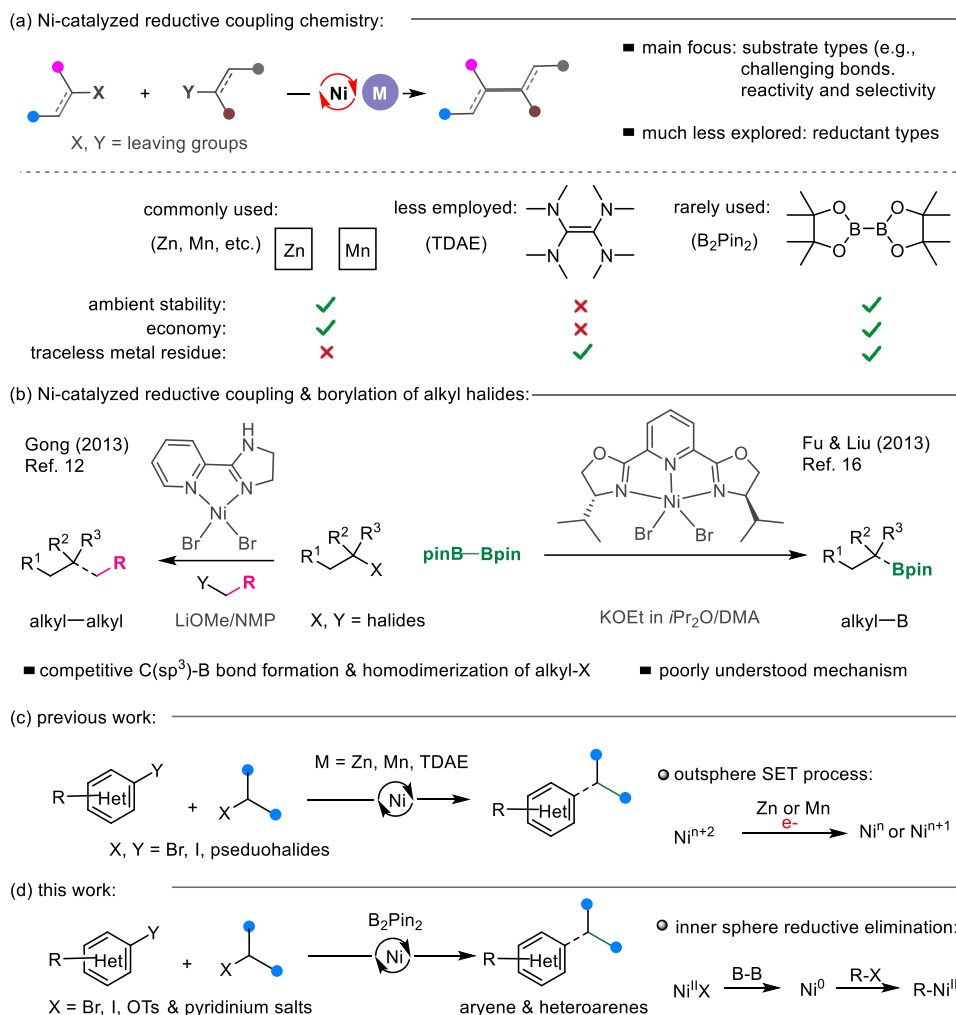


The chemistry herein stresses the use of economic and environmentally friendly (bispinacolato)diboron, as the non-metallic reductant that enables the reductive cross-coupling of alkyl electrophiles with aryl/vinyl halides to afford C(sp<sup>3</sup>)–C(sp<sup>2</sup>) bond forming products. The present method displays equivalent coupling efficiencies to those reported ones using Zn and Mn as the terminal reductants that have predominated the field of cross-electrophile coupling. Our mechanistic studies support that B<sub>2</sub>Pin<sub>2</sub>-mediated reduction of Ni<sup>II</sup> to Ni<sup>0</sup>, and a radical-chain process emphasizing interception of an alkyl Ni(0) may operate to give alkyl–Ni<sup>I</sup> followed by oxidative addition of ArX to give a key alkyl–Ni<sup>III</sup>–Ar intermediate prior to ejection of the product. We believe the present study offers insight into the use of B<sub>2</sub>Pin<sub>2</sub> as a non-metallic reductant that does not involve a SET reduction process.

## Introduction

The transition metal-catalyzed reductive coupling of alkyl electrophiles with carbon electrophiles, known as cross-electrophile coupling chemistry has evolved to a privileged synthetic platform that significantly advances the fields of C(sp<sup>3</sup>)-C coupling chemistry.<sup>1-3</sup> In this vein, the use of metallic reductants in particular Zn and Mn predominates the field that may encounter issues of scalability and metallic impurities in pharmaceuticals.<sup>4</sup> Despite these potential drawbacks, these two versatile reductants are potent to reduce the catalyst to its low-valent states via single or two electron reduction, and thus warrant numerous elegant types of transformations with emphasis on the Ni-catalyzed coupling of alkyl electrophiles with different electrophiles, e.g., alkyl-/ally-, aryl-/vinyl-, and acyl halides, as well as acid anhydrides and CO<sub>2</sub>.<sup>3</sup> Recent advances have also been capitalized on accommodating alkyl-NHPI esters, -Katritzky salts, -ammonium salts and -oxalates as the alkyl coupling partners, permitting effective transformation of the C-C, C-N and C-O bonds into value-added C(sp<sup>3</sup>)-C and C(sp<sup>3</sup>)-heteroatom bonds.<sup>5-9</sup> In a sharp contrast, meagre efforts have been devoted to the development of non-metallic reductants that outcompete Zn and Mn. Towards this end, Weix has advanced tetra(dimethylamino)ethylene (TDAE) as an organic reductant that displayed moderate efficiencies in the Ni-catalyzed arylation of alkyl halides with aryl halides.<sup>10</sup> Unfortunately, the tedious preparation of moisture and air sensitive TDAE hindered its practicality in reductive coupling chemistry. Although Hazari has made significant efforts to modify the structure of TDAE, a more synthetically useful TDAE derivative has not been disclosed.<sup>11</sup>

Our laboratory has initially reported B<sub>2</sub>Pin<sub>2</sub> as a terminal reductant to induce effective chemoselective cross-electrophile coupling of a primary and a secondary alkyl halide (Figure 1).<sup>12-13</sup> However, use of B<sub>2</sub>Pin<sub>2</sub> in Ni-catalyzed cross-electrophile coupling has not been extended to C(sp<sup>3</sup>)-C(sp<sup>2</sup>) bond forming process. This is not surprising, as B<sub>2</sub>pin<sub>2</sub> is incapable of reducing Ni species via SET as opposed to that of Zn, Mn and TDAE, and thus may exhibit narrow reaction scope due to intrinsic mechanistic limitation. On the other hand, the use of B<sub>2</sub>Pin<sub>2</sub> as the terminal reductant to mediate Ni-catalyzed cross-electrophile coupling is beneficial; B<sub>2</sub>Pin<sub>2</sub> is economic and easy to be removed, and thus it does not produce metallic traces post the purifications as opposed to Zn and Mn.<sup>14,15</sup> However, the challenges are noted. First, the mechanism of using B<sub>2</sub>Pin<sub>2</sub> as the reductant is poorly understood. Second, under Ni-catalyzed reaction conditions, alkyl halides are known to undergo markedly competing alkyl-Bpin forming process that terminates the reductive coupling event.<sup>16</sup> Herein, we present an unprecedented B<sub>2</sub>Pin<sub>2</sub>-mediated reductive arylation/vinylation of alkyl halides/Katritzky salts with aryl/vinyl halides that effectively afford C(sp<sup>3</sup>)-C(sp<sup>2</sup>) bonds, wherein highly competitive homodimerization of alkyl halides and formation of alkyl-Bpin products were effectively inhibited (Figure 1). Moreover, we provide comprehensive mechanistic studies to elucidate the reaction details. The role of B<sub>2</sub>Pin<sub>2</sub> was found to reduce the L<sub>n</sub>Ni<sup>II</sup>X<sub>2</sub> to L<sub>n</sub>Ni<sup>0</sup>. The reaction was suggested to involve a radical chain-process in which formation of a key alkyl-L<sub>n</sub>Ni<sup>III</sup>(Ar)X intermediate may arise from trapping an alkyl radical by L<sub>n</sub>Ni<sup>0</sup> to give L<sub>n</sub>Ni<sup>I</sup>-alkyl followed by oxidative addition of ArX to the Ni<sup>I</sup> species. In the meantime, the interception of the alkyl radical with L<sub>n</sub>Ni<sup>II</sup>(Ar)X derived from oxidative addition of ArX to L<sub>n</sub>Ni<sup>0</sup> may parallelly operate to give the key Ni(III) intermediate.

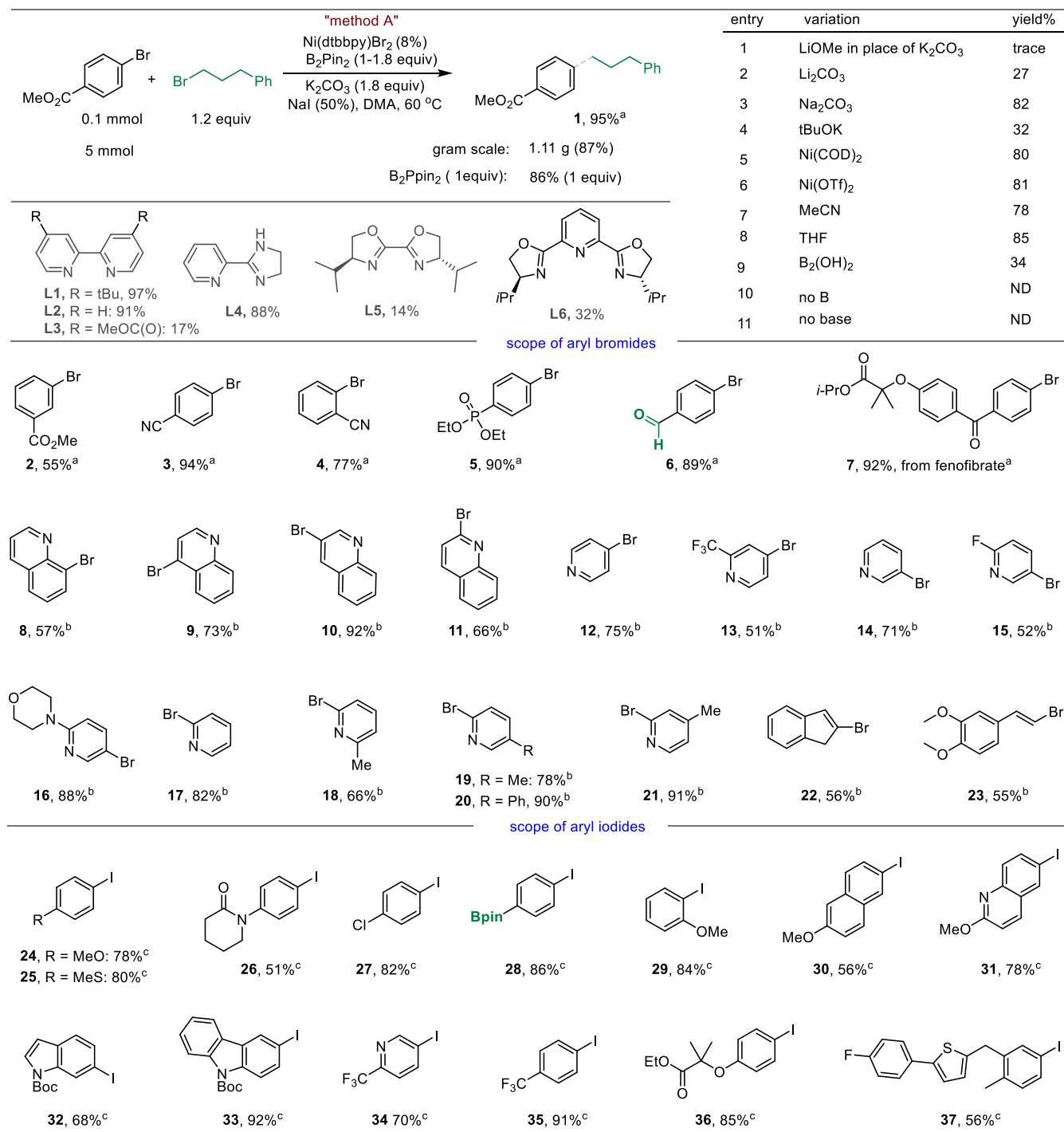


**Figure 1.** Brief summary of the current focuses of Ni-catalyzed cross-electrophile coupling with emphasis on the reductants.

We initiated our investigation on the coupling of methyl 4-bromobenzoate with (3-bromopropyl)benzene using Ni as the catalyst and B<sub>2</sub>Pin<sub>2</sub> as the reductant. Following the standard conditions developed for alkyl–alkyl bond formation (Figure 1b and Scheme S1),<sup>17</sup> trace amount of coupling product **1** was detected alongside with dimerization of alkyl halides and recovered aryl halides accounting for the mass balance. After extensive screening of the reaction parameters, we eventually identified the optimized reaction conditions that employed 8 mol% of Ni(dtbbpy)Br<sub>2</sub>, 1.2 equivs of B<sub>2</sub>Pin<sub>2</sub> and of K<sub>2</sub>CO<sub>3</sub>, and 50 mol% of NaI as the additive in *N,N*-dimethyl acetamide (DMA) at 60 °C (method A, Figure 2). The use of LiOMe to replace K<sub>2</sub>CO<sub>3</sub> resulted in trace amount of the product, whereas other bases including Li<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub> and KO*t*Bu were inferior, indicating the key role of bases in the aryl–alkyl forming event (Figure 2 and Table S1).<sup>17</sup> Other nickel sources (Table S1), solvents (Table S1), and diboron (Table S1) did not lead to better results. Other bipyridine ligands were generally effective (e.g., **L2**, Figure 2),<sup>17</sup> except for those electron-withdrawing groups (e.g., **L3**). Engagement of 2-(4,5-dihydro-1H-imidazol-2-yl)pyridine **L4**, biox and pybox ligands (**L5–L6**) were not as effective as **L1**. Control experiments showed the necessity of diboron, base and Ni for the coupling reaction (Figure 2 and Table S1). When the reaction was run on gram-scale using 5 mmol of ArBr, the yield was slightly reduced to 87%, indicative of the robustness of the method (Figure 2).

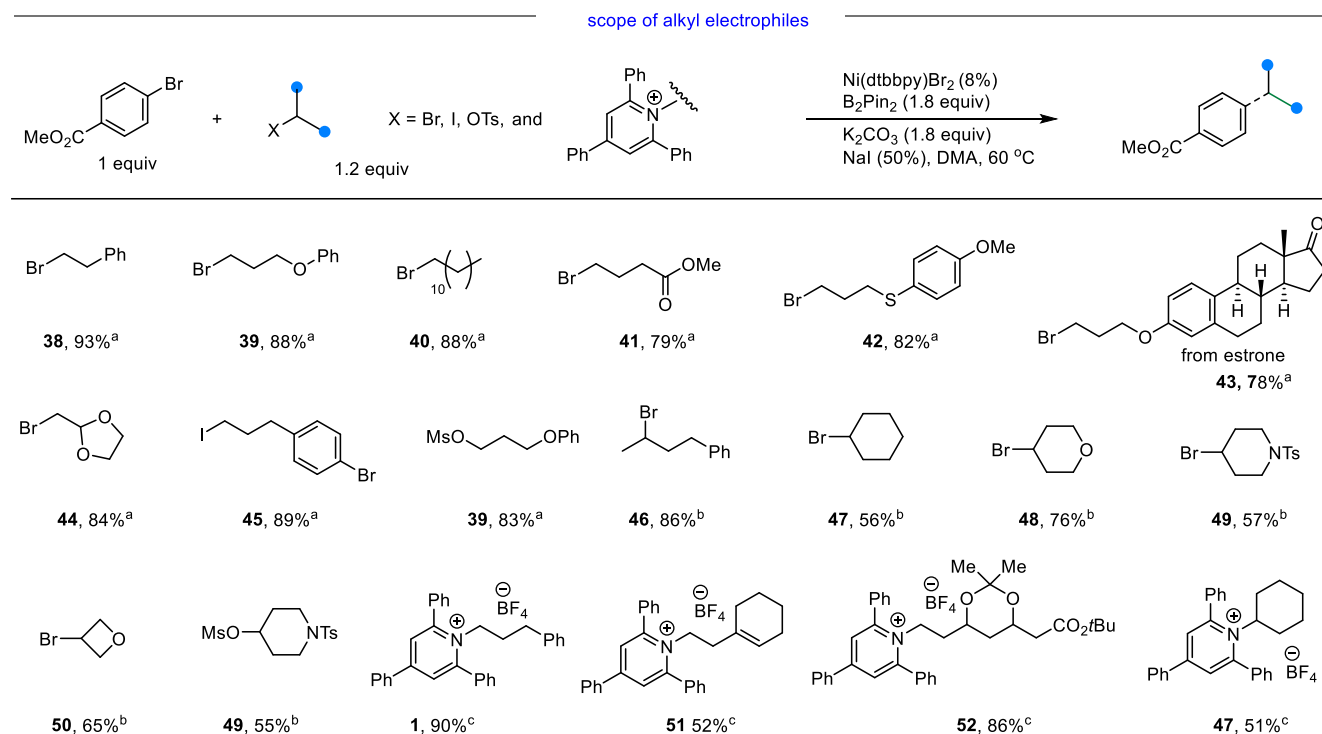
The compatibility of aryl halides was next examined with the standard method A (Figure 2) using (3-bromopropyl)benzene as the coupling partner. A brief screening of the electron-deficient arenes

suggested that ester-, cyano-, phosphoryl-, aldehyde-, and ketone-decorated aryl bromides were all competent to deliver the products **2–7** in moderate to excellent yields. The *meta*-substitution pattern seemed to be an important factor to deteriorate the yield when comparing the *para*- and *meta*-ester-containing products **1** and **2**, likely due to enhanced electron-deficient effect in the former. The alkylation of a bromo-analog of fenofibrate proved to be highly efficient giving **7** in 82% yield. We then shift our attention to heteroarenes. Coupling of the 2-, 3-, 4-, and 8-bromoquinolines was satisfactory, giving the products **8–11** in good results. More importantly, the 4-, 3-, and 2-bromopyridines and their derivatives were found highly effective to give the products **12–21**. The pyridines decorated with substituents at C2 or C6 such as 2-F in **15** and 2-CF<sub>3</sub> in **13**, and 6-methyl in **18** were moderately effective, likely due to enhanced steric repulsive effect by the neighboring groups with respect to nitrogen. Noteworthy is the viability of 2-bromopyridine and its analogs for the arylation process that are notoriously difficult substrates in the Zn-mediated cross-electrophile couplings due to easy formation of bipyridine products.<sup>18</sup> The present method was also suitable for vinyl bromides as manifested by the examples of **22** and **23**. For electron-rich arenes, use of aryl iodides were necessary to promote the transformation by adding 2 equiv of NaI and 50 mol% of tetrabutylammonium iodide (TBAI) (Figure 2). Good to excellent yields were obtained for **24–30**. Comparable results were observed for 4- and 2-methoxy arenes **25** and **26**, indicating that ortho-substitution pattern is marginally influential. The chloro- and Bpin- groups were tolerated as in **27–28**. Heteroarenes such as 6-odo-2-methoxyquinoline, iodoindole, 9H-carbazole, 2-CF<sub>3</sub>-5-iodopyridine and 1-iodo-4-(trifluoromethyl)benzene were all compatible with the method, as shown by the examples of **32–35**. Finally, alkylation of the iodo analog of bioactive deschloroclofibrate, and iodo-(fluorophenyl)methylbenzylthiophene gave **36** and **37** in 85% and 56% yields, respectively.



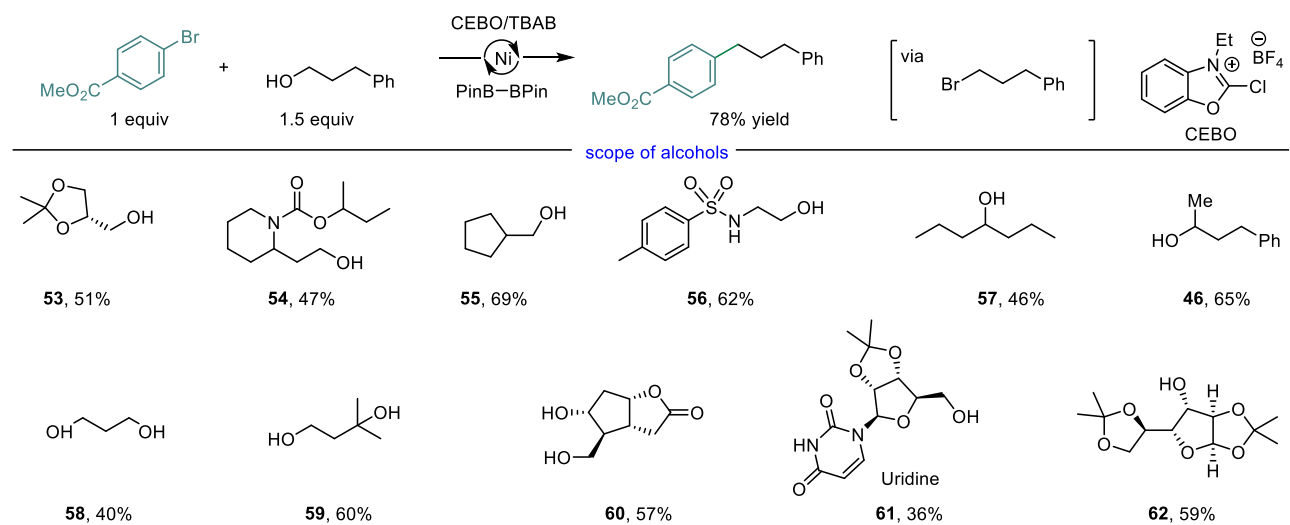
**Figure 2.** Optimization of the reaction conditions and scope of aryl halides. Note: (a) standard Method A was used for electron-deficient aryl bromides; (b) for heteroaryl bromide, a similar procedure to the standard method A was used, except that dtbpy (2.7 mg, 10 mol %) and NiCl<sub>2</sub>(Py)<sub>4</sub> (3.6 mg, 8 mol %) displaced (dtbbpy)NiBr<sub>2</sub>, and NaI (30 mg, 2 equiv), TBAI (18 mg, 0.5 equiv) were employed; (c) for electron rich aryl iodides, a similar procedure to the standard method A was used except that NaI (30 mg, 2 equiv), TBAI (18 mg, 0.5 equiv) and alkyl bromide (1.5 equiv) were employed.

Next, we studied the coupling efficiencies for the reaction methyl 4-bromobenzoate with a wide range of alkyl electrophiles. The primary and secondary alkyl bromides, iodides and mesylates were generally good to high yielding as evident by the examples of **38–50**, wherein the cyclic secondary alkyl electrophiles appeared to less effective (Figure 3). The method was also suitable for a range of alkyl–Katritzky pyridinium salts generating **1, 47, 51–52** in moderate to good yields (Figure 3).



**Figure 3.** Scope of alkyl electrophiles. Note: (a) unless otherwise noted, standard method A was used; (b) for the coupling of aryl halides with secondary alkyl bromides, a similar procedure to the standard method A was used, except that  $\text{Ni}(\text{OTf})_2$  (8 mol %), dtbpy (10 mol %) displaced  $\text{NiBr}_2(\text{dtbbpy})$ , and NaI (2 equiv), TBAI (0.5 equiv) and alkyl bromide (1.5 equiv) were employed; (c) for the coupling of alkyl-pyridinium salts, a similar procedure to the standard method A was used, except NaI (1 equiv), and alkyl-pyridinium salt (1.5 equiv) were employed.

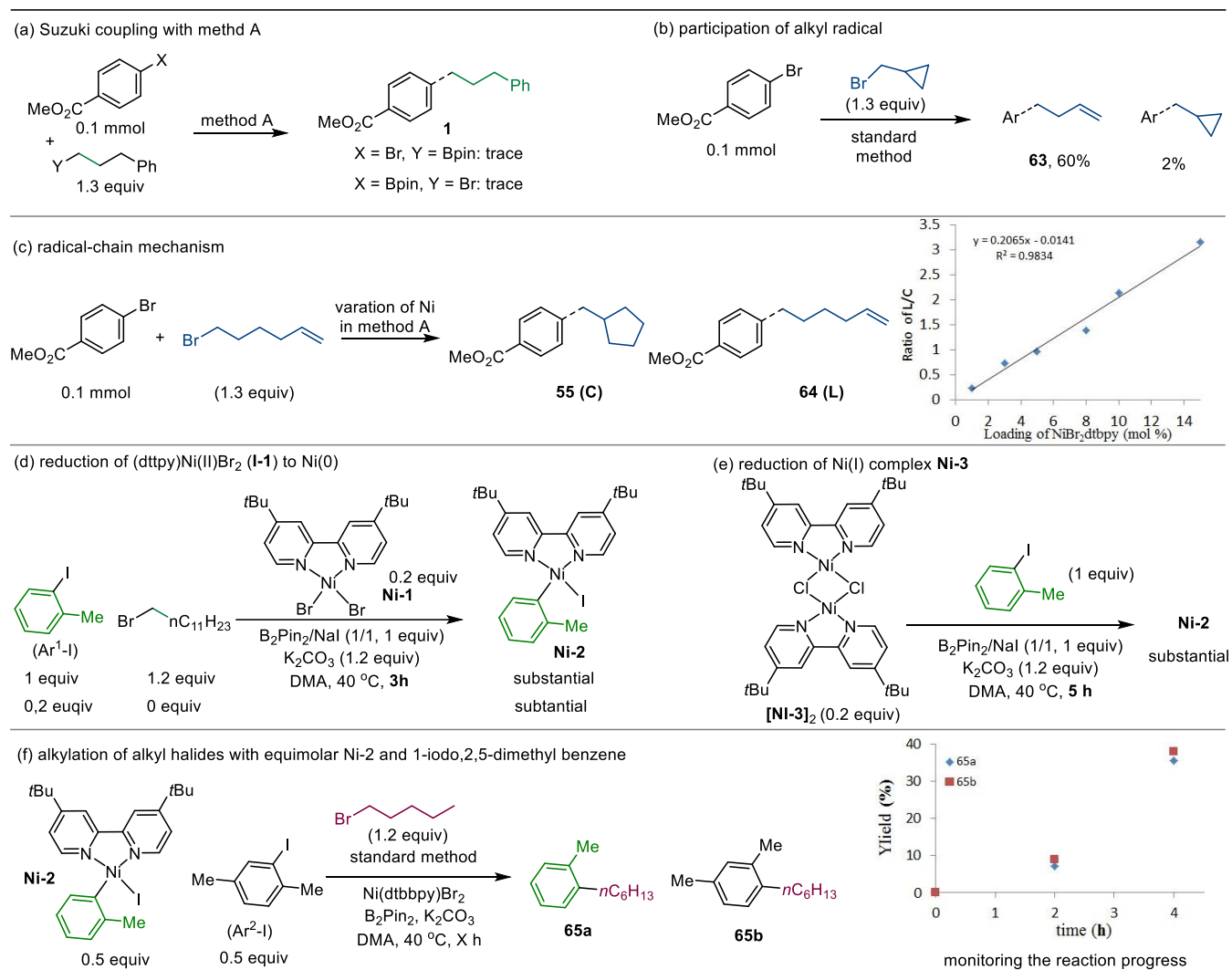
Finally, we combined our in-situ halogenation of alcohols method with the diboron-mediated coupling process, and developed a protocol for an in situ arylation of alcohols.<sup>19</sup> The previous report showed that CEBO/halide source was a powerful handle to convert the primary and secondary alcohols to their halide counterparts within 1–5 min. Such a technique enabled us to undertake a quick screening of a variety of primary and secondary alcohols to couple with methyl 4-bromobenzoate to give **53–57** in synthetically useful yields. The unprotected diols were also compatible with the diboron-mediated reductive coupling conditions, offering **58–60** in reasonably good results. The method was also showcased by facile functionalization of uridine and diacetone-D-glucose to give **61** and **62**.



**Figure 4.** Formal coupling of alcohols and diols with aryl halides. Note, Method B was used: alcohol (1.5 equiv) was treated with CEBO (1.5 equiv) and TBAB (1.5 equiv) in CH<sub>3</sub>CN (0.2 mL) for 5 min, before addition of the rest of ingredients as described in method A including 8 mol% NiBr<sub>2</sub>(dtbpy), 180 mol% B<sub>2</sub>Pin<sub>2</sub>, 180 mol% K<sub>2</sub>CO<sub>3</sub>, 50 mol% NaI, DMA (0.4 mL). The reaction was run at 60 °C.

## Mechanistic Studies

To understand the details of the reaction process, we first evaluated the possibility of in situ formation of organoboron ensued by a Suzuki mechanism. The reactions of (4-methoxycarbonyl)phenyl-Bpin with (3-bromopropyl)benzene, as well as phenylpropyl-Bpin with methyl 4-bromobenzoate did not give the coupling product **1** (Figure 5a), thus a mechanism of in situ Suzuki process was excluded. Next, bromocyclopropyl methane was used to couple with methyl 4-bromobenzoate. The reaction primarily furnished the ring-opening product **63**, implying alkyl radical nature of the method (Figure 5b). The coupling of methyl 4-bromobenzoate with 6-bromohex-1-ene as a radical clock was examined to give a mixture of the cyclized and linear products **55** and **64**. A linear dependence of their ratios on the concentration of Ni catalyst was observed, indicative of a radical-chain process, in which diffusion of alkyl radical to the bulk solution was suggested (Figure 5c).

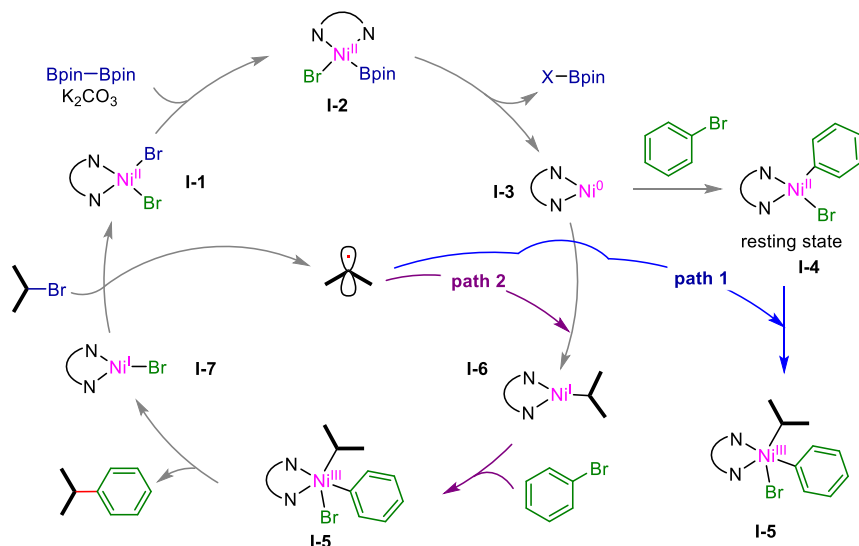


**Figure 5.** Mechanistic considerations.

Perhaps a more instructive result lies in the detection of substantial amount of (dtbpy)Ni<sup>II</sup>(Ar<sup>1</sup>)X (complex **Ni-2**) in the reaction mixture of 1 or 0.2 equiv of 2-methyl iodobenzene (Ar<sup>1</sup>-I) with or without (3-bromopropyl) benzene in the presence of 0.2 equiv of (dtbpy)Ni<sup>II</sup>Br<sub>2</sub> (complex **Ni-1**) or [dtbpyNi<sup>I</sup>Cl]<sub>2</sub> (**Ni-3**) and stoichiometric amount of B<sub>2</sub>Pin<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub> and NaI in DMA after 5 hours (Figures 5d and 5e, S1 and S3). A control experiment showed that the reduction of (dtbpy)NiBr<sub>2</sub> with B<sub>2</sub>Pin<sub>2</sub> in the absence of Ar<sup>1</sup>-I but with COD led to appreciable amount of (dtbpy)Ni<sup>0</sup>(COD) after 1 h (Figure S2). The collective results indicated that L<sub>n</sub>Ni<sup>II</sup>X<sub>2</sub> (**I-1**) can be effectively reduced to L<sub>n</sub>Ni<sup>0</sup> (**I-3**) by B<sub>2</sub>Pin<sub>2</sub> under the present reductive coupling conditions, likely through a L<sub>n</sub>Ni<sup>II</sup>(Bpin)X (**I-2**) (Scheme 1).<sup>20</sup> We then carried out a control experiment by submitting an equimolar mixture of **Ni-2** and 2,4-dimethyl bromobenzene (Ar<sup>2</sup>-I) (0.5 equiv) to the catalytic reaction containing 1.2 equiv of hexyl bromide, and observed that formation of product **65a** derived from Ar<sup>2</sup>-I was slightly preferred over **65b** arising from **Ni-2** (Figure 5f); a control study indicated that **Ni-2** was fairly stable in the absence of Ar<sup>2</sup>-I and hexyl bromide within 5 hours (Figures 5f and S1). These results suggested a well-established radical-chain mechanism that highlights trapping alkyl radical with L<sub>n</sub>Ni<sup>II</sup>(Ar)X (**I-4**) to give alkyl-L<sub>n</sub>Ni<sup>III</sup>(Ar)X (**I-5**) prior to reductive elimination of the alkyl-aryl product, should not account for a major catalytic path for this coupling event (Path 1, Scheme 1).<sup>21</sup> In Path 1, oxidative addition of ArX to L<sub>n</sub>Ni<sup>0</sup> (**I-3**) to give L<sub>n</sub>Ni<sup>II</sup>(Ar)X (**I-4**) is indispensable; thus, formation of **65a** would be outcompete with that of **65b**, because the concentration of **Ni-2** should be much higher than that of (dtbpy)Ni<sup>II</sup>(Ar<sup>2</sup>)I (**Ni-**



2'). The latter was formed in situ by oxidative addition of  $\text{Ar}^2\text{-I}$  to  $(\text{dttpy})\text{Ni}^0$ . Alternatively, we proposed that the interception of an alkyl radical with  $\text{L}_n\text{Ni}^0$  (**I-3**) to form  $\text{L}_n\text{Ni}^{\text{I}}\text{-R}_{\text{alkyl}}$  (**I-6**) was possible (path 2) or simultaneously operate with Path 1. Subsequently, oxidative addition of aryl halides to **I-6** leads to a key  $\text{Ar-L}_n\text{Ni}^{\text{III}}(\text{X})\text{-R}_{\text{alkyl}}$  (**I-5**) that delivers the coupling product associated with  $\text{L}_n\text{Ni}^{\text{I}}\text{X}$  (**Ni-7**). The subsequent halide abstraction of alkyl halide with **I-7** produces alkyl radical that diffuse to the bulk solution to combine with  $\text{L}_n\text{Ni}^0$  (**I-3**), and the associated  $\text{L}_n\text{Ni}^{\text{II}}\text{X}_2$  (**I-1**) was reduced by  $\text{B}_2\text{Pin}_2$  to afford  $\text{Ni}^0$  (**I-3**). This mechanistic scenario proposed in the present work appears to be supported by Rueping and Cavallo's recent DFT studies on the photo-induced/Ni-catalyzed  $\text{C}(\text{sp}^3)\text{-H}$  arylation with aryl halides, which favors oxidative addition of  $\text{ArX}$  to  $\text{L}_n\text{Ni}^{\text{I}}\text{-alkyl}$  over  $\text{ArX}$  to  $\text{L}_n\text{Ni}(0)$ .<sup>22</sup>



**Scheme 1.** Possible reaction paths for the reductive coupling event.

## Conclusion

In summary, we have illustrated that  $\text{B}_2\text{Pin}_2$  as the effective terminal reductant to mediate the Ni-catalyzed cross-electrophile coupling of alkyl electrophiles with aryl/vinyl halides to afford  $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^2)$  bonds. The method avoids the use of routine metallic reductants, and thereby is more environmentally benign and easy to scale up. The generality of the reaction was elucidated by a wide range of examples of electron-rich aryl iodides and electron-deficient aryl bromides including a number of heteroarenes, and alkyl electrophiles including halides, tosylates and Katritzky salts. Our mechanistic studies indicated that  $\text{B}_2\text{Pin}_2$  effectively reduced  $\text{Ni}(\text{II})$  salt to  $\text{Ni}(0)$  likely through ligand exchange followed by reductive elimination process, which differs from the electron-transfer reduction by metallic reductants. The second feature of the reaction mechanism is that the reaction may proceed through a radical chain process that emphasizes trapping the radical with  $\text{L}_n\text{Ni}^0$ , although the well-established mechanism involving interception of an alkyl radical with  $\text{L}_n\text{Ni}^{\text{II}}(\text{Ar})\text{X}$  may simultaneously operate. The use of diboron ester as the reductant may evoke more reductive coupling methodologies including those failed with the metallic reductants.

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## Competing interests

The authors declare no competing financial interests.

## Data availability

All data supporting the findings of this study are available within the paper and its Supplementary Information files.

## Additional information

Supplementary information and compound characterization data are available in the online version of the paper. Reprints and permissions information is available online at [www.nature.com/reprints](http://www.nature.com/reprints).

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