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Nickel-catalyzed cross-coupling of unactivated alkyl halides using bis(pinacolato)diboron as reductant†

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The use of bis(pinacolato)diboron as the terminal reductant allows the efficient Ni-catalyzed coupling of unactivated secondary and primary alkyl halides, generating the C(sp^3)–C(sp^3) coupling products in good yields. The mild catalytic conditions display excellent functional group tolerance, and good chemoselectivities which require only 1.5 equiv. of primary bromides for the coupling with secondary bromides. Preliminary mechanistic studies suggest that an *in situ* organoborane/Suzuki process is not likely. It was identified that the base and ligand have more profound impact on selecting this reductive coupling pathway. The good chemoselectivity appears to be evoked by the formation of Ni–Bpin catalytic intermediates, which demands matched sizes and reactivities of the alkyl halide coupling partners for optimal coupling efficiency.

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Introduction

The catalytic formation of C(sp^3)–C(sp^3) bonds is generally realized *via* transition-metal-catalyzed cross-coupling of alkyl electrophiles and organometallic nucleophiles.[1–10] The nickel-catalyzed methods in particular appear to be highly effective for the coupling on sp^3 carbon electrophiles, including sterically hindered secondary alkyl halides.[6–8] Although these conventional protocols are ideal in the sense of chemoselectivity, extra steps of conversion of the electrophilic precursors into alkylmetallic nucleophiles are generally required. In some cases, the formation of alkyl nucleophiles could be difficult, *e.g.*, for those bearing β-leaving groups.[9,10]

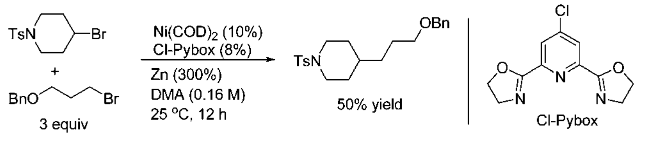
On the other hand, direct reductive coupling of two alkyl electrophiles can afford an alternative yet more facile method for the construction of alkyl–alkyl compounds,[11–13] considering alkyl halides are generally more accessible and easy-to-handle than alkyl nucleophiles. However the major challenge of this strategy resides in the poor selectivities between the two coupling alkyl electrophiles. In our previous study, although the use of zinc powder as the terminal reductant gave the coupling products in moderate yields, one of the coupling halides need to be 3 equiv.[13] Significant amounts of highly competitive homocoupling side reactions are observed, *e.g.*, >2 equiv. of ((3-bromopropoxy)-methyl)benzene underwent homocoupling in the reaction shown in Scheme 1, due in part to a statistically controlled mechanism. The Ni/Zn-catalytic conditions thus cannot effectively bias the two structurally similar alkyl coupling partners.

Herein, we report the efficient cross-coupling of two unactivated alkyl halides, employing bis(pinacolato)diboron as the reductant, with which good coupling yields can be achieved using only 1.5 equiv. of primary bromides for the coupling with secondary bromides. To the best of our knowledge, this work should represent the first efficient coupling of unactivated alkyl halides using boron as the terminal reductant.[14] Our initial studies indicated that the *in situ* Suzuki mechanism is not operative, which bypasses the formation of alkyl boronate esters as evidenced in the recent Ni-, Pd-, and Cu-catalyzed borylation of alkyl halides (Scheme 2).[15]

Results and discussions

Homocoupling of secondary and primary bromides

We first studied the homocoupling of unactivated alkyl halides **1a** and **2a** (Table 1), and identified that NiI$_2$, NMP (*N*-methylpyrrolidone) and LiOMe were superior to other Ni sources, solvents and bases.[16] Examination of the ligands indicated that **7a** was optimal for **1a** at 45 °C (Table 1, entry 3), and **8a** was optimal for **2a** using reduced catalyst and ligand loading (Table 1, entry 4), producing **3** and **4** in 74% and 99% yields, respectively.[16] The primary alkyl tosylate-, iodo-, and chloro analogs **2b–d** delivered **4** in 94% (45 °C), 70%, and 70% (with



Scheme 1 Coupling of ((3-bromopropoxy)methyl)benzene and 4-bromo-1-tosylpiperidine.

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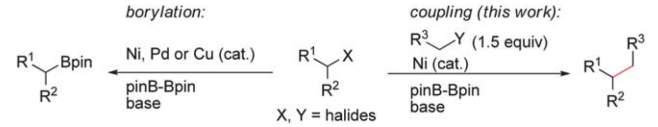
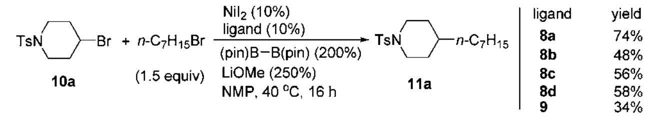
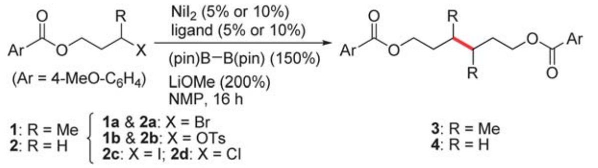


Scheme 2 Alkyl borylation *vs.* alkyl–alkyl coupling.



Scheme 3 Cross-coupling of **10a** and *n*-heptylbromide.

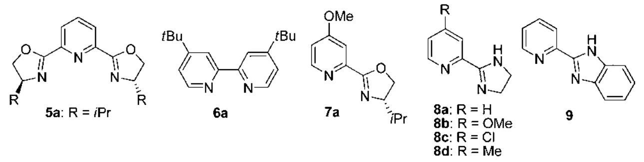
Table 1 Optimization for the dimerization of **1** and **2**[a]



				Yield[b] (%)	
Entry	X (**1** or **2**)	Ligand	°C	**3** (R = Me)	**4** (R = H)
1	Br (**1a** or **2a**)	**5a**	30	35	80
2	Br (**1a** or **2a**)	**6a**	30	22[c]	NA[d]
3	Br (**1a** or **2a**)	**7a**	45	74	86
4	Br (**1a** or **2a**)	**8a**	30	50	99[e]
5	OTs (**1b** or **2b**)	**8a**	45	NA[d]	94
6	I (**1c** or **2c**)	**8a**	30	NA[d]	70
7	Cl (**1d** or **2d**)	**8a**	80	NA[d]	70[f]

[a] **1** or **2** (100 mol%, 0.16 M in NMP), NiI_2 (10 mol%), ligand (10 mol%), $(Bpin)_2$ (150 mol%), LiOMe (200 mol%), NMP (1 mL), 16 h. [b] Isolated yields; for **3**, an inseparable mixture of diastereomers was collected. [c] HPLC yield (see the ESI†). [d] Not available. [e] 5% NiI_2 and 5% ligand were used. [f] Similar conditions to **2a** except 1 equiv. of Bu_4NBr was added.

Bu_4NBr) yields, respectively (Table 1, entries 5–7). Possible iodo/tosylate exchange may account for the reactivity of **2b** as $Ni(COD)_2$ was ineffective.[16]



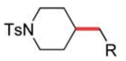
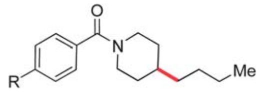
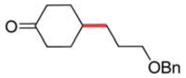
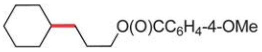
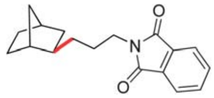
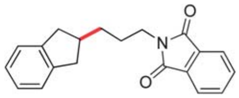
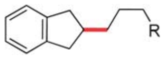
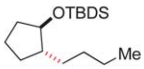
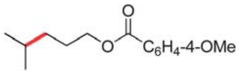
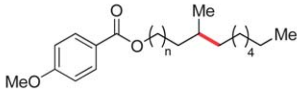
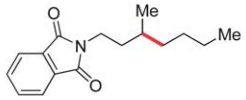
Cross-coupling of secondary and primary halides

(1) Cross-coupling of secondary and primary bromides. We next examined whether cross-coupling between a 2° and a 1° alkyl halide is feasible. To our delight, under the optimized reaction conditions for **2a** (Table 1, entry 4), the desired coupling product **11a** was obtained in 50% yield using only 1.5 equiv. of *n*-heptyl bromide for the coupling with **10a**. Raising the temperature to 40 °C, doubling the concentration of **10a** in NMP, and using 2 equiv. of $B_2(Pin)_2$ and 2.5 equiv. of LiOMe boosted the yield to 74% (Scheme 3). The use of 2 equiv. of *n*-heptyl bromide slightly increased the yield to 77%. Tuning the ligand structures as in **8b–d** and **9** did not yield better results. The use of bis(neopentyl glycolato)diboron and bis(hexylene glycolato)diboron gave **11a** in 50% and 68% yields, respectively. Under the optimized conditions, the use of *n*-heptyl bromide as the limiting regent for the coupling with 1.5 equiv. of **10a** only delivered **11a** in 46% yield, implying that the intrinsic selectivity arising from the substrates and catalysts takes effect.

Under the optimized reaction conditions, the scope and limitations of alkyl bromides were explored, affording **12–28** (Table 2). Both cyclic and open-chain secondary alkyl bromides were generally competent providing the coupling products in moderate to good yields. Notably, substrates containing β-leaving groups also afforded the coupling products **21–24** in reasonably good results (Table 2, entries 10–13). In general, the side reactions for the primary halides primarily arose from homocoupling, whereas those for the secondary bromides were from hydrodehalogenation and homocoupling, along with recovered starting materials (*vide infra*). The reactions tolerated a range of functional groups, including ester, acteal, ketone, amide containing NH proton (Table 2, entry 11), cyanide, and silyl ether. However, the sterically more congested primary bromides, and secondary bromides lacking in polar functional groups appeared to be less efficient as evident in **15**, **19–20** and **25** (Table 2, entries 4, 8–9, 14).[17]

(2) Cross-coupling involving alkyl iodides, chlorides and tosylates. Interestingly, in a sharp contrast to bromocyclohexane (Table 2, entry 8), the coupling of **2a** with iodocyclohexane under the standard conditions generated **19** in 60% yield (Table 3, entry 1). A 1.5 to 1 molar ratio of iodocyclohexane to **2a** further boosted the yield to 77% (Table 3, entry 2). The generality of using iodo surrogates for unfunctionalized secondary bromides can be evidenced in the efficient synthesis of **29**, **20** and **25** (Table 3, entries 3–5). The effectiveness of 5-bromopentyl 4-methoxybenzoate (Table 3, entry 3) under these modified conditions suggests an inductive effect on primary bromides is not crucial. Application of the modified methods to the sterically bulky primary iodide, *e.g.*, 1-iodo-2-methylpropane for the coupling with secondary bromide **10a** was not successful (Table 3, entry 6). Next, we examined the coupling efficiency of secondary bromide **10a** with *n*-heptyl chloride, tosylate, and iodide (Table 3, entries 7–9). It was revealed that only the primary tosylate gave a moderate coupling yield. The chloride (in the presence of Bu_4NBr) and iodide analogs were ineffective. In contrast, the coupling of iodo analog **10b** with *n*-butyl iodide generated **11b** in a 43% yield, implying that a matched reactivity between the two coupling partners is an important factor for better cross-coupling efficiency (Table 3, entry 10).

Table 2 Coupling of secondary with primary alkyl bromides[a]

Entry	Product		Yield[b]
1		**12**, R = $Ph(CH_2)_2$	79
2		**13**, R = $BnO(CH_2)_2$	75
3		**14**, R = (1,3-dioxolan-2-yl)methyl	80
4		**15**, R = *i*Pr	40[c]
5		**16**, R = H	85
6		**17**, R = CN	83
7		**18**	70
8		**19**	15
9		**20**	45[d]
10		**21**	63
11		**22**, R = CbzNH	74
12		**23**, R = 4-MeO-$C_6H_4C(O)O$	74
13		**24**	61
14		**25**	Trace
15		**26**, *n* = 1	70
16		**27**, *n* = 2	60
17		**28**	67

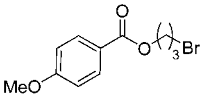
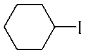
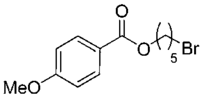
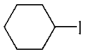
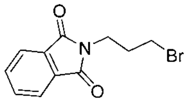
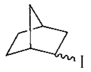
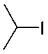
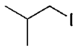
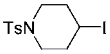
[a] Standard reaction conditions: secondary bromide (100 mol%, 0.32 M in NMP), primary bromide (150 mol%), NiI_2 (10 mol%), **8a** (10 mol%), $(Bpin)_2$ (200 mol%), LiOMe (250 mol%), NMP (0.5 mL), 40 °C, 16 h. [b] Isolated yields. [c] The yield was estimated by NMR analysis of an inseparable mixture containing the product of hydrodehalogenation of **10a**. [d] *Exo* : *endo* > 20 : 1.

Cross-coupling of secondary with secondary, and primary with primary halides

The cross-coupling of **2a** and *n*-heptyl bromide or (3-bromopropoxy)benzene which possess similar steric demands gave the coupling products **30** and **31** in moderate yields (Table 4, entries 1–3). The ratio of 1 : 1.5 or 1.5 : 1 of the coupling partners did not seem to be important (Table 4, entries 1–3). The tosylate analog **2b** generated comparable coupling results (Table 4, entries 4–5). The coupling yields for **2a** with 1-bromo-2-methylpropane and the more hindered 1-bromo-2,2-dimethylpropane were both low, with the former being better (Table 4, entries 6–7). This is possibly due to low reactivity of hindered primary bromides. It was interesting, however, to note that in contrast to a moderate yield for the coupling of 1-iodo-2-methylpropane and **2a** (Table 4, entry 8), reactions of 1-iodo-2,2-dimethylpropane with primary bromides afforded **33** and **34** in high yields, suggesting that a steric effect is a pivotal factor for the origin of selectivity (Table 4, entries 9–10). The much improved coupling efficiency for 1-iodo-2,2-dimethylpropane as compared to the bromo-analog is supportive of a matched reactivity between the two coupling partners being important (Table 4, entries 7 and 9).

The coupling of two secondary halides, such as **10a** and cyclohexylbromide was not satisfactory (Table 4, entries 11–13); only 20% of the desired product **35** was observed. The secondary iodide and bromide were primarily converted into hydrodehalogenation byproducts.[16]

Table 3 Coupling involving alkyl iodides, tosylates and chlorides[a]

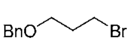
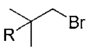
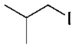
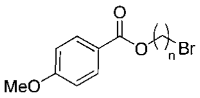
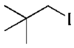
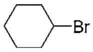
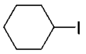
Entry	R^1X	R^2Y	R^1X/R^2Y	Product	Yield[b] (%)
1			1.5 : 1	**19**	60
2			1 : 1.5		77
3			1 : 1.5	**29**	66
4			1 : 1.5	**20**	65[c]
5	**2a**		1 : 1.5	**25**	50
6	**10a**		1 : 1.5	**15**	Trace
7	**10a**	n-$C_7H_{15}Cl$	1 : 1.5	**11a**	Trace
8	**10a**	n-$C_7H_{15}OTs$	1 : 1.5	**11a**	48
9	**10a**	n-$C_7H_{15}I$	1 : 1.5	**11a**	Trace
10	**10b**: 	n-C_4H_9I	1 : 1.5	**11b**	43

[a] Reaction conditions as in Table 2. [b] Isolated yield. [c] *Exo* : *endo* > 20 : 1.

Side reactions in the cross-coupling process

In order to understand the details of the reactions, we tracked the reaction progress of **10a** with 1.5 equiv. of ((3-bromopropoxy)methyl)benzene ($BnO(CH_2)_3Br$) (Table 2, entry 2). During the course of the reaction, in addition to formation of the product **13**, the primary bromide gradually dimerized, whereas **10a** was transferred into homocoupling and hydrodehalogenation byproducts (Fig. 1). At 16 h, the yield for **13** was 75% (with respect to 1 equiv. of **10a**). While ~40% of the primary bromide (with respect to 1.5 equiv. of primary bromide) was converted into the homocoupling product, ~15% of which is recovered; ~10% of **10a** was recovered along with <10% of the homocoupling and ~5% of the hydrodehalogenation

Table 4 Cross-coupling of primary with primary and secondary with secondary alkyl halides[a]

Entry	R^1X	R^2Y	R^1X/R^2Y	Product	Yield[b] (%)
1	**2a**	n-$C_7H_{15}Br$	1 : 1.5	**30**	55
2			1.5 : 1		52
3	**2a**		1 : 1.5	**31**	52
4	**2b**	n-$C_7H_{15}Br$	1 : 1.5	**30**	50
5			1 : 1.2		48
6	**2a**		1 : 1.5	**32**, R = H	34
7			1 : 1.5	**33**, R = Me	19
8	**2a**		1 : 1.5	**32**	45
9			1 : 1.5	**33**, $n = 3$	74
10			1 : 1.5	**34**, $n = 5$	80
11	**10a**		1 : 1.5	**35**	20
12	**10a**		1 : 1.5	**35**	10
13	**10b**		1 : 1.5		5

[a] Reaction conditions as in Table 2. [b] Isolated yield.

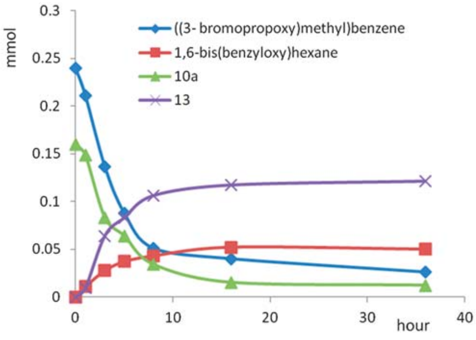


Fig. 1 Reaction profile of **10a** with ((3-bromopropoxy)methyl)benzene.

byproducts. Interestingly, >0.3 equiv. of $(Bpin)_2$ can be recovered. The use of 1.7 equiv. of $(Bpin)_2$, however, slightly diminished the yield to 70%. The reaction seems to slow down after 8 h and almost stops after 16 h, leaving ~10% of both halides being recovered even after 36 h.[18]

Interestingly, under the same standard reaction conditions in the absence of **10a**, $BnO(CH_2)_3Br$ rapidly dimerized within 1 hour (~90%), whereas **10a** in the absence of $BnO(CH_2)_3Br$ was gradually converted into the hydrodehalogenation product (>70%) within 16 hours (Fig. 2).[16] This observation indicates that the homocoupling rate for the primary bromide is significantly slowed down when the secondary bromide is present, and the coupling of two secondary halides is not favored, possibly due to steric hindrance.

The collective data of product distribution for different reactions that support side reactions of primary halides generally arises from homocoupling (Tables S13 and S14†),[16] whereas the side reactions of secondary halides comprise homocoupling and hydrodehalogenation. More importantly, substantial amount of unreacted $(Bpin)_2$ (>0.3 equiv.) and secondary bromides can be recovered in many examples in Tables 2–4.[16]

Mechanistic considerations

(1) Non-*in situ* Suzuki process. Fu has demonstrated that borylation of secondary alkyl bromides is kinetically more favored than primary alkyl bromides under $NiBr_2$/**5a**-catalyzed conditions.[15a] *In situ* Suzuki coupling is therefore a possible explanation for the selective coupling in this method. The coupling of alkyl bromides **2a**, **10a** and 3-phenylpropyl bromide with alkyl-Bpin **36** and **37** in the presence of $(Bpin)_2$ did not provide the Suzuki coupling products. Rather, the alkyl-Bpin derivatives were primarily recovered along with the products of homocoupling of the primary alkyl bromides or hydrodehalogenation of **10a** (Scheme 4).[16] These observations suggest that alkyl-Bpin does not participate in the reductive coupling process, and therefore an *in situ* alkyl-Bpin/Suzuki sequence is less plausible. Thus, the coupling of **10a** with **38** reasonably afforded **39** in good yield.

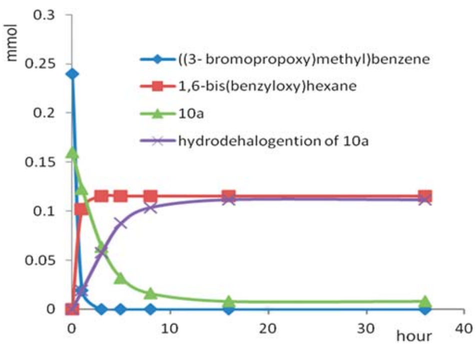
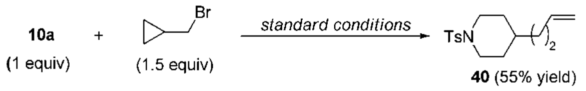
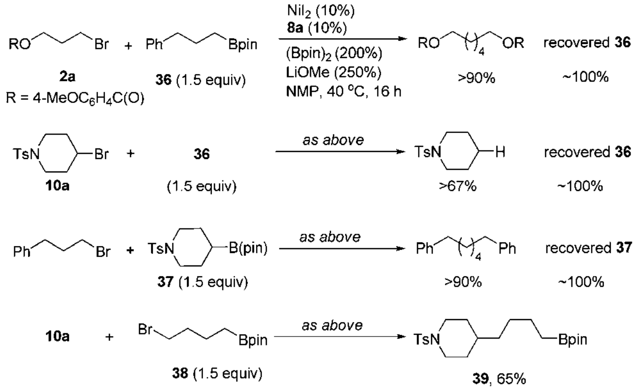


Fig. 2 Reaction profiles of **10a** and ((3-bromopropoxy)methyl)benzene that were independently run under the standard cross-coupling reaction conditions.

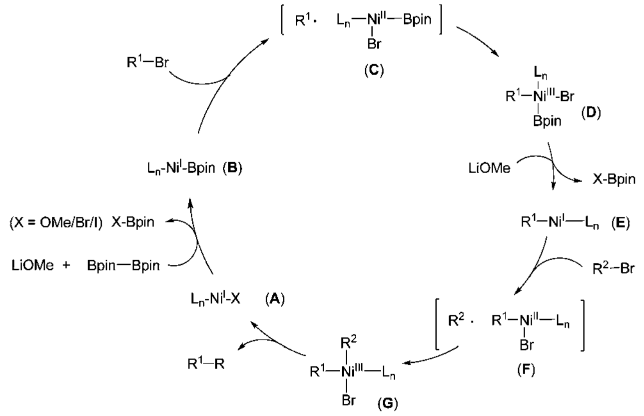
(2) Radical process. Moreover, the coupling of **10a** with (bromomethyl)cyclopropane furnished ring opening product **40** in 55% yield (eqn (1)), suggesting that alkyl radical intermediates were generated during the course of coupling.[19,20] The involvement of alkyl radicals has been suggested in the oxidative addition of $R_{alkyl}{}^1$–Ni^I or Bpin–Ni^I intermediates to $R_{alkyl}{}^2$–X in the recent mechanistic considerations on Ni-catalyzed Miyaura borylation, and alkyl–alkyl Negishi and Suzuki coupling reactions.[15a,21,22]

 (1)

(3) Proposed catalytic cycle. We proposed a catalytic cycle as in Scheme 5. Borylation of the Ni^I–X complex (**A**) offers a Bpin–Ni^I species **B**, which undergoes a one electron transfer to R^1–X, leading to R^1 radical and a Ni^{II} intermediate **C**, followed by rapid combination to afford Bpin–$Ni^{III}(R^1)$–Br (complex **D**) (Scheme 5).[15a] Subsequent elimination of Bpin–X (X = Br or OMe, *etc.*) gives an R^1–Ni^I species **E**, which oxidatively adds to R^2–Br, involving rapid combination of the R^2 radical and a Ni^{II} complex **F** to produce an R^1–Ni^{III}–R^2 intermediate **G.** Reductive elimination of **G** gives the product and regenerates Ni^I–X complex **A.** In contrast to Fu's proposal in the Ni-catalyzed borylation of alkyl halides, the elimination of R^1–Bpin from complex **D** may become energetically disfavored under our reaction conditions.[15a]



Scheme 4 Coupling of alkyl bromides with alkyl-Bpin.

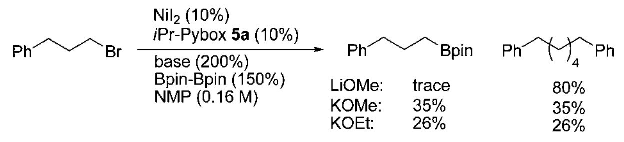


Scheme 5 Proposed reaction pathways.

(4) Alkyl borylation *vs.* reductive coupling. Investigation of the key factors favoring Fu's borylation and our reductive coupling products reveals that the bases and ligands are more significant in altering the product formation. Using (3-bromopropyl)benzene as the model substrate and *i*Pr-Pybox **5a** as the ligand, the trace amount of borylation of (3-bromopropyl)benzene using LiOMe in our procedure can be boosted to 26% using KOEt, and 35% using KOMe. This clearly demonstrates that the lithium cation plays an important role in reductive homocoupling (Scheme 6).[16] In addition, even with KOMe being the base, the dimerization product of (3-bromopropyl)benzene was obtained in 60% yield using **8a** as the ligand.

Therefore, the use of **8a** and LiOMe without premixing with $(Bpin)_2$ in NMP may facilitate formation of complex **E** from complex **D**. We speculate that reductive elimination of Br–Bpin from complex **D** is less likely. If it occurs, subsequent conversion of Br–Bpin into the more stable MeOBpin may be crucial. Alternatively, complex **E** may directly arise from nucleophilic attack of methoxide on the boron of complex **D**.

(5) Origin of the cross-coupling selectivity. The present Ni/$(Bpin)_2$ reductive cross-coupling method is effective for reactions between secondary and primary halides, and between hindered primary iodide and a less hindered primary bromide, wherein the more reactive alkyl halides are in excess. It however is not efficient for the coupling between two secondary halides varying polar substituents, and between hindered primary and secondary halides, as well as between a tertiary and a primary bromide.[23] Hence, only matched sizes and reactivities of the alkyl halides deliver the optimal cross-coupling selectivities.



Scheme 6 Comparison of the effect of bases.

Conclusions

In summary, we present a mild, easy-to-handle Ni-catalyzed reductive coupling of two alkyl halides displays high chemoselectivity between primary and secondary alkyl halides, which allows excellent functional group tolerance, and provides alkyl–alkyl coupling products in good to excellent yields. The coupling efficiency can be higher considering that a substantial amount of $(Bpin)_2$ (>0.3 equiv.) and secondary bromides may be recovered.[16] Given that the known Ni-catalyzed Suzuki method for the construction of $C(sp^3)$–$C(sp^3)$ bonds requires excess alkylboranes (>1.5 equiv.),[8] and Ni/Cu-catalyzed formation of alkyl-Bpin generally requires excess pinB–Bpin (1.2–1.5 equiv.),[15] the current method that avoids the extra step of preparation of alkylboranes may be practically useful in terms of atom economy. Our preliminary studies suggest that an *in situ* alkylboronate ester/Suzuki process is less likely. Instead, we propose a mechanism involving a double oxidative addition of alkyl halides to Ni^I. With suitable choices of base and ligands, the formation of Ni–Bpin complexes may be the key to differentiating the coupling alkyl partners.

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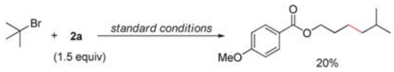

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