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Nickel-Catalyzed Ipso-Borylation of Silyloxyarenes via C−O Bond Activation

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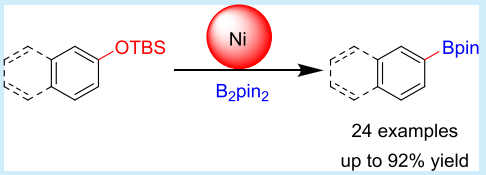
ABSTRACT: The conversion of silyloxyarenes to boronic acid pinacol esters via nickel catalysis is described. In contrast to other borylation protocols of inert C−O bonds, the method is competent in activating the carbon−oxygen bond of silyloxyarenes in isolated aromatic systems lacking a directing group. The catalytic functionalization of benzyl silyl ethers was also achieved under these conditions. Sequential cross-coupling reactions were achieved by leveraging the orthogonal reactivity of silyloxyarenes, which could then be functionalized subsequently.

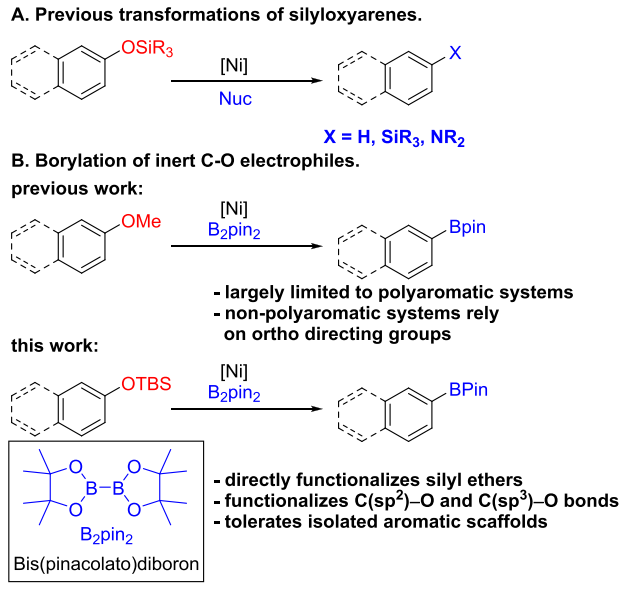


In recent years, employing Earth-abundant base metals including nickel for catalysis has been of great interest due to their ability to provide a more sustainable and affordable option while offering distinctive reactivity compared with precious metal alternatives.[1] In pursuit of this goal, much has been learned regarding the special properties of nickel that differentiate it from its congener palladium, such as nickel's propensity to activate low-reactivity C−O bonds.[2] Developing cross-coupling reactions that employ C−O electrophiles is desirable due to the abundance and diversity of phenol derivatives that are commercially available and present in natural products. Furthermore, the reactivity of the C−O bond can be modulated greatly depending on the protecting group being employed.[3a]

Taken together, aryl halides and phenol derivatives provide a wide range of reactivity and stability, which presents opportunities for orthogonal reactivity among different substrate classes utilized in cross-couplings.[3b,c] This enables functionally dense aryl scaffolds possessing differentiated electrophilic sites to be engaged in sequential couplings via judicious selection of catalyst type. Whereas a diverse range of effective cross-coupling methods have been developed utilizing aryl halides, triflates, and pivalates, methods employing low-reactivity aryl C−O electrophiles such as simple ethers often require highly reactive organometallic coupling partners such as Grignard reagents, extended naphthol-derived electrophiles, and/or directing groups that promote reactivity.[4] To bridge this gap, we have explored silyloxyarenes as coupling partners. Although silyloxyarenes have most commonly seen usage in reactions with activated nucleophilic coupling partners,[5] recent reports from our lab show that electron-rich nickel *N*-heterocyclic carbene (Ni-NHC) catalyst systems facilitate the reduction, silylation, and amination of silyloxyarenes in a manner that is inclusive of isolated aromatic systems without the need for *ortho*-directing groups.[6,7] In this report, we describe the application of this strategy in silyloxyarene borylations, as aryl boronic acid pinacol esters serve as excellent handles for downstream functionalization[8] and serve as precursors for medicinally relevant boronic acids (Scheme 1).[9]

Traditional synthetic organic methods to access aryl boronic acids involve the treatment of borates with organolithium reagents.[10] Attractive methods have also been described for the light-mediated and transition-metal-catalyzed reactions ena-

Scheme 1. Couplings of Aryl Ethers



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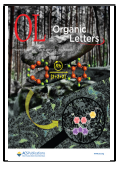

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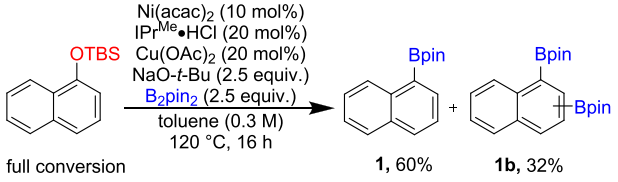
bling the borylation of aryl halides and aryl C−H bonds.[11] More recently, C−O electrophiles have been utilized as precursors to aryl boronic acids, although opportunities for improvement include avoiding easily hydrolyzed activating groups and providing improved reactivity with isolated aromatic ring substrates.[12−16]

To address the above limitations regarding borylation of C−O bonds, silyloxyarenes offer a number of promising attributes. They offer ease of synthesis and possess well-understood reactivity profiles, owing to detailed investigations of silyl ethers as protecting groups. This latter understanding gives rise to predictable strategies to tune their reactivity and stability across a range of reaction conditions,[17] enabling them to be carried through several synthetic steps, functionalized without additional deprotection and activation steps, leaving them available for further functionalization. Given the balance between the stability and reactivity of silyloxyarenes in comparison to other inert C−O electrophiles, this study sought to enable the inclusion of substrates that go beyond naphthyl systems while using attractive diboron coupling partners.

Optimization efforts utilizing *tert*-butyl dimethylsilane (TBS) protected 2-napthol as a model substrate were first explored as TBS groups provided an ideal balance of reactivity and stability in previous functionalizations of silyloxyarenes. Conditions were also guided by previous studies wherein electron-rich Ni-NHC catalyst systems were shown to be effective in conjunction with *tert*-butoxide bases in toluene using $Cu(OAc)_2$ to aid the transmetalation step (Scheme 2).[6,7,18] Under these conditions, however, moderate yields and

Scheme 2. Preliminary Hit

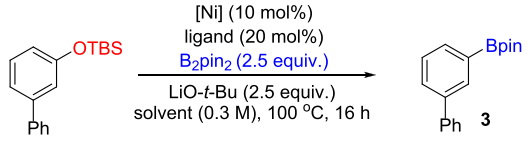


overborylation of the desired product were observed, providing a mixture of regioisomers (**1b**, Scheme 2) along with borylation of the toluene solvent.[19,20] Competing borylation of C−H bonds was not observed in borylations of isolated aromatic rings (*vide infra*).

Further optimization was conducted with a silylated 3-phenylphenol derivative as the model substrate, as we anticipated that optimization using this substrate would address the challenges of C−O activations in biphenyls and isolated aromatic systems. To eliminate solvent-derived side product formation, nonarene solvents were investigated, starting with ethereal solvents that matched the boiling point profile for the requisite reaction temperature (Table 1, entries 1 and 2). Cyclopentyl methyl ether (CPME) as the solvent greatly enhanced the yield of the desired product and eliminated solvent-derived side products. Furthermore, it was found that, in this solvent, $Cu(OAc)_2$ was no longer required to promote the reaction, though it did not hinder yields (Table 1, entry 3). However, nickel and ligand were essential for starting material conversion (Table 1, entries 4 and 5).

Representative Ni(0) and Ni(II) salts were screened, but were found to not be as effective as $Ni(acac)_2$ (Table 1, entries 6 and 7). Phosphine ligands were ineffective (Table 1, entry 8),

Table 1. Optimization for the Borylation of Silyloxyarenes



entry	metal	ligand	solvent	yield (%)[a]
1	$Ni(acac)_2$	IPr^{Me}·HCl	Dioxane	32
2	$Ni(acac)_2$	IPr^{Me}·HCl	CPME	82[b]
3	$Ni(acac)_2$	IPr^{Me}·HCl	CPME	80
4	none	IPr^{Me}·HCl	CPME	0
5	$Ni(acac)_2$	none	CPME	0
6	$Ni(cod)_2$	IPr^{Me}·HCl	CPME	48
7	$NiBr_2$	IPr^{Me}·HCl	CPME	49
8	$Ni(acac)_2$	PCy_3	CPME	0
9	$Ni(acac)_2$	IPr·HCl	CPME	57
10	$Ni(acac)_2$	IPr^{*OMe}·HCl	CPME	5.0
11	$Ni(acac)_2$	IPr^{Me}·HCl	CPME	72[c]
12	$Ni(acac)_2$	IPr^{Me}·HCl	CPME	32[d]
13	$Ni(acac)_2$	IPr^{Me}·HCl	CPME	41[e]
14	$Ni(acac)_2$	IPr^{Me}·HCl	CPME	80[f]
15	$Ni(acac)_2$	IPr^{Me}·HCl	CPME	0[g]

[a]Yields were determined by ^{1}H NMR with CH_2Br_2 as internal standard. [b]$Cu(OAc)_2$ (20 mol %) was added. [c]NaO-*t*-Bu used instead of LiO-*t*-Bu. [d]KO-*t*-Bu used instead of LiO-*t*-Bu. [e]B_2pin_2 (2.0 equiv), LiO-*t*-Bu (2.0 equiv). [f]B_2pin_2 (3.0 equiv), LiO-*t*-Bu (3.0 equiv). [g]HBpin used instead of B_2pin_2.

and incorporation of methyl groups on the NHC backbone were essential for optimal reactivity as notable yield decreases were observed with IPr·HCl. Although IPr^{*OMe}·HCl had been effective in reductions of silyloxyarenes, it was not effective in borylations (Table 1, entries 9 and 10). Bases were next explored as yields can vary greatly in the functionalizations of low-reactivity C−O with the cation playing a Lewis acidic role to aid oxidative addition.[18] LiO-*t*-Bu was optimal as NaO-*t*-Bu delivered product in slightly lower yields and KO-*t*-Bu provided low yields (Table 1, entries 3, 10−12). Equivalents of B_2pin_2 were reduced to minimize overborylation, but yields were greatly reduced, while increasing B_2pin_2 offered a neglible change in yield (Table 1, entries 13 and 14). Alternatively, pinacol borane (HBpin) provided none of the desired product (Table 1, entry 15).

With optimized conditions in hand, the scope for the ipso-borylation of silyloxyarenes was explored (Scheme 3). The reaction scope was broad, providing good to excellent yields for a variety of silyloxyarenes without deviating from the standard conditions. Although a control experiment indicated that silyloxyarenes can react with aryl boronic acid pinacol esters, in no case was the Suzuki byproduct derived from further reaction of the aryl boronic acid pinacol ester (Aryl BPin) observed. For naphthyl and biphenyl systems, full conversion was generally observed, wherein the remaining mass balance could be attributed to overborylation of the desired product, resulting in a mixture of regioisomers. However, trace quantities of overborylation were typically observed for isolated aromatic systems. Unfortunately, optimization efforts did not improve conversion of starting material to the desired product in the case of naphthyl systems; however, it is worth noting that borylation can be achieved at both the 1 and 2 position of the naphthyl unit (compounds **1** and **2**, Scheme 3). A more favorable product distribution was

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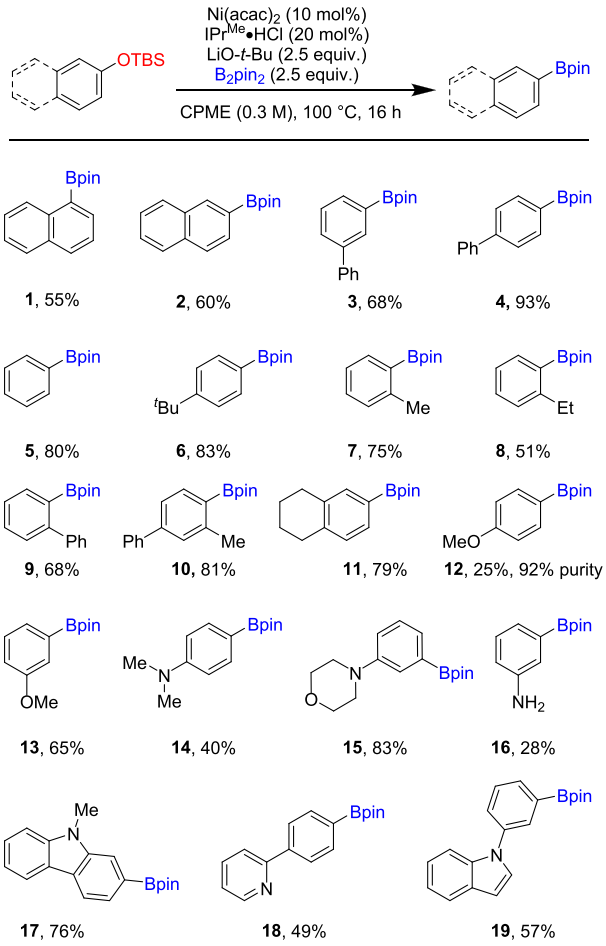
Scheme 3. Scope for Borylation of Silyloxyarenes

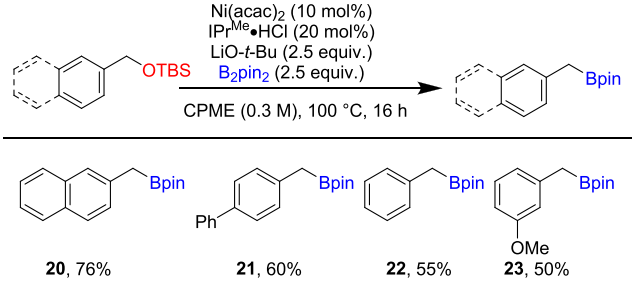


observed with the less activated biphenyl (compound **3**, Scheme 3) systems, although reduced yields due to over-borylation were still observed to some extent. A biphenyl system possessing substitution at the 4 position proved to be less susceptible to this issue, providing an excellent yield of the desired product (compound **4**, Scheme 3).

Notably, the reaction was effective with isolated aromatic systems, and in these cases, the remainder of the mass balance was typically starting material and small quantities of proto-deboronation product (compounds **5** and **6**, Scheme 3). The process proved to be tolerant of sterics both at the *ortho* position and at other sites around the ring either in isolated aromatics (compounds **7** and **8**) or with biphenyl substrates (compounds **9** and **10**, Scheme 3). Tolerance to sterics was improved when biphenyl scaffolds were subjected to reaction conditions (compounds **9** and **10**, Scheme 3). Substrates bearing electron-donating groups (EDGs) were examined, demonstrating that oxygen and nitrogen groups could be incorporated (compounds **13**, **15**, Scheme 3); however, when the EDG was at the *para* position, decreases in yield were observed (compounds **12**, **14**, Scheme 3). Notably, methyl ethers, which can serve as electrophiles in subsequent coupling reactions, were tolerated as illustrated by products **12** and **13**. Although in moderate yield, the reaction proceeded on an unprotected aniline (compound **16**, Scheme 3) and a variety of heterocycles including indoles, carbazoles, and pyridines in good yields (compounds **17**–**19**, Scheme 3).

Benzylic silyl ethers were also effective substrates, providing good yields of benzyl Bpins, even in the case of simple isolated aromatic substrates (compounds **21** and **22**, Scheme 4).

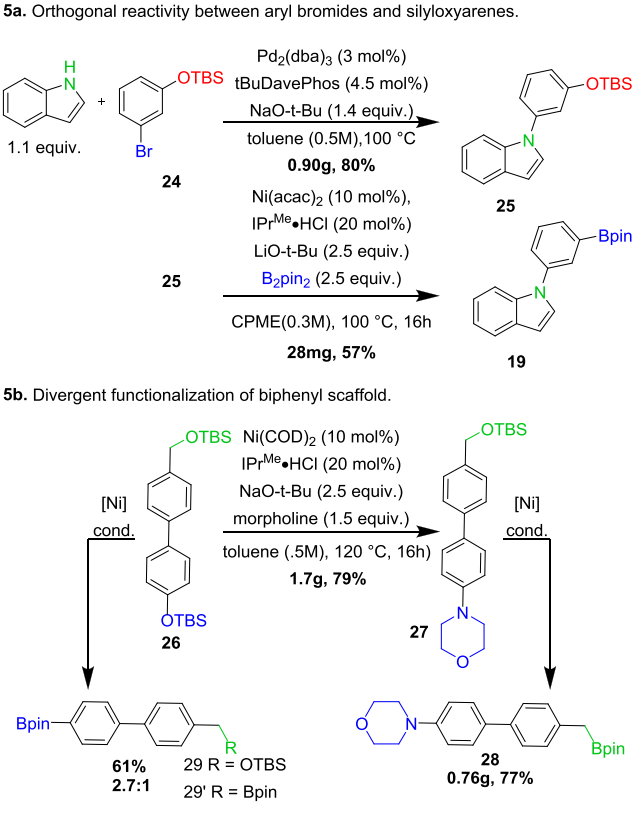
Scheme 4. Examples of C(sp^3)–O Borylation



Notably, an electron-rich methoxy group was tolerated in this series as well (compound **23**, Scheme 4). While yields for benzylic substrates are moderate, the borylation of benzylic methyl ethers that contain isolated aromatic systems have not been demonstrated, representing an advancement in the area.[16] Although the reaction conditions performed well on a range of substrates, the reaction did have limitations, including substrates where aryl fluorides (Table S1) or isolated aromatic systems possessing ester and amide functionalities are present (Table S3).

To highlight the synthetic utility of this method, the orthogonal reactivity of silyloxyarenes in the presence of competing functional groups commonly used in cross-couplings was examined with an eye toward leveraging this capability in chemoselective couplings (Scheme 5). First, the stability of silyloxyarenes under palladium catalysis was shown,

Scheme 5. Synthetic Demonstrations



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as **24** (Scheme 5a) underwent Buchwald−Hartwig amination to afford **25** (Scheme 5a) in good yield.[21] The unfunctionalized silyloxyarene participated in the borylation reaction under standard conditions to afford **19** (Scheme 5a) in moderate yield. Second, experiments were carried out to determine if the borylation of silyloxyarenes is selective for either the C(sp^2)−O or the C(sp^3)−O bond (Scheme 5b). To probe this question, **26** (Scheme 5b) was subjected to the standard borylation conditions, which resulted in the formation of **29** (Scheme 5b) in good yield. However, diborylation of both silyloxy groups was also observed, resulting in a mixture of **29** and the analogous diborylated product. Scaffold **26** (Scheme 5b) was further derivatized by amination,[7] which resulted in a good yield of **27** (Scheme 5b) with no evidence of overamination. The C(sp^3)−O bond could be subsequently functionalized to afford the borylated compound in good yield **28** (Scheme 5b). Overall, this represents a modular process, which highlights the diversity of functional groups that can be installed on biphenyl core scaffolds, which are ubiquitous in pharmaceuticals. For example, the structure **28** represents a fragment related to the core structure of fexaramine, which is a drug currently under investigation as an agonist of the farnesoid X receptor.[22]

A plausible mechanism for this reaction involves a traditional Ni(0)/Ni(II) cycle, wherein oxidative addition to the silyloxyarene would occur, followed by transmetalation of the diboron species and reductive elimination from the borylated arene. However, in recent years, an increasing number of mechanistic studies regarding the functionalization of low-reactivity of C−O bonds suggest that alternative mechanisms involving Ni(I) species or Ni(0) ate complexes may be operative.[4a,23−25]

In summary, an effective nickel-catalyzed ipso-borylation of silyl ethers has been developed.[26] This method provides rare demonstrations of the direct functionalization of the C−O bond of silyloxyarenes and is distinguished by the inclusion of several isolated aromatic substrates including those with heterocyclic functionality. These features address several limitations regarding alternative approaches for the catalytic functional group interconversion of low-reactivity C(sp^2)−O bonds to C(sp^2)−Bpin products. The orthogonality of this method to other classes of arene and heteroarene cross-couplings was demonstrated by chemoselective Buchwald−Hartwig amination of an aryl bromide followed by borylation of a silyloxyarene functionality. Additionally, in another bifunctional substrate, initial chemoselective amination of a silyloxyarene group was followed by borylation of a benzyloxysilane functionality. This method represents a promising technology for the functionalization of silyl protected phenols including those with isolated aromatic ring systems while possessing orthogonal reactivity to other classes of aryl electrophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01280.

Synthetic details and spectral data (PDF)

FAIR data, including the primary NMR FID files, for compounds **1**−**23**, **25**, **27**−**29** (ZIP)

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Notes

The authors declare no competing financial interest.

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