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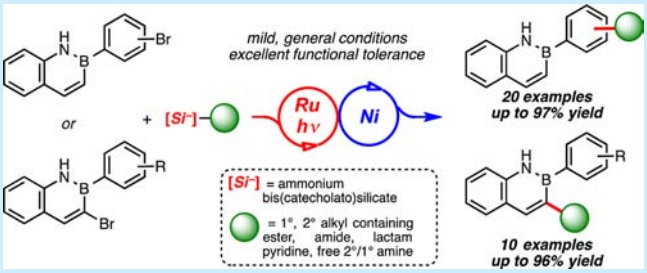
Accessing Elaborated 2,1-Borazaronaphthalene Cores Using Photoredox/Nickel Dual-Catalytic Functionalization

Matthieu Jouffroy, Geraint H. M. Davies, and Gary A. Molander*

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

Supporting Information

ABSTRACT: A highly effective method for derivatizing 2,1-borazaronaphthalene cores using ammonium alkylbis(catecholato)silicates via photoredox/nickel dual catalysis is reported. By forging C_{sp^3}–C_{sp^2} bonds via this approach, alkyl fragments with various functional groups can be introduced to the azaborine core, affording previously inaccessible heterocyclic isosteres in good to excellent yields. The base-free, room-temperature conditions outlined allow sensitive functional group tolerance, even permitting the cross-coupling of unprotected primary and secondary amines.



Azaborines are boron-, nitrogen-, and carbon-containing heteroaromatic compounds that have been recognized as viable isosteric species for aryl and heteroaryl cores.[1] The B–N bond serves as a replacement for a C=C bond in arenes, and substitution in this manner affords molecules having similar, but *not identical*, electronic and steric properties.[2] Consequently, B–N/C=C isosterism has attracted the attention of medicinal chemists because it allows the introduction of structural and electronic variety to existing drug templates and may enhance the potency of biologically active molecules, leading to new therapeutics.[3]

Recently, we developed a rapid synthetic route to 2,1-borazaronaphthalenes,[4] in addition to methods for further elaborating the structural diversity of these cores.[5] Post-annulation modifications included nucleophilic substitution of 2-(chloromethyl)-2,1-borazaronaphthalene (Scheme 1a)[6] and various Pd-catalyzed functionalization processes (Scheme 1b).[7] Additionally, alkyl groups could be introduced at the 3-position of the naphthyl azaborine via Ni-catalyzed reductive coupling of primary and secondary alkyl iodides (Scheme 1c).[8] This latter protocol enabled the formation of C_{sp^3}–C_{sp^2} bonds between the naphthalene isostere core and *an alkyl chain*. The introduction of functionalized alkyl moieties is attractive, particularly for medicinal chemistry applications.[9] Addition of such groups could provide a means of increasing solubility of drug candidates, hence improving their ADME (absorption, distribution, metabolism, and excretion) properties.[10] Unfortunately, current conditions for incorporation of alkyl chains have several drawbacks, among them the need for excess terminal reductant, intolerance of protic functional groups, and the limited accessibility/high cost of alkyl iodides.

Very recently, our group and others reported a new synthetic paradigm to enable the formation of C–C bonds under extremely mild reaction conditions, i.e., visible light photoredox/Ni dual catalytic cross-coupling.[11,12] Utilization of this reaction manifold has allowed the formation of C_{sp^3}–C_{sp^2} bonds between benzylic,[11a,13] secondary alkyl,[12a,13] primary alkyl,[13] α-alkoxy,[11d,12a,f] and α-amino[11b,12c,d,f] C_{sp^3}-hybridized radical precursors with a variety of (hetero)aryl and/or alkenyl halide electrophiles. These radical precursors are oxidizable species such as organotrifluoroborates, carboxylic acids, and alkylsilicates. The latter, specifically ammonium alkylbis(catecholato)silicates,[13a,b] represent practical, highly versatile radical precursors because of their low oxidation potentials, the innocuous byproducts generated during single electron transfer (SET)-mediated fragmentation, and the near-neutral reaction conditions. Taken together, photoredox/Ni dual catalysis employing ammonium alkylsilicates offers a cross-coupling approach that possesses excellent functional group tolerance and ease of operation.[13a,b] With this newly developed paradigm in mind and the goal of accessing more highly elaborated and functionalized 2,1-borazaronaphthalene cores, we assessed whether these substrates were amenable to this means of C_{sp^3}–C_{sp^2} bond formation.

From the outset, we chose to focus our study on azaborines having an aryl ring off the boron atom because such derivatives have been found to possess enhanced stability relative to those possessing other substituents on boron. Using the previously reported reaction conditions for the cross-coupling of aryl bromides with silicates [2 mol % of $[Ru(bpy)_3](PF_6)_2$, 5 mol % of $[NiCl_2(dme)]$, 5 mol % of dtbbpy in DMF (0.1 M)], the reaction of 2-(4-bromophenyl)-2,1-borazaronaphthalene **1a** with cyclohexylsilicate[13a] affords coupled product **2a** in 97% isolated yield (Scheme 2) (dtbbpy: 4,4′-di-*tert*-butyl-2,2′-dipyridyl; bpy: 2,2′-dipyridyl). Substrate **1a** was further coupled with various silicates, affording alkylated azaborines **2b–n** in

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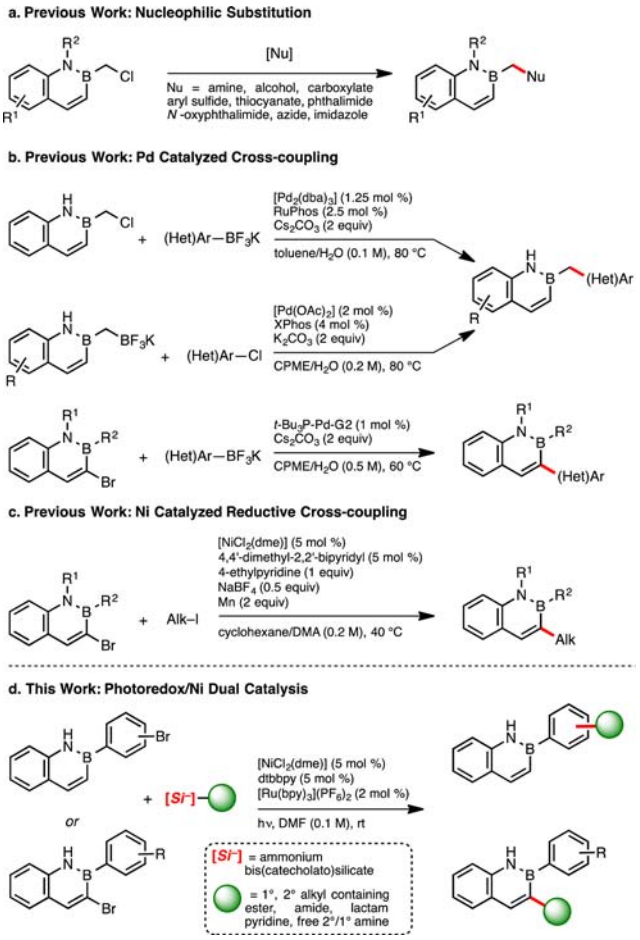
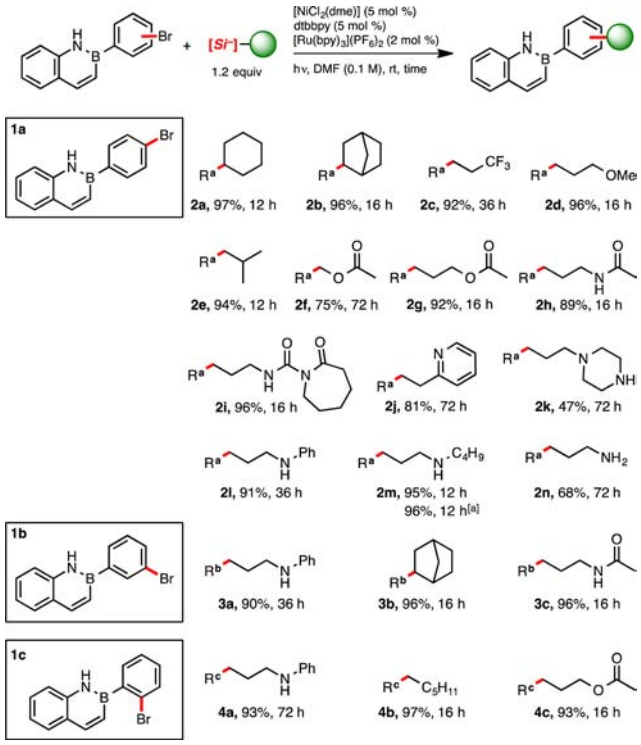
Scheme 1. 2,1-Borazaronaphthalene Functionalization by (a) Nucleophilic Substitution; (b) Pd Catalyzed Cross-Coupling; (c) Ni Catalyzed Reductive Cross-Coupling; (d) Photoredox/Ni Cross-Coupling



excellent yield with both secondary and primary alkylsilicates. Isobutyl, bicyclic, and 3,3,3-trifluoropropyl fragments were amenable to cross-coupling (**2b−c**,**e**) as were radicals containing various functional groups, including an ether (**2d**), ester (**2f**,**g**), amide (**2h**), and even a lactam (**2i**).[14] Alkylsilicates containing Lewis basic residues such as pyridyl (**2j**), phenylalkylamino (**2l**), and secondary alkylamino (**2m**) were similarly well tolerated. In the case of piperazine (**2k**)- and primary amine (**2n**)-containing silicates, lower yields were obtained (47% and 68%, respectively), with unreacted bromoazaborine remaining even after extended reaction time. The rationale for the lower yield observed using the unprotected piperazine and the previously successful 3-aminopropylsilicate remains elusive.[13a] Despite this, the late-stage incorporation of these basic substituents may be highly attractive to medicinal chemists seeking to improve the ADME properties of prospective azaborine targets. To assess the robustness of the described protocol further, the synthesis of the amine-containing compound **2m** was scaled to 1 g (3.5 mmol). Neither the yield nor the reaction time was compromised in this transformation, confirming the scalability of this reaction.

The azaborine scope was further extended to *meta*- and *ortho*-substituted 2-(bromophenyl)-2,1-borazaronaphthalenes (Scheme 2, **1b** and **1c**, respectively). It appeared that the positioning of the bromine atom on the *B*-aryl group did not

Scheme 2. Photoredox Cross-coupling of Ammonium Alkylbis(catecholato)silicates with 2-(Bromophenyl)-2,1-borazaronaphthalenes

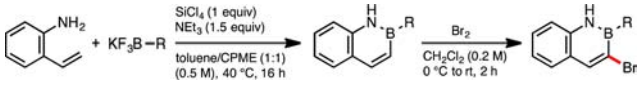


[a]Reaction carried out on 3.5 mmol using blue LEDs; all other reactions were carried out on a 0.5 mmol scale of **1**.

affect the reaction, affording coupled products **3a−c** and **4a−c** in excellent yields. Interestingly, *ortho*-substituted azaborines (**1c**, **4a−c**) were isolated as oils, whereas nearly all other compounds (with the exception of **2k**) were obtained as fluffy powders. This disparity is most likely due to a perturbation of the molecular packing caused by the steric constraints imparted by *ortho* substitution. Positioning of an alkyl chain at this position on the *B*-aryl group likely prevents coplanarity, disrupting intermolecular π-stacking.

Next, we examined the photoredox/Ni cross-coupling performed directly on the azaborinyl ring itself. Therefore, a series of 3-bromo-2-phenyl-2,1-borazaronaphthalene derivatives were prepared in high yield via selective electrophilic bromination (Scheme 3).[4]

Scheme 3. Synthesis of Brominated 2,1-Borazaronaphthalene Cores



Brominated azaborines **1d−h** were found to be excellent electrophiles in this type of cross-coupling, affording coupled product in good to excellent yields (Scheme 4). Indeed, a variety of groups could be installed at the 3-position on the azaborine core (**5a−f**, **6−9**). Notably, reaction times were often shorter when these couplings were performed. Such acceleration may be due to improved rates of oxidative addition into the C−Br bond, illustrating the lower aromatic character of the azaborines relative to that of all-carbon arenes. Substitution on

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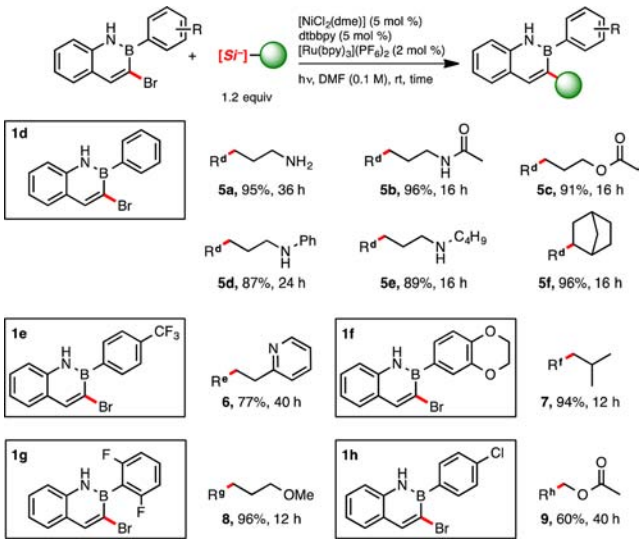
Scheme 4. 2,1-Borazaronaphthalene Scope with both Primary and Secondary Ammonium Alkylbis(catecholato)silicates



the aryl group off the boron did not seem to affect cross-coupling. *B*-4-(Trifluoromethyl)phenyl (**1e**) and *B*-benzodioxanyl substituents (**1f**) were both well tolerated, affording coupling products **6** and **7** in good and excellent yields, respectively. An *o*-difluoro-substituted azaborine (**1g**) did not impede the reaction and afforded the corresponding alkylated product **8** almost quantitatively. Whereas selectivity can sometimes be problematic when dihalogenated systems in transition-metal-catalyzed cross-couplings are used, total selectivity for the bromine over the chlorine was observed in the case of **1h**, leaving the latter intact for further modification.

In conclusion, several 2,1-borazaronaphthalene derivatives were efficiently alkylated using ammonium alkylsilicates via photoredox/Ni dual catalysis. This selective, high-yielding, and very mild approach to azaborinyl functionalization enables the rapid construction of a library of naphthalene isosteres with numerous types of functional groups at room temperature and near-neutral conditions. In fact, the modular nature of constructing the borazaronaphthalene core, combined with the selective and regiocomplementary means of elaborating this core, provide a means to access chemical space in a manner that is challenging, if not impossible, to achieve in the parent naphthalene systems themselves. The methods outlined in this report add further to this versatility and may allow enhancement of ADME properties of target structures, thus improving their viability as potential isosteres for drug molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00466.

Experimental procedures, compound characterization data, and NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gmolandr@sas.upenn.edu.

Notes

The authors declare no competing financial interest.

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