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Stereospecific Coupling of Boronic Esters with N-Heteroaromatic Compounds

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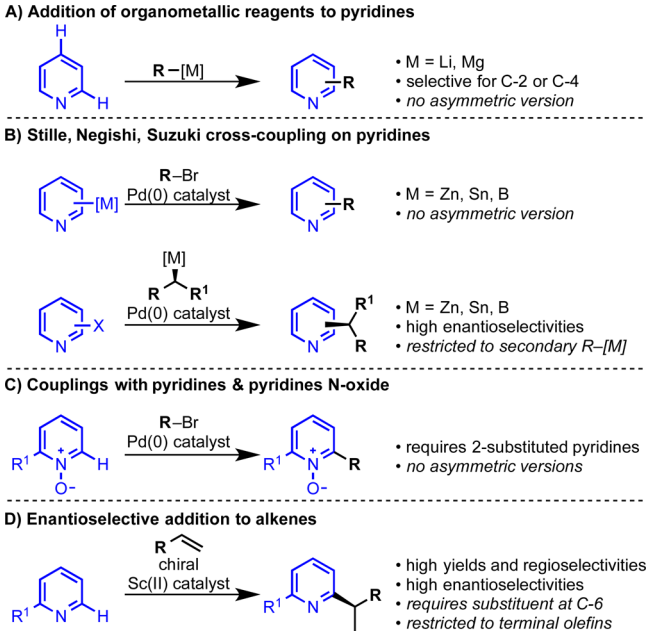
Supporting Information

ABSTRACT: A protocol for the stereospecific coupling of chiral secondary and tertiary boronic esters with lithiated N-heteroaromatics is described. The process involves initial boronate complex formation followed by addition of Troc-Cl, which activates the nitrogen and induces 1,2-migration. Oxidative workup furnishes the coupled product with >98% es.

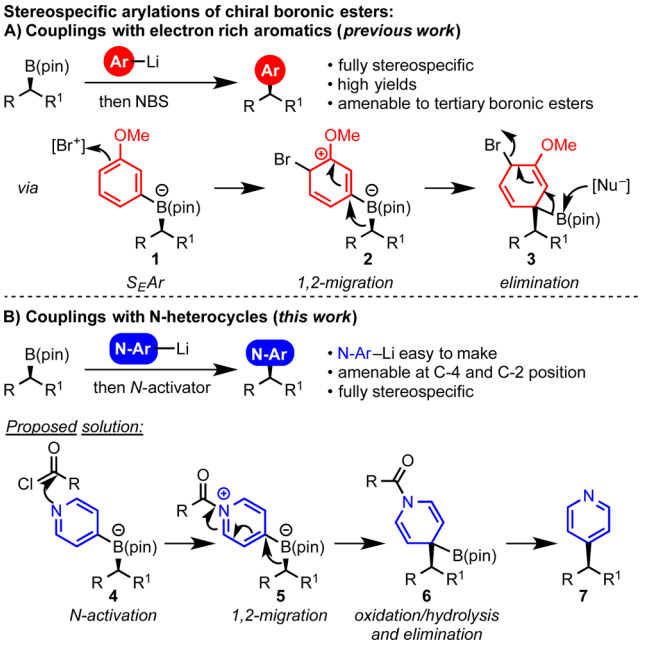
From medicines to materials, six-membered ring nitrogen-containing heterocycles have found broad application,[1] which in turn has stimulated numerous methods for their synthesis. Some of the common methods include addition–elimination reactions[2,3] (Scheme 1A), Stille[4]/Kumada[5]/Negishi[6]/Suzuki–Miyaura[7] cross-coupling (Scheme 1B), and C–H activation followed by addition to an alkene/alkyne or aryl halide (Scheme 1C, D).[8,9] In most cases sp^2–sp^2 bonds are created, limiting the methodology to achiral (flat) molecules. However, recent awareness of the greater clinical success of sp^3-rich heteroaromatic compounds has fueled demand for methods that create chiral molecules bearing heterocyclic motifs.[10] In fact, sporadic examples of sp^2–sp^3 couplings creating such compounds have been reported and are illustrated in Scheme 1, but enantioselective protocols are rare and limited in scope.[4b,6e,f,7e−h,9j] The development of a general method for the asymmetric synthesis of substituted *N*-heteroaromatics using chiral (3D) cross-partners remains a challenging goal.

We recently reported a novel strategy for the stereospecific coupling of secondary and tertiary boronic esters with aryl lithium reagents (Scheme 2a).[11,12] The strategy involved formation of boronate complex **1** followed by S_EAr reaction with NBS, which triggered a stereospecific 1,2-migration–elimination sequence (**2** → **3**). The methodology showed very broad scope in terms of the boronic ester that could be employed but was limited to coupling with electron rich aromatics. In order to extend this protocol to electron deficient heteroaromatics (e.g., pyridines and quinolines), a different method for activation

Scheme 1. Previous Couplings of Pyridines Creating sp^2–sp^3 Bonds



Scheme 2. Previous Stereospecific Coupling of Electron Rich Aromatics with Boronic Esters and Proposed Work



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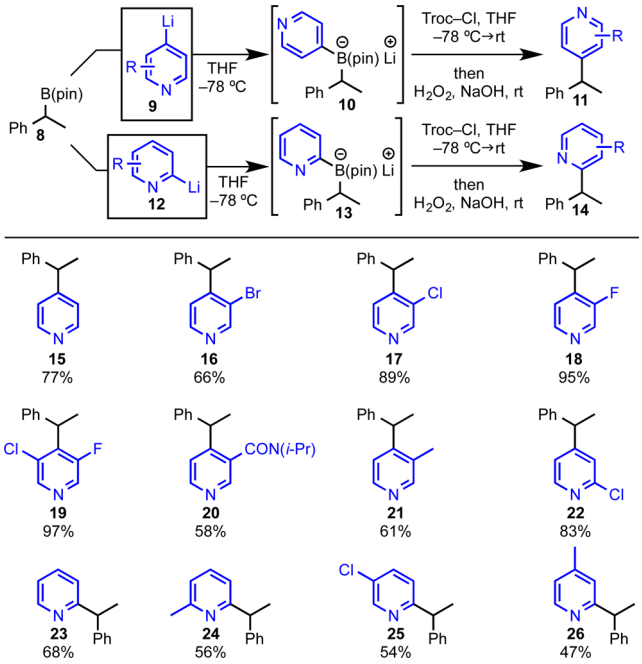
of the boronate complex was required. We reasoned that activation of the N atom by a carbonyl group[13] of a related boronate complex **4** would create an electrophilic intermediate **5**, which would trigger a 1,2-migration (**5** → **6**, Scheme 2b). This step is mechanistically related to intermolecular nucleophilic addition of boronate complexes to iminium or amidinium ions.[14] Subsequent oxidation and rearomatization (**6** → **7**) should then provide the heteroaryl-coupled product with high enantiospecificity. In this communication we describe our success in achieving this goal.

We initiated our studies by reacting 4-lithiopyridine **9** (generated by I–Li exchange)[15] with secondary boronic ester **8** and investigated different N-activators, stoichiometry, and reaction conditions (Scheme 3, see SI for details). From these

Scheme 3. Coupling of 2- and 4-Lithiated Pyridines[a]



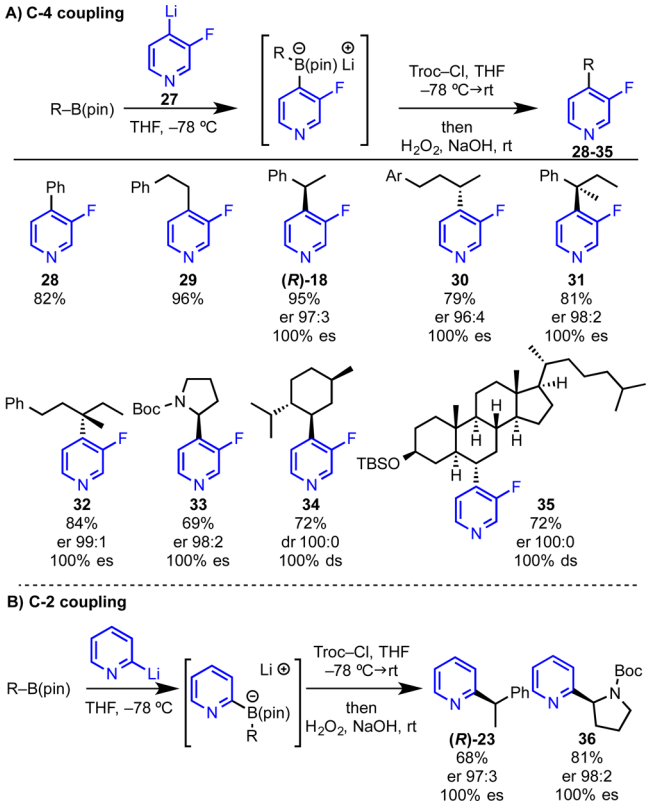
[a]Typical conditions: Het–Li (1.25 equiv), R–B(pin) (1.0 equiv), −78 °C, Troc–Cl (2.5 equiv), −78 °C to rt, H_2O_2–NaOH, rt.

studies, a general protocol emerged consisting of Troc-Cl addition at low temperature (−78 °C) followed by oxidative hydrolysis with basic H_2O_2 at room temperature. Under this set of conditions the coupled product **15** was obtained in 77% yield. The unique effectiveness of Troc-Cl in promoting this process is attributed to its ability to promote both the 1,2-migration and the final hydrolysis/rearomatization process by increasing the electrophilic character of both the iminium ion **5** and the carbamate intermediate **6** (Scheme 2B). With optimized conditions for the C-4 coupling, the scope of the reaction was investigated using boronic ester **8** (this boronic ester was chosen as it leads directly to 1,1-diarylalkyl products, a privileged pharmacophore in medicinal chemistry[16]) and a series of differentially substituted pyridines. As described in Scheme 3, after lithiation[17] and B-ate complex formation (**10**), exposure to Troc-Cl and oxidative workup furnished a series (**15**–**22**) of 3,4-/2,4-disubstituted and 3,4,5-trisubstituted pyridines in high yields.

Mechanistically, C-2 lithiated pyridines were expected to behave similarly to the C-4-lithiated pyridines and so were also explored (Scheme 3). Pleasingly, C-2 lithiation[18] of pyridine followed by addition of boronic ester **8** gave the intermediate boronate complex **13**, which, under our optimized conditions, furnished the desired C-2 alkylated product **23** in 68% yield. The process was again extended to a series of substituted pyridines thus giving access to 2,6-, 2,5-, and 2,4-disubstituted products **23**–**26** in moderate to good yields. The yields for coupling at the C-2 position were generally lower than for coupling at the C-4 position, perhaps reflecting the greater steric hindrance of the pyridine nitrogen and therefore reduced rates of acylation.

Having evaluated the substitution pattern of the pyridine ring, 4-lithio-3-fluoropyridine **27** was selected to evaluate the scope of the boronic ester coupling partner. As shown in Scheme 4A, both

Scheme 4. Stereospecific Coupling of 2- and 4-Lithiated Pyridines[a]



[a]Typical conditions: Het–Li (1.4 equiv), R–B(pin) (1.0 equiv), −78 °C, Troc–Cl (3.3 equiv), −78 °C to rt, H_2O_2–NaOH, rt.

aryl and primary alkyl boronic esters worked well and yielded products **28** and **29**. More importantly, enantioenriched secondary and tertiary boronic esters could be coupled in high yields and complete stereospecificity ((*R*)-**18**, **30**–**35**). The high yield and stereospecificity that was achieved with tertiary boronic esters is particularly noteworthy due to the challenges that these sterically hindered substrates present in traditional cross-coupling processes.[12] The broad scope of the process was further illustrated by the heteroarylation of 2-pyrrolidinyl-, menthyl-, and *β*-cholesteryl boronic esters in high yields and excellent stereospecificity (**33**–**35**).

However, the coupling of 2-lithiopyridine was more limited in its scope (Scheme 4B). While both the secondary benzylic and pyrrolidinyl boronic esters coupled in high yield (68% and 81%, respectively) and with perfect enantiospecificity ((*R*)-**23** and

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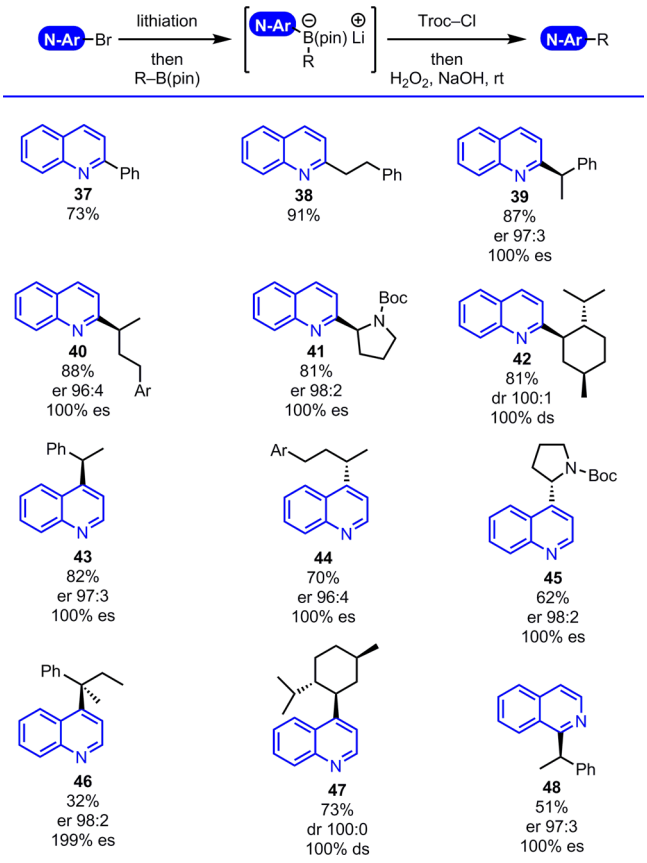
36), tertiary boronic esters failed, returning starting materials instead. This could be due to the increased steric hindrance around the nitrogen of the boronate complex, inhibiting acylation.

We were keen on extending this methodology to other N-heterocycles and so explored the coupling of lithiated quinolines and isoquinolines (Scheme 5). Pleasingly, under our standard

Scheme 5. Stereospecific Coupling of Quinolines and Isoquinolines[a]

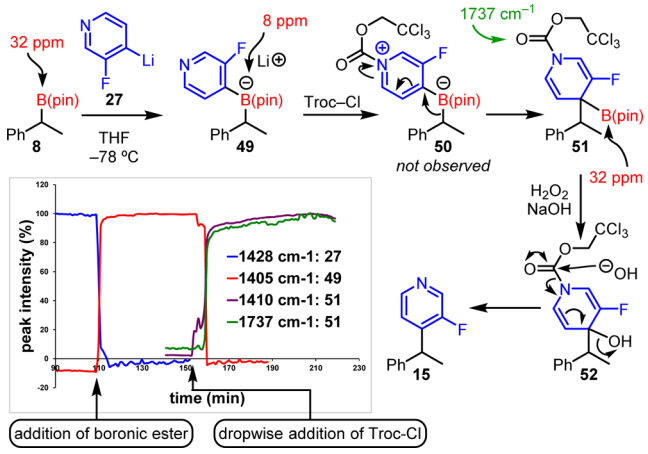


[a]Typical conditions: Het–Li (1.7 equiv), R–B(pin) (1.0 equiv), −78 °C, Troc–Cl (3.3 equiv), −78 °C to rt, H_2O_2–NaOH, rt.

conditions, 2-lithioquinoline (generated by Br–Li exchange)[18] coupled with a broad array of boronic esters, including PhB(pin), primary alkyl, secondary benzylic, secondary alkyl, pyrrolidinyl, and hindered cyclic boronic esters in good yield (**37**–**42**) and complete stereospecificity. Despite the increased steric hindrance around the quinoline nitrogen due to both the boronate complex and the additional ring, high yields were nevertheless obtained, perhaps reflecting the greater ease of the 1,2-migration step due to the lower aromatic character of the system. However, the more hindered tertiary boronic esters proved to be a step too far and did not couple, probably because of the severe steric crowding around the N atom of the quinoline boronate complex, which would inhibit the acylation step. In addition, 4-lithioquinoline[19] (generated by Br–Li exchange) reacted with a range of representative boronic esters (secondary, pyrrolidinyl- and menthyl boronic esters) and gave the coupled products in high yields and complete stereospecificity (**43**–**47**). This time, it was possible to use the tertiary benzylic boronic ester to form the quaternary heterocycle **46**, again with complete enantiospecificity albeit in moderate yield (32%). The methodology was further expanded to 2-lithio-isoquinoline,[18] which, with our standard benzylic boronic ester (*R*)-**8**, furnished **48** in good yield and excellent enantiospecificity.

The mechanism of the reaction was briefly explored. The reaction shown in Scheme 6 was followed by ^{11}B NMR. The

Scheme 6. Mechanistic Studies through Analysis of Intermediates by ^{11}B NMR and React-IR



initial boronic ester **8** was observed at 32 ppm, and this peak shifted to 8 ppm upon addition of 4-lithiopyridine **27**, indicative of the formation of the boronate complex **49**. Upon addition of Troc-Cl, the signal at 32 ppm reappeared but is assigned to the new boronic ester **51**.[20] Subsequent oxidation gave the alcohol **52**, which finally underwent hydrolysis of the carbamate group and rearomatization. The reaction was also monitored by React-IR. This showed that reaction of 4-lithiopyridine **27** (blue line) with boronic ester **8** forming boronate complex **49** (red line) was essentially instantaneous. Dropwise addition of Troc-Cl at −78 °C also resulted in extremely rapid carbamate formation with concomitant/concerted 1,2-migration leading to intermediate **51** (green/purple lines). This study shows the high reactivity of the intermediates involved in the coupling reaction.

In conclusion, a novel method for the stereospecific coupling of secondary and tertiary boronic esters with lithiated six-membered ring N-heterocycles has been developed. This approach consists of lithiation of an N-heterocycle and addition of a boronic ester resulting in formation of a boronate complex. Subsequent addition of Troc-Cl results in acylation of the nitrogen heterocycle which triggers 1,2-migration. Oxidative workup finally gives the coupled product with complete stereospecificity. The new method adds to the growing arsenal of methods for asymmetric synthesis, with particular application to the increasing demand for creating chiral molecules containing heteroaromatic motifs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07842.

Detailed experimental procedure, characterization data for new compounds, and ReactIR data (PDF)

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Notes

The authors declare no competing financial interest.

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(20) The C4-dihydropyridyl boronic ester **51** proved to be too unstable and so could not be fully characterized. However, we succeeded in isolating and fully characterizing a related C2-dihydropyridyl boronic ester. See SI for full details.

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