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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% ee.

ABSTRACT:

From medicines to materials, six-membered ring nitrogen-containing heterocycles have found broad application, which in turn has stimulated numerous methods for their synthesis. Some of the common methods include addition−elimination reactions, Stille/Kumada/Negishi/Suzuki−Miyaura cross-coupling, and C−H activation followed by addition to an alkene/alkyne or aryl halide. In most cases sp2−sp3 bonds are created, limiting the methodology to achiral (flat) molecules. However, recent awareness of the greater clinical success of sp3-rich heteroaromatic compounds has fueled demand for methods that create chiral molecules bearing heterocyclic motifs. In fact, sporadic examples of sp3−sp3 couplings creating such compounds have been reported and are illustrated in Scheme 1, but enantioselective protocols are rare and limited in scope. 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). The strategy involved formation of boronate complex followed by SEAr reaction with NBS, which triggered a stereospecific 1,2-migration−elimination sequence. 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 formation of boronate complex followed by S2Ar 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...
of the boronate complex was required. We reasoned that activation of the N atom by a carbonyl group 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. 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 (generated by 1-Li exchange) with secondary boronic ester 8 and investigated different N-activators, stoichiometry, and reaction conditions (Scheme 3, see SI for details). From these studies, a general protocol emerged consisting of Troc-Cl addition at low temperature (−78 °C) followed by oxidative hydrolysis with basic H₂O₂ 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 acylation process.15

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 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 stereoselectivity ((R)-18, 30–35). The high yield and stereoselectivity 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. The broad scope of the process was further illustrated by the heteroarylation of 2-pyrrolidinyl-β-methyl- and β-cholesteryl boronic esters in high yields and excellent stereoselectivity (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 (S)-24), secondary benzylic and pyrrolidinyl boronic esters coupled in moderate to good yields (63% and 72%, respectively) and with perfect enantiospecificity ((R)-25 and (R)-26).
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 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 (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 11B NMR. The 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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