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Alkyl Group Migration in Ni-Catalyzed Conjunctive Coupling with C(sp^3) Electrophiles: Reaction Development and Application to Targets of Interest

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Cite This: https://dx.doi.org/10.1021/acs.orglett.9b04453 Read Online

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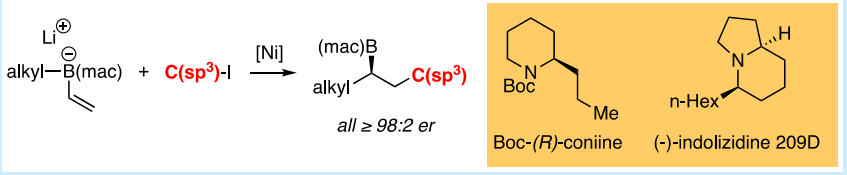
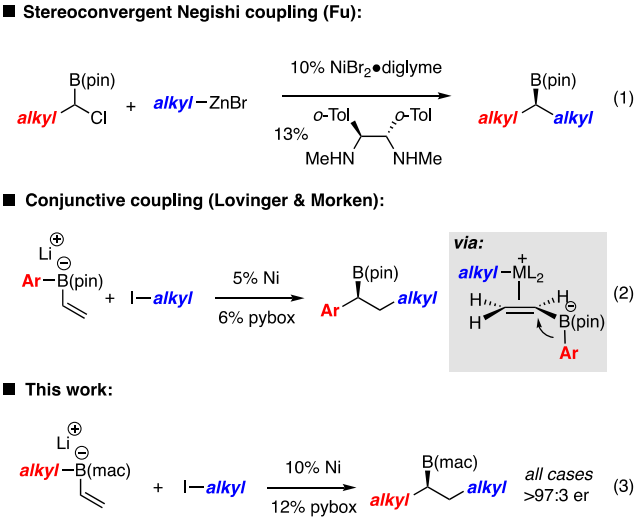


ABSTRACT: A catalytic conjunctive cross-coupling reaction is developed that allows the construction of chiral organoboronic esters from alkylboron ate complexes and alkyl iodide electrophiles. The process occurs most efficiently with a Ni/Pybox-comprised catalyst and with an acenapthoquinone-derived boron ligand. Because of the broad functional group tolerance of this reaction, it can be a versatile tool for organic synthesis. Applications to the construction of (*R*)-coniine and (−)-indolizidine 209D are described.

Organoboronic acid derivatives are useful reagents in organic synthesis,[1] are important structures in medicinal chemistry[2] and chemical biology,[3] and have found applications in sensor technology and material science.[4] One can prepare organoboron compounds with a variety of a different methods; however, there are gaps in synthetic methodology that hinder access to certain structural classes. This is especially the case if one wishes to use catalytic reactions to construct compounds with boron-containing stereogenic centers.[5] For instance, while a number of reactions can produce secondary boronic esters in a catalytic enantioselective fashion, most of these transformations, as a consequence of their underpinning reaction mechanism, will lead to specialized products that contain sp^2 carbons, directing groups, carbonyls, or other particular functional groups at defined locations. In so far as we are aware, the asymmetric catalytic Negishi coupling of α-chloroboronic esters (Scheme 1, eq 1) developed by Fu is the only process able to furnish nonracemic secondary organoboronic esters containing simple alkyl substituents.[6] In this paper, we present an alternate catalytic enantioselective route to nonfunctionalized organoboronic esters and show that a number of functional groups can be included at sites necessary to enable subsequent chemical synthesis.

The conjunctive cross-coupling between organic electrophiles and alkenylboron "ate" complexes (Scheme 1, eq 2) is an efficient process that can furnish enantiomerically enriched organoboronic esters in a catalytic fashion.[7,8] This reaction occurs by way of a 1,2-metalate shift wherein a substituent attached to the boron atom migrates to the α-carbon of the adjacent alkene with concomitant C−M bond formation occurring at C_β (see Scheme 1 inset).[9] While initial studies employed palladium catalysts and C(sp^2) electrophiles, the use of nickel complexes in conjunction with a pyridylbisoxazoline (pybox) ligand as the catalyst allowed for the use of C(sp^3) electrophiles and promised to broaden the scope of this reaction substantially.[10] A critical limitation of the Ni/pybox-

Scheme 1. Conjunctive Cross-Coupling with Alkenylboron Ate Complexes



Received: December 12, 2019

https://dx.doi.org/10.1021/acs.orglett.9b04453
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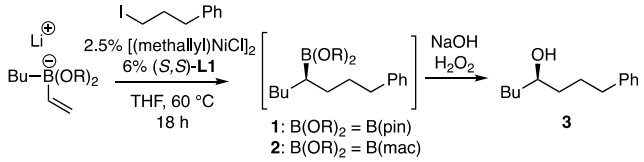
catalyzed process, however, was that aliphatic boron substituents were found to be recalcitrant migrating groups, and therefore, the reaction was limited to construction of benzylic boronic esters. In this study, we examine the Ni/pybox-catalyzed coupling of C(sp^3) electrophiles with alkyl(vinyl)boron-derived ate complexes (Scheme 1, eq 3) and show that the boron ligand can be tuned to facilitate an effective reaction.

Examination of the conjunctive coupling between a pinacolato alkylboron-derived ate complex and (3-iodopropyl)benzene demonstrated the lack of reactivity with this class of boron reagent. Whereas the analogous phenyl-derived ate complex undergoes coupling in 70% yield (data not shown), as depicted in Table 1 (entry 1) when the migrating group is an *n*-butyl chain, the product obtained upon oxidation of **1** is formed in only 4% yield. Examination of the byproducts in entry 1 showed that one competing side reaction is the alkylation of the pinacol ligand with the electrophile. To avoid this circumstance, we considered other boron ligand frameworks that might be either less basic or more sterically encumbered. As depicted in entries 2 and 3, replacement of pinacol with a neopentylglycolato group resulted in only 6% product yield, whereas use of acenapthoquinone-derived "mac"[11] ligand led to a substantial improvement in reaction outcome: after oxidation of the boronic ester intermediate (**2**), the alcohol was isolated in 35% yield. Subsequent optimization led to further improvements: the use of increased catalyst loading (10% catalyst), the use of THF/DMSO mixture as the reaction solvent, and the use of [(TMEDA)Ni(*o*-tol)Cl] as the source of Ni ion resulted in a process that reproducibly delivered the conjunctive coupling product in about 65% yield and 99:1 enantiomer ratio when conducted at room temperature (entry 9).

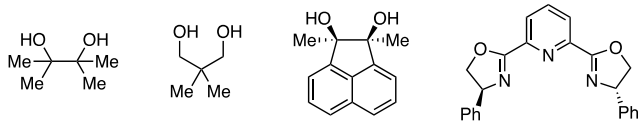
With a workable catalytic system that allows the migration of aliphatic groups in conjunctive couplings with aliphatic electrophiles, we surveyed a number of other substrates. As depicted in Scheme 2, migrating chains that bear functional groups such as an alkene (**4**), ether (**5**), ketal (**6**), and carbamate (**21**) are accommodated in this reaction. In contrast to the Pd-catalyzed process that allows migrations of secondary and tertiary aliphatic groups,[7a,b,f] the Ni-catalyzed process appears to be much more sensitive to steric effects: migration of an isopropyl group from a B(mac)-derived ate complex occurred in only 32% yield. Of note, use of the pinacol derived ate complex could improve the yield of these more hindered substrates (**18**–**20**); however, the overall efficiency of these reactions still remains modest.

In terms of the electrophile, the experiments in Scheme 2 suggest that the alkyl iodide component could have silyl (**9**) and alkyl ethers (**10**, **11**), ketals (**13**), esters (**14**), and Boc-protected amines (**15**). It was also found that the alkyl iodide itself could contain a pinacol boronic ester and, in the case of

Table 1. Optimization of Ni-Catalyzed Conjunctive Coupling of a C(sp^3) Electrophile with an Alkyl(vinyl)boronate Complex.[a]

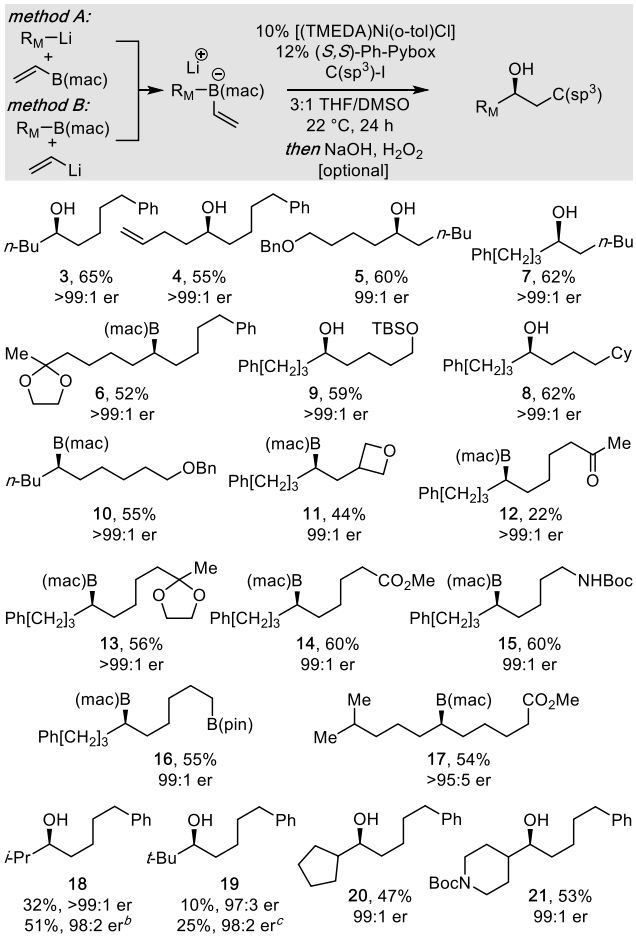


entry	$(OR)_2$	modifications	yield of **3** (%)	er
1	pin	none	4	n/d
2	neo	none	6	n/d
3	mac	none	35	99:1
4	mac	5% $Ni(cod)_2$	16	n/d
5	mac	5% $NiBr_2$·glyme	11	n/d
6	mac	5% [methallyl)NiCl]$_2$[Ni], 12% **L1**	41	n/d
7	mac	5% [methallyl)NiCl]$_2$, 12% **L1**, 3:1 THF/DMSO	53	99:1
8	mac	10% [(TMEDA)Ni(*o*-tol)Cl], 12% **L1**, 3:1 THF/DMSO	55	99:1
9	mac	10% [(TMEDA)Ni(*o*-tol)Cl], 12% **L1**, 3:1 THF/DMSO, rt	65	>99:1



[a]Yield refers to isolated yield of purified product. er refers to the enantiomeric ratio and was determined by SFC chromatography on a chiral stationary phase.

Scheme 2. Scope of Ni-Catalyzed Conjunctive Coupling with B(mac)-Derived Ate Complexes[a]



[a]Yield refers to isolated yield of purified product. er refers to the enantiomeric ratio and was determined by SFC chromatography on a chiral stationary phase. [b]Reaction employed the pinacol-derived boronate. [c]Reaction with the pinacol-derived boronate and at 45 °C.

https://dx.doi.org/10.1021/acs.orglett.9b04453
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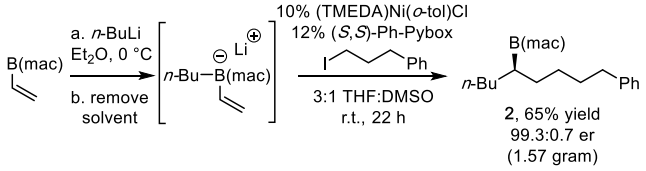
16, provides a route to a 1,6-diboronate. Lastly, while secondary iodides proved reactive (11), they gave lower yields than primary electrophiles (12% yield with cyclopentyl iodide, data not shown).

To assess the usefulness of the Ni(pybox)-catalyzed conjunctive coupling in preparative synthetic chemistry, we first examined the ability of this process to proceed effectively on larger scale. As depicted in Scheme 3, when 1.56 g of

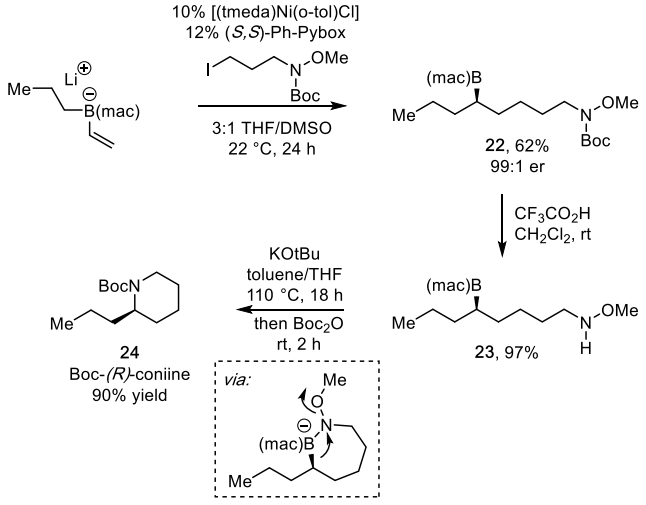
Scheme 3. Gram-Scale Conjunctive Coupling



vinylB(mac) was treated with *n*-BuLi, followed by the catalyst and (3-iodopropropyl)benzene in THF/DMSO at room temperature for 22 h, the conjunctive coupling product **2** was isolated in 65% yield and with an enantioselectivity of 99.3:0.7 er. That the selectivity and efficiency for this process so closely mirror that observed on smaller scale bodes well for the general use of this reaction in chemical synthesis.

To learn whether the conjunctive coupling might accommodate reactive functional groups that would be useful in the preparation of relevant alkaloid synthesis targets, we examined preparation of motifs that could participate in boronic ester amination or reductive amination. In the first scenario, the synthesis of enantiomerically enriched Boc-protected coniine[12] was addressed. To access this structure, an alkyl iodide bearing an alkoxyamine was employed in the conjunctive coupling. In this case, product **22** (Scheme 4) was accessed in good yield

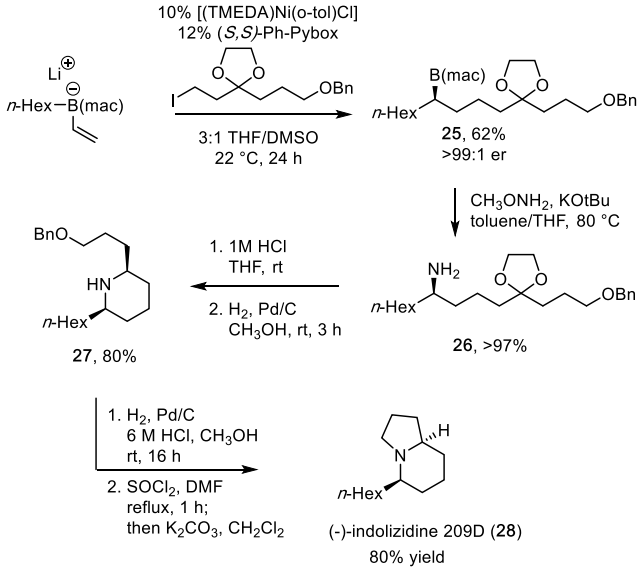
Scheme 4. Preparation of (*R*)-Coniine by Ni-Catalyzed Conjunctive Cross-Coupling



and outstanding enantioselectivity. Subsequent removal of the Boc carbamate, followed by intramolecular amination[13] of the organoboronic ester, and Boc protection (to facilitate isolation) delivered the product **24** in an efficient fashion.

As an alternate route to alkaloid natural products, we considered the reductive amination applied to substrates derived from conjunctive coupling. As shown in Scheme 5, (−)-indolizidine 209D[14] was prepared by conducting the

Scheme 5. Preparation of (−)-Indolizidine 209D by Ni-Catalyzed Conjunctive Cross-Coupling



coupling with an electrophile bearing appropriately positioned ketal and benzyl ether functional groups. This reaction delivered compound **25** in good yield and >99:1 er. Subsequent amination of the boronic ester (to give **26**), followed by ketal hydrolysis and imine reduction provided piperidine **27**, which was then converted to the target **28** by a known route[14c] involving debenzylation and substitution at the primary carbon.

In conclusion, the use of the "mac diol" ligand allows alkyl boronic ester-derived ate complexes to participate in highly selective conjunctive coupling reactions with aliphatic electrophiles. The reaction can be conducted on preparative scale and can accommodate a range of useful organic functional groups. We anticipate that these features will make this process useful to the synthetic chemist.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04453.

Procedures, characterization and spectral data(PDF)

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https://dx.doi.org/10.1021/acs.orglett.9b04453
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NIH (R35-GM1217140).

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