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COMMUNICATION

Benzylation of Imines with Activated Boronate Nucleophiles

Michael R. Hollerbach,[a] Jacob C. Hayes,[a] and Timothy J. Barker*[a]

Abstract: Benzylation reactions of *N*-tosyl imines and *N*-*tert*-butanesulfinyl imines using benzylboronic acid pinacol ester are reported. *s*-Butyllithium was used to activate the boronic ester, rendering it nucleophilic. The reaction was compatible with electronically diverse substituents on the imine in both substrate classes. Good diastereoselectivity was observed in additions to *N*-*tert*-butylsulfinylaldimines. The diastereoselectivity observed in these reactions is consistent with an open transition state for the addition. Examples of a secondary alkylboronic ester nucleophile and a *N*-*tert*-butanesulfinyl trifluoromethylketimine electrophile are also included.

Introduction

Organoboron reagents have been used extensively to form carbon-carbon bonds.[1] The reaction between allylboron reagents and carbonyls or imines with and without catalysts has provided access to homoallylic alcohols and amines in high enantioselectivity and has been a very successful way to perform this transformation.[2] Despite the success of allylboron reagents in 1,2-addition reactions, the use of benzylboron reagents and other alkylboron reagents in a similar reaction is less common.[3],[4],[5]

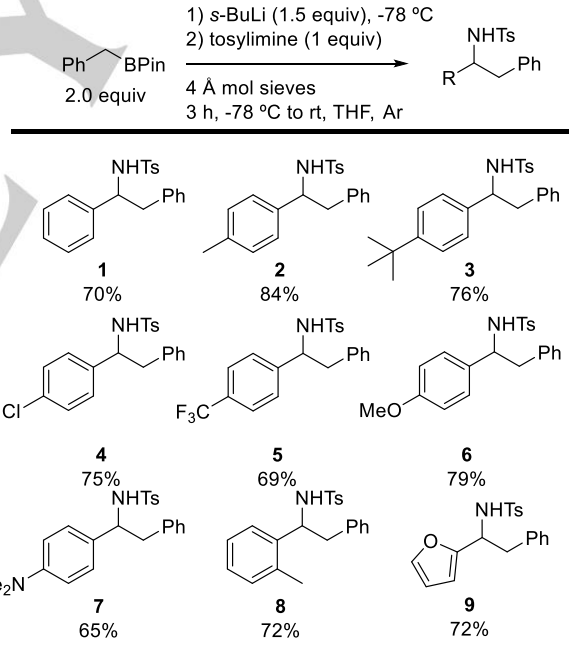
Imines are an attractive class of electrophiles, because addition reactions between organometallic reagents and imines provide α-branched amines in a straightforward manner.[6] Additionally, the diastereoselective addition to a chiral imine provides access to enantiomerically enriched amines, a direct approach to a medicinally relevant class of amines. Specifically, homobenzyl amines are present in a number of HIV protease inhibitors, including Fosamprenavir and Darunavir. Previously, benzyl Grignard reagents,[7] benzylzinc reagents,[7b, 8] benzylltrimethylsilanes,[9] and tetrabenzylhafnium[10] have been employed as nucleophiles with imines. A new synthetic approach, starting from a benchtop stable organometallic reagent such as an organosilicon or organoboron that upon activation can be rendered nucleophilic is attractive. A Rh-catalyzed addition of secondary benzylic trifluoroborates salts to *N*-sulfonylimines has also been reported.[3c] Notably, *N*-*tert*-butanesulfinylimine were unreactive under these conditions. We sought to develop a 1,2-addition of benzylboronic esters to several classes of imines including *N*-tosylimines and *N*-*tert*-butanesulfinyl imines.

Alkylboronic esters can be activated with organolithium reagents to form the more nucleophilic alkylboronate species.[11] Aggarwal has previously employed aryllithium reagents to activate alkylboronic esters and their subsequent reactions in numerous enantiospecific transformations.[12] Previously, we have demonstrated benzylboronic acid pinacol ester (BnBpin) can be activated by an alkyllithium reagent, rendering it nucleophilic toward aldehydes.[13]

Results and Discussion

Using our previously developed conditions for activation of BnBpin with *s*-BuLi employing *N*-tosylimines, good yields were observed of the amine products (Table 1). The reaction proved insensitive to substituents on the aromatic ring with both electron-donating and electron-withdrawing substituents well-tolerated, as seen in products **5**-**7**. Additionally, the *o*-tolyl imine reacted well, affording product **8** in 72% yield. A reaction with the imine derived from furfural provided an 72% yield of the heteroaromatic amine product **9**. A reaction using $BnBF_3K$ in place of BnBpin under the standard conditions did not provide any of the desired product.

Table 1. *N*-Tosyl Imines Substrate Scope.



Next, (*R*)-*N*-*tert*-butanesulfinyl imines were examined as electrophiles, providing the opportunity for a diastereoselective reaction. As the *N*-*tert*-butanesulfinyl imines are not as activated as the *N*-tosyl imines, the reactions proceeded slower but

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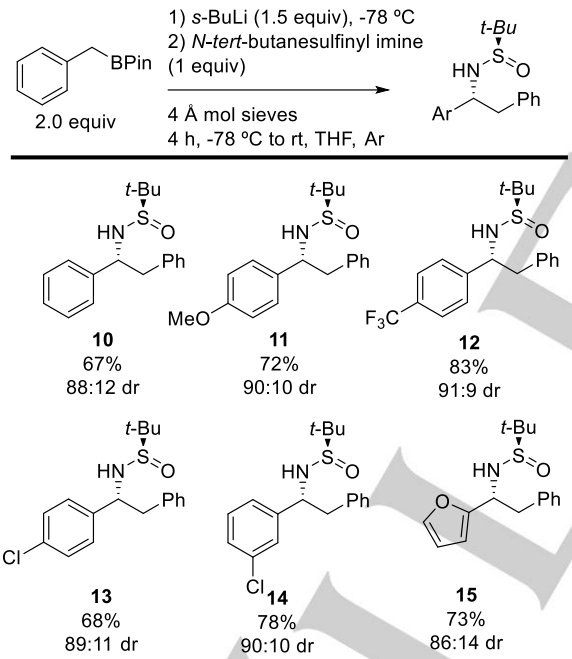
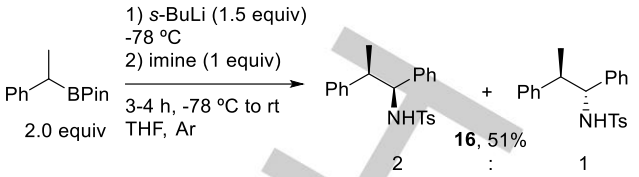
provided the products in good yields across electronically diverse substrates (Table 2). This reaction with *N-tert*-butanesulfinyl imines was found to be more sensitive to substituent effects, with the imine derived from 4-trifluoromethylbenzaldehyde providing the highest yield of product **12** (83%) with a diastereomeric ratio of 91:9. The imine derived from furfural provided the desired amine product in 73% yield (86:14 d.r.). With the six *N-tert*-butanesulfinyl imines examined, the diastereomeric ratio observed ranged from 83:17–90:10. The diastereoselectivity observed was very close to that previously reported with benzyl zinc[8a] and benzyl silicon[9b] nucleophiles when using common substrates. The absolute configuration of the products was determined by comparison to previously reported data of the products that had rigorously established the configurations and by analogy for other examples.[8a] With a proposed tetracoordinate boron nucleophile, the reaction is expected to proceed through an open transition state which is consistent with the observed stereochemistry of the products.[8a] The previously mentioned Rh-catalyzed addition of alkylboron reagents did not work with *N-tert*-butanesulfinyl imines, suggesting these boronate are a more reactive nucleophile.[3c]

Table 2. *N-tert*-Butanesulfinylimine Substrate Scope.

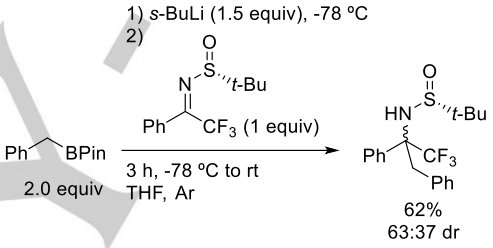


To expand the scope of nucleophiles, the branched benzylboronic ester was also examined with an *N*-tosyl imine (Scheme 1). The product was isolated in a modest yield (51%, 2:1 d.r.). Previously this branched product had been made in a Rh-catalyzed reaction that also gave a 2:1 dr, however the major diastereomer is different under our reaction conditions.[3c] This observed difference in selectivity can be attributed to a closed vs open transition state in the respective mechanisms.



Scheme 1. Addition with a Branched Nucleophile.

Finally, a *N-tert*-butanesulfinyltrifluoromethylketamine was examined as a substrate to examine this nucleophile with a more sterically hindered imine electrophile (Scheme 2). The reaction provided a 62% yield of the desired product. The diastereomeric ratio for the reaction was 63:37. While this reaction was less diastereoselective than in the additions to the aldimines, this reaction is one of the first examples of a benzyl addition to this class of ketamines to the best of our knowledge.



Scheme 2. *N-tert*-Butanesulfinyl Ketimine Electrophile.

Conclusion

In summary, the nucleophilic 1,2-addition of benzylic boronic esters to imines has been demonstrated. Electron-donating and electron-withdrawing groups were well-tolerated with both imine classes. The diastereoselectivity observed in the reaction with the *N-tert*-butanesulfinylimines was consistent with that previously observed with other benzyl nucleophiles going through an open transition state. Branched alkylboronic esters was a competent nucleophile in the reaction, and a reaction with a trifluoromethylketimine was also demonstrated. Further studies on the use of alkylboronic esters as nucleophiles are underway in our laboratory.

Experimental Section

General Procedure for Benzyl Addition to *N*-Tosyl Imines: An oven dried round-bottom flask was charged with 4 Å molecular sieves and a magnetic stir bar, flame dried under vacuum, covered with a new septum and sealed thoroughly with Parafilm. The flask was allowed to cool under vacuum and purged three times with argon before adding benzylboronic acid pinacol ester (223 µL, 1.0 mmol, 2.0 equiv.) and 4 mL of THF. The contents were cooled to -78 ˚C under increased argon flow before addition of *sec*-butyllithium (0.75 mmol, 1.5 equiv., 1.2 M in hexanes) and allowed to stir at that temperature for 30 minutes. Subsequently, tosylimine (0.50

mmol, 1 equiv.) was added at -78 ˚C as a solution in THF (2 mL). The reaction was removed from the bath after an additional 15 minutes and allowed to warm to room temperature while stirring for 3 hours. The reaction was quenched with 0.2 ml sat. NH_4Cl and concentrated under reduced pressure and isolated by column chromatography, eluting with hexanes/ethyl acetate.

General Procedure for Benzyl Addition to (*R*)-*N*-*tert*-Butanesulfinyl Imines: An oven dried round-bottom flask was charged with 4 Å molecular sieves and a magnetic stir bar, flame dried under vacuum, covered with a new septum and sealed thoroughly with Parafilm. The flask was allowed to cool under vacuum and purged three times with argon before adding benzylboronic acid pinacol ester (223 µL, 1.0 mmol, 2.0 equiv.) and 4 mL of THF. The contents were cooled to -78 ˚C under increased argon flow before addition of *sec*-butyllithium (0.75 mmol, 1.5 equiv., 1.2 M in hexanes) and allowed to stir at that temperature for 30 minutes. Subsequently, *tert*-butylsulfinyl imine (0.50 mmol, 1 equiv.) was added at -78 ˚C as a solution in THF (2 mL). The reaction was removed from the bath after an additional 15 minutes and allowed to warm to room temperature while stirring for 4 hours. The reaction was quenched with 0.2 mL sat. NH_4Cl and concentrated under reduced pressure. The diastereomeric ratio of the product was determined by inverse-gated no NOE ^{13}C NMR[14] and ^{1}H NMR of the unpurified material before being isolated by column chromatography, eluting with hexanes/ethyl acetate.

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Keywords: diastereoselectivity • boron • nucleophilic addition • chiral auxiliaries

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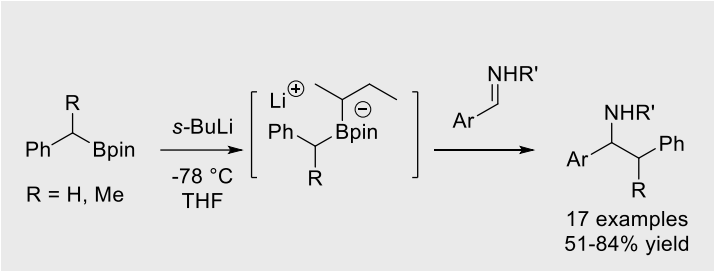

Key Topic Nucleophilic Boron

*Michael R. Hollerbach and Timothy J. Barker** **Page No. – Page No.**

Title Benzylation of Imines with Activated Boronate Nucleophiles

An in situ generated benzylboronate nucleophile reacts with two classes of imines. *N-tert*-Butanesulfinyl imines react diastereoselectively.