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Communication

The Acid Promoted Petasis Reaction of Organotrifluoroborates with Imines and Enamines

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The acid promoted addition of organotrifluoroborate salts to imine and enamine electrophiles is reported. Use of the preactivated trifluoroboronate complex bypasses the need for α -hetero substitution on the electrophile component, greatly expanding the scope of the Petasis borono-Mannich reaction. A variety of vinyl, aromatic and heteroaromatic trifluoroborate salts undergo addition with good efficiency under mild reaction conditions. The reaction is amenable for use with a variety of carbamate protected imine and enamine electrophiles, achieving for the first time the effective coupling with aliphatic aldehydes.

Introduction

Following the initial literature report by Petasis¹, the borono-Mannich reaction has found widespread use in the chemical community as a useful three component coupling reaction, generating highly functionalized amine product from simple aldehyde, amine and boronic acid precursors (eq 1).² Subsequent to this first report, much work has been devoted to expanding the scope of this transformation, with recent catalyzed^{3,4}, of metal "traceless"⁵ reports and enantioselective⁶⁻⁸ variants highlighting the prominence it has achieved as a synthetic tool. However, a common limitation of this process is the need for a pendant heteroatom on the iminium intermediate, which is required to facilitate intramolecular addition of the resulting boronate species (Eq.

Petasis Reaction: Aryl Group Transfer Following Activation (eq 1)



This work: Expansion of Electrophile Scope using BF₃K salts (eq 2)



component of this transformation to glyoxylate⁹, α -hydroxy¹⁰,

1, **TS-1**). This requirement has effectively limited the aldehyde salicylaldehyde¹¹ and heteroaromatic species¹². We postulated that starting from a pre-activated boron species, namely an organotrifluoroborate salt, would eliminate this requirement for intramolecular activation by rendering the transformation intermolecular in nature, thereby expanding the scope and utility of this transformation (Eq. 2, **TS-2**). Herein we report the successful realization of this strategy with the addition of a variety of organotrifluoroborate salts to imine and enamine electrophiles.

Earlier reports of the organocatalytic Friedel-Crafts alkylation of α , β -unsaturated aldehydes with aryl trifluoroborate salts¹³ effectively demonstrated the utility of these species as mild, easily handled coupling partners. While previous work¹⁴⁻¹⁶ has shown that trifluoroborate salts undergo π -nucleophilic addition reactions through the proposed intermediacy of their dihalogenated equivalents under Lewis acid catalysis, this mode of activation faces the same limitation as more traditional Petasis systems in that pre-association with the electrophile is required before addition occurs. We wondered if the electrophile was instead subjected to Brønsted acid activation and the trifluoroborate salt was allowed to remain as the boronate species, one could overcome this limitation and obtain reactivity with non- α -heteroatom functionalized electrophiles.

Results and discussion

Towards this end, the reaction of potassium *trans*styryltrifluoroborate, camphorsulfonic acid (CSA) and a variety of differentially protected benzaldehyde imines was evaluated (Table 1). It was found that only the carbamate protected imine gave desired product (entry 4, 12% yield) so this substrate was chosen for further optimization. Solvent polarity was found to play a key role in the observed levels of reactivity with highly polar solvents such as acetonitrile giving the

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Table 1 Evaluation of Parameters for Trifluoroborate Addition

Ph H electrophile		KF ₃ B Ph H sol	HX (1 eq) vent (0.1M) 23 °C	HN - R Ph Ph coupling product	
entry	R	НХ	solvent	time (h)	% conv.
1	PMP	camphorsulfonic acid	THF	24	0
2	Ts	camphorsulfonic acid	THF	24	0
3	benzyl	camphorsulfonic acid	THF	24	0
4	Boc	camphorsulfonic acid	THF	24	12
5	Boc	camphorsulfonic acid	CH_2Cl_2	24	36
6	Boc	camphorsulfonic acid	toluene	24	16
7	Boc	camphorsulfonic acid	MeCN	4	40
8	Boc	dichloroacetic acid	MeCN	4	68
9	Boc	trifluoroacetic acid	MeCN	4	86

^aConversion determined by GLC analysis relative to an internal standard.

greatest levels of conversion over shorter reaction times (entry 7, 40% yield). This result can be directly attributed to solubility effects as homogenous solutions of potassium trifluoroborate salt are only obtained in solvents with high dielectric constants. It was observed during the course of these reactions that a significant amount of hydrodeboration was occurring in the acidic reaction media and it was postulated that this was leading to the low observed yields. Switching from the highly acidic CSA (pKa = -2.17) to trifluoroacetic acid (TFA, pKa = -0.25) seems to support this hypothesis as significantly less hydrodeboration was observed and resulted in a corresponding increase in yield (entry 9, 86% yield, 4 h). Interestingly, no deprotection products were observed despite the use of strong acids.

While trans-styryl boronic acid derivatives are known to be particularly reactive in Petasis systems, we were pleased to find that a diverse range of trifluoroborate salts also participate in this reaction (Table 2). The less electron-rich cis and trans methyl vinyl organotrifluoroborates both undergo intermolecular addition in this system (entries 2-3, 63-68% yield) with retention of olefin geometry. Electron rich heterocycles such as furan, N-Boc-pyrrole and 4methylthiophene also undergo addition with good levels of reactivity (entries 5-7, 73-82% yield) with the use of cryogenic conditions serving to retard the rate of competing hydrodeboration of the trifluoroborate starting material. Similarly, in the case of electron-rich aromatics such as 4methoxyphenyl trifluoroborate, dichloroacetic acid is used in place of TFA to limit this competing hydrodeboration pathway (entry 8, 79% yield).

Having shown that benzaldehyde derived imines react well with a variety of organotrifluoroborate nucleophiles, we next turned our attention to the goal of exploring the applicability of this methodology to diverse electrophile frameworks. In addition to the parent benzaldehyde imine, both the electron-rich 4-methoxy and electron-poor 4-trifluoromethyl substituted imines undergo reaction with good levels of efficiency (Table 2, entries 1–2, 78-83% yield) while substitution at the *meta* position is also well tolerated (entry 3,



^aPerformed with dichloroacetic acid ^bPerformed at –20 °C.

Table 3 Reaction Scope with Aryl Imines and Aliphatic Enamines



95% yield). In addition to substituted phenyl systems, heteroaromatic imines also undergo net styrene addition with

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with good levels of reactivity (Table 2, entries 4–5, 65–99% yield).

After demonstrating the success of this protocol with aromatic electrophiles, we next turned our attention towards applying this methodology to aliphatic systems with the aim of accomplishing our goal of expanding the scope of this transformation to encompass a wide range electrophiles. To our satisfaction, it was found that easily prepared alkyl enamines also undergo reaction with styryl trifluoroborate, through their imine tautomer, upon exposure to trifluoroacetic acid in excellent yields and relatively short reaction times (Table 3, entries 6-10, 89-98% yield). It should also be noted that both the tert-butyl (Boc) and benzyl (Cbz) carbamate Nprotecting groups can be used, with both furnishing the desired addition products with high levels of reactivity (entries 6–7). The use of such alkyl enamines represents a particularly valuable transformation, as this opens up an entirely new class of previously non-reactive substrates to Petasis functionalization.

In order to demonstrate of the intermolecular nature of the organotrifluoroborate addition, it was shown that a fully substituted cyclic enamine **1** can also undergo styryl addition under standard reaction conditions (Eq 3). This result supports that an alternative pathway, coordination to the imine nitrogen and subsequent intramolecular nucleophile delivery, is not taking place as the cyclic substrate has no open coordination site.

Trifluoroborate Addition with Fully Substituted Cyclic Enamine



55% yield

Much to our surprise, initial results revealed that though unable to participate in a π -nucleophilic addition mechanism, potassium benzyl trifluoroborate also undergoes addition, albeit in moderate yield (Eq 4). Due to the inability of this substrate to participate in a Friedel-Crafts type mechanism, this intriguing result raises the possibility of alternative mechanisms for trifluoroborate addition including anionic, rearrangement and radical addition pathways. In the anionic mechanism, polarization of the boron-carbon bond would lead to a localization of negative charge on the benzylic carbon, which could behave as a carbanionic nucleophile. An alternative mechanism, reminiscent of the classical Petasis mechanism, is that of intramolecular rearrangement of the benzylic group following coordination to the imine nitrogen. There is also the possibility of a one-electron radical addition mechanism, as it has been shown that a similar class of imine electrophiles are susceptible to such radical fragmentation pathways¹⁷ and organotrifluorborates have been shown susceptible to single-electron oxidation events to generate benzylic radicals¹⁸. In order to determine which reaction mechanism is in effect, a Hammett study probing the role of imine electronics on the rate of addition was undertaken (Figure 2).

For this study a number of variously substituted imines were synthesized and the initial rate of their reaction with benzyl trifluoroborate at 0 °C was measured. If this reaction is proceeding through a two-electron mechanism, one would expect to see correlation with two electron Hammett constants. Conversely, if it proceeds through a one-electron mechanism, then better correlation should be seen with the single-electron Hammett constant σ •.

Figure 2. Hammett Study of Potassium Benzyl Trifluoroborate Addition





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As seen in Figure 2, better correlation is obtained with σ , indicating that this addition proceeds through a two-electron pathway. This suggests that either the anionic or rearrangement pathways are in effect for the addition of benzyltrifluoroborate.

In an attempt to render this transformation enantioselective, the reaction of *trans*-styryltrifluoroborate with a number of electrophiles containing chiral auxiliaries was examined (Figure 3). While the chiral carbamate protected substrates in equation 5 were able to undergo trifluoroborate addition with moderate levels of reactivity, no diastereomeric preference was observed.¹⁹

Figure 3 Chiral Auxiliary Approach to Asymmetric Induction



Conclusions

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In conclusion, we have demonstrated the first use of organotrifluoroborate salts as nucleophiles in the Petasis borono-Mannich reaction. Furthermore, through the use of these commercially available, air and moisture stable boronate salts we have been able to greatly expand the scope of electrophiles used in this synthetically valuable and versatile transformation.

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