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Synthesis of *N,N*-alkylated α-tertiary amines by coupling of α-aminoalkyltrifluoroborates and Grignard reagents

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Supporting Information Placeholder

ABSTRACT: The cross-coupling of α-aminoalkyltrifluoroborates and Grignard reagents to form *N,N*-substituted α-tertiary amines (ATAs) is reported. Key to the success of this reaction is the unexpected oxidation of the α-aminoalkyltrifluoroborate to the corresponding iminium cation by commercially available Barluenga's reagent. Various Grignard reagents added smoothly, enabling the synthesis of a variety of ATAs, which are of high value for medicinal chemistry and drug development. Many of the reported examples are not accessible by the established methods.

Amines adjacent to a tertiary carbon center – often referred to as α-tertiary amines (ATAs) – are an attractive motif for bioactive molecules and pharmaceuticals.[1] A few methods for the synthesis of these structures have been reported in the literature, but most are limited to ATAs with no substituents other than a single protecting group (tosyl, carbamate) on the N-atom. Frequently used strategies involve the addition of organometallic reagents to activated ketimines, as reported by Ellman, Shibasaki and others, C–H aminations, used by DuBois and Baran or rearrangements leading to the carbamate protected α-tertiary amine.[2] Examples for the synthesis of *N,N*-alkylated ATAs are rare and far less general, although several promising methods have been reported in the past years, for example, the copper/titanium-catalyzed one-pot coupling of amines, ketones and alkynes reported by Larsen and co-workers.[3]

We recently reported the facile synthesis of trifluoroborate iminiums (TIMs) from secondary (cyclic) amines and potassium acyltrifluoroborate (KAT) reagents[4] and studied the addition of Grignard reagents to these compounds to provide α-aminoalkyltrifluoroborates.[5] Based on the existing literature, these compounds looked to be an ideal coupling partner in cross-coupling reactions to give ATAs. For example, Molander and others reported conditions for the Suzuki–Miyaura coupling of α-aminomethyltrifluoroborates or α-(acylamino)benzylboronic esters with aryl halides using palladium catalysis (Figure 1).[6] Unfortunately, these conditions completely failed in our attempts to cross-couple the more sterically demanding α-aminoalkyltrifluoroborates with aryl halides. Numerous attempts to generate a radical from the α-aminoalkyltrifluoroborates in the α-position to the nitrogen atom using literature known procedures[7] followed by trapping with radical acceptors were also unsuccessful.

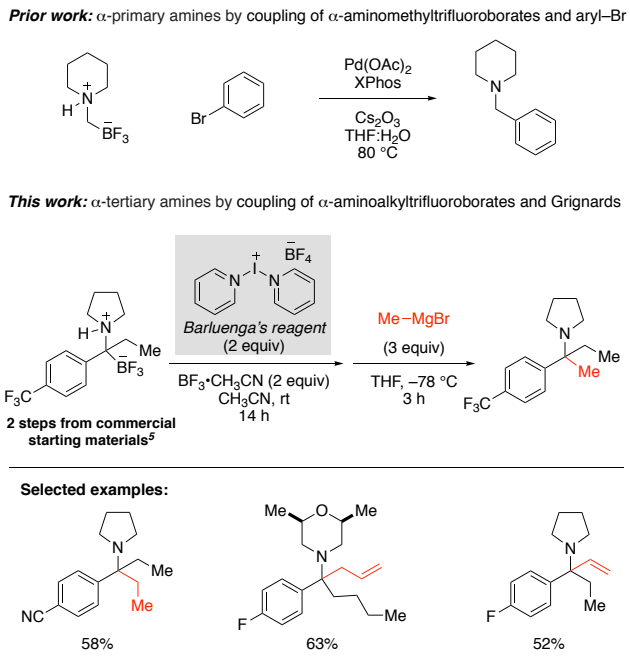


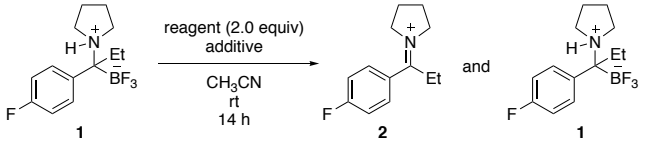
Figure 1. α-Aminoalkyltrifluoroborates for the synthesis of *N,N*-alkylated α-tertiary amines (ATAs)

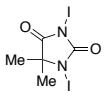
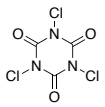
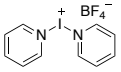
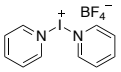
Therefore, we decided to change our strategy, suggesting that formal cross coupling by mild, room temperature oxidative iminium formation followed by nucleophilic addition could be possible. We now document the successful implementation of this strategy via a chemically and mechanistically unexpected oxidation of the α-aminoalkyltrifluoroborates with Barluenga's reagent, an iodonium species (Figure 1). To our surprise, this reaction does not proceed via boron or ni-

trogen oxidation, but rather, iodination of a distal site followed by the breakdown of this intermediate to the iminium.

By generating the iminiums under these somewhat acidic, non-dehydrative conditions, they can be cleanly formed and subjected to nucleophilic addition by Grignard reagents to form the tetrasubstituted carbon. In contrast, iminium salts generated by ketone/amine condensations are not well compatible with the subsequent addition of Grignard or organolithium reagents, as shown by Böhme in his studies on the addition of organolithium or Grignard reagents to iminium salts generated from ketones and ammonium perchlorates.[8]

Table 1. Reaction optimization for the oxidation step



entry	reagents	additive	ratio 2:1[a]
1		–	57:23
2	ICl[b]	–	47:53
3		BF_3•CH_3CN	90:10
4		BF_3•CH_3CN	35:65
5		BF_3•CH_3CN	messy
6		BF_3•CH_3CN	100:0
7		–	0:100

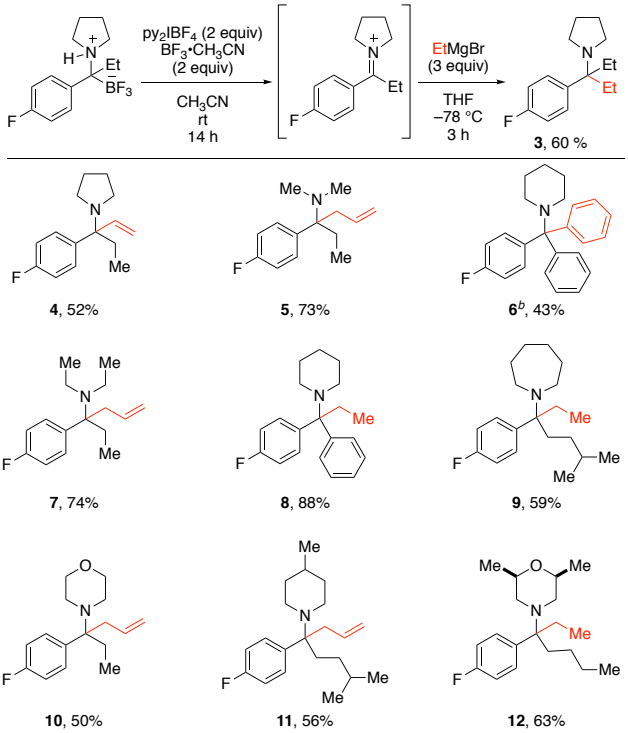
[a]From ^{1}H-NMR, 0.1 mmol scale; [b] 5.0 equiv were used

We first sought to establish efficient, reliable conditions for the oxidation of the α-aminoalkyltrifluoroborate to the iminium and screened various oxidizing reagents and conditions (Table 1). Our original hypothesis for iminium formation relied on *N*-halogenation, in analogy to our recently reported amide formation from N–Cl amines. This inspired a screen of polar halogenating reagents, and indeed, some success was found with *N*-iodosuccinimide, and ICl (entries 1–2). Interestingly, *N*-bromosuccinimide gave the iminium only in the presence of BF_3•CH_3CN (entry 3). Further exploration of I^+ reagents to investigate this finding in more detail was appealing, and we screened various commercially available I^+-reagents (entry 4 and entries 6–7). Ultimately, Barluenga's reagent (bis(pyridine)iodonium(I) tetrafluoroborate; py_2IBF_4)[9] in combination with Lewis acids proved to be the most general and highest yielding reaction condition (entry 6).

This finding led to a general protocol for the iminium-formation/Grignard addition: a 0.1 M solution of the α-aminoalkyltrifluoroborate in CH_3CN was treated with 2.0 equiv of Barluenga's reagent and 2.0 equiv of BF_3 and stirred for 14 h.[10] The iminiums formed in this manner are stable to concentration and solvent exchange, allowing the addition to proceed in THF with 3.0 equiv of the Grignard reagent at –78 °C.[11] We found that 3.0 equiv of Grignard reagent are optimal to drive the reaction to full conversion. To suppress undesired side reactions, cooling the reaction to –78 °C provided the best results. The reaction proceeds in moderate to good yield for most of the substrates tested (Scheme 1).

To our surprise, the iminium formation requires at least one aromatic substituent at the carbon center; fully aliphatic substrates gave no conversion. Differently substituted amine moieties led to comparable results. The reaction tolerates both acyclic (**5**, **7**) and cyclic secondary amines (**3**, **4**, **6** and **8**–**12**). Pyrrolidines and piperidines worked similarly well as morpholines or even larger rings, such as azepanes. Various Grignard reagents added smoothly to the iminium formed from the α-aminoalkyltrifluoroborates (**3**–**12**). The highest yields were achieved using allyl Grignard reagents; alkyl and vinyl Grignard reagents added in moderate to good yield.

Scheme 1. Substrate scope for the coupling of α-aminoalkyltrifluoroborates and Grignard reagents[a]

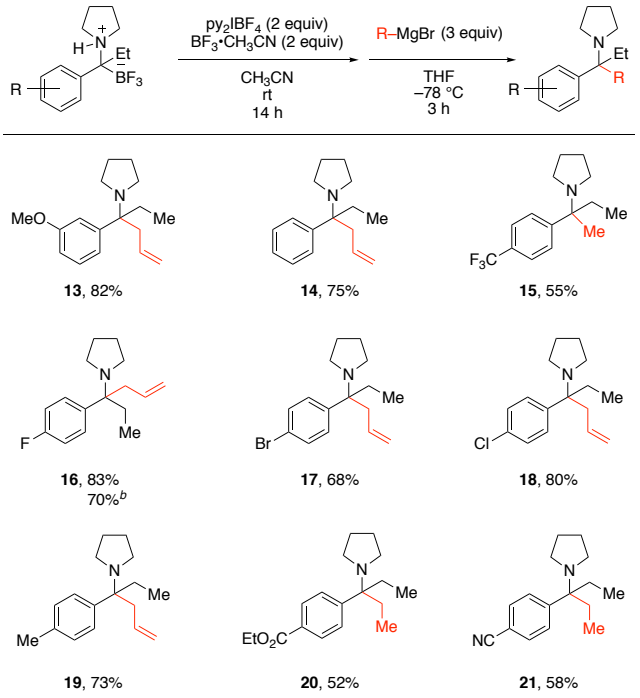


[a]Reactions were performed on a 0.5 mmol scale using the indicated α-aminoalkyltrifluoroborate (1.0 equiv) and the Grignard reagent (3.0 equiv); yields of analytically pure compounds after chromatography are given; [b]PhLi (3.0 equiv) was used

More sterically demanding Grignard reagents including isopropyl or aryl Grignards add to the iminium as well, but the conversion drops, and the overall efficiency of the reaction decreases. If the more reactive aryl Lithium reagent is chosen, the reaction proceeds in satisfying yields, which enabled the efficient synthesis of the triaryl substituted ATA **6**. Identical conditions could be used to scale up the reaction to a gram scale (**16**, Scheme 2).

To investigate the functional group tolerance and the impact of the electronic properties of the aromatic substituent, substrates bearing various functionalities on the aromatic moiety were synthesized and tested under our general conditions (Scheme 2). Unlike some metal-catalyzed cross couplings, the reaction tolerates aromatic halogens (**16**, **17**, **18**) and, if an alkyl Grignard is chosen, aromatic esters (**20**) and nitriles (**21**). The overall oxidation/addition process takes place on substrates substituted with electron-poor and electron-rich aromatics.

Scheme 2. Substrate scope for coupling of α-aminoalkyltrifluoroborates[a]



[a]Reactions were performed on a 0.5 mmol scale using the indicated α-aminoalkyltrifluoroborate (1.0 equiv) and the Grignard reagent (3.0 equiv); yields of analytically pure compounds after chromatography are given; [b]reaction was performed on a 1 g scale (4.0 mmol)

Finally, we investigated the mechanism of the reaction in light of the requirement of an aromatic moiety on the carbon center. Having discounted *N*-iodination or oxidation of the BF_3 moiety, we hypothesized that an electrophilic aromatic substitution-elimination mechanism might be operative (Figure 2).[9, 12, 13]

In this mechanism, Barluenga's reagent is first activated by BF_3. Next, the aromatic group is iodinated in the *meta* position to the aminoalkyltrifluoroborate moiety to form **22**. This position is prone to electrophilic addition due to both the electron-withdrawing nature of the aminoalkyltrifluoroborate substituent and steric reasons. Elimination of iodine and BF_3 leads to cation **23**, which loses a proton to form iminium **2**.

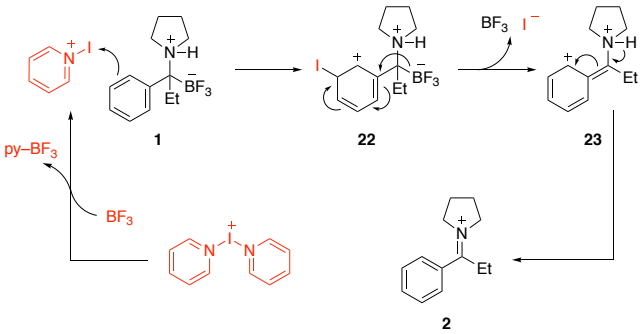


Figure 2. Proposed mechanism for the oxidation step of the reaction; BF_3 activates the Barluenga's reagent

To confirm this hypothesis, the rates of iminium formations of a set of α-aminoalkyltrifluoroborates containing differently substituted aromatic moieties were probed by NMR. A clear trend could be observed: substrates with electron-poor aromatics converted slower to the iminium cation than substrates with more electron-rich aromatic groups.[14] A Hammett-plot analysis using the literature values for σ_{meta} parameters[15] showed a linear relationship (Figure 3).

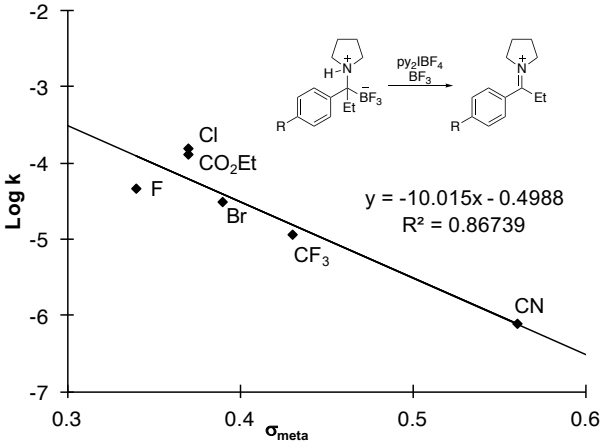


Figure 3. Hammett-plot analysis of the kinetic data. Reaction constants k of differently substituted substrates were measured using ^{1}H-NMR. A linear relationship between Log k and literature values for σ_{meta} is clearly observed

In summary, we have documented a convenient method for the synthesis of *N,N*-alkylated α-tertiary amines via oxidative generation of iminiums from α-aminoalkyltrifluoroborates. We have postulated an unexpected mechanism for the iminium formation featuring transient iodination of a distal aromatic site. Further advances in

this chemistry will expand access to *N,N*-alkylated α-tertiary amines for drug discovery and development and provide a useful method for the generation of synthetically valuable ketone-derived iminiums.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF)

AUTHOR INFORMATION

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(10) For specific cases, it is possible to further optimize the reaction and possibly apply less Lewis acid or Grignard reagent

(11) The nature of the counter ion is unknown. ^{1}H-NMR and ^{19}F-NMR studies suggest pyr–BF_3^- as the possible counter ion, but others as I^- cannot be excluded.

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