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$B(C_6F_5)_3$ mediated arene hydrogenation/transannulation of *para*-methoxyanilines†

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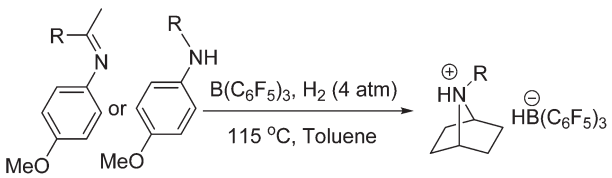
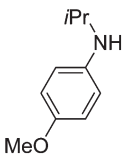
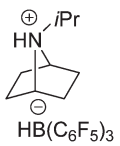
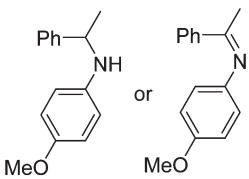
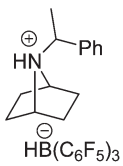
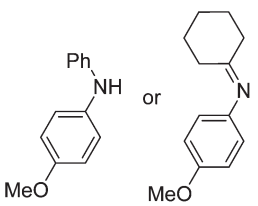
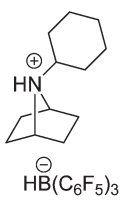
The stoichiometric reaction of *para*-methoxyanilines and $B(C_6F_5)_3$ under H_2 results in reduction of the N-bound phenyl ring(s), and subsequent transannular ring closure with elimination of methanol, affording the respective 7-azabicyclo[2.2.1]heptane derivatives.

Frustrated Lewis pair (FLP) chemistry has seen considerable growth since its discovery,[1] particularly in the fields of H_2 activation and hydrogenation.[2] While initial reports of these metal-free hydrogenations were limited to the reduction of imines,[3] protected nitriles, and aziridines,[4] the scope has broadened dramatically to include enamines, silyl enol ethers,[5] N-heterocycles,[6] olefins,[7] poly-arenes,[8] alkynes,[9] ketones,[10] and aldehydes.[11] In addition to these catalytic reductions, we have reported the stoichiometric FLP reduction of anilines to afford cyclohexylammonium derivatives.[12] These unique main group-mediated aromatic reductions can be extended to include pyridines and other N-heterocycles.[13] In an effort to further explore the scope of these remarkable metal-free aromatic reductions, herein we report the finding that *para*-methoxy substituted anilines undergo tandem hydrogenation and intramolecular cyclization with $B(C_6F_5)_3$, presenting a unique route to 7-azabicyclo[2.2.1]heptane derivatives.

A toluene solution of $B(C_6F_5)_3$ and the substituted aniline *p*-$CH_3OC_6H_4NH(i\text{Pr})$ was pressurized with H_2 (4 atm) and heated at 115 °C for 48 h. Upon workup, a new white crystalline product **1** was isolated in 87% yield (Table 1, entry 1). Indeed, the ^1H NMR spectrum indicated loss of aromatic resonances, and showed a diagnostic broad singlet at 4.29 ppm with the corresponding $^{13}C\{^1H\}$ resonance at 64.7 ppm. These data inferred the presence of two equivalent bridgehead CH groups of the bicyclic ammonium cation. The ^{11}B NMR spectrum revealed a doublet (J = 88 Hz) at −25 ppm, and resonances at −134, −164, and −167 ppm were observed in the ^{19}F NMR spectrum, consistent with the presence of the $[HB(C_6F_5)_3]$ anion. An X-ray diffraction study confirmed that **1** was indeed the bicyclic product isolated as $[C_6H_{10}NH(iPr)][HB(C_6F_5)_3]$ (Fig. 1a).

Table 1 Hydrogenation and transannulation reactions of *para*-methoxyanilines



Entry	Starting material	Product	Isolated yield
1			**1:** 87%
2			**2:** 51% (N–C) 63% (N=C)
3			**3:** 36% (Ph) 63% (Cy)

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†Electronic supplementary information (ESI) available: Spectroscopic and preparative details have been deposited. Crystallographic data have been deposited see: CCDC 1046629-1046633. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5dt00921a

‡These authors contributed equally and should be both deemed "first author".

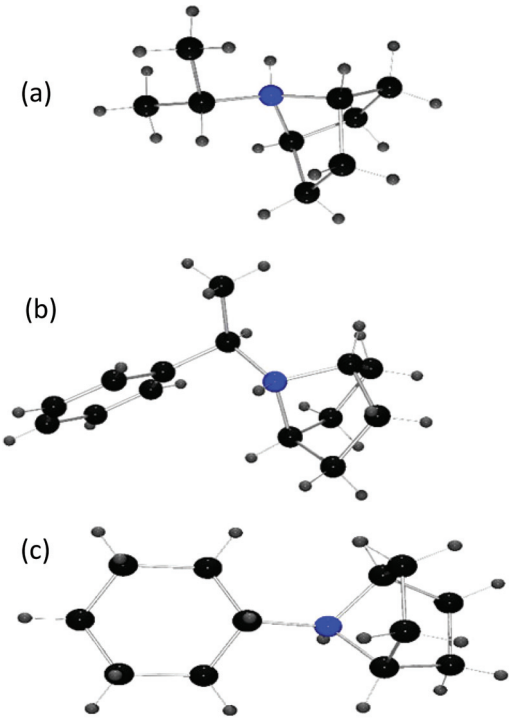
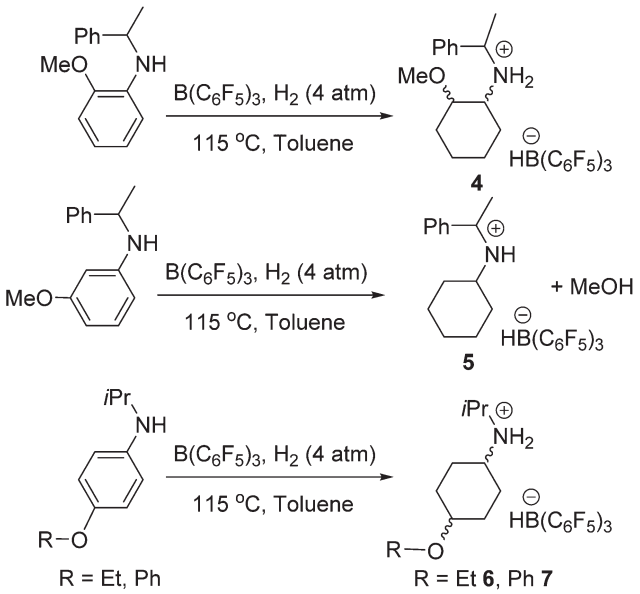


Fig. 1 POV-ray depiction of the cations of (a) **1**, (b) **2**, (c) **3** (N, blue; H, gray; C, black).



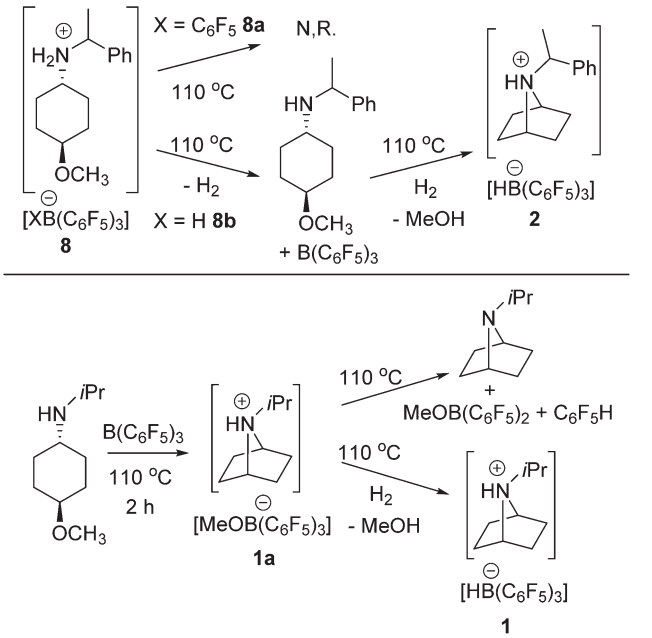
Scheme 1 Synthesis of compounds **4–7**.

In a similar fashion, the reaction of *p*-$CH_3OC_6H_4NHCH(CH_3)Ph$ with $B(C_6F_5)_3$ under H_2 at 115 °C afforded the product $[C_6H_{10}NHCH(CH_3)Ph][HB(C_6F_5)_3]$ **2** in 51% isolated yield (Table 1, entry 2). In this case, the ^1H NMR spectrum showed two inequivalent doublet of doublets at 4.47 and 3.74 ppm that are attributable to the bridgehead protons of the bicyclic cation, with corresponding $^{13}C\{^1H\}$ NMR resonances observed at 65.2 and 64.7 ppm, respectively. In addition, the ^{11}B and ^{19}F NMR spectra were consistent with the presence of $[HB(C_6F_5)_3]$ as the counter anion and the formulation was also confirmed by single crystal X-ray crystallography (Fig. 1b). Compound **2** was also isolated in 63% yield from the corresponding reaction of the imine *p*-$CH_3OC_6H_4N{=}C(CH_3)Ph$ (Table 1, entry 2).

Under analogous conditions, the bis-aryl substrate *p*-$CH_3OC_6H_4NHPh$ yielded the bicyclic product **3** in 40% isolated yield (Table 1, entry 3). ^1H NMR analysis showed that both N-bound aromatic rings were reduced, resulting in a cyclohexyl-substituted 7-aza-bicyclo[2.2.1]heptane ammonium product $[C_6H_{10}NHCy][HB(C_6F_5)_3]$. This formulation was also confirmed through a single crystal X-Ray diffraction study (Fig. 1c). The same product was isolated when starting from the imine substrate $CH_3OC_6H_4N{=}Cy$ in 56% yield (Table 1, entry 3).

The *ortho*- and *meta*-methoxy substituted amines $CH_3OC_6H_4NHCH(CH_3)Ph$ were independently reacted with $B(C_6F_5)_3$ and H_2 using the above protocol. In both cases, while hydrogenation of the N-bound phenyl group was observed, no transannular attack followed. The *ortho*-substituted amine gave a mixture of *cis* and *trans*-[*o*-$CH_3OC_6H_{10}NH_2CH(CH_3)Ph$]-$[HB(C_6F_5)_3]$ **4** in 92% isolated yield while the *meta* precursor gave rise to C–O bond cleavage yielding $[C_6H_{11}NH_2CH(CH_3)Ph]$-$[HB(C_6F_5)_3]$ **5** in 65% isolated yield (Scheme 1). Similarly, replacement of *para*-methoxy substituent on the aromatic ring by ethoxy and phenoxy substituents in the precursor anilines did not lead to bicyclic products. In these cases, only hydrogenation of the N-bound aromatic ring was observed affording the cyclohexylammonium salts [*p*-$EtOC_6H_{10}NH_2(iPr)$]-$[HB(C_6F_5)_3]$ **6** and [*p*-$PhOC_6H_{10}NH_2(iPr)$] $[HB(C_6F_5)_3]$ **7**, respectively (Scheme 1).

The mechanism through which these bicyclic products were formed was further investigated. To this end, a toluene solution of the independently-synthesized ammonium-borate salt [*trans*-4-$CH_3OC_6H_{10}NH_2CH(CH_3)Ph$][$B(C_6F_5)_4$] **8a** was heated at 110 °C (Scheme 2, top). No reaction was evidenced by ^1H, ^{11}B and ^{19}F NMR spectroscopy. However, addition of [*trans*-4-$CH_3OC_6H_{10}NH_2CH(CH_3)Ph$][$HB(C_6F_5)_3$] **8b** at 110 °C prompted release of H_2 as evidenced by the ^1H NMR signal at 4.5 ppm. Furthermore, after heating at 110 °C for 12 h compound **1** was isolated (Scheme 2, top). This observation infers that ring closing yielding the 7-azabicyclo[2.2.1]heptane ammonium cation does not proceed by intra- or intermolecular protonation of the methoxy group but rather that transannular attack proceeds *via* intramolecular nucleophilic attack of the *para*-carbon by free amine, facilitated by borane capture of the methoxide fragment. To further support this proposed mechanism, the independently synthesized amine *trans*-4-$CH_3OC_6H_{10}NH(iPr)$ was treated with an equivalent of $B(C_6F_5)_3$ in the absence of H_2. Interestingly, after heating for 2 h, the reaction resulted in quantitative formation of compound **1** with a borane-methoxide anion $[C_6H_{10}NH(iPr)]$ $[CH_3OB(C_6F_5)_3]$ **1a** (Scheme 2, bottom). ^1H NMR spectra showed the diagnostic resonances for the bridgehead CH protons at 4.13 ppm con-



Scheme 2 Reactions of *trans*-[4-$CH_3OC_6H_{10}NH_2CH(CH_3)Ph$]-[$XB(C_6F_5)_3$] (X = C_6F_5 **8a**; H **8b**) (top) and *trans*-4-$CH_3OC_6H_{10}NH$*i*Pr (bottom).

sistent with the formation of the 7-azabicyclo[2.2.1]heptane ammonium cation. A sharp ^{11}B resonance at −2.42 ppm and ^{19}F resonances at −135, −162 and −166 ppm were consistent with the formation of the borane-methoxide anion [$CH_3OB(C_6F_5)_3$]. This formulation of **1a** was further confirmed by an X-ray diffraction study (Fig. 2).

While heating of **1a** for 2 h at 110 °C in the absence of H_2 resulted in amine liberation and rapid degradation of the borane to $CH_3OB(C_6F_5)_2$ and C_6F_5H, in the presence of H_2 **1a** is transformed to **1** with the liberation of CH_3OH (Scheme 2, bottom). This observation infers that the ammonium cation protonates the methoxide bound to boron, liberating methanol and regenerating $B(C_6F_5)_3$, which undergoes FLP type H_2 activation with the amine (Scheme 2, bottom). ^1H NMR spectroscopy confirmed the presence of methanol as a reaction product (see ESI†). Interestingly, a similar protonation pathway has been previously proposed by Ashley and O'Hare[14] in the stoichiometric hydrogenation of CO_2 using 2,2,6,6-tetramethylpiperidine and $B(C_6F_5)_3$. Additionally, Ashley *et al.*[11] have recently proposed that metal-free carbonyl reduction of aldehydes also proceed through protonation of $B(C_6F_5)_3$-alkoxide bonds.

One can also envision the combination of $[CH_3OB(C_6F_5)_3]^-$ and $B(C_6F_5)_3$ acting as an FLP to activate H_2. To probe this, a toluene solution of $[NEt_4][CH_3OB(C_6F_5)_3]$ and 5 mol% $B(C_6F_5)_3$ was exposed to H_2 (4 atm) at 110 °C. After heating for 2 h, the ^1H, ^{11}B and ^{19}F NMR data revealed complete consumption of the $[CH_3OB(C_6F_5)_3]$ anion and the emergence of $[NEt_4]$-$[HB(C_6F_5)_3]$ and CH_3OH (see ESI†). This latter mechanism provides an alternative path to the anion of **1**.

Regardless of the mechanism of methanol liberation, the cleavage of the B–O bond in this case stands in contrast to previous work from our group[4] and the groups of Erker,[15] Repo and Rieger[16] where robust B–O bonded products are derived from reactions of oxygen based substrates and FLPs. Indeed, in our own efforts to effect aliphatic ketone reduction in toluene, borinic esters were obtained from the stoichiometric combination of ketones and $B(C_6F_5)_3$ under H_2.[17] It is interesting however that ketone hydrogenation to alcohol has been recently achieved by both our group and that of Ashley employing ethereal solvents. In these cases, hydrogen bonding of the protonated ketone with the solvent, preclude protonation of the B–C bond of the generated $[HB(C_6F_5)_3]$. In a similar sense, the intermediate ammonium cation of **1a** selectively protonates the oxygen of the anion en route to **1**.

Collectively these data infer that compounds **1–3** are formed by initial hydrogenation of the aniline arene ring affording the cyclohexylamine. Although the amine and borane can activation H_2 to give the ammonium salt, at elevated temperatures this is reversible allowing the borane to activate the methoxy substituent and induce transannulation (Scheme 3). Subsequent conversion of the generated

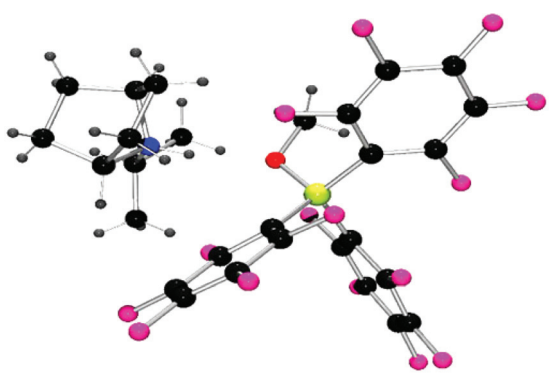
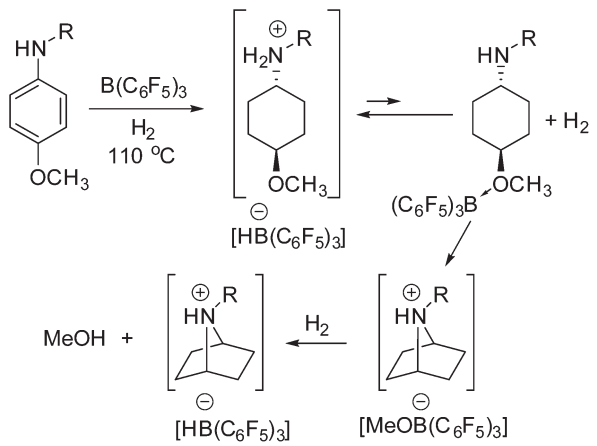


Fig. 2 POV-ray depiction of **1a**. (B, yellow-green; O, red; F, deep pink; N, blue; H, gray; C, black).



Scheme 3 Overall proposed mechanism for the formation of 7-azabicyclo[2.2.1] heptane derivatives.

methoxy-borate anion to the hydridoborate anion proceeds under H_2.

The formation of **1**, **1a**, **2** and **3** represent, to the best of our knowledge, the first examples of a one-pot synthesis of 7-azabicyclo[2.2.1]heptane derivatives. Traditional synthetic methods to 7-azabicyclo[2.2.1]heptanes include Diels–Alder cycloaddition of pyrroles and alkenes or alkynes, or multi-step intramolecular cyclizations of 4-aminocyclohexane derivatives.[18] These traditional methods are typically low-yielding or require several protecting group manipulations.

Conclusions

In summary, heating the combination of *para*-methoxy substituted anilines and $B(C_6F_5)_3$ under H_2 provides a one-pot tandem arene hydrogenation-transannular ring closure reaction affording 7-azabicyclo[2.2.1]heptane ammonium salts. Although the oxophilic $B(C_6F_5)_3$ facilitates this reaction by abstracting methoxide, subsequent reaction with H_2 affords methanol and the hydridoborate anion. Research is continuing to design and develop application of this and other tandem FLP-mediated transformations.

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