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Branched Amine Synthesis via Aziridine or Azetidine Opening with Organotrifluoroborates by Cooperative Brønsted/Lewis Acid Catalysis: An Acid-Dependent Divergent Mechanism

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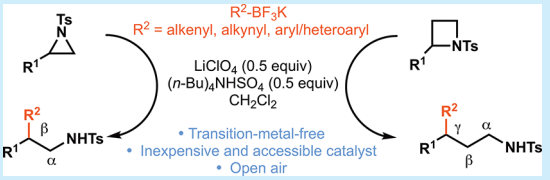
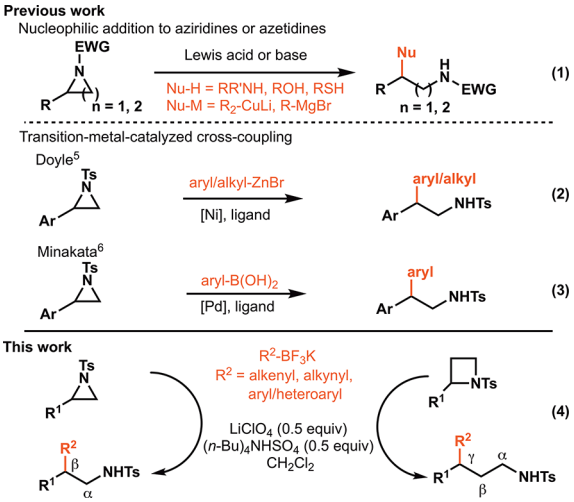
Supporting Information

ABSTRACT: A practical catalytic method to synthesize β,β- and γ,γ-substituted amines by opening aziridines and azetidines, respectively, using alkenyl, alkynyl, or aryl/heteroaryl trifluoroborate salts is described. This reaction features simple open-flask reaction conditions, the use of transition-metal-free catalysis, complete regioselectivity, and high diastereoselectivity. Preliminary mechanistic studies suggest that carbocation formation is disfavored. Stereoretentive addition is favored with Brønsted acid present, while stereoinversion is favored in its absence, indicating divergent mechanisms.



Amines with β- or γ-branching constitute an important motif for a large number of small molecules with biological properties, some of which serve as candidates for the treatment of nervous system disorders such as Parkinson's and Alzheimer's diseases.[1] Several strategies have been conceived to construct these molecules. A powerful strategy to synthesize β,β- or γ,γ-substituted amines has been nucleophilic addition to the substituted position of aziridines[2] or azetidines,[3] respectively, catalyzed by Lewis acids or Lewis bases (Scheme 1, eq 1). Though several types of nucleophiles have been successfully employed to make C−C bonds, carbanions such as organolithium cuprates or Grignard reagents have been most prominently used.[4] Examples of neutral carbon π-nucleophiles are rare, especially with azetidines.[3] Furthermore, these approaches usually exhibit poor regioselectivity due to competitive nucleophilic attack at the two carbons of the aziridine.

Scheme 1. Synthesis of β,β- and γ,γ-Substituted Amines



Another efficient approach to synthesize substituted amines is transition-metal-catalyzed cross-coupling of aziridines (Scheme 1, eqs 2 and 3). Specific metals and ligands are needed for fine control over the selectivity of these reactions. For instance, Doyle developed nickel catalysts to promote the cross-coupling between aryl or alkylzinc reagents to *N*-sulfonylaziridines with complete regioselectivity at the substituted position.[5] The use of an electron-deficient alkene ligand was crucial to prevent β-hydride abstraction. Aryl boronic acids were successfully used for a palladium-catalyzed coupling, as later reported by Minakata,[6] where the bond formation occurs with excellent stereochemical inversion. Although these reactions represent significant advances, which even allow the generation of quaternary stereocenters[5c] or an enantioselective transformation,[5d] they require complex and sometimes expensive ligands. Moreover, transition-metal catalysts often require inert atmospheres and exclusion of water, and limited tolerance of halogenated substrates is seen. Additionally, no examples of using alkynyl or alkenyl nucleophiles as coupling partners with aziridines at the substituted carbon have been reported, nor are there examples of transition-metal-catalyzed cross-couplings to azetidines to afford γ,γ-substituted amine.

In addition to the above-mentioned limitations to synthesizing substituted amines, it is crucial to remove contaminating metals in many chemical processes, especially in the pharmaceutical industry.[7] Transition-metal-free conditions are consequently of interest to reduce cost and environmental impact.[8] Coincidentally, organotrifluoroborates have recently gained increasing attention due to their wide functional group tolerance, bench-

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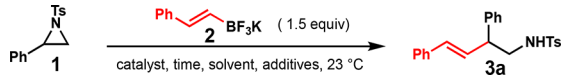
stability, low toxicity, and easy access from commercial sources. Therefore, a reaction to afford substituted amines under transition-metal-free conditions from organotrifluoroborates, an unprecedented reaction, would be highly attractive for organic synthesis. Herein, we describe a general method to synthesize both *β*,*β*- and *γ*,*γ*-substituted amines by nucleophilic ring opening of aziridines and azetidines, respectively, using organotrifluoroborate salts as nucleophiles under cooperative Lewis/Brønsted acid catalysis (Scheme 1, eq 4). This approach provides straightforward, high-yielding, and scalable access to substituted amines with a wide range of readily available organotrifluoroborates under very simple conditions.

With the successful employment of organotrifluoroborate salts as nucleophiles in our previous works,[9] we hypothesized that a similar nucleophilic addition to aziridines or azetidines would occur in the presence of a suitable Lewis acid or Brønsted acid. The investigation began by testing the reaction between readily available styrenyl trifluoroborate **2** and styrene-derived *N*-tosylaziridine **1** with various catalysts. After extensive screening, we found that some Lewis acids such as $Bi(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, or $InCl_3$ could promote the reaction to afford *β*,*β*-substituted amine **3a** with complete regioselectivity, but in low yield (Table 1, entry 1). Promisingly, amine **3a** could be obtained

Table 1. Effects of Varying Reaction Conditions[10]



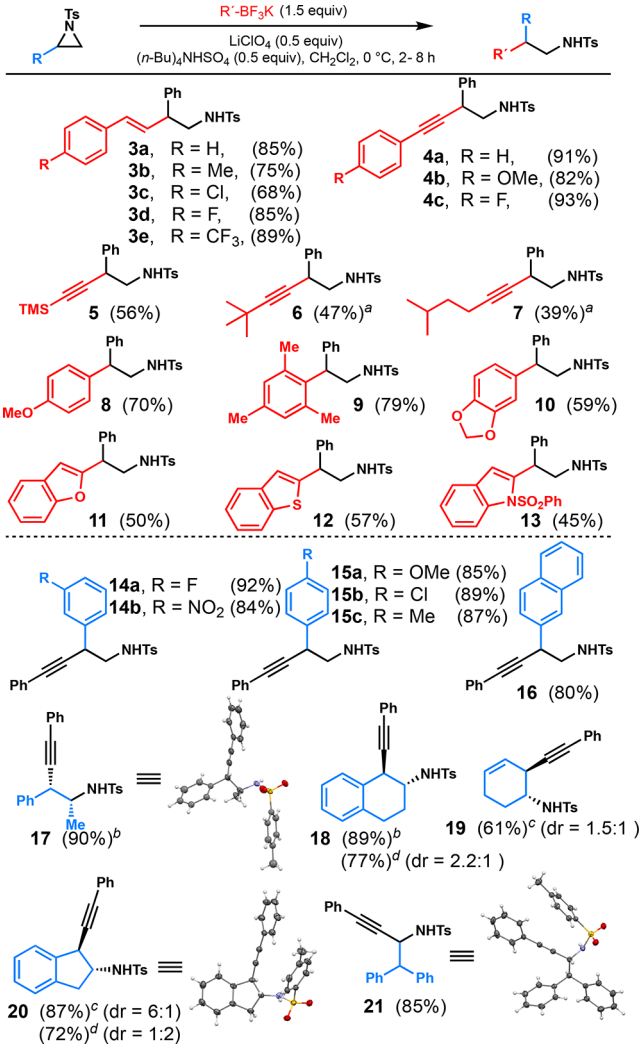
entry	catalyst	time (h)	solvent	co-catalyst	yield (%)[a]
1	LA[b]	12	CH_2Cl_2		17−22
2	$LiClO_4$	12	CH_2Cl_2		61
3	LiCl	12	CH_2Cl_2		45
4	$LiPF_6$	12	CH_2Cl_2		28
5	LiOTf	12	CH_2Cl_2		18
6	$LiClO_4$	12	MeCN		51
7	$LiClO_4$	12	THF		trace
8	$LiClO_4$	12	PhMe		60
9	$LiClO_4$	6	CH_2Cl_2	$(n\text{-Bu})_4NHSO_4$	77
10		24	CH_2Cl_2	$(n\text{-Bu})_4NHSO_4$[c]	66
11	$LiClO_4$	6	CH_2Cl_2	**$(n\text{-Bu})_4NHSO_4$**	85[d]

[a]Via ^1H NMR integration relative to an internal standard. [b]LA = $Bi(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, and $InCl_3$. [c]0.5 equiv. [d]Isolated yield, 0.5 equiv of $LiClO_4$ at 0 °C.

in >60% yield in the presence of $LiClO_4$ under open air conditions at room temperature (Table 1, entry 2). When switching to other lithium salts, the reaction yields did not improve (Table 1, entries 3−5). Only toluene gave results similar to dichloromethane but not for all substrates (Table 1, entries 6−8). The addition of $(n\text{-Bu})_4NHSO_4$ increased the reaction yield to 77% (Table 1, entry 9).[9b] Interestingly, we later found that $(n\text{-Bu})_4NHSO_4$ provided the product in 66% yield without lithium salts (Table 1, entry 10). Further optimization showed that the adduct **3a** was obtained in 85% yield at 0 °C catalyzed by $LiClO_4$ and $(n\text{-Bu})_4NHSO_4$ (Table 1, entry 11).

To investigate the scope of this reaction, we first varied the alkenyl trifluoroborate (Scheme 2). Yields were generally high and not significantly affected by aryl ring *para* substituents (**3b**−**e**). When alkynyl trifluoroborates instead of alkenyl trifluoroborates were used, the products were obtained in even higher yields (**4a**−**c**), even though alkynyl boronates are often sensitive to acidic conditions. It should be noted that there are no previous

Scheme 2. Scope of the Reaction with Aziridines



[a]24 h at 60 °C. [b]Obtained as a single diastereomer. [c]Yield reported for the mixture of diastereomers. [d]Reaction conducted with $(n\text{-Bu})_4NHSO_4$ omitted.

examples using alkynyl/alkenylzinc reagents or alkynyl/alkenyl boronates for this transformation. Ethynyltrimethylsilane borate reacted as well to give **5** in 56% yield. Less reactive aliphatic alkynyl borates required a higher temperature and longer time to afford adducts **6** and **7**. Aryl and heteroaryl borates to afford synthetically useful *β*,*β*-biaryl amines were next tested. The $LiClO_4/(n\text{-Bu})_4NHSO_4$ catalytic system also promoted the nucleophilic addition of electron-rich aromatic borates (**8**−**13**) in moderate to good yields. The steric hindrance of *o*,*o*-disubstitution on a mesityl nucleophile was not an issue (**9**). Heteroaryl borates afforded products **11**−**13** in acceptable yields.

Next, the aziridine scope was investigated with phenylethynyl trifluoroborate and a variety of aziridines. The reactions proceeded smoothly to give products in good to excellent yields with complete regioselectivity and high diastereoselectivity in all but one substrate. Aziridines with aromatic rings bearing either an electron-donating or an electron-withdrawing group reacted similarly (compare **14** and **15** to **4**). 2-Naphthylaziridine reacted as well to give **16** in 80% yield. The reaction is not limited to monosubstituted aziridines; 1,2-disubstituted aziridines performed similarly. The aziridine derived from *trans*-*β*-methylstyr-

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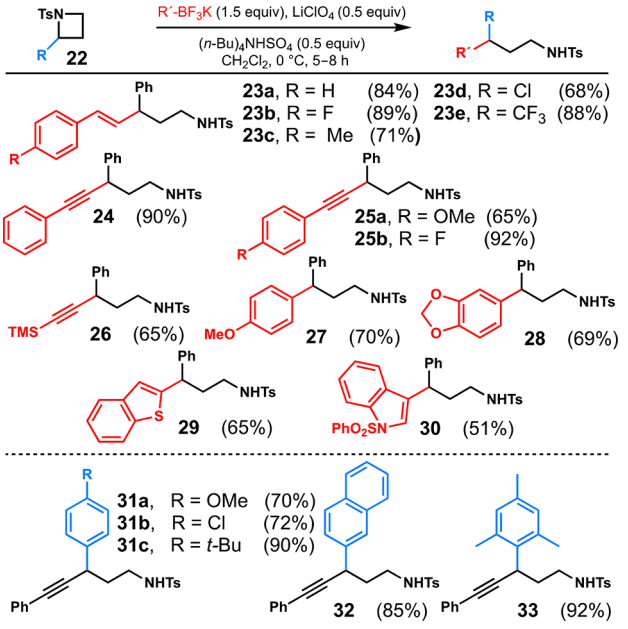
ene provided exclusively *syn*-**17** in 90% yield. Aziridines derived from dialin and indene gave *trans*-products **18** and **20** as the major diastereomers, respectively, in excellent yields. It should be noted that the major diastereomers of **17** to **20** were formed by stereoinversion in the nucleophilic addition. Surprisingly, the absence of $(n\text{-Bu})_4NHSO_4$ produced significantly more *cis* product, which was the major product for **20**. Interestingly, the aziridine derived from *trans*-stilbene underwent a 1,2-phenyl shift prior to the nucleophilic addition to afford adduct **21** in 85% yield, which was confirmed by single-crystal X-ray crystallography. An allylic substrate gave homoallylic amine **19** in 61% yield with a *trans*/*cis* ratio of 1.5:1. Unfortunately, aziridines with saturated aliphatic substituents did not afford β-amine products.

Because the intrinsic ring strain of aziridines is believed to facilitate the formation of the new C−C bond, we looked next to *N*-tosylazetidine electrophiles since they exhibit similar ring strain to aziridines.[11] The azetidine **22** (R = Ph), which could easily be accessed by reported procedures,[12] reacted with various trifluoroborates to afford a variety of γ,γ-substituted amines (Scheme 3). Styrenyl trifluoroborate gave γ,γ-substituted amine

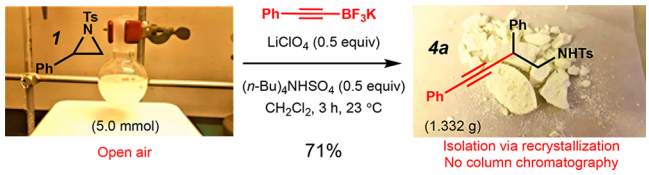
Scheme 3. Scope of the Reaction with Azetidines



23a in 84% yield. Again, reaction yields were largely unaffected by the substituents at the *para*-position of the aromatic ring (**23b**−**e**). As was the case for aziridines, alkynyl trifluoroborates generally afforded product in good to excellent yields (**24**−**26**). Though ethynyltrimethylsilane trifluoroborate reacted less well, product **26** was still obtained in a useful 65% yield. A range of electron-rich aromatic and heteroaromatic nucleophiles afforded γ,γ-biaryl products **27**−**30** with satisfactory yields. The scope of the reaction with regard to the azetidine was also investigated. With the representative phenylethynyl trifluoroborate, good to excellent yields of the products **31**−**33** were obtained for all azetidines, even with a sterically hindered mesitylene (**33**).

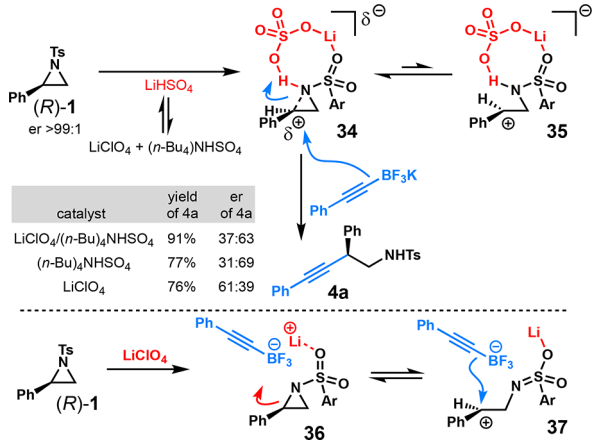
To highlight the practicality of this method to synthesize substituted amines, the reaction was conducted with 5 mmol (>1 g) of aziridine **1** and phenylethynyl trifluoroborate under open-air conditions at room temperature. It proceeded cleanly and was complete in 3 h to afford **4a** in 71%, which was obtained by simple recrystallization (Scheme 4).

Scheme 4. Large-Scale Production of Amine 4a



To gain insight into the reaction mechanism, enantiomerically pure aziridine (*R*)-**1** was reacted with phenylethynyl trifluoroborate under the optimized conditions. The product **4a** was obtained in 91% yield with an enantiomeric ratio of 37:63 (Scheme 5). The partial loss of enantioenrichment in the product

Scheme 5. Proposed Reaction Mechanisms



4a suggests that the reaction initially proceeds via an intermediate with significant carbocationic character. While $(n\text{-Bu})_4NHSO_4$ gave a similar outcome, when using only $LiClO_4$ as the catalyst, a surprising inverted enantiomeric ratio of 61:39 was seen. In the presence of HSO_4^-, primarily stereoinversion is seen (**17**−**20**), while $LiClO_4$ alone must then favor stereoretention. When the aziridine (*R*)-**1** was treated with the co-catalysts and without the organoborate nucleophile, a slow racemization of the aziridine was observed (see the Supporting Information (SI)). The rate of nucleophile addition to (*R*)-**1** (>60% within 5 min) is much faster than that of racemization (99% to 25% ee in 14 h).

On the basis of the results of these control experiments, a proposed mechanism is shown. Since the combination of $LiClO_4$ and $(n\text{-Bu})_4NHSO_4$ gives a significant reaction rate acceleration compared to $LiClO_4$ or $(n\text{-Bu})_4NHSO_4$ alone, it is possible that ion exchange between $LiClO_4$ and $(n\text{-Bu})_4NHSO_4$ occurs to generate bifunctional catalyst $LiHSO_4$ in situ.[13] The coordination of $LiHSO_4$ to aziridine **1** could form species **34** where partial bond fragmentation has been initiated. An intermolecular nucleophilic attack of the organotrifluoroborate then generates amine **4a**. The proposed carbocation intermediate **35** is evident from the slow loss of enantioenrichment of (*R*)-**1** in control experiments. However, the observed diastereoselectivity in the formation of **17**−**20** suggests that an S_N2-like mechanism predominates in the attack of **34**. To explain the stereoretention observed with only $LiClO_4$, we hypothesize that the trifluoroborate is initially located on the same face as the lithium-coordinated tosamide through electrostatic attraction in the nonpolar solvent.[14] When the aziridine opens, C−C bond formation would then take place from that face. More detailed control experiments to evaluate this case are ongoing.

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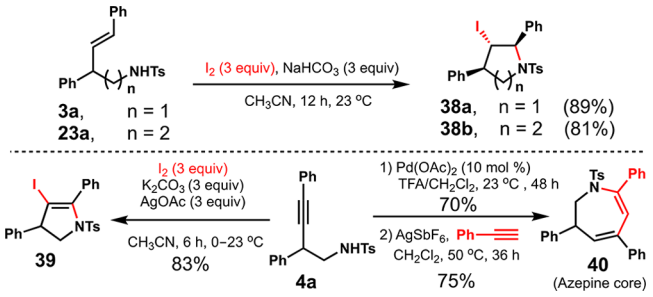
To illustrate the utility of the reaction products, iodocyclization and cycloaddition transformations have been performed (Scheme 6). In the presence of I_2 and $NaHCO_3$, the products **3a** and **23a** smoothly underwent iodocyclization to form iodo-substituted pyrrolidine **38a** and piperidine **38b** in 89% and 81% yields, respectively.[15] When using alkynyl amine **4a** for iodocyclization, AgOAc was needed to improve the reaction rate and yield;[16] the iodopyrroline **39** was thus obtained in 83% yield. Importantly, azepine derivatives can be constructed efficiently and selectively. After a γ-amino ketone intermediate was formed by a hydration reaction of the amine **4a**, it underwent a $AgSbF_6$-catalyzed [5 + 2]-cycloaddition with phenylacetylene to afford synthetically useful azepine **40** in 75% yield.[17]

Scheme 6. Product Transformations



In conclusion, we report a general procedure to synthesize β,β- and γ,γ-substituted amines by nucleophilic ring opening of aziridines and azetidines under transition-metal-free and open-air conditions. A range of substituted amines could be straightforwardly accessed from readily available alkynyl, alkenyl, aryl, and heteroaryl trifluoroborates. A mechanistic proposal has been made on the basis of control experiments. The reaction products can be easily transformed to useful amine scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01394.

Complete experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 1841874−1841876 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(10) See the Supporting Information for a list of experiments.

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(13) Attempts to synthesize $LiHSO_4$ were made. However, it is extremely hygroscopic and difficult to purify.

(14) A control experiment with excess fluoride present (KHF_2) showed no impact on reactivity, indicating that the boron of the nucleophile remains coordinatively saturated. Consequently, Lewis acid/Lewis base coordination for facial direction is unlikely.

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