Anodic Benzylic C(sp3)-H Amination: A Unified Access to Pyrrolidines and Piperidines

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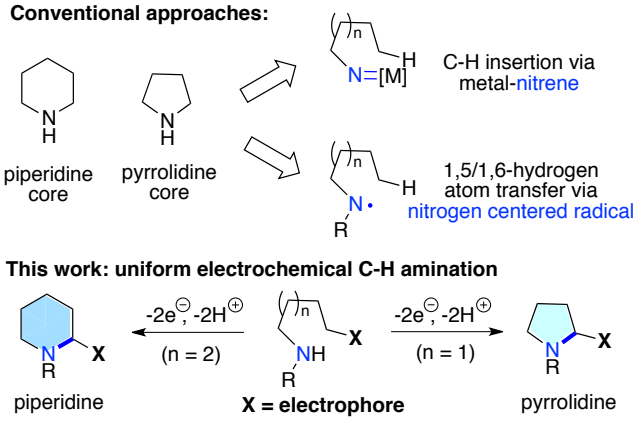
An electrochemical aliphatic C-H amination strategy was developed to access the important heterocyclic motifs of pyrrolidines and piperidines within a uniform reaction protocol. The mechanism of this unprecedented C-H amination strategy involves an anodic C-H activation to generate a benzylic cation, which is efficiently trapped by the nitrogen nucleophile. The applicability of the process is demonstrated for 40 examples comprising both 5- and 6-membered ring formation.

Pyrrolidines and piperidines are among the most significant saturated nitrogen heterocycles in Nature, being present in numerous natural products.[1] They also exhibit essential pharmacophoric properties and thus constitute prominent molecular components in pharmaceutical structure development.[2] Their nature as saturated aminated heterocycles renders them ideal representatives of the "escape from flatland" concept.[3] The quest for new accesses towards this class of compounds has been a constant source for synthetic innovation. Recently, the direct functionalization of aliphatic C-H bonds has been identified as a logical strategy for the formation of such higher-functionalized molecules.[4] Within this context, molecular catalysts have demonstrated conceptual utility for certain intramolecular C-H amination reactions, which have been developed to an impressive extent based on transition metal catalysis.[5] Therein, the formation of new alkyl-nitrogen bonds is predominantly based on nucleophilic nitrogen groups[6] and metal nitrene insertions[7] into aliphatic hydrocarbon bonds. Despite high levels of efficiency, such metal-catalysed reactions commonly rely on non-carbon spacer units activating and/or stabilizing the nitrogen atom involved in the C-H amination reaction. This generates heterocycles that differ from naturally occurring cycloamines. Recent advances in the area have overcome this limitation.[8] Still, extended use of precious metal promoters are considered problematic due to removability of trace metal impurities or economic reasons. Aliphatic C-H bond amination can also be achieved by catalytic versions[9] of classic amidyl radical chemistry.[10] Despite the impressive advance, no general environmentally benign synthesis concept is currently available that would reach out for both five- and six-membered ring formation in intramolecular C-H amination.[11]



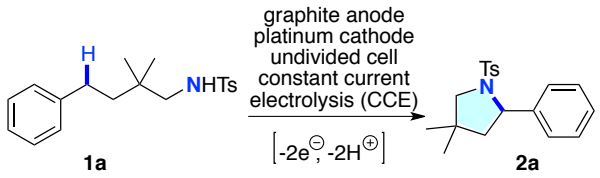
Scheme 1 Aliphatic C-H amination

We have now envisioned an electrochemical strategy to selectively and sustainably access pyrrolidines and piperidines within a unified protocol. This approach employs a suitably positioned electrophoric group to direct C-H amination within electrochemical oxidation. Synthetic organic electrochemistry has recently attracted a lot of attention and is recognized as an environmentally benign methodology in the tool kit of the organic chemist.[12,13] While the formation of pyrrolidines and piperidines by intramolecular electrochemical amination of electron-rich alkenes is well known and has been extensively studied,[14] until now the corresponding anodic amination of unfunctionalised aliphatic C-H bonds remains a notably underdeveloped field.[15]

Initial experiments were carried out using similar conditions reported in literature for the electrochemical generation of nitrogen centred radicals.[14a-c] We rationalized that the anodic formation of amidyl radicals should lead to a 1,5-H transfer[8a,f] and subsequently to the desired pyrrolidines. Starting from model compound **1a**, optimization studies were performed in an undivided cell, using a graphite rod anode and a platinum cathode.[16] A constant current of 5 mA and a charge of 2.2 F were applied. Using methanol or mixtures of methanol and THF with

$LiClO_4$ as supporting electrolyte and sodium methoxide as base the desired pyrrolidine **2a** was only obtained in yields of up to 25% (Table 1, entries 1 and 2). Changing the supporting electrolyte to Et_4NOTs and Bu_4NPF_6 did not improve the yield (Table 1, entries 3 and 4). We then altered the solvent to 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). HFIP has proven beneficial in electroorganic transformations due to its ability to stabilize and enhance the lifetime of anodically generated reactive intermediates such as radical cations.[17, 18] To reduce the fluorine footprint, HFIP can be redistilled.

Table 1 Optimization of electrolysis conditions.



Entry	Electrolyte	Additive	Yield [%] 1a	2a
1	0.1 M $LiClO_4$/MeOH	0.5 eq. NaOMe	56	23
2	0.1 M $LiClO_4$, 60% MeOH/THF	0.5 eq. NaOMe	57	25
3	0.1 M Et_4NOTs/MeOH	0.5 eq. NaOMe	87	trace
4	0.1 M Bu_4NPF_6/MeOH	0.5 eq. NaOMe	92	trace
5	0.1 M Bu_4NPF_6/HFIP	-	n.d.	67
6[a]	0.1 M Bu_4NPF_6/HFIP	-	n.d.	61
7[b]	0.1 M Bu_4NPF_6/HFIP	-	n.d.	52
8[c]	0.1 M Bu_4NPF_6/HFIP	-	n.d.	77
9[d]	0.1 M Bu_4NPF_6/HFIP	-	trace	70
10[c]	0.1 M Bu_4NPF_6, 50% CH_3CN/HFIP	-	trace	24
11[c]	0.05 M Bu_4NPF_6/HFIP	-	n.d.	65
12[c]	0.1 M Et_4NOTs/HFIP	-	-	53
13[c]	0.1 M Bu_4NBF_4/HFIP	-	n.d.	85
14[c]	0.05 M Bu_4NBF_4/HFIP	-	n.d.	68
15[c]	0.2 M Bu_4NBF_4/HFIP	-	n.d.	70
16[c,e]	0.1 M Bu_4NBF_4/HFIP	-	n.d.	80
17[f]	0.1 M Bu_4NBF_4/HFIP	-	n.d.	73

Isolated yields. 0.2 mmol substrate; I = 5 mA, 2.2 F; [a] 2.0 F; [b] 2.4 F; [c] I = 2.5 mA; [d] I = 1.5 mA; [e] 1.0 mmol substrate scope; [f] 3.0 mmol substrate scope; n.d. = not determined.

The use of HFIP as solvent led to dramatically improved yields of up to 67% of **2a** (Table 1, entry 5). Having identified HFIP as optimum solvent for this electrochemical transformation, the amount of charge was varied in the range of 2-2.4 F (Table 1, entries 6 and 7) as well as the applied current (1.5-5 mA, Table 1, entries 5, 9 and 13). Furthermore, the effect of the concentration of the supporting electrolyte was investigated (Table 1, entries 14 and 15). The best yield (Table 1, entry 13) of the corresponding pyrrolidine **2a** was obtained by using a 0.1 M Bu_4NBF_4/HFIP electrolyte, a current of 2.5 mA and 2.2 F. To test the robustness of the reaction, experiments at 1 and 3 mmol scale of substrate **1a** (0.33 g and 1 g, respectively) were conducted without any change in reaction conditions leading to 73-80% of isolated **2a** (Table 1, entries 16 and 17). This demonstrates that the cyclization proceeds equally efficient at higher substrate concentration.

With the optimized electrolysis conditions in hand, we explored the scope of the reaction (Figure 1). Different sulphonyl protecting groups on the nitrogen are tolerated including 4-nosyl, mesyl and SES (**2a-d**). The possible use of SES and Ns is important in order to access the corresponding free pyrrolidines under mild conditions.

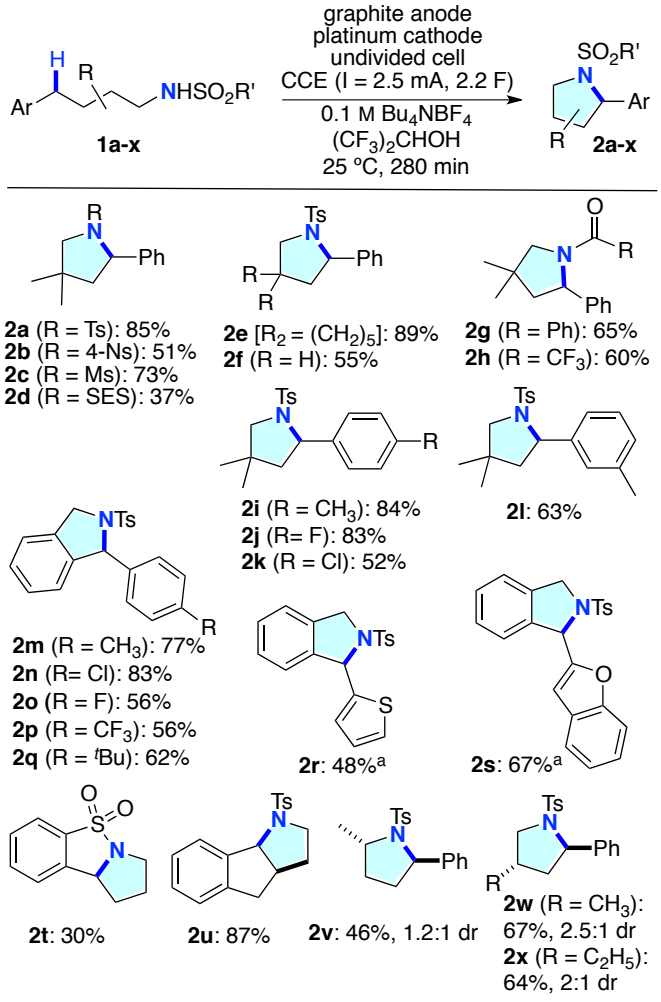
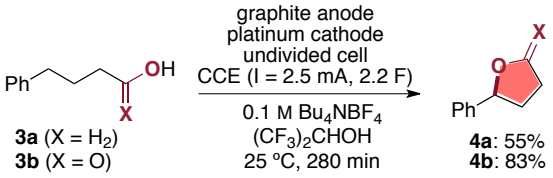


Figure 1 Electrochemical synthesis of pyrrolidines: scope. [a] With I = 1 mA.

Furthermore, it is possible to perform the transformation with modified backbone (**2e**) and without any substitution in the alkyl backbone (**2f**), demonstrating that a Thorpe-Ingold effect is not required, although in this case the isolated yield is slightly lower (55%) compared to the similar substrates **2a** and **2e**. Not only sulphonyl but also carbonyl substituents at the nitrogen functionality can be employed to yield the corresponding amides in good yields (**2g,h**). Typical organic substituents including methyl, chloro and fluoro groups are well tolerated on the arene as demonstrated for derivatives **2i**-**k**. The C-H amination scope also includes substrates with a phenyl backbone. The corresponding isoindolines **2m**-**2q** are formed in very good yields tolerating chloro, fluoro, alkyl as well as trifluoromethyl substitution in the 4-position of the aryl moiety. For the case of heteroarene substitution, **2r** and **2s** are formed in considerable yields tolerating the electron-rich thiophene and benzofurane cores, respectively. In addition, transannular cyclisations are possible as demonstrated for **2t**. Diastereomerically pure pyrrolidine **2u** was obtained as a result of cyclic stereocontrol. In the case of substrates bearing mono-substitution in the alkyl chain, acyclic stereocontrol with a diastereomeric excess of up to 2.5:1 for the *trans*:*cis*-ratio was observed (**2v**-**2x**). These latter experiments provided a first indication that the cyclization most likely occurs through a planarised benzylic cation allowing for minor diastereoselection. Besides the main interest in amination reactions, the possibility to include oxygen nucleophiles to trap the anodically generated benzylic cation was briefly explored (Scheme 2). Under standard conditions, cyclization of 4-phenyl butanol **3a** was straightforward to provide 2-phenyl tetrahydrofurane **4a**. In the same manner, 4-phenyl butanoic acid **3b** generated the 5-membered lactone **4b** in high yield.[19]



Scheme 2 Electrochemical oxygenative cyclization.

The scope of the C-H amination reaction could be directly expanded to the formation of piperidines **6a-q**. Figure 2 displays several examples of such a 6-membered ring formation under the mild and operational simple electrochemical conditions. The cyclization proceeds well for tosylamides **5a,b** with different backbone substitution and for **5c** with a functionalized benzenesulfonamide. As expected, common functional groups are well tolerated as substituents at the 4- and the 3-position of the arene group demonstrating the broad scope of the transformation (**6d**-**6j**). A substrate with a phenyl backbone efficiently yielded the corresponding tetrahydroisoquinoline **6k** in excellent yield of 81%. The reaction could also be applied to generate the new benzo-fused bicycle **6l**. The stereochemistry of the piperidine formation is comparable to the observations from pyrrolidine formation. Amination under cyclic stereocontrol proceeds with 100% selectivity as determined for **6m** and **6n**, while acyclic stereocontrol provides a slight preference for the *trans*-diastereoisomer (**6o**,**p**). Although in lower yield, the amination conditions could also be extended to the synthesis of piperazine **6q**.

Figure 2 Electrochemical synthesis of piperidines: scope.

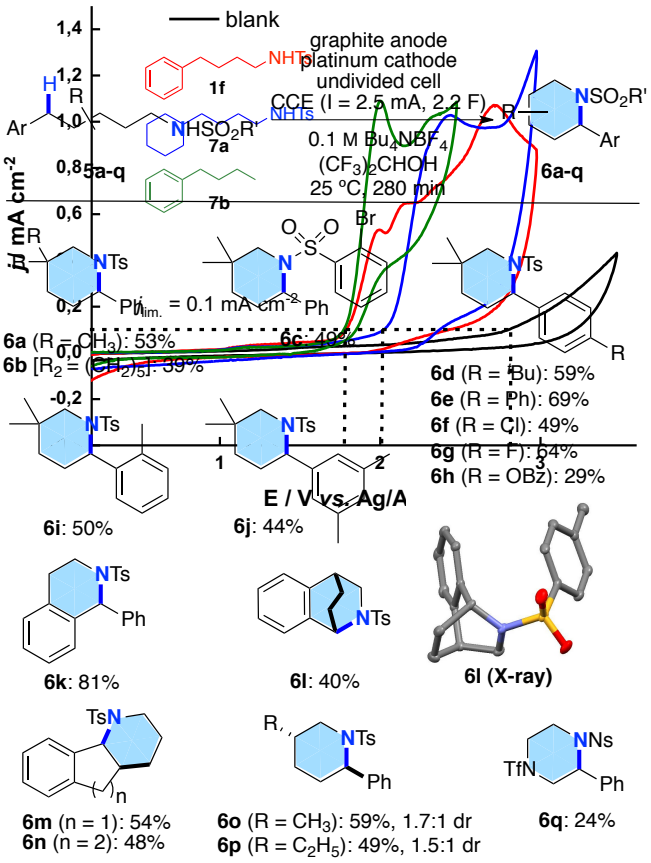


Figure 3 Cyclic voltammetry of **1f** (3 mM, red line), **7a** (3 mM, blue line) and **7b** (3 mM, green line). The voltammogram for the blank electrolyte is shown for comparison (black line). Working electrode: glassy carbon; counter electrode: platinum wire; reference electrode: Ag/0.01 M $AgNO_3$ in 0.1 M Bu_4NClO_4; scan rate: 50 mV s^{-1}.

In order to study the mechanistic aspects of the process, we performed cyclic voltammetric studies of model compounds **1f** (Figure 3, red line), **7a** (Figure 3, blue line) and **7b** (Figure 3, green line) in 0.1 M Bu_4NBF_4/HFIP. Each solution contained a concentration of 3 mM of the corresponding substrate. By comparing the oxidation potentials of the three model substrates **1f**, **7a** and **7b** it should be possible to determine whether the amine functionality or the aromatic core is oxidized first. Initially, the CV of the blank electrolyte 0.1 M Bu_4NBF_4/HFIP (black line) was measured demonstrating the outstanding stability of HFIP based electrolytes towards anodic oxidation.[20] Significant degradation of the electrolyte only starts at 2.80 V vs. $Ag/AgNO_3$ with a cut-off current density for oxidation defined as $j_{lim.}$ = 0.1 mA cm^{-2}. Compound **1f** bearing both the aromatic core and the amino functionality is irreversibly oxidized at a potential of 1.79 V vs. $Ag/AgNO_3$. The oxidation for tosylamide **7a** without the aromatic core is 230 mV higher at 2.02 V vs. $Ag/AgNO_3$ whereas the oxidation of model compound **7b** takes place at 1.77 V vs. $Ag/AgNO_3$. Furthermore, the CV of pyrrolidine product **2f** was measured,[16] which reveals that oxidation of **2f** takes place at 1.88 V vs. $Ag/AgNO_3$. This is 90 mV above the oxidation of substrate **1f** thus ensuring clean

product formation. Although not investigated at present, redox mediators may allow for additional selectivity increase for electron-rich substrates.[12h] The results depicted in Figure 3 allow for a conclusion regarding the mechanism of the electrochemical intramolecular C-H amination (Figure 4).

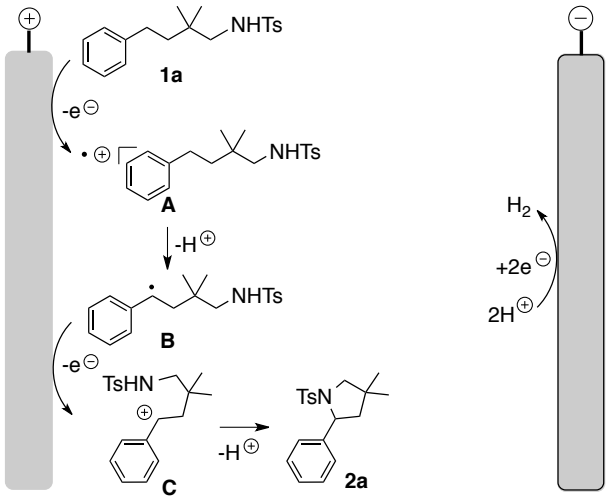
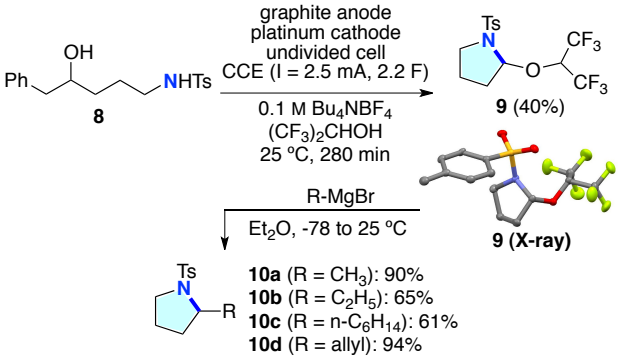


Figure 4 Proposed mechanism with **1a** as representative substrate.

Interpreting the data from cyclic voltammetry, the aromatic core was identified as the functional group, which is engaging in the initial oxidation. This is evidenced by the comparable oxidation potentials of phenyl-containing compounds **1f** and **7b**, while oxidation of the aliphatic tosylamide **7a** occurs at significantly higher potentials.[21] This concludes that from the involved aryl and tosylamide functional groups the former one acts as electrophore at the outset of the reaction. Upon single electron transfer (SET), an aromatic radical cation **A** is thus formed. Because of the positive charge, the acidity of the benzylic hydrogens is dramatically increased by several magnitudes of order.[22] Thus, deprotonation occurs readily leading to benzylic radical **B**. Such benzylic radicals are as a rule oxidized at lower potentials than the corresponding neutral substrate **1a**.[23] Further SET generates a benzylic cation **C**, which is efficiently trapped by the nucleophilic tosylamide. The formation and trapping of a benzylic cation is further supported by our observation of diastereomeric excesses in the cases of acyclic stereocontrol with compounds **1u-w, 5o,p**. In contrast, C-N bond formation involving radical pathways provides equal mixtures of diastereomers.[9]

Finally, electrochemical oxidation of alcohol **8** leads to C-C cleavage and provides the 2-alkoxylated pyrrolidine **9**.[16] The same compound can be accessed through a Shono oxidation[24] of *N*-tosyl pyrrolidine in the presence of HFIP (52% yield). Compound **9** serves as a versatile synthon for Grignard addition to provide access to pyrrolidines with elusive 2-substitution outside the aryl motif (Scheme 3).[25]

Scheme 3 Electrochemical access to 2-substituted pyrrolidines.



Conclusions

To conclude, we have developed a mild and atom-economical intramolecular C(sp³)-H amination to access pyrrolidine and piperidine scaffolds under uniform reaction conditions. This unprecedented C-N bond formation has been enabled by use of an anodic C(sp³)-H bond activation. The resulting straightforward heterocycle synthesis provides an attractive green alternative to existing protocols and is compatible with a diverse range of functional groups.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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An electrochemical C-H amination process enables the sustainable unified access to the heterocyclic classes of pyrrolidines and piperidines.