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Electrochemical Scaled-up Synthesis of Cyclic Enecarbamates as Starting Materials for Medicinal Chemistry Relevant Building Bocks

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Abstract. The electrochemical Shono oxidation of Boc-protected cyclic amines was revised. The conditions for scalable electrochemical synthesis of cyclic enecarbamates were found. The developed protocol included recycling of the full range of used reagents, favoring to E-factor reduction according to Green Chemistry requirements. The method opened the way for the convenient preparation of previously uncommon materials, which could become useful synthetic intermediates. Their synthetic potential was evaluated in [2+1] and [2+2] cycloadditions as well as electrophilic functionalization. Moreover, functionalized enecarbamates with carbonyl groups in β-position were used as latent 1,3-bielectrophiles in classical heterocyclizations. In a case of the hydrazine, the corresponding unusually decorated pyrazoles were prepared. The proposed methodology is a straightforward tool for the design and synthesis of Medicinal Chemistry relevant building blocks. As examples, 5-fluoro pipecolic and 3-fluoro isonipecotic acids were synthesized starting from Boc-protected esters of the pipecolic and the isonipecotic acids respectively; the 5-step approach to pyrazole containing α-aminoacids with different linkers between the aminoacidic and pyrazole moieties was elaborated based on the cheapest commercially available racemic and chiral cyclic α-aminoacids; the convenient approach to the functionalized tetrahydropyrido[3,4-d]pyridazines was proposed starting from Boc-protected ester of the isonipecotic acids.

Keywords: Electrochemistry; Green Chemistry; Cyclic enecarbamates; Shono oxidation; Scale up; Cyclopropanation; Recyclization; Medicinal chemistry; Building blocks

Introduction

Modern organic synthesis and drug discovery strongly influence each other.[1] Innovation in synthetic chemistry allows successful solving problems in all phases of drug discovery,[2] on the other hand, the medicinal chemistry poses more and more complex challenges to synthesis.[3] Moreover, the challenges contradict each other. Current Medicinal Chemistry needs access to new chemical space, especially based on new and unusual scaffolds.[4] However, in spite of newly appeared approaches,[5] medicinal chemists prefer to use a limited number of well-known robust procedures in their synthetic planning, especially in parallel (library) synthesis.[6] The comparable analysis showed, that the combination of the above-mentioned reactions did not allow to achieve the desired complexity of new drugs,[7] which were more close to the natural compounds.[8] Usually, the complexity and novelty of the compound libraries come from the building blocks, which now become more diverse and sophisticated.[9] Access to diverse and unique BB collections has a tremendous impact on the speed and scope of different Medicinal Chemistry projects.[10] Taking into account the speed and cost-effectiveness of BB delivery,[11] producers of new BB prefer to use synthetic sequences based on the reliable transformations and easy accessible cheap starting materials. Therefore, effective, but not optimized or adapted for multigram scale synthesis, new approaches do not attract the attention of BB producers, even if they lead to unique Medicinal Chemistry

relevant chemotypes. These new chemotypes begin to be actively used only after the innovative development of the multigram synthesis of the key intermediates. The bright example of such recent chemical difficulties overcoming is the development of key intermediates synthesis for the straightforward installation of the saturated bioisosteres of benzene.[12] Nevertheless, there are many original novel structural motifs, which still need cost and time optimization for active use. As a part of our ongoing efforts on the adaptation of existing and developing of new effective approaches to the advanced building blocks for medicinal chemistry,[13] we turned our attention to the chemistry of cyclic enecarbamates I. These compounds are known from 1969[14] and find application in academician investigations as starting materials for natural products and bioactive molecules synthesis in mg scales.[15] Some representative examples of compounds made from cyclic enecarbamates are shown on Figure 1.

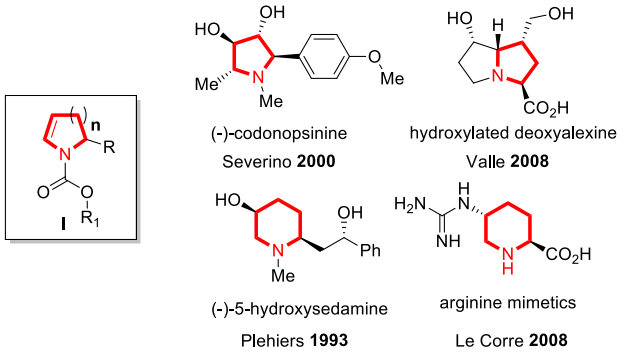
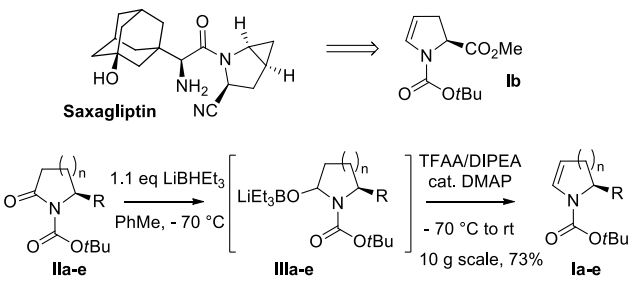


Figure 1. Examples of natural products and bioactive compounds obtained from cyclic enecarbamates **I**.

The industrial application of cyclic enecarbamates chemistry started from the anti-diabetic drug ***Saxagliptin*** which was co-developed in 2007 by Bristol-Myers Squibb and AstraZeneca. The synthesis of the drug was based on cyclopropanation chemistry of the key intermediate **I**. In a course of the project the preparative approach to cyclic enecarbamates was elaborated based on one-pot conversion of the lactam carbamates type **II** to target products by reduction with $LiBEt_3H$, and *in situ* dehydration with TFA-DIPEA (Figure 2).[16] The approach was scaled up to 100 kg of key intermediates **Ia,b**. But the development of eco-friendly protocols is still needed.



a: R = H, n = 1; **b**: R = CO_2Me, n = 1; **c**: R = H, n = 2; **d**: R = CO_2Me, n = 2; **e**: R = H, n = 3

Figure 2. One-pot conversion of lactam carbamates to cyclic enecarbamates.

The methodology developed had an impact on the availability of cyclic enecarbamates and, therefore, on the investigation of their properties. It was demonstrated on the compound **Ia** as an example.[17] The reported approach was used in our company for the synthesis of Medicinal Chemistry relevant trifluoromethyl substituted 3-azabicyclo[n.1.0]alkanes.[18] In this research specific behavior of five-membered lactams in the $LiBEt_3H$ reduction step was detected. The scale up procedure didn't work on cyclic lactams other than 5-membered ones. The same results were obtained independently by other researchers. When the above-mention protocol was used for cyclic lactams containing more than 5 atoms in the ring significantly lower yields were obtained.[19] Meanwhile, the Reaxys database[20] analysis showed that significant applicability was found only for two cyclic enecarbamates **Ia** and **Ic** from the representative set. Moreover, very interesting boc-3,4-dihydro-morpholine **If** is still unknown. Previously only corresponding Cbz-derivative[21] and, by analogy, 3,4-dihydro-2H-1,4-oxazine-3-carboxylic acid derivatives[22] were synthesized through cyclization in mg scales. The E-molecules[23] search showed that only 3 compounds were commercially available from reliable suppliers and only the parent compound **Ia** was available in up to 100 g quantity. However, the price of **Ia** does not allow to generate a cost-effective design of Medicinal Chemistry relevant building blocks on its base (Figure 3).

In order to expand our initial stock in a cost-effective way by multigram quantities of diverse cyclic enecarbamates for the further design and synthesis of Medicinal Chemistry relevant building blocks, we started to search for a new approach to these compounds. We have chosen an approach based on organic electrochemistry, which becomes popular either in industrial or laboratory scales.[24]

Results and Discussion

In our previous project directed to the synthesis of 3-oxadiazolyl/triazolyl morpholines, we successfully used modified Shono oxidation[25] of Boc-protected morpholine **1a** to corresponding 3-methoxy derivative **2a** on 40g scale.[26] The products of the Shono oxidation were close structural analogues of compounds of type **3** and also could be converted to desired enecarbamates by methanol elimination.[27] Therefore, we decided to investigate the Boc-morpholine electrochemical oxidation more deeply in order to obtain still unknown compound **3a** (Scheme 1).[28]

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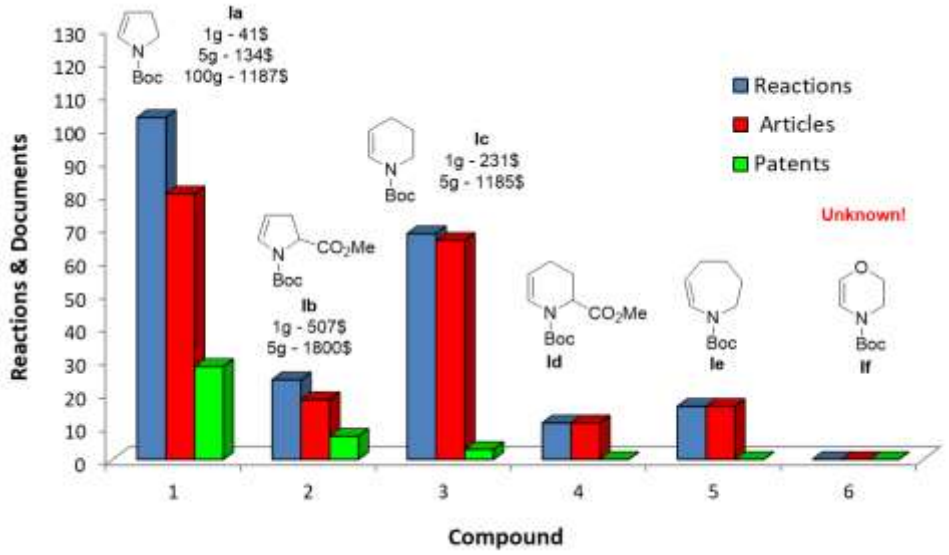


Figure 3. Reaxys and E-molecules data for representative cyclic enecarbamates.

Key points for the optimization were taken from our previous experience and literature data.[25] As the first estimation of whether the reported procedure could be applied to electrochemical oxidation of new Boc-protected amines, electrochemical properties of Boc-protected morpholine (**1a**) were evaluated by cyclic voltammetry (CV) and compared with the reported CV curves for Boc-protected pyrrolidine.[29] MeCN was chosen as a solvent in order to see the potentials of the first steps of compounds oxidation with minimal influence of possible subsequent reactions; the evolution of CV curves upon addition of MeOH was also studied (see SI for details).

The oxidation of **1** in MeCN solution on GC electrode started at 1.81 V, and the shoulder on CV curve was found at E = 2.40 V with Bu_4NBF_4 (TBATBF) as the supporting electrolyte; hereinafter all potentials are given *vs.* Ag/AgCl (the CV curve is presented on Figure 4 and details are provided in the SI). This process could be associated with one- or two-electron oxidation of **1**, leading to the formation of radical cation or cationic enecarbamate.[29a] The current values at this potential almost did not change upon the repeated scans, it can be concluded that there was no noticeable adsorption of the reaction products on the electrode. Also, these current values were proportional to the concentration of **1**, indicating that the process was controlled by Randles–Ševćik law.[29a] The addition of methanol (in the concentration range between 0.01 M and 0.4 M) to 0.01 M solution of **1** did not cause a change of the peak current, indicating that reaction of the oxidized species with methanol was not the rate-limiting stage of the electrochemical oxidation. Thus, it can be concluded from the CV measurements that oxidation of **1** occurred at E at the level of 2.40 V and GC surface is not passivated in the course of the process. The behavior of **1** was quite similar to the properties of previously reported Boc-protected pyrrolidine,[29b] and in view of this similarity, we used the electrolysis conditions reported in [25] as the first step in search of optimized conditions for electrolysis of **1**.

The first attempts to carry out preparative electrolysis of **1a** were performed at constant current using tetraethylammonium tosylate as the background electrolyte; different combinations of the electrodes

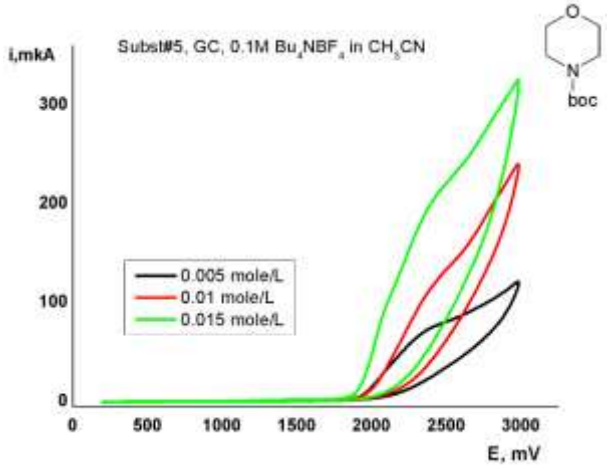
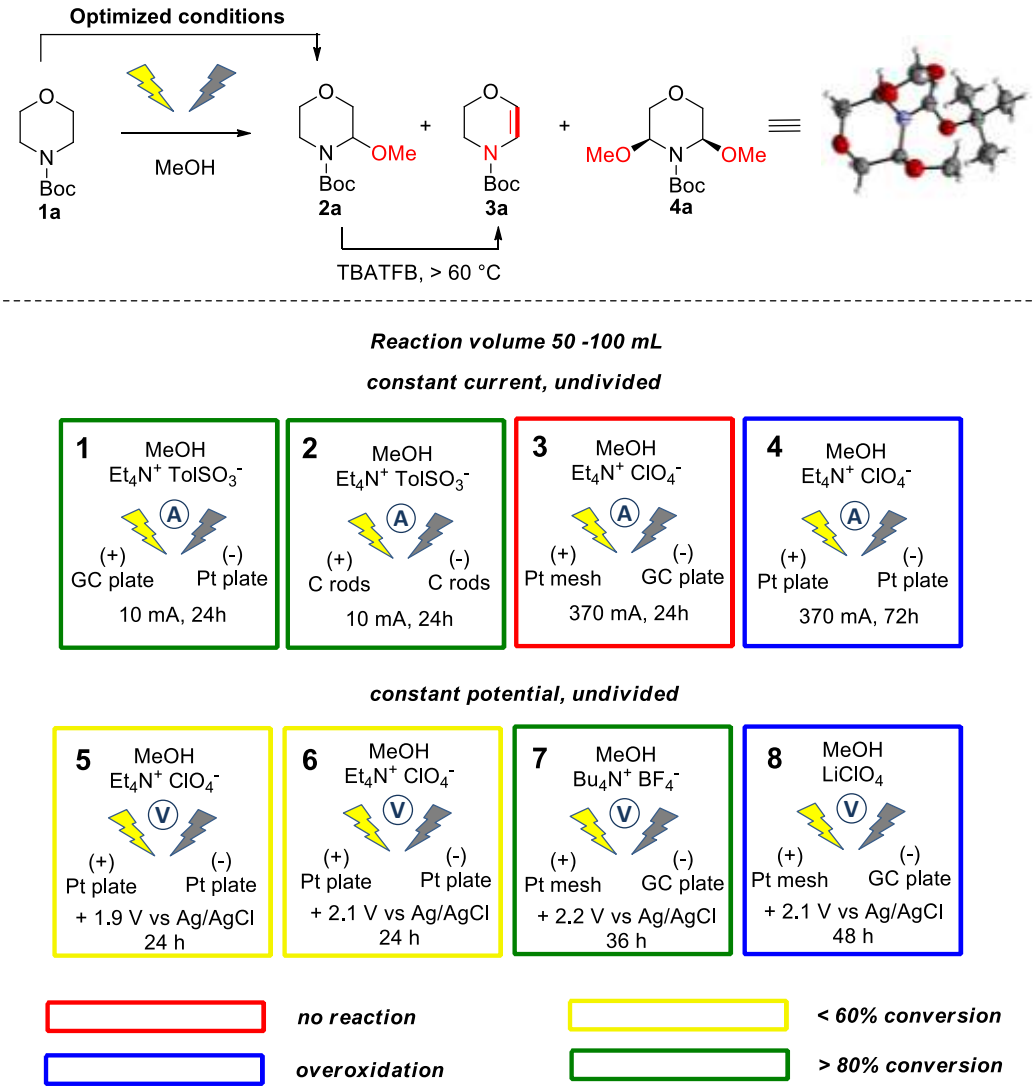


Figure 4. CV curves for **1** in MeCN solution on GC electrode at three different concentrations; the supporting electrolyte - Bu_4NBF_4.



Scheme 1. Optimization of Shono oxidation protocol for the Boc-morpholine **1** as a model substrate.

were tested (boxes 1 and 2 on Scheme 1). After consumption of 3.6 F/mole of electricity in both experiments, high conversion values and good yields of the target product were obtained. In theory, 2 F/mol is required for Shono oxidation.[29a] However, a higher quantity of electricity is used for this process (4 F/mole)[29a], which can be partially consumed for methanol oxidation. Both GC and carbon electrodes appeared to be suitable for electrochemical synthesis of enecarbamate **3a** (Scheme 1).

In this study, we did not intend to perform a systematic examination of the influence of the reaction conditions on the conversion of **1a**, since the aim was just to develop a multi-gram protocol for the enecarbamate preparation. So, in order to minimize efforts, further experiments were directed on testing some ideas, based on comparison with literature data or reasonable assumptions.

The aim of the second step was to check if tetraethylammonium tosylate could be replaced by tetraethylammonium perchlorate, because preparative electrochemical oxidative methoxylation of a similar compound, N,N-diethylbenzamide at the presence of perchlorate (Bu_4NClO_4) was much more efficient compared to a similar process in a solution of tosylate (EtN_4OTs).[29a] Being aware of success, we used Et_4NClO_4 and also changed the electrodes: Pt mesh was used as anode while GC plate was used as cathode (box 3 on Scheme 1). Surprisingly, this attempt failed, no reaction occurred. To check if the reaction was possible in these conditions (Pt electrode and Et_4NClO_4 as supporting electrolyte), we repeated the experiment with an increased quantity of electricity reaction time (4.0 F/mol instead of 3.6 F/mol, (box 4 on Scheme 1). In this case, Pt mesh was changed by Pt plate: the idea was to minimize by-products formation, but again this idea was not fruitful, and the reaction

ended up with the formation of di-methoxy-Boc-morpholine **4a** in a near 70% yield. The structure of **4a** was proven by single-crystal X-ray structure determination. Production of this species could be considered as consequent two-step 4-electron oxidation of Boc-protected morpholine; the second oxidation step can be occurred due to the increase of methoxy-Boc-morpholine concentration in course of the process as well as due to continuous growth of the process potential in galvanostatic mode. The second reason seemed to be more probable, because the formation of **4a** was not observed in the cases of previous experiments (boxes 1 and 2), where the reaction mixture after a certain time contained a high concentration of "semi-oxidation intermediate" **3a**, but no product of further oxidation could be detected.

On the results of the previous experiment (box 4 on Scheme 1) in order to control oxidation potential electrochemical oxidation of **1** was carried out in potentiostatic mode (box 5 on Scheme 1) at constant potential 1.9 V using the same Pt electrodes and the same Et_4NClO_4 as the supporting electrolyte. In order to minimize the formation of **4a** the potential was chosen at the level close to the lowest acceptable value, estimated from CV experiments, as described above, taking into account that (1) oxidation of the previously reported N-Boc-proline methyl ester in MeOH occurred at a lower potential than in MeCN, see SI for details, and (2) it was recently shown that irreversible oxidation of organic compounds in tetrafluoroborate electrolyte occurred at a slightly higher potential than in perchlorate electrolyte.[29c] An additional reason for the use of lower potential was the minimization of possible methanol oxidation (the methanol oxidation onset was *ca.* 2.3 V in 0.4 M solution in MeCN, see SI for details). However, in pure methanol, the oxidation apparently starts at lower potential. The conversion of **1** in these experiments was less than 60% and the selectivity with respect to compound **3a** was good. In order to increase the conversion, an attempt to raise the potential to 2.1 V was performed (box 6 on Scheme 1), but it did not cause significant improvement. Notably, on the grounds of the experiments shown in boxes 4-6 (Scheme 1), Et_4NClO_4 could be considered as a suitable supporting electrolyte, because the desired enecarbamate formed. However, our expectations of very high yields in perchlorate solutions were overestimated.

In addition, a significant disadvantage of Et_4NClO_4 was its potential explosivity. Tetraborofluoride salts seemed to be a suitable safe alternative.[29d] On the next step (box 7 on Scheme 1) we decided to perform electrolysis in potentiostatic mode at potential 2.2 V using TBATBF and the same electrodes as in box 3 (Scheme 1). The potential was slightly increased compared to the previous experiments (box 6 on Scheme 1) because, as mentioned above, oxidation in tetrafluoroborate electrolyte was expected to occur at slightly higher potential.[29c] The reaction time was 1.5 times increased. As a result, we got more than 80% conversion of **1** and good selectivity with respect to formation of the desired compound **3a**. Unexpectedly, it was found the MeOH elimination from **2a** during the evaporation of the solution giving the crude desired carbamate **3a** was very efficient compared to the previous experiment. This effect was attributed to the catalytic action of TBATBF, and this feature was taken into account in the selection of conditions for multi-gram electrolysis.

Finally, we decided to check if lithium perchlorate (box 8 on Scheme 1) could be used instead of tetraethylammonium salts (boxes 3, 5 and 6 on Scheme 1), because $LiClO_4$ was successfully used several times in Shono oxidation processes.[30] Electrolysis of **1** in potentiostatic mode at 2.1 V in $LiClO_4$ solution (the same potential as in box 6 with Et_4NClO_4) led to the formation of di-methoxy-Boc-morpholine **4a** in 48 h. Thus, $LiClO_4$ appeared to be suitable however in a quick test we did not find any advantage over Et_4NBF_4.

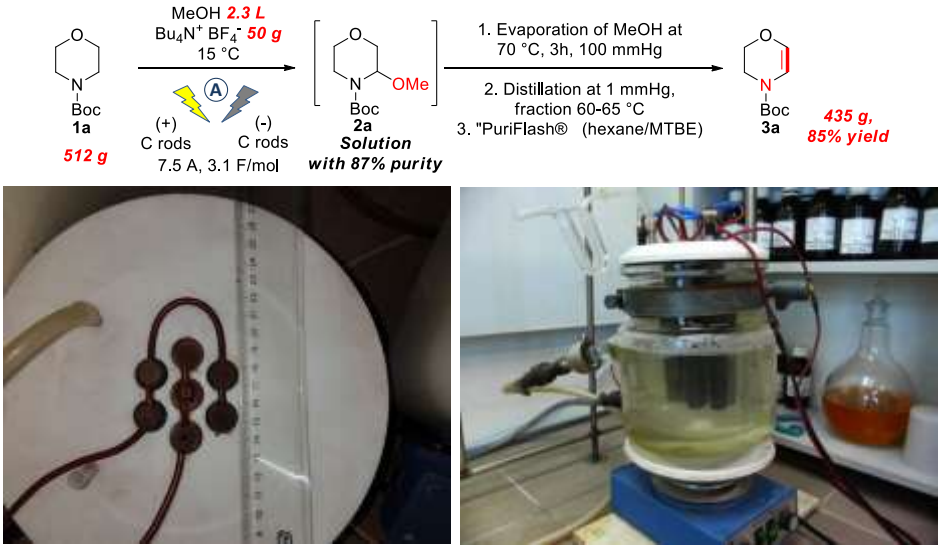
Notably, in the experiments described above, we did not find any preference for a certain type of the electrodes, since the reaction proceeded (and high conversions were achieved) on all types of the electrodes tested.

Among the tested conditions the cases, shown in boxes 1, 2 and 7, were the most promising for target enecarbamate **3a** formation. For multi-gram scale electrolysis galvanostatic mode was chosen because control of constant current was simpler than control of constant potential. TBATBF was chosen, first of all, due to its catalytic effect in the transformation of **2a** to **3a**. Using in-house made electrochemical cell with 7 graphite rod electrodes (150 mm, d = 12 mm, see pictures on scheme 2) the transformation of ca. 0.5 kg of Boc-protected morpholine **1** was performed in 2.3 L MeOH under constant 7.5 A current with 50 g of TBATBF as the supporting electrolyte leading to the solution containing ca. 87% of pure compound **2**. The reaction course was additionally monitored by TLC. Thereby, 87 % yield was achieved at the consumption of 3.1 F/mol of electricity, 14 % less than in small-scale experiments described above. We can note that a scale-up of the synthesis resulted in lower electricity consumption. The obtained solution was evaporated at 70 °C. The isolation/purification procedures included distillation with further flash chromatography purification affording target compound **3** in 85% preparative yield (Scheme 2). The purified compound **3** according to the described procedure possessed good stability and could be kept at normal conditions for 1 year without decomposition. These data indicate that the compound **3a** becomes attractive advanced intermediate due to cost-effective synthesis and good storage ability. Moreover, it should be noted, that all

reagents and solvents were recovered by distillation and TBATBF was recovered by simple crystallization from EtOAc. The developed method can be considered as more ecofriendly compared to previously reported for enecarbamates type **3a**.

The developed protocol was tested on other Boc-protected cyclic amines, which could lead to cyclic carbamates not accessible in the multigram scale by $LiBEt_3H$/TFA - DIPEA protocol. The electrochemical behavior of the compounds **1d** (as a racemic mixture or as pure enantiomers R or S), **1e**, and **1f**, evaluated by CV, was quite similar to the properties of **1a**. In the case of all these compounds irreversible oxidation occurred at potentials slightly higher than in the case of **1a** (2.6, 2.6 and 2.45 V, respectively, compared to 2.4 V for **1a**, see SI for details). In the case of **1f**, some signs of electrode passivation were found which can be caused by adsorption of the reaction products.

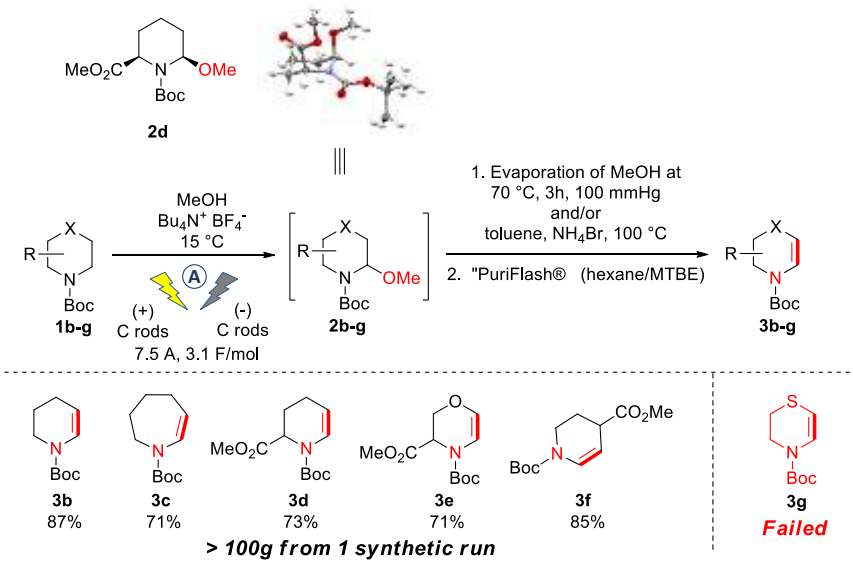
For the preparative electrolysis of these compounds, the same conditions were chosen as for **1a**. Since the electrolysis was carried out in galvanostatic mode, no



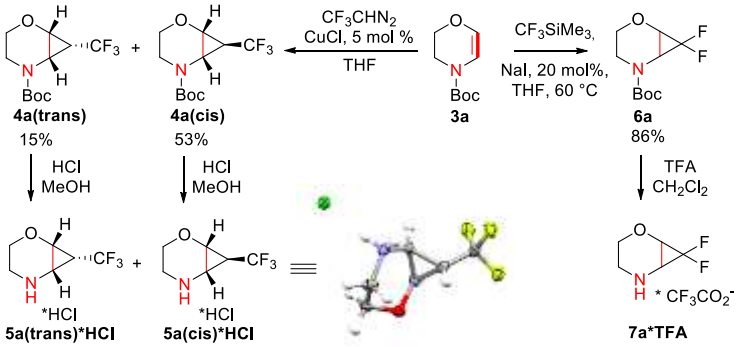
Scheme 2. Optimized conditions and machinery for multigram scale Shono oxidation with further obtaining of encarbamate **3a**.

corrections associated with higher oxidation potentials were made. The results of the tests are shown on Scheme 3. Among 6- and 7-membered substrates all gave high preparative yields on more than 100 g scale except thiomorpholine. In the latter case, the sulfur oxidation was the major process instead of the expected enecarbamate formation. It should be noted that cyclic amides considered in this study did not tend to undergo dealkylation, which can occur in the case of non-cyclic analogues.[24d-f] In cases of piperidine-based compounds, the preparative yield on the methanol elimination step was higher when the crude product after methanol evaporation was additionally heated at 100 °C in toluene at the presence of NH_4Br (such treatment was not required in the case of other compounds reported herein, since they underwent demethoxylation at the presence of TBATBF, *vide supra*). Similarly to Boc-3,4-dihydro-morpholine **3**, all obtained cyclic carbamates exhibited excellent storage ability. Thus, it can be concluded that the electrochemical Shono oxidation of Boc-protected cyclic amines followed by methanol elimination is the best method for the cyclic enecarbamates production for further commercialization.

It should be noted that all methoxy-derivatives type **2** reported herein can be isolated using a slightly modified procedure, see SI for details. Electrochemical methoxylation of all α-substituted Boc-dialkylamines **1**, studied in this work, resulted in



Scheme 3. The scope of the multigtam Shono oxidation/elimination protocol.



Scheme 4. [2+1] cycloadditions of *N*-Boc-3,4-dihydro-morpholine **3a**.

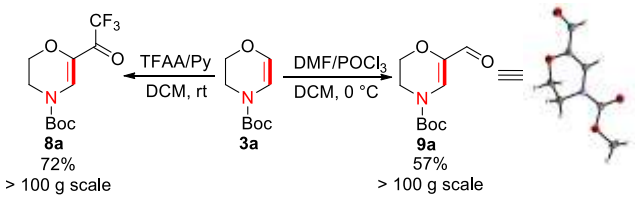
the formation of *cis*-isomers in respect of R and OMe substituents position to the heterocyclic ring, as it could be concluded by NMR analysis of all compounds and X-ray structures of two representatives, **2d** and **4a**.

All abovementioned carbamates obtained in multigram quantities by described protocol become available and attractive starting materials for the design and synthesis of Medicinal Chemistry relevant building blocks based thereon. Firstly, the most interesting Boc-3,4-dihydro-morpholine **3** was tested in our in-house program directed to the synthesis of innovative fluorine-containing building blocks, particularly in [2+1] cycloaddition reactions with fluorine-containing carbenes/carbenoids. The compound **3** was subjected to CuCl-mediated trifluoromethyl cyclopropanation with CF_3CHN_2.[18] The reaction afforded the mixture of Boc-protected diastereomers **4a(cis)** and **4a(trans)** in ca. 4 : 1 ratio; deprotection of these compounds by treatment with HCl in MeOH led to final amines **5a(cis)** and **5a(trans)**. The structure of **5a(cis)** was confirmed by X-ray single crystal analysis (Scheme 4). The compound **3a** was also subjected to difluorocyclopropanation by Me_3SiCF_3 – NaI system in THF,[13c] affording corresponding fused difluorocyclopropane **6a**. Deprotection of **6a** by TFA led to TFA salt of amine **7a**, which possessed increased stability in comparison with non-oxygenated analogues.[31] The compound could be stored at –10 °C for several months (Scheme 4).

The compound **3a** also was tested in [2+2] cycloadditions with ketenes, used in our in-house building block programs,[32] their reactions with non-oxygenated cyclic enecarbamates were described.[33] In a case of compound **3a**, bearing donors from both sides of double bonds, the reaction with 2-methylprop-1-en-1-one generated from isobutyryl chloride/Et_3N

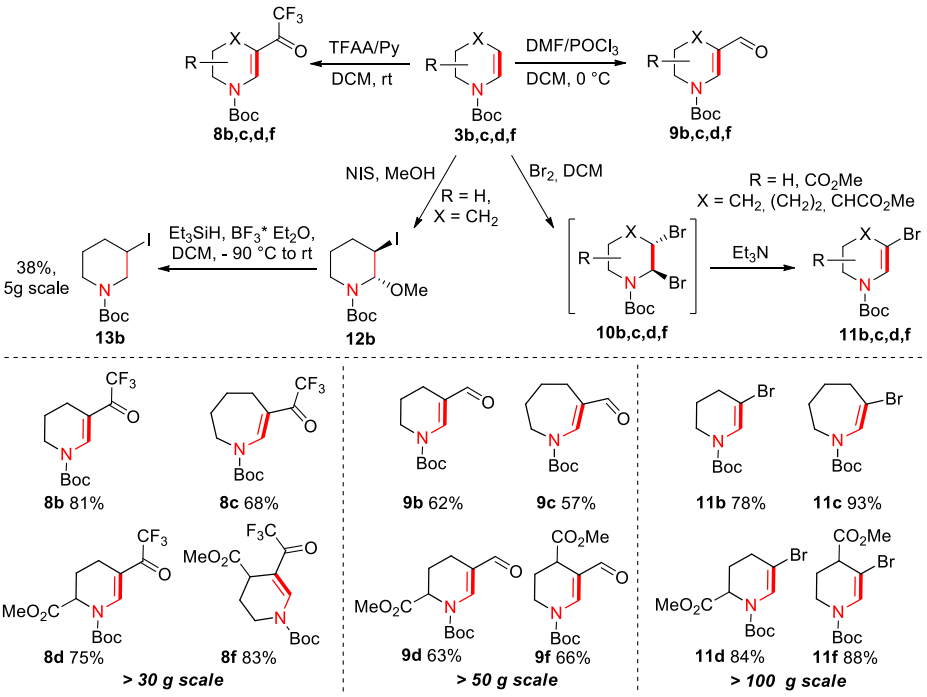
was not regioselective. Moreover, fragmentation of the fused cyclobutanone products upon chromatographic separation occurred evidencing for its instability in such conditions.

The electrophilic substitution reactions were tested for compound **3a**. The direction of such reactions was unclear because **3a** was the compound bearing both enecarbamate and vinyl ether functions. In classical reactions of electrophilic substitution, such as trifluoroacyclation by TFAA and Vilsmeier–Haack formylation, compound **3a** behaved as enecarbamate giving compounds **8a** and **9a**, respectively. The regiochemistry of the products was unambiguously solved by X-ray diffraction study of the compound **9a**. Both these reactions were scaled up to 100 g giving functionalized derivatives in good preparative yield (Scheme 5). The trifluoroacyclation by TFAA and Vilsmeier–Haack formylation of other enecarbamates **3b-d**, **f** proceeded smoothly giving the corresponding products **8b-d**, **f** and **9b-d**, **f** in good preparative yields on 30-50 g scale (Scheme 6), similarly to the abovementioned **3a**.



Scheme 5. Electrophilic substitution in *N*-Boc-3,4-dihydromorpholine **3a**.

In a course of this project, the new method for preparation of Br-containing enecarbamates was developed based on the bromination of cyclic enecarbamates **3b-f** (Scheme 6). Previously electrochemical bromination of such carbamates in MeOH was proposed by Shono leading to β-brominated enecarbamates **11** through addition product type **12**.[34] It was also reported that addition products type **12** could be prepared by enecarbamate treatment with NBS in MeOH.[15d] However, this approach could not be applied for preparation of the



Scheme 6. Electrophilic substitution in cyclic encarbamates.

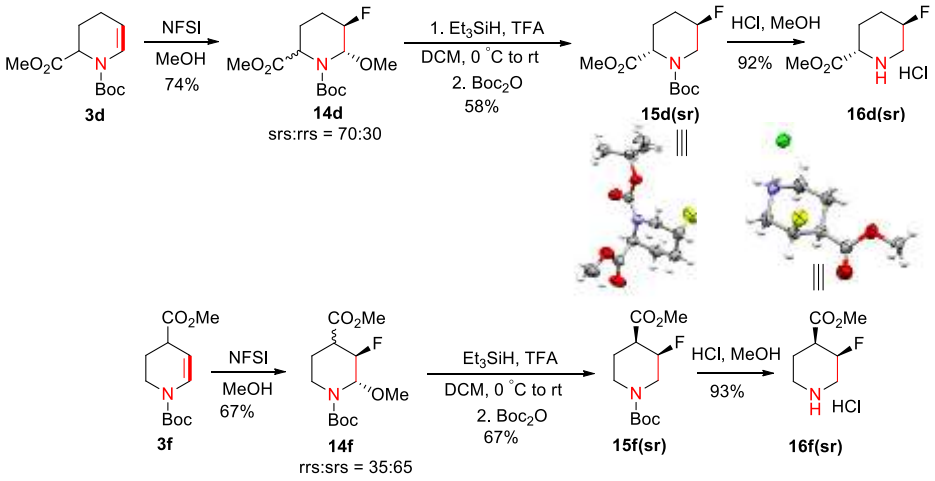
Br-containing enecarbamate **11**, because basic treatment of the addition product type **12** led to bromine elimination.[27] We optimized and scaled up the one-pot synthesis of β-brominated enecarbamates **11** for more than 100 g in excellent preparative yield. The protocol included carbamate treatment by Br_2 in DCM leading to its addition to double bond giving **10** followed by elimination of one bromine at the presence of TEA. The approach allowed us to obtain the β-brominated enecarbamates **11** on 100 g scale from one synthetic run.

In the frame of this project, we also tried to develop a preparative method for the introduction of iodine to β-position of the corresponding Boc-dialkylamines leading to the compounds type **13** (Scheme 6). These compounds are valuable synthetic intermediates. Previously they were prepared by iododecarboxylation in a small scale.[35] In our case, we tested the sequence

of enecarbamate iodination in methanol followed by removal of the methoxy group by Et_3SiH - $BF_3{\cdot}Et_2O$ system.[15d] The latter two-step sequence appeared to be preparative on 5 g scale from starting compound **3b**, however, the yield was 38%.

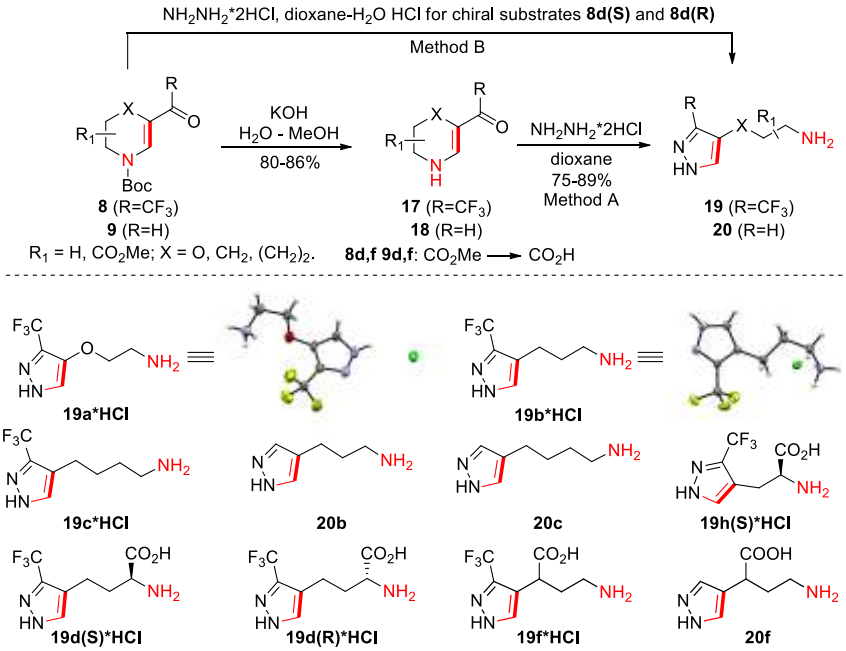
In spite of low yields of MeO-group reductive removal in iodo derivatives type **12b**, we decided to use a similar approach for the fluorine atom introduction into the cycle. The treatment of encearbamates **3d** and **3f** bearing ester function by Selectfluor in MeOH led to addition products **14d** and **14f**, respectively, as the mixtures of hardly separable diastereomers (Scheme 7). Further reduction of the fluorinated products by Et_3SiH - $BF_3{\cdot}Et_2O$ led to orthogonally protected (N-Boc, CO_2Me) fluorinated aminoacids **15d** and **15f** as diastereomeric mixtures. In the case of **15d** *trans*-isomer was dominating, while in the case of **15f** the mixture contained *cis*-isomer as the major component. These diastereomers were easily separated from the minor isomers by column chromatography. The configurations of both major isomers were unambiguously determined by single-crystal X-ray diffraction analysis of **15d** and **16f** derivatives. This approach was scaled up to 30 g of both compounds, which are fluorinated analogues of important for Medicinal Chemistry pipecolic and isonipecotic acids (Scheme 7). It should be noted that the 5-fluoropipecolic acid was previously synthesized in our company starting from *trans*-N-benzyl-2,5-dicarbomethoxy pyrrolidine and it was based on morph-DAST mediated rearrangement leading to ring expansion. However, the rearrangement product was minor,[36] therefore, this acid was not used in our Medicinal Chemistry program.

The next milestone in the study was the utilization of formylated and trifluoroacylated encarbamates as latent bielectrophilic synthons for heterocyclization.[37] The simplest hydrazine hydrate was chosen as model binucleophlic reagent for recyclization. Firstly, we chose heterocyclization protocols described earlier for 4-trifluoroacetyl-2,3-dihydropyrroles bearing CO_2Me group at the nitrogen atom and applied such protocol to the Boc-protected compounds **8** and **9**.[38] In our case, the abovementi-

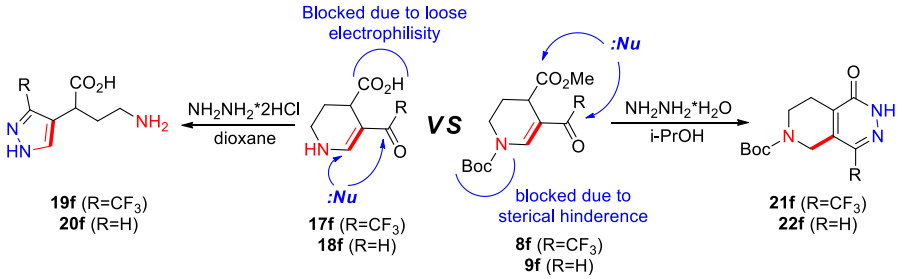


Scheme 7. Synthesis of 5-fluoro pipecolic and 3-fluoro isonipecotic acids.

oned methods worked, but the yields of the desired products were low. It could be explained by the lower activity of the latent cyclic electrophilic center due to the significant steric hindrance of the Boc group in comparison with the CO_2Me one. As a consequence, transacetylation of hydrazine hydrate by Boc occurred. In order to improve the yield, the special Boc-deprotection procedure was elaborated for the compounds **8** and **9** by KOH in water at rt by analogy with alkaline Boc-deprotection of N-protected aromatic heterocycles.[39] In the case of functionalized encarbamates bearing ester function **8d**, **8f**, **9d**, and **9f** the Boc deprotection was accomplished by hydrolysis of the esters. Further treatment of the deprotected compounds **17** and **18** by $NH_2NH_2{\cdot}2HCl$ in dioxane lead to clean recyclization to pyrazoles **19** and **20** respectively. The structures of the compounds **19a** and **19b** (as hydrochlorides) were confirmed by single crystal X-ray analysis. In the case of substrates type **17** and **18** bearing CO_2H functions the reactions provided corresponding amino acids **19d**,**f** and **20f** (Scheme 8). This approach was easily scaled up to 100 g in the case of all above-mentioned pyrazoles. Notably, for functionalized Boc-3,4-dihydro-morpholine **3** previously not reported pyrazoles linked with OCH_2CH_2 group at the 4th position were obtained, which are of high interest for Medicinal Chemistry. But in the case of chiral substrates obtained from both enantiomers of enecarbamate **3d** this approach dramatically failed due to full racemization.



Scheme 8. Recyclization reaction of functionalized carbamates **8, 9** to pyrazoles **19, 20**.



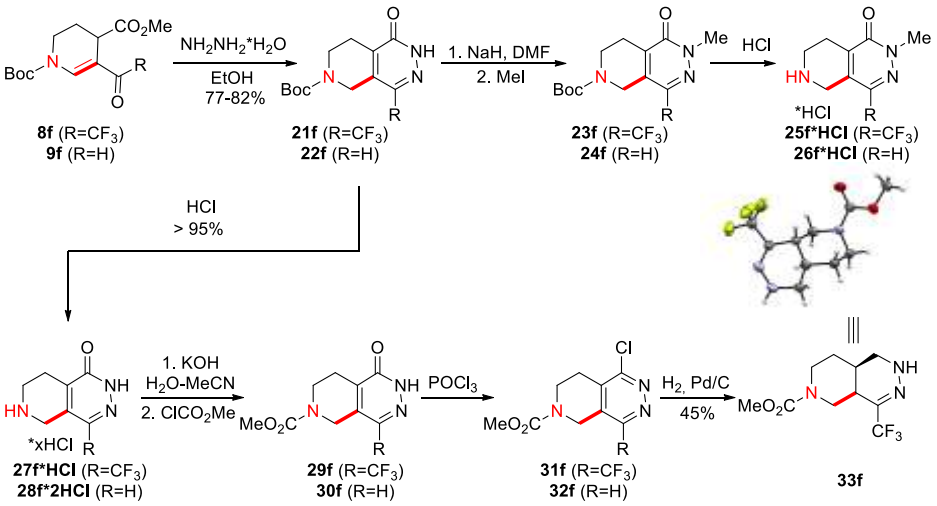
Scheme 9. Behavior difference of the compounds 8f and 9f in the reaction with binucleophiles.

Therefore, for these substrates, the alternative recyclization protocol was developed, this new protocol was based on slow acidic Boc-deprotection during the reaction. It was found that reflux with hydrazine dihydrochloride in 10% solution of HCl in water-dioxane during 20 h were the best conditions. Using such conditions both enantiomers of pyrazolyl-containing aminoacids **19d** were synthesized in 80% (for S) and 83% (for R) yields on 10 g scale respectively (Scheme 8). The efficacy of elaborated approach was also demonstrated by the synthesis of the aminoacid **19e(S)** from the well-known, commercially available 5-membered enecarbamate – (R)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid (see SI).

Taking in mind that Boc-group at the nitrogen atom blocked the nucleophilic attack in reactions of **8** and **9,** were decided to try redirection of the regioselectivity in the heterocyclization reaction with binucleophiles in a case of isonipecotic acids derivatives **8f** and **9f**. The representative illustration of this idea is shown on Scheme 9. In the case of Boc-deprotected derivative with carboxylic function at the 4th position, only push-pull enaminone fragment was able to react with the nucleophiles due to the high reactivity of the enamine function in comparison with the non-electrophilic carboxylic group. In the case of NH_2NH_2 such reactivity pattern was proven by exclusive formation of the pyrazole derivative **19f** and **20f** (see scheme 8). Vice versa, in the case of Boc-protected ester derivatives **8f** and **9f**, the cyclic electrophilic center is "blocked" by sterically hindered Boc-group while the ester function was electrophilic. Therefore, we expected that the reaction with $NH_2NH_2{\cdot}H_2O$ had to lead to tetrahydropyrido[3,4-d]pyridazin-1(2H)-one derivatives.

Indeed, isonipecotic acid derivatives **8f** and **9f** reacted with 3 eq of $NH_2NH_2{\cdot}H_2O$ in *i*-PrOH under reflux selectively affording tetrahydropyrido[3,4-d]pyridazin-1(2H)-ones **21f** and **22f**, which crystallized from the reaction mixture upon cooling (Scheme 10). These reactions were easily scaled up to

60 g and the products became good starting materials for the design of the tetrahydropyrido[3,4-d]pyridazine libraries with several diversity points. It should be noted, that tetrahydropyrido[3,4-d]pyridazin-1(2H)-one building blocks were developed by us earlier [40], but the previously reported sequence of steps included photochemical chlorination with autoclave pyridine hydrogenation over freshly prepared PtO_2, which limited the scale of the synthesis of key parent compound **22f** to 5 g from 1 synthetic run.



Scheme 10. The synthesis of building blocks based on tetrahydropyrido[3,4-d]pyridazine scaffold starting from isonipecotic acid derivatives **8f** and **9f**.

Therefore, the method proposed by us earlier did not allow the wide use of the above-mentioned building block in our Medicinal Chemistry programs. The Boc protected compounds **21f** and **22f** could be easily alkylated at N2-position giving (after deprotection) blocks type **23f** and **24f** bearing N6 amino function. This sequence opened the door for the tetrahydropyrido[3,4-d]pyridazin-1(2H)-one based libraries *via* parallel synthesis with diversity points at N2 and N6 positions. Alternatively, change of the Boc-protection to more stable CO_2Me the reaction with $POCl_3$, allowed to obtain 1-chloro tetrahydropyrido[3,4-d]pyridazines **31f** and **32f**, which were the key BB for the tetrahydropyrido[3,4-d]pyridazine based libraries with diversity points at C1 and N6 positions *via* nucleophilic substitution at C1/deprotection/nitrogen functionalization at N6. However, when we tried to prepare the parent C1-unsubstituted compound via reductive dechlorination of **31f** with H_2 over Pd/C, we found that the hydrogenation at 40 atm led to the product of quite selective partial reduction of pyrazine ring **33f** - new Fsp^3-rich scaffold. Its structure was proven by single crystal X-ray diffraction study.

Conclusion

As a result of this study, we showed that the well-known electrochemical Shono oxidation of Boc-protected cyclic amines leading to the synthesis of corresponding carbamates could be optimized and scaled up to 0.5 kg from 1 synthetic run. This improvement opens the door to the active use of these compounds as starting materials possessing excellent storage ability for the design and synthesis of Medicinal Chemistry relevant building blocks on its base. This opportunity was previously not available (except five-membered encarbamates) because of the limited accessibility of these compounds in gram scale. Notably, the developed protocol complies with the current Green Chemistry requirements.

The parent *N*-Boc-3,4-dihydro-morpholine was synthesized for the first time and its chemical properties were tested in [2+1], [2+2] cycloadditions as well as electrophilic substitutions. The novel, unique building blocks based on 2-oxa-5-azabicyclo[4.1.0]heptane framework as well as functionalized *N*-Boc-3,4-dihydromorpholines were obtained. In the case of encarbamates, derived from Boc-protected esters of pipecolic and isonipecotic acids, the stereoselective (*trans*-, in the case of pipecolic acid, and *cis*-, in the case isonipecotic acid) introduction of the fluorine atom in the 5^{th} and the 3^{rd} position, respectively, was developed based on electrophilic fluorination by Selectfluor with subsequent MeO-group reductive removal by Et_3SiH. All obtained cyclic encarbamates were subjected into Vilsmeier–Haack formylation and trifluoroacyclation affording latent 1,3-bielectrophilic compounds, which

were investigated in classical heterocyclization with hydrazine. Thus, the method for preparation of the corresponding pyrazoles, decorated by unusual manner including chiral examples, was developed. In the case of enecarbamate derived from Boc-protected ester of isonipecotic acids, the efficient synthetic route to tetrahydropyrido[3,4-d]pyridazine derivatives was elaborated.

The developed procedures are simple, cheap and time-effective. Therefore, the reaction sequences developed in this investigation were involved into REAL building block program[41] and building blocks synthesized were input into REAL database program[42]. This investigation meets the criteria of "translational chemistry" proposed by P. Baran[43] and means almost immediately introduction the results into market as building blocks, advanced synthetic intermediates as well as using the innovative protocol developed in P@D projects without significant optimization.

Experimental Section

General information. The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on automated melting point system. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for Protons and 126 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400 MHz for protons, 101 MHz for Carbon-13, and 376 MHz for Fluorine-19). Tetramethylsilane (^{1}H, ^{13}C) or C_6F_6 (^{19}F) were used as standards. Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, their results were found to be in good agreement (±0.4%) with the calculated values. Preparative HPLC analyses were done on an Agilent 1200. Mass spectra were recorded on Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). Preparative chromatography was performed on "interchem"PuriFlash® machine. CCDC-1982686 (**2d**), CCDC-1982687 (**4a**), CCDC-1982688 (**5a(*cis*)**), CCDC-1982689 (**9a**), CCDC-1982690 (**15d(sr)**), CCDC-1982691 (**16f(sr)**), CCDC-1982693 (**19a**), CCDC-1982694 (**19b**), CCDC-1982692 (**33f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Detailed experimental procedure for the synthesis of all compounds as well as its characterization is available in the supporting information. The representative examples of general protocols are given below.

Procedure A. *Typical protocol for cyclic enecarbamates synthesis from Boc-protected cyclic amines* ***N*-Boc-3,4-dihydro-morpholine 3a**. N-boc morpholine (512.0 g, 2.73 mmol) and tetrabutylammonium tetrafluoroborate (50.0 g, 0.15 mol) were dissolved in dry MeOH (2400 mL) and the solution obtained was placed into a 3L undivided cell with a cooling mantle equipped with seven graphite rod electrodes (150 mm, d 12mm, see pictures). The mixture was cooled down to 15 °C and then electrolyzed under a constant current 7.5A (initial potential was raised from 17V to 21V progressively). After 3.1 F/mol, the mixture was concentrated in vacuum and heated for 3 hours at 70 °C under reduced pressure (100 mm Hg) in a rotary evaporator. The reaction course was additionally monitored by TLC. Then the mixture was extracted twice with EtOAc (500 mL). EtOAc layer washed twice with 200 mL of water, dried over Na_2SO_4 and concentrated under reduced pressure, distilled at 1 mm, collected fraction 60-65 ºC, The desired product was purified by flash chromatography in "interchem"PuriFlash® (in a gradient from ratio $CHCl_3$/MeCN 1:0 to 0:1). The enecarbamate **3a** was obtained as a colourless liquid (435.0 g, 85% yield).

Procedure B. *Synthesis of* **(1R*,6S*,7R*)-7-(trifluoromethyl)-2-oxa-5-azabicyclo[4.1.0]heptane 5a(trans)** and **(1R*,6S*,7S*)-7-(trifluoromethyl)-2-oxa-5-azabicyclo[4.1.0]heptane 5a(cis)**. CF_3CHN_2 (5 eq; obtained as described in ref 18) was gradually blown off by an inert gas from the generator flask and passed through a drying tube ($MgSO_4$) into a vessel containing a stirring mixture of **3a** (18.5 g, 0.1 mol) and anhydrous CuCl (0.5 g, 5 mmol) in CH_2Cl_2 (300 mL). The reaction was monitored by ^{1}H NMR spectroscopy. After the starting material had disappeared, trifluoromethyldiazomethane bubbling was immediately stopped. The reaction mixture was filtered off and concentrated in vacuo. The oily residue was purified by flash column chromatography with a hexane/EtOAc mixture (4:1) as an eluent to afford isomer **4a(trans)**, (R_f~0.5) as a yellow oil in 53% yield (14.2 g) and **4a(cis)** (R_f~0.35) as a light yellow solid in 15% yield (4.0 g, m.p.=73-75 ºC). The separated isomers were dissolved in saturated HCl solution in dioxane[44] and stirred overnight at rt. The reaction mixture was evaporated and the residue was triturated with a mixture of MTBE/MeCN (4/1). The precipitates formed were filtered off and dried. The desired products obtained in 94% (**5a(*trans*)**, 10.1 g, beige powder, m.p. = 111-113 ºC) and 96% (**5a(*cis*)**, 2.9 g, beige powder, m.p. 116-118 ºC) yields respectively as hydrochlorides.

Procedure C. *Synthesis of* **7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane 7a**.[13c] Sodium iodide (3.0 g, 0.02 mol) was added to a solution of **3a** (18.5 g, 0.1 mol) in anhydrous THF (200 mL) under an argon atmosphere and heated to reflux. Trimethyl(trifluoromethyl)silane (57.0 g, 0.4 mol) was added dropwise for 8 hours. The reaction mixture was heated overnight. Then, the additional trimethyl(trifluoromethyl)silane (28.5 g, 0.2 mol) was added, and the reaction mixture was refluxed for an additional 24 hours. When the conversion was complete, the solvent was evaporated, and the crude product was distilled under reduced pressure. The product was formed and purified by flash column chromatography hexane/EtOAc 9:1. The compound **6a** was obtained in 86% yield (20.2 g). The obtained product was dissolved in TFA and heated at 60 ºC for an hour. The precipitates formed was filtered off

and dried. The desired product **7a** obtained in 91% yield as trifluoroacetate (22.6 g).

Procedure D. *Typical protocol for trifluoroacylation of cyclic enecarbamates.* **Tert-butyl 5-(2,2,2-trifluoroacetyl)-3,4-dihydropyridine-1(2H)-carboxylate 8b**. The corresponding encarbamate **3b** (92.0 g, 0.5 mol) was dissolved in 800 mL of DCM and dry pyridine (47.5 g, 0.6 mol) was added. The solution obtained was cooled down to 10 ºC and then TFA (63.0 g, 0.55 mol) was added dropwise at 10-15 ºC for 1 hour and then left for 16 hours at rt. After that, the reaction mixture poured into a cold 5% solution of $NaHCO_3$ and the desired product extracted 2x300 mL of DCM, washed with water 200 mL, then 20% water solution of citric acid 2x200 mL, and water again 500 mL. The organic layer was dried under Na_2SO_4. The solvent was removed under reduced pressure. The crude product formed with 90% purity. The desired product was purified by flash chromatography in "interchem"PuriFlash® (in a gradient from ratio hexane/MTBE 9:1 to 0:1). The final compound **8b** (113.1 g, 81% yield) was obtained as a yellow crystalline powder.

Procedure E. *Typical protocol for Vilsmeier–Haack formylation of cyclic enecarbamates.* **Tert-butyl 6-formyl-2H-1,4-oxazine-4(3H)-carboxylate 9a**. A solution of dry DMF (110 g, 1.5 mol) in 540 mL of DCM was placed into a three-neck round flask equipped with a mechanic stirrer and and $POCl_3$ (184 g, 1.2 mol) was added dropwise at 5-15 ºC. After that, the reaction mixture stands by for 10 min and 500 mL of methylene was added, the mixture was cooled down to 0 ºC and solution of morpholine encarbamate **3a** (219.0 g, 1.01 mol) in 200 mL of DCM was added dropwise at 0 ºC. Afterward, the reaction mixture was stood for 1 hour at 10 ºC and 2 hours at rt. The solution was poured into 3 kg of ice with 7.2 mol of 1M KOH, extracted 3x200 mL of DCM, washed with brine and dried under anhydrous Na_2SO_4. The desired product was purified by flash chromatography in "interchem"PuriFlash® (in a gradient from ratio $CHCl_3$/MeCN 1:0 to 0:1). Aldehyde **9a** was isolated as beige powder (122.8 g, 57% yield, m.p. = 130ºC).

Procedure F. *Typical protocol for the formation of 3-bromoenecarbamates*. **1-tert-butyl 2-methyl 5-bromo-3,4-dihydropyridine-1,2(2H)-dicarboxylate 11d**.[45] The encarbamate **3d** (96 g, 0.3 mol) was dissolved in 800 mL of DCM and Br_2 (50 g, 0.31 mol) was added dropwise at –50-60 ºC. After that, the reaction mixture was stirred for 15 min with further dropwise addition of TEA (61 g, 0.6 mol) at –50-60 ºC. The bath was removed and the reaction mixture was stirred for 2 h. Then, the reaction mixture was poured into a cold 5% solution of $Na_2S_2O_3$, washed with water (500 mL) and the organic layer was dried under Na_2SO_4, the solvent was removed under reduced pressure and the crude product was formed with 86% purity. The desired product was purified by flash chromatography in "interchem"PuriFlash® (in a gradient from ratio $CHCl_3$/MeCN 1:0 to 0:1). The desired bromide **11d** was obtained in 84% yield (80.7 g).

Procedure G. *Typical protocol for the formation of 3-iodo-2-methoxy derivatives*. **(2S*,3R*)-tert-butyl 3-iodo-2-methoxypiperidine-1-carboxylate 12b**. The encarbamate **3b** (18.5 g, 0.1 mol) was dissolved in 400 mL of 0.5M solution of NaOMe in MeOH. Then the solution of I_2 (25.5 g, 0.1 mol) in DCM 400 mL was added dropwise to the stirring reaction mixture at rt for a 1 hour. Then the mixture was stirred at rt for an additional half an hour. After that, the 20% solution of Na_2SO_3 in water (500 mL) was added. The mixture obtained was stirred for 5 minutes and then, extracted with DCM 2x500 mL. The organic layer was separated and dried under Na_2SO_4, the solvent was removed under reduced pressure and the crude product was formed. The residue was solved in hexane (400 mL) and placed to a freezer at -20 ºC for 24 hours. The precipitate formed was filtered off, washed with hexane 3x50mL and dried. The iodide **12b** was obtained in 63% yield (21.5 g). The iodide obtained was dissolved in DCM (200 mL), and mixed with in $BF_3{\cdot}Et_2O$ (9 g, 0.07 mol). The reaction mixture was cooled to -90 ºC and Et_3SiH was added dropwise under this temperature. After that the reaction mixture was warmed up to rt. The solvent was removed under reduced pressure and the crude product was formed. The desired product was purified by flash chromatography in "interchem"PuriFlash® (in a gradient from ratio $CHCl_3$/MeCN 1:0 to 0:1). The desired iodide **13b** was obtained in 38% yield (7.1 g).

Procedure H. *Typical protocol for the formation of 3-fluoro-2-methoxy derivatives*. **(2S*,5R*,6S*)-1-tert-butyl 2-methyl 5-fluoro-6-methoxypiperidine-1,2-dicarboxylate 14d**. The enecarbamate **3d** (24.1 g, 0.1 mol) was dissolved in 100 mL CH_3CN/MeOH (ratio 2:1) and Selectfluor (39.0 g, 0.11 mol) was added. After the reaction mixture was stirred at rt for 14 hours. After the reaction completed (monitored by TLC), the solvent was removed by evaporation. 300 mL of water was added and the desired product was extracted with ethyl acetate (3x100 mL). Combined organic layers were dried over $MgSO_4$ and evaporated. The product was purified by flash column chromatography with a hexane/EtOAc (9:1) mixture as eluent. The desired fluoride **14d** was obtained in 74% yield (21.6 g). as a mixture of diastereomers. The products also can be used in the next step without further purification.

Procedure I. *Typical protocol for the formation of 3-fluoro derivatives*. **(2S,5R)-methyl 5-fluoropiperidine-2-carboxylate 16d(srs).** The compound **14d** (29.1 g, 0.1 mol) was dissolved in 200 mL of DCM and triethylsilane (19.8 g, 0.17 mol) was added. Then the reaction mixture was cooled to 0 ºC and TFA (114.0 g, 1.0 mol) was added dropwise to the stirring reaction mixture at 0 ºC for 2 hours. After, the mixture was warmed up to rt and stirred at rt for 48 hours. The solvent was removed at 40 ºC and MeOH (200 mL), TEA (50.6 g, 0.5 mol) and BOC-anhydride (32.7 g, 0.15 mol) were added to the residue. The obtained reaction mixture was stirred overnight, and MeOH was evaporated. The product was formed and purified by flash chromatography in "interchem"PuriFlash® (in a gradient from ratio $CHCl_3$/MeCN 1:0 to 0:1). The compound **15d(srs)** was obtained in 58% yield (15.2 g). The product was dissolved in saturated solution of acidic dioxane at rt.

The precipitate formed as hydrochloride was filtered off, washed by ether (2x50 mL) and dried. The product **16d(srs)** was obtained in 92% yield (13.9 g) as a white powder.

Procedure J. *Typical protocol for the recyclization of trifluoroacetyl and formyl derivatives to pyrazoles.* **2-((3-(trifluoromethyl)-1H-pyrazol-4-yl)oxy)ethanamine 19a.** Compound **8a** (140.6 g, 0.5 mol) was dissolved in MeOH (1 L) and the solution of KOH (42.0 g) in 200 mL of water was added. The reaction mixture was stirred for 48 hours at rt. After that, MeOH was removed under reduced pressure and water was acidified with citric acid and stood by for 1.5 hours. The precipitate formed was filtered off, washed with water (2x100 mL) and dried in exicator under P_2O_5. The product **17a** was obtained as a yellowish solid in 86% yield (78.0 g, m.p. = 205-208 ºC). Compound **17a** can be used in the next step without additional purification. The product **17a** (72.0 g, 0.4 mol) was dissolved in EtOH 1 L in Erlenmeyer flask, then the reaction mixture was refluxed with hydrazine hydrate (60.0 g, 1.2 mol) for 4 hours. After that, the solvent was removed under reduced pressure, extracted with methylene-water to remove the excess of hydrazine. The organic layer was evaporated and 3 eq of 31% water solution of HCl was added. Then the solvent was removed under reduced pressure again. The desired amine **19a** was crystallized from CH_3CN and obtained as the hydrochloride in 88% yield (81.5 g) as a yellow powder.

Procedure K. *Synthesis of optically pure S and R* **2-amino-4-(3-(trifluoromethyl)-1H-pyrazol-4-yl)butanoic acids 19d(S) and 19d(R).** The product **8d** (R or S isomer) (134.9 g, 0.4 mol) was dissolved in DXN (500 mL) in the three-neck round flask equipped with a mechanic stirrer. After that, hydrazine dihydrochloride (47.0 g, 0.4 mol) and 10% water solution of HCl (0.5 L) were added. The reaction mixture was stirred for 16 hours at 70 ºC. The solvent was removed under reduced pressure. The corresponding amine **19d** was crystallized from CH_3CN and obtained as the hydrochloride in 83% yield (78.7 g) with 95% ee (m.p. = 210-212 °C). 0.1% FA-ACN 30-40% ACN 7 min. Zorbax Eclipse-plus C18 4.6*100 mm, 3.5 mkm with Marfey's Reagent EE 95.3%.

Typical protocols for the synthesis of tetrahydropyrido[3,4-d]pyridazines

Procedure L. *Synthesis of compounds 21f and 22f.* **tert-butyl 1-oxo-4-(trifluoromethyl)-1,2,7,8-tetrahydropyrido[3,4-d]pyridazine-6(5H)-carboxylate 21f.** Compound **8f** (168.7 g, 0.5 mol) was dissolved in *i*-PrOH (1,5 L) in Erlenmeyer flask equipped with a condenser and hydrazine hydrate (40 g, 0.8 mol) was added. Then the reaction mixture was refluxed for 4 hours. After that, *i*-PrOH was removed under reduced pressure and the residue was diluted by water 500 mL and extracted by DCM 3x200 mL. The organic layer was separated and the solvent was removed in vacuo. The desired product **21f** was crystallized from EtOAc and obtained as a white powder in 88% yield (140.5 g).

Procedure M. *Synthesis of compounds 27f and 28f.* **4-(trifluoromethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyridazin-1(2H)-one 27f.** Piridazinone **21f** (64 g, 0.2 mol) was suspended in EtOH (400 mL) and 3 eq of 31% water solution of HCl was added. Then the reaction mixture was refluxed for an hour. After that, EtOH was removed under reduced pressure. The desired product **27f** was crystallized from CH_3CN and obtained as a yellow powder in 97% yield (49.6 g, m.p. = 176 ºC) as hydrochloride.

Procedure N. *Synthesis of compounds 25f and 26f.* ***2*-methyl-4-(trifluoromethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyridazin-1(2H)-one 25f**. Piridazinone **21f** (64.0 g, 0.2 mol) was dissolved in DMF (200 mL). Then NaH (5 g, 0.21 mol) was added and MeI (28.4 g, 0.2 mol) was added dropwise for an hour. The reaction mixture was stirred overnight. After that 20 mL of water was added and the solvent was removed under reduced pressure. Hexane (200 mL) was added to the residue. The suspension was stirred and the hexane was decanted from the precipitate. Then the residue was dissolved in EtOAc (500 mL) and washed by water 2x200. The organic layer combined and the solvent was removed under reduced pressure. The crude product was treated with MTBE, and then was crystallized from MTBE and washed by the mixture MTBE/hexane 1:1. The corresponding product **23f** was obtained as a white powder in 40% yield (26.7 g). The BOC-deprotection was performed the same as described in procedure M. The desired product **25f** was obtained as a beige powder in 94% yield (20.3 g) as hydrochloride.

Procedure O. *Synthesis of compounds 31f and 32f.* **Methyl 1-chloro-4-(trifluoromethyl)-7,8-dihydropyrido[3,4-d]pyridazine-6(5H)-carboxylate 31f**. Piridazinone **27f** (51.0 g, 0.2 mol) was dissolved in CH_3CN:H_2O mixture (1:1, 1 L) and KOH (18.0 g, 0.45 mol) was added. The reaction mixture was cooled to 5 ºC and methyl chloroformate (21 g, 0.22 mol) was added dropwise to the stirring solution during 1 h. Then the solvent was removed under reduced pressure and water (500 mL) was added to the residue. The desired product was extracted from the suspension obtained by DCM (3x200 mL). The organic layer combined and the solvent was removed under reduced pressure. The corresponding product **29f** was crystallized from EtOAc and obtained as a white powder in 68% yield (37.7 g). Compound **29f** (27.7 g, 0.1 mol) was mixed with $POCl_3$ (92 g, 0.6 mol) in the three-neck round flask equipped with a mechanic stirrer. The reaction mixture was stirred for 3 hours at 80 ºC. The excess of $POCl_3$ was removed in vacuo and caramel-like syrup was obtained. This residue was poured into 3 kg of ice with of 25% water solution of NH_3 (10 mol), extracted 3x300 mL of DCM, washed with brine and dried under anhydrous K_2CO_3. The organic layer combined and the solvent was removed under reduced pressure. The residue was dissolved in 300 mL of DCM and flashed through 6 cm of the silica gel pad. The solvent was removed again. The product **31f** was obtained as a yellowish solid in 92% yield (54.4 g, m.p. = 121 ºC).

Procedure P. *Synthesis of 33f.* **Methyl 4-(trifluoromethyl)-1,4a,5,7,8,8a-hexahydropyrido[3,4-d]pyridazine-6(2H)-carboxylate 33f**. **31f** (5.0 g, 0.017 mol) was dissolved in 60 mL of MeOH in 100 mL

autoclave, 2 g of 10% Pd(C) was added. The mixture was blow off with hydrogen to scavenge air and autoclave was closed. The reduction of **31f** was performed with TEA (1.89 g, 0,019 mol) under 40 atm and 40 ºC for 6 h. The mixture was filtered off, the solution was evaporated, the residue was diluted by water 100 mL and extracted by DCM 2x30 mL. The solvent was evaporated under reduced pressure. The desired product was recrystallized from MTBE and obtained as a beige powder in 45% yield (3.18 g, m.p. = 137 ºC).

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FULL PAPER

Electrochemical Scaled-up Synthesis of Cyclic Enecarbamates as Starting Materials for Medicinal Chemistry Relevant Building Blocks

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