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C(sp^3)–C(sp^3) Bond Formation *via* Electrochemical Alkoxylation and Subsequent Lewis Acid Promoted Reactions

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Abstract: A two-step transition metal-free methodology for the C(sp^3)–C(sp^3) functionalisation of saturated *N*-heterocyclic systems is disclosed. First, aminal derivatives are generated through the anodic oxidation of readily accessible carboxylic acids. Then, in the presence of $BF_3 \cdot OEt_2$, iminium ions are unmasked and rapidly alkylated by organozinc reagents under flow conditions. Secondary, tertiary and quaternary carbon centers have been successfully assembled using this methodology. Such an approach is especially relevant to drug discovery since it increases C(sp^3)-functionalities rapidly within a molecular framework. As proof of concept, our methodology was applied to derivatization of peptides and an API.

Keywords: Electrochemistry; Flow chemistry; Transition-metal free; Drug discovery; Organozinc reagents

Although C(sp^3)–C(sp^3) bond formation is fundamental in medicinal and organic chemistry, it remains a key challenge. In particular, incorporating C(sp^3)-moieties into bioactive molecules is essential to escape from the "flatland" in drug discovery programs.[1] For instance, quaternary carbon centres are highly relevant owing to the new 3D chemical diversity they can bring.[2] Several transition-metal catalysed alkyl-alkyl cross-coupling reactions have been reported to achieve this goal.[3] Unfortunately, despite their synthetic benefits, these reactions usually require toxic and expensive transition metal catalysts such as Ni, Pd or Ir, which makes them unappealing from a green chemistry point of view.[4] The growing impetus of the chemical community for developing ecologically friendlier methodologies has prompted us to investigate the combined use of electrosynthesis with low-toxicity organometallics. Indeed, electrosynthetic organic chemistry has been shown to be an outstanding technology for developing more sustainable methodologies in medicinal chemistry.[5] This green and valuable tool uses electricity, one of the cheapest reagents, to achieve complex organic transformations.[6]

Many drug-like lead compounds are embedding *N*-heterocyclic scaffolds such as pyrrolidines, morpholines or piperazines.[7] The ability for late-stage functionalisation of nitrogen-containing systems with C(sp^3)-fractions tremendously speeds up the drug discovery process by rapidly opening new chemical spaces with promising biological activity.[8]

We have previously reported the electrochemical methoxymethylation of α-alkoxy carboxylic acids to synthesize MOM-type ethers in a practical, green, safe and scalable method either in batch or flow.[9] Based on this precedent, we investigated the anodic generation of aminals from α-nitrogen carboxylic acid derivatives. A Lewis acid-promoted generation of an iminium ion, followed by an organometallic reagent addition would lead to the rapid formation of functionalized *N*-heterocycles.[10] The high functional group compatibility of organozinc derivatives makes them more suitable than Grignard reagents[11] to introduce a new C(sp^3)–C(sp^3) center on the nitrogen-containing

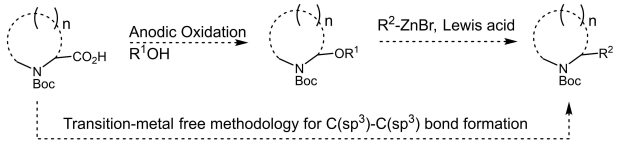
scaffolds. Our general approach is depicted in Scheme 1.

We began by electrochemically oxidising *N*-Boc-protected proline in methanol using our previously developed conditions (Scheme 2). Much to our delight, **1a** was isolated in 90% yield without the need for any purification. 3-Substituted proline aminal derivatives were produced in excellent yields (**1b** and **1c**) following the same procedure. Furthermore, morpholine and piperazine derivatives proved to be compatible and their aminals were successfully electrosynthesised (**1e** and **1f**). Alternatively, direct Shono oxidation can be used for the preparation of these intermediates as demonstrated with piperidine analogue **1d**.[12]

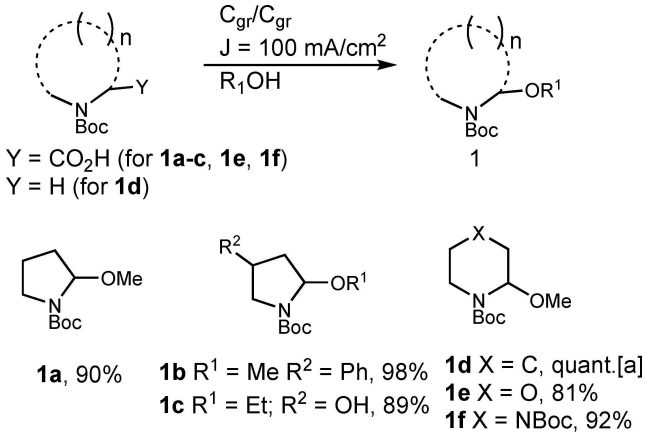
With the optimal electrochemical conditions for the formation of aminals in hand, we then focused our attention on the addition of organozinc derivatives, prepared using our previously reported protocol,[13] on to the iminium ion formed from **1a** promoted by the presence of a Lewis acid.[8] For our initial screening, **1a** and benzylzinc bromide were selected as model substrates. They were reacted in the presence of an array of Lewis acids in batch (see Table S1 in Supporting information). Among them, $BF_3 \cdot OEt_2$ led to the best results. However, adding the Lewis acid portionwise over 5 minutes increased the yield from 25 to 54%, which highlighted the need for a controlled delivery of this acid in the reaction media. This result prompted us to consider flow chemistry as an alternative for a better control of the reaction parameters. As shown in Table 1, a residence time of 1 min was enough to improve the yield obtained in previous batch experiments (Entry 1). Nevertheless, best conditions were obtained when the reaction was run at room temperature and just 1 equivalent of $BF_3 \cdot OEt_2$ (Entry 4). Under these conditions starting material was completely consumed and provided the best balance regarding isolated yield. Increasing the equivalents of Lewis acid or organozinc reagent did not improve the reaction outcome (See supporting info for more details).

We then explored the reaction scope and limitations of this new methodology. A wide range of functionalized organozinc reagents were used in the presence of **1a** (Table 2). At first, we investigated the use of substituted benzylic zinc reagents. Coupling products were obtained in reasonable to good yield with a wide variety of substituents, including halides (**5** and **6**), products bearing electron-withdrawing groups such as cyano, trifluoromethyl, sulfone and ester (**7**–**10**), or *p*-*tert*-butyl moiety as an electron-donating group (**11**). *Ortho* and *meta* functionalized benzylic derivatives also led the desired products in good yields (**12**–**15**). Additionally, allyl organozinc reagent also provided the desired product **16**.

One of the main challenges in organic synthesis is formation of all-carbon-substituted quaternary carbon atoms.[14] Remarkably, this methodology allowed the formation of challenging quaternary carbon centres. Tertiary cyclobutyl, lactones, cyclohexyl and THP groups bearing ester and cyano groups were successfully used to prepare the corresponding coupling products (**22**–**27**) where a new sterically demanding tertiary-quaternary carbon-carbon bond is been formed.

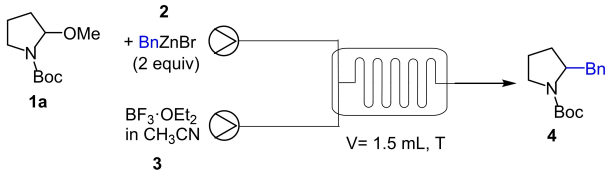


Scheme 1. General approach to obtain α-functionalised nitrogenated systems.



Scheme 2. Electrochemical alkoxylation. [a]Compound **1d** was obtained by Shono oxidation of *N*-Boc piperidine (reaction conditions see Supporting Information).

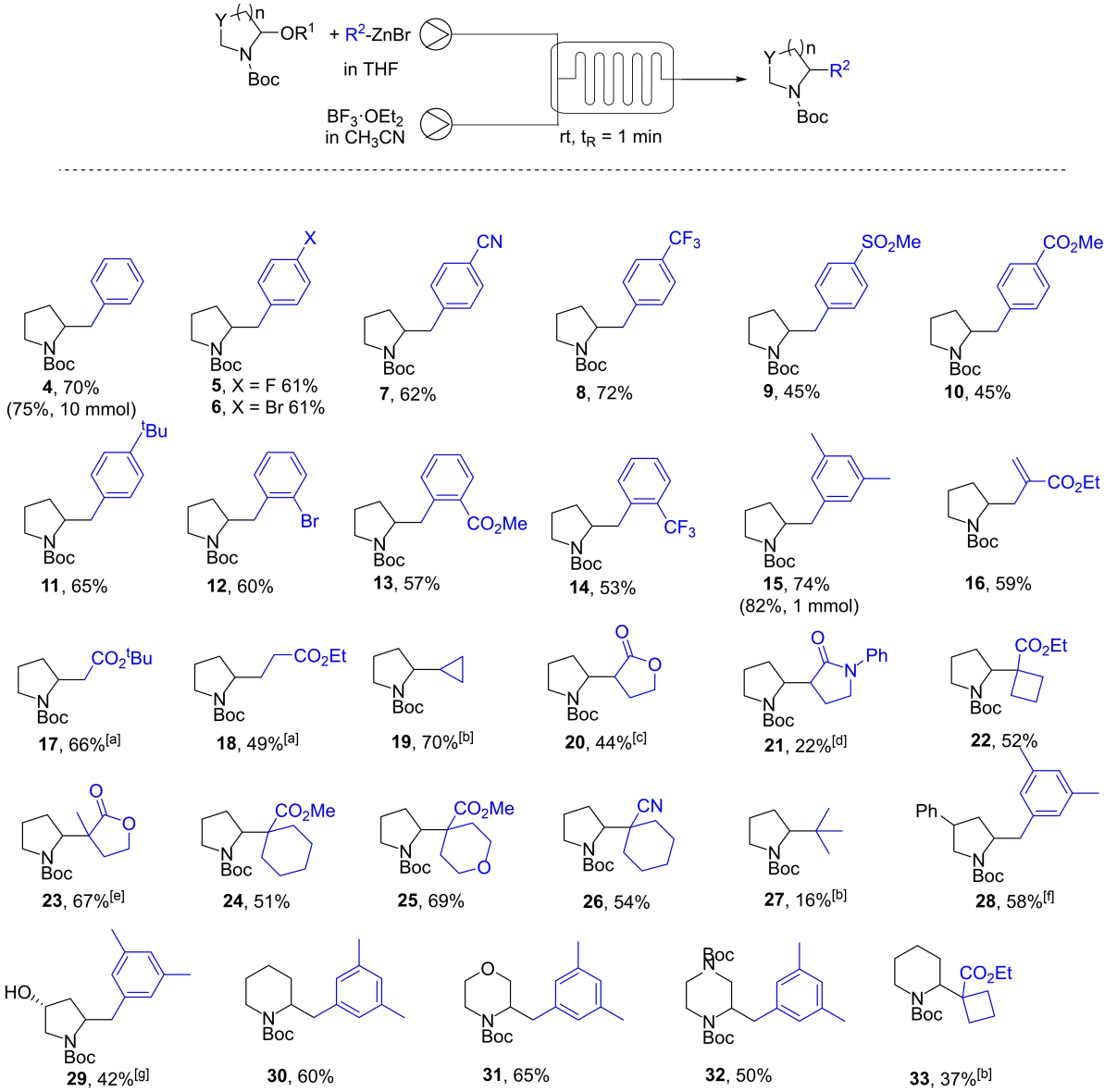
Table 1. Flow reaction screening.



Entry	T (°C)	t_R (min)	Equiv. $BF_3 \cdot OEt_2$	Yield[a]
1	0	1	1	61%
2	0	2	1	63%
3	0	5	1	60%
4	**rt**	**1**	**1**	**71%(70%)**
5	rt	1	1.2	70%(66%)
6	rt	1	1.5	71%(67%)

[a] Yield was determined by NMR using 1,3,5-trimethoxybenzene as internal standard (isolated yield in brackets).

Table 2. Reaction scope.



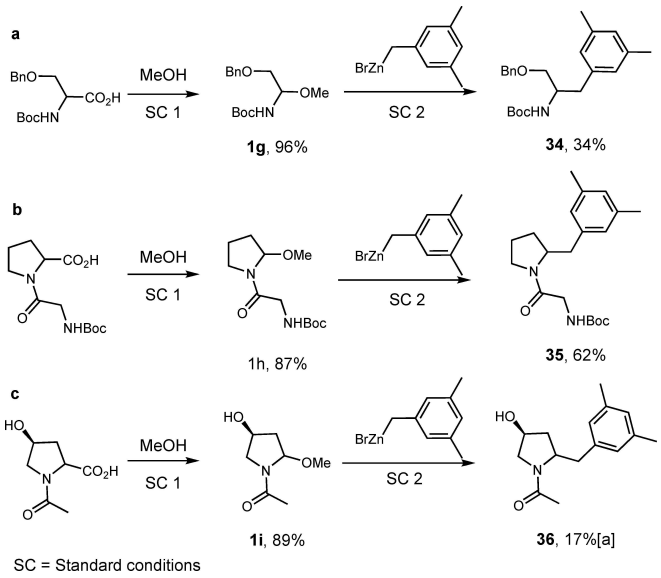
[a] 3 equiv. of RZnBr were added.
[b] 2 equiv. of $BF_3 \cdot OEt_2$ were added.
[c] Obtained as RR,SS/RS,SR mixture 55/45.
[d] Obtained as RR,SS/RS,SR mixture 50/50.
[e] Obtained as RR,SS/RS,SR mixture 33/67.
[f] Obtained as RR,SS/RS,SR mixture 40/60.
[g] Obtained as 2R,4R/2S,4R mixture 30/70.

Finally, we investigated the use of substituted pyrrolidines and other nitrogen heterocyclic systems. Placing a phenyl group at *3*-position of the pyrrolidine generated the expected coupled product **28** as a mixture of diastereomers. Ethoxy aminals can also be used in this method as demonstrated with compound **29** again as mixture of diasteroisomers. It is noteworthy that in both examples the major diasteroisomer formed is the one where the organozinc is added to the core at the opposite side of the group present in it. This will open the possibility to explore an enantioselective version of the reaction in the future. Similar reaction conditions allowed for the preparation of piperidine, morpholine and piperazine derivatives **30**, **31**, **32** and **33**.

Further demonstrating the applicability of the method, the scalability of the reaction was demonstrated with compounds **4** and **15** at 10 and 1 mmol scale, respectively. The observed improvement in yield was associated with the longer steady state obtained. These results evidence the usefulness of this transformation even in gram scales. For the 10 mmol scale reaction a 5 mL PFA coil and a T-mixer were used instead of the chip. This opens the possibility to use much larger reactors for a future industrial scale up.

We then investigated the use of aliphatic aminals as starting materials, especially peptide derivatives (Scheme 3). Boc-L-Ser benzyl ester anodically decarboxylated to form the aminal **1g** in excellent yield. The second step, involving the addition of the organozinc reagent, led to the formation of the desired open-chained product **34**. Similarly, starting from Boc-Pro-Gly-OH allowed the preparation of the functionalized dipeptide derivative **35**. This extends the scope of this methodology to more complex peptide scaffolds. Finally, as an example of late-stage functionalization, we applied our methodology to the functionalization of oxaceprol, an anti-inflammatory drug agent used to treat arthritis, chronic joint disorders and inflammation of connective tissues.[15] Decarboxylation of oxaceprol leads to the formation of the corresponding aminal **1i**. The reaction of this aminal with 3,5-dimethyl benzyl organozinc afforded the coupled compound **36**. Such a practical, rapid and mild late-stage functionalization opens the door to a high degree of molecular diversity.

In summary, we have developed a rapid C(sp^3)–C(sp^3) bond formation for the late-stage functionalisation of saturated N-heterocyclic systems. The critical step of this methodology relies on forming stable aminal derivatives through anodic decarboxylation, which are then easily coupled to an organozinc reagent in the presence of a Lewis acid. This procedure allows the access to complex structures in two steps and only one chromatographic purification from affordable compounds. For instance, homologation of amino acids or formation of quaternary-tertiary carbon-carbon bonds usually requires a multistep process to be achieved. Most of the compounds shown above can be considered as enriched C(sp^3) scaffolds with two or more points for diversification, very attractive from a medicinal chemistry point of view. Furthermore, this methodology can be also applied for late-stage functionalization of peptides and API. Further application and expansion of this methodology to industrial scale will be matter of future publications.



Scheme 3. Application of the methodology in late stage functionalization. [a]Obtained as 2S,4S/2R,4S; mixture 31/69.

Experimental Section

General Procedure for the Electrochemical Decarboxylation Reaction

An undivided electrochemical cell (total volume of 10 mL) equipped with two rectangular-shaped graphite electrodes (5 cm × 1 cm) connected to an Electrasyn 2.0 setup was used for the electrochemical decarboxylation. The carboxylic acid (3 mmol) was dissolved in 5 mL of dried alcohol (MeOH or EtOH) and neutralized with KOH (3 mmol). The solution was then sonicated for 10 minutes to ensure its homogeneity. The Electrasyn 2.0 was set up in galvanostatic mode with an alternating (every 30 s) current of 100 mA. The solution was then electrolyzed for 7 F/mol. The methanolic solution was then washed with a 1 M KOH solution in water (50 mL) and extracted with DCM (3 × 50 mL). The organic layers were combined, washed with a saturated sodium carbonate solution (50 mL), dried over Na_2SO_4, and carefully concentrated under reduced pressure to yield the aminal without the need for any further purification.

General Procedure for the Lewis Acid Organozinc Addition

A solution of the alkoxylated derivative (0.4 mmol, 1 equiv.) with the corresponding solution of R–ZnBr (prepared following General Procedure 2, see Supporting Information; 2 equiv.) was mixed using a T-mixer with a solution of $BF_3 \cdot OEt_2$ (0.2 M; 1 equiv.) in dry CH_3CN in a 1.5 mL microreactor at 0.75 mL/min each line (rt, $t_R = 1$ min). The reaction mixture was quenched in NH_4Cl solution (5 mL, 2 M) and it was then extracted with AcOEt (3 × 10 mL). The organic layers were combined and dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. The crude was purified by flash column chromatography using the indicated solvent mixtures giving rise to the corresponding coupling product.

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