C–H Functionalization *via* Iodine-mediated Electrocatalysis and C–N Bond Formation

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Abstract:

The access of heterocyclic compounds via direct amination of C-H bonds are of vital interest because of their role in pharmaceutical and natural products. The combination of molecular iodine and electricity activates benzylic C-H bond and facilitates the amination process via intramolecular C-N bond formation. Iodine works as a mediator for the formation of C-N bond via activation of a distance C-H bond through intermediate N-I bond under electrochemical conditions, so iodine can be called electrocatalyst. Under both batch & flow electrochemistry conditions, similar results were obtained in cyclization product with 77 & 78% yields respectively. However, in case of annulation reaction higher yield was obtained with 99% conversion under flow electrochemical conditions using our design of home-made flow microreactor. In both electrochemical transformations, cyclization as well as annulation reaction, no photocatalyst was used. Notably, flow reactions work under safe & environmentally friendly conditions, and continuous products are obtained.

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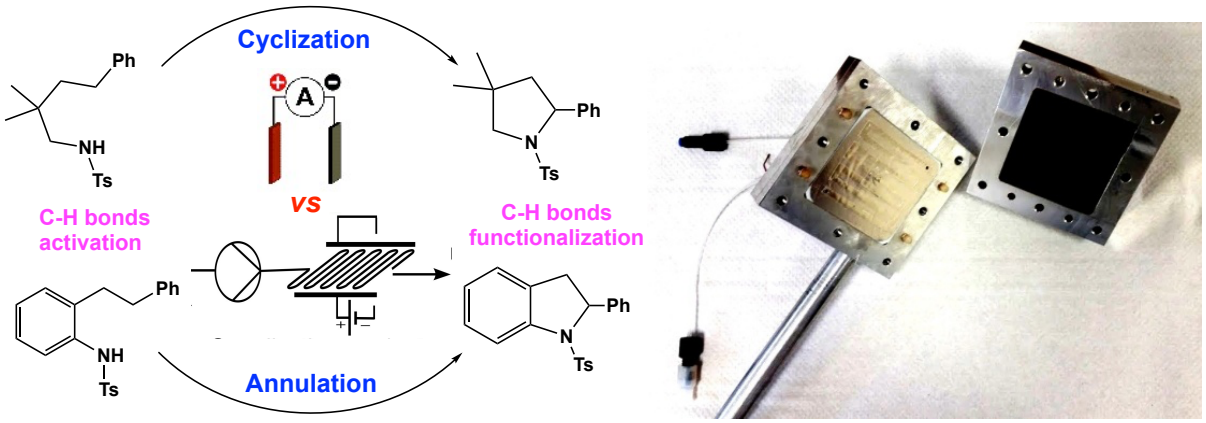


Introduction

The research field of electroorganic synthesis is growing fast due to its green and sustainable nature as it originates from renewable electricity.[1-4] Further its merging with other enabling technologies has increased its applications in organic synthesis.[5-9] Now, many of challenging chemical transformations and new bonds formation are possible under ambient and environmentally benign conditions.[10,11] Due to the great importance, the study of new C-N bonds for the synthesis of pyrrolidines and other heterocyclic structures has been explored for many decades, in addition, the development of a new methodology to obtain highly selective reactions is one of the most important areas in synthetic organic chemistry. Electrochemistry in general is the study of chemical reactions that occur at the interface of an electrode, usually a solid metal or a semiconductor, and an ionic conductor, the electrolyte. Electrochemical cells have two conductive electrodes (the anode and the cathode). The anode is defined as the electrode where oxidation occurs and the cathode is the electrode where the reduction takes place. A electrode reactions have their own specific factors for controlling selectivity, therefore both electrochemical and ordinary chemical factors make the control of electrochemical reactions more complicated.[12] These reactions involve electrical charges moving between the electrodes and the electrolyte. Electrochemical reactions allow the introduction and removal of electrons in organic molecules, and may also reverse the polarity of known functional groups. Electrons can be added to electron-deficient functional groups to convert them into nucleophiles, or removed from electron-rich functional groups to convert them into electrophiles. Thus, these reactions are interesting because their availability creates the potential to develop entirely new synthetic strategies for the construction of more complex molecules, being able to be framed in the green chemistry.

The Hofmann–Löffler reaction is an example of C(sp^3)–H bonds functionalization that proceeds via generation of remote intramolecular free radical intermediate. In this reaction, cyclic amine is formed via decomposition of N-halogenated amine under strongly acidic, thermal and photochemical conditions.[13] In 2015, Martínez et al[14] reported amination of saturated hydrocarbons using Hypervalent iodine as a catalysing moiety. During the iodine catalysis, radical chain is formed that works within the various oxidation states of iodine (I/III). This method is an efficient and provide alternative to the conventional metal-catalyzed transformations. However, O'Broin et al in 2016,[15] presented an efficient method for the intramolecular C(sp^3)–H bonds amination of aliphatic compounds in the presence of N-Iodosuccinimide (NIS) as a promoter. Light was used as source for activation of promotor. This

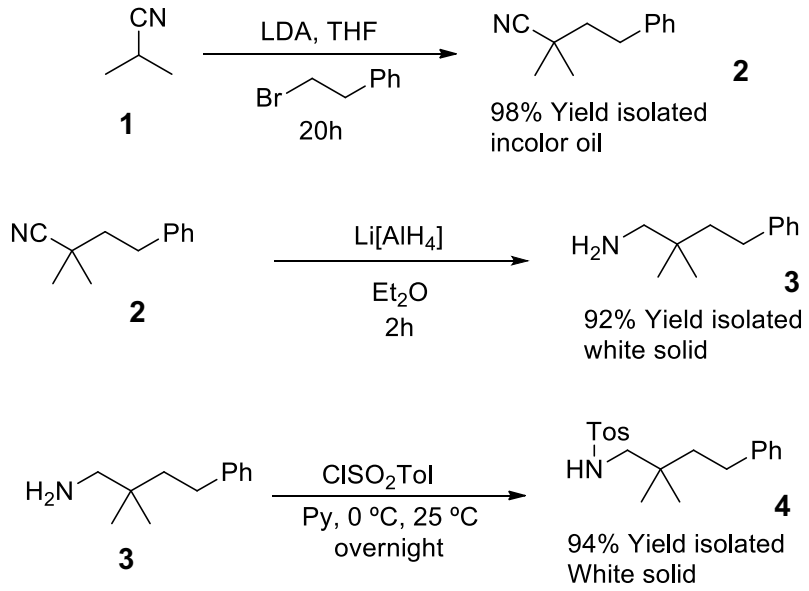
iodine-mediated Hofmann−Löffler synthetic methodology using NIS, is economic and can be used under convenient conditions for broad substrate scope as compared to hypervalent iodine reagents. Otherwise, Meng et al in 2017,[16] reported remote amination of C(sp^3)–H bonds using copper as a catalyst and obtained selective products. This mythology was applied successfully for primary, secondary, and tertiary C–H bonds and high yields were obtained. By this method, a wide range of pyrrolidines were synthesized via direct amination of tosylamine. This methodology has importance in achieving to actively utilize remotely formed carbon radicals and forms C–N bonds in the presence of copper complex. In 2017, Becker et al[17] published a work in which the cooperative role of molecular iodine and photoredox catalysis has been highlighted. This method was used to achieve intramolecular benzylic C(sp^3)–H amination in the presence of light. In this method and in the presence of visible light, iodine plays a role of catalyst for the generation of C-N bond via activation of remote C(sp^3)-H bond. In this methodology, TPT known as photoredox catalyst helps in reoxidation of the molecular iodine catalyst. The important step of this transformation was cleavage of intermediate N-I bond which was rationalized by computational chemistry and the presence of other species such as active iodine (hypoiodite) was identified by Raman spectroscopy.. In 1990, Shono et al,[18] reported electrochemical synthesis of α-(tosylamino) aldehyde acetals and pyrrolidine derivatives in methanol containing KX salts (X = Br, I). In this anodic oxidation, by changing the reaction conditions, selectivity of the products can be increased. The electrochemical cell used in this electrolysis was equipped with platinum electrodes (2 cm x 2 cm) and reaction was performed under constant current of 50 mA/cm2, and in a water bath, a cooling system.

Herein, aim is to develop a potentially metal-free approach for the direct functionalization of unactivated C–H bonds and investigate C–N bond formation reactions using electrochemistry. The use of Electrochemistry provides the substitution of metallic, expensive and toxic catalysts, allowing synthetic paths with an even cheaper source. The objective of the work emphesizes to synthesize new heterocyclic derivatives containing nitrogen, in the structure through new C-N bonds, using electrochemistry as the source of electrons.

DISCUSSION OF RESULTS

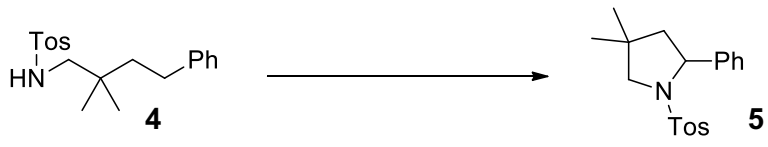
In the dry round bottom flask, was added the corresponding nitrile **1** in THF and adding dropwise LDA with a external ice cooling bath. The solution was stirred for 30 min and after which time the corresponding bromide was added and stirred at room temperature for 12 h.

The nitril product **2** was obtained in 98% yield (Scheme 1). For the reduction reaction, a dry round bottom flask and a reflux condenser were used. $LiAlH_4$ in Et_2O was added carefully and the mixture was cooled to 0 °C with an external ice cooling bath. The nitrile **2** is dissolved in a small volume of Et_2O and carefully added to the suspension. The mixture is heated at reflux for 2 h and then cooled with ice-bath to quent. The amine product **3** was obtained in 92% yield. The respective amine **3** was dissolved in pyridine and the respective sulfonyl chloride is added at 0 ºC. The solution was stirred overnight at 25 ºC. The product **4** was obtained in 94% yield (Scheme 1).



Scheme 1. Synthesis of correspondent nitril, amine & N-Tosylated product.

To access the target product **5**, Initially, the batch electrochemistry (Figure 1A) was used (Scheme 2, Table 1).



Scheme 2. Synthesis of 4,4-dimethyl-2-phenyl-1-tosylpyrrolidine**.**

It was observed the formation of product using electrochemistry (entry 0) as an oxidizing environment, providing a clean and inexpensive synthesis, with a great economy of atoms since there is no need to use hypervalent iodine as oxidizing source, this being very interesting

condition and of great interest for green chemistry. Thus, it was decided to explore the Electrochemical reactions (Table 1).

Table 1. Screening of the reactions in Batch Electrochemistry.

Entry	I_2 (%)	Time (hours)	Solvent	Current (mA)	Electrolyte (1 eq.)	Yield %[a]
0	2.5	0.5	HFIP	54 mA (1F)	nBu_4NBF_4	38
1	2.5	1h	HFIP	54mA	nBu_4NBF_4	52
2	2.5	5h	HFIP:DCM (1:1)	05 mA	nBu_4NBF_4	15
3	2.5	1h	HFIP:DCM (1:1)	20mA	nBu_4NBF_4	68
4	2.5	1h	HFIP:DCM (1:1)	27mA	nBu_4NBF_4	66
5	2.5	2h	HFIP:DCM (1:1)	54mA	nBu_4NBF_4	-[b]
6	2.5	1h	HFIP:DCM (1:1)	54mA	nBu_4NBF_4	77
7	5	1h	HFIP:DCM (1:1)	54mA	nBu_4NBF_4	72
8	2.5	1h	HFIP:DCM (8:2)	54mA	nBu_4NBF_4	55

.[a]Obtained by NMR. [b]Decomposition of reagents.

Various tests were carried out, with different conditions, where it was observed that the use of HFIP as a solvent provided the formation of the desired product (entry 0 – Table 1). After 30 minutes using in the electrochemical system, the product formation was observed in 38% yield via NMR conversion, whereas when the time of reaction was increased to 1h under the same conditions, an increase was achieved for 52% yield via conversion (entry 1 – Table1). But when the same reaction condition was carried out with time of 2 hours, no products were obtained, and the decomposition of the products and reagents was observed (entry 5). However, when a 1:1 ratio of HFIP:DCM was used, an increase in the reaction yield to 77% yield via NMR conversion was observed (entry 6). For all these tests, 1 equivalent of *n*Bu_4NBF_4 was used. Other tests were performed, varying conditions, but unfortunately no better results were obtained, being the reactional condition of entry 6 the best result obtained in batch electrochemistry.

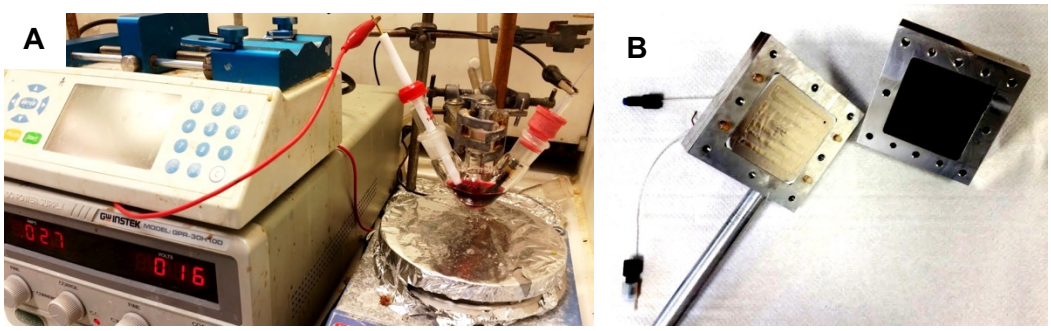


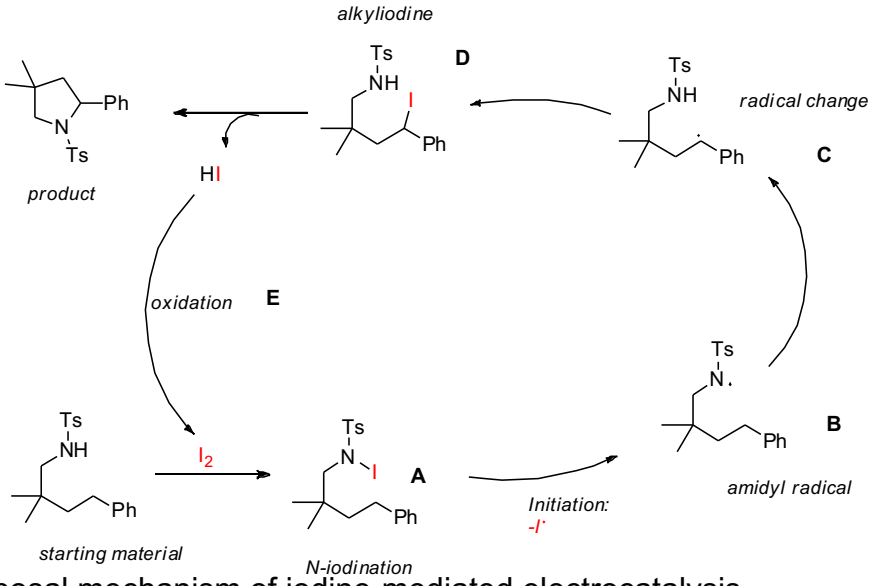
Figure 1. Process for Electrosynthesis: **A**: batch electrochemistry, **B**: flow electrochemical reactor.[11]

Similar results to batch electrochemistry were obtained using home-made flow electrochemical reactor (Table 2, Figure 1B). However, working under safer conditions and continous product formation using reactor is advantigous as compared to batch electrochemistry.

Table 2. Screening of the reactions in flow electrochemistry.

Entry	Solvent (0.05M)	Electrodes	Current (mA)	Rate ml min^{-1}	Yield %[a]
1	HFIP:DCM (1:1)	Pt ano | C cat	10	0.1	-[c]
2	HFIP:DCM (1:1)	Pt ano | C cat	25	0.05	70
3	HFIP:DCM (1:1)	Pt ano | C cat	30	0.05	65
4	HFIP:DCM (1:1)	Pt ano | C cat	30	0.1	78
5	HFIP:DCM (1:1)	C ano | Pt cat	30	0.1	15
6	HFIP:DCM (1:1)	Pt ano | C cat	33	0.1	67
7	HFIP:DCM (1:1)	Pt ano | C cat	35	0.1	58
8	HFIP:DCM (0.25:0.75)	Pt ano | C cat	30	0.1	74
9	HFIP:DCM (0.25:0.75)	Pt ano | Ni cat	30	0.1	73
10	HFIP:THF (0.25:0.75)	Pt ano | C cat	30	0.1	Traces[c]
11	HFIP:DCE (0.25:0.75)	Pt ano | C cat	30	0.1	-[b]
12	HFIP:DCE (0.25:0.75)	Pt ano | C cat	20	0.1	57
13	ACN	Pt ano | C cat	20	0.1	-[c]
14	ACN	Pt ano | C cat	30	0.1	-[c]

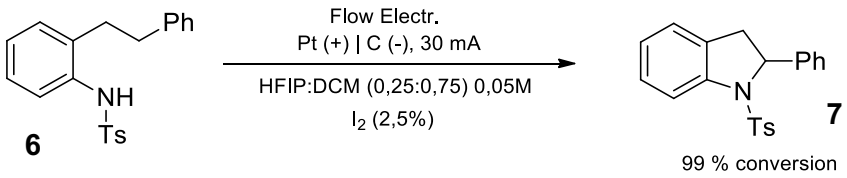
[a]Obtained by NMR conversion, using 2.5 % of I_2. [b]Decomposition of reagents. [c]Just starting material.



Scheme 3. Proposal mechanism of iodine-mediated electrocatalysis.

In the first stage, we propose the N-iodination **A** followed by the formation of the radical amidyl intermediate **B**. After the radical change of position **C** followed by the C-iodination **D**, as well as the substitution and elimination of HI, which is regenerated by the anode surface of the electrode **E**, regenerating the iodine and forming the desired product.

The flow electrochemical reaction was aslo performed with different substrate **6**, aiming to apply this methodology for amination to obtain annulation product **7** (scheme 4).



Scheme 4.

According to the 400 MHz NMR spectrum (**Figure 2**) of the crude, the formation of product **7** was observed with 99% conversion (Scheme 4). With this result it is possible to conclude that aromatic amines present better performance, being possible to use this methodology for the synthesis of indole and indoline derivatives.

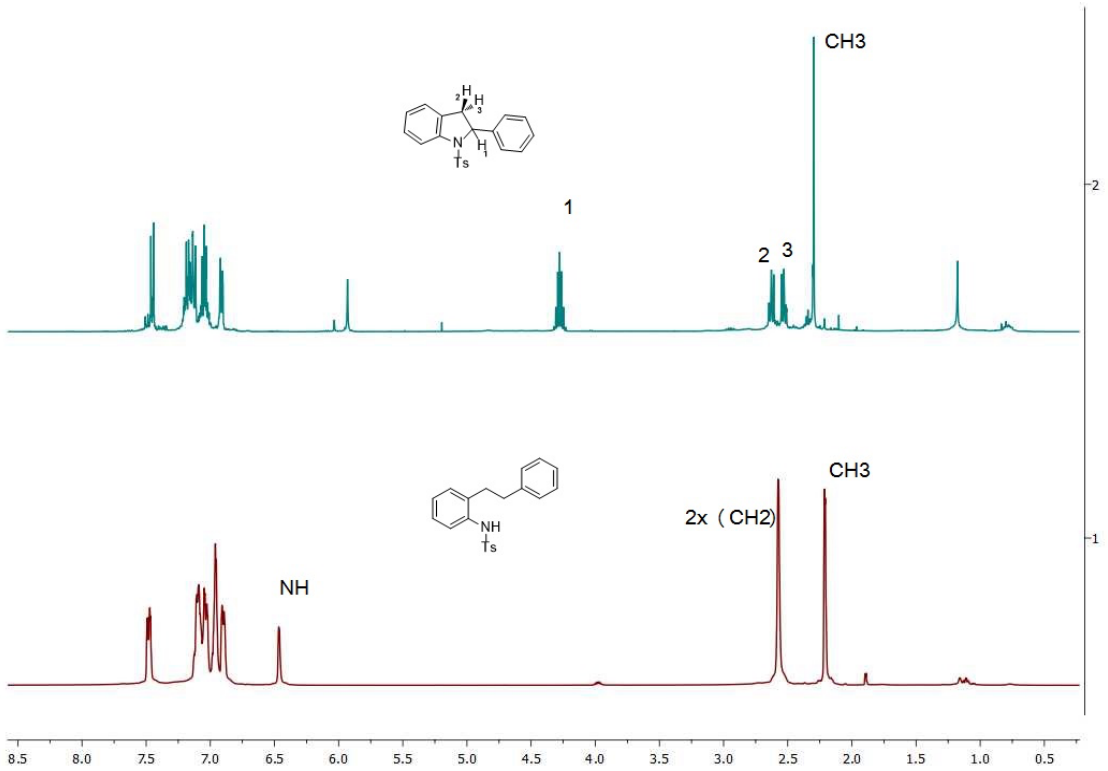


Figure 2.

CONCLUSION

Using an electrochemical reactor we demonstrated an economical route and with greater advantages using electrochemistry as an oxidizing medium. We present an electrochemical oxidative amination of saturated hydrocarbons catalyzed by iodine. The reaction demonstrates to be simple and clean in mild conditions, without the use of external oxidants or metals, being this the model electrochemical methodology that uses electrochemistry for the Hofmann-Löffler reaction. The methodology still presents several limitations, being necessary to carry out more test reactions to discover the scope of the best reactional condition. However, the use of electrochemistry for the synthesis of these compounds has been shown to be very efficient and this could be more promising in future using flow electrochemical microreactor.[11,19,20]

Acknowledgements

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Supporting Information

^{1}H spectra were obtained on Bruker DPX-300 and DPX-400 spectrometers, operating on the 300 MHz and 400 MHz frequencies, respectively. The chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS, used as an internal standard for ^{1}H NMR spectra). The number of hydrogens deduced from the relative integral and the coupling constant (*J*), expressed in Hertz (Hz), are given in parentheses.

*Synthesis of 2,2-dimethyl-4-phenylbutanenitrile **2**.*

A dry round bottom flask equipped with a stirrer bar is charged with the corresponding nitrile compound (1.0 equiv) and THF. LDA (2.6 mL, 2M, 1.0 equiv) is added drop wise at -78 ºC and the solution is stirred for 30 min. After that period, the corresponding bromide (1.2 equiv) is added in a single portion and the mixture is stirred at room temperature for 12h. A saturated aqueous solution of NH_4Cl is added and the resulting mixture is extracted with CH_2Cl_2 (3x). The organic layer is dried over $MgSO_4$ and the solvent is evaporated under reduced pressure. The crude product is purified by chromatography (silica gel, n-hexane/ethyl acetate) 98% Yield isolated, incolor oil.

*Synthesis of 2,2-dimethyl-4-phenylbutan-1-amine **3**.*

A dry round bottom flask equipped with a stirrer bar and a reflux condenser is charged with $LiAlH_4$ (3 equiv), Et_2O is added carefully and the mixture is cooled to 0 ºC with an external ice/water cooling bath. The crude nitrile (1 equiv) is dissolved in a small volume of Et_2O and added carefully to the $LiAlH_4$ suspension. The mixture is heated to reflux for 2h and cooled to 0 ºC afterwards. A solution of NaOH (10% in water) is added carefully until a white solid precipitates. After filtration the solvent is evaporated under reduced pressure. The crude product is purified by chromatography (silica gel, n-hexane/ethyl acetate) 92% Yield isolated, White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 – 7.27 (m, 2H), 7.21 – 7.19 (m, 3H), 2.60 – 2.52 (m,4H), 1.24 (s, 2H), 1,56 – 1,50 (m, 2H), 0.95 (d, *J* = 0.94 Hz, 6H).

*Synthesis of 2 N-(2,2-dimethyl-4-phenylbutyl)-4-methylbenzenesulfonamide **4**.*

The amine (1 equiv) is dissolved in pyridine and the respective sulfonyl chloride (1.5 equiv) is added at 0 ºC. The solution is stirred overnight at 25 ºC. CH_2Cl_2 is added, and the

mixture is washed three times with a hydrochloride solution (10% HCl in water). The organic layer is dried over $MgSO_4$ and the solvent is evaporated under reduced pressure. The crude product is purified by chromatography (silica gel, n-hexane/ethyl acetate) 94% Yield isolated, White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.30 - 7.20 (m, 2H), 7.21-7.18 (m, 1H), 7.17-7.14 (m, 2H), 4.71 (s, 1H), 2.76 (d, *J* = 6.9 Hz, 2H), 2.54 - 2.49 (m, 2H), 2.44 (s, 3H), 1.54 - 1.50 (m, 2H), 0.95 (s, 6H). Exact Mass (calc.): 331.1606, TLC Mass (found): 332.2 $(M+H)^+$, 155.0 (100).

4,4-dimethyl-2-phenyl-1-tosylpyrrolidine ***5***.

The flow product was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1, v/v) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.26 (m, 4H), 7.26 – 7.18 (m, 3H), 4.72 (dd, *J* = 9.4, 7.3 Hz, 1H), 3.45 (dd, *J* = 10.4, 1.5 Hz, 1H), 3.35 (d, *J* = 10.4 Hz, 1H), 2.40 (s, 3H), 2.03 (ddd, *J* = 12.8, 7.3, 1.5 Hz, 1H), 1.73 (dd, *J* = 12.8, 9.4 Hz, 1H), 1.06 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.1, 143.0, 135.9, 129.4, 128.3, 127.4, 127.1, 126.6, 63.9, 62.0, 51.6, 38.2, 26.2, 25.8, 21.6. Exact Mass (calc.): 329.1449, TLC Mass (found): 330.2$(M+H)^+$, 184.0 (100).