SCIENTIFIC LETTER N°11

Edito

Cette année, AtlanChim Pharma fête ses 14 ans d'existence. 14 belles années durant lesquelles nous vous avons accompagné sur des projets divers et variés où nous avons pu vous apporter notre expertise en synthèse chimique à façon et en marquage à froid.

Cherchant continuellement à répondre à vos nouvelles problématiques, nous avons récemment développé un savoir-faire dans la synthèse dite « Food Grade ». Nous avons ainsi poussé la traçabilité mise en place chez AtlanChim Pharma tout en maîtrisant l'environnement de travail au laboratoire ainsi que les réactifs et solvants utilisés. Ce référentiel (HACCP) correspond à un cahier des charges très spécifique des fabricants et fournisseurs de produits alimentaires qu'il convient de respecter pour toute utilisation (en rapport avec la chaîne alimentaire) à des fins olfactives et gustatives.

Dans le cadre de notre veille scientifique, le Professeur **Jacques LEBRETON** vous propose un article dédié au cycle pyrrole, au travers des différentes avancées synthétiques développées ces dernières années.

L'équipe d'AtlanChim Pharma grandissant, nous vous invitons à lire à la suite de cet article le portrait de Flavie JANVIER, technicienne chimiste, qui a rejoint récemment notre équipe.

Nous vous souhaitons une agréable lecture et à très bientôt pour de nouvelles demandes de synthèse !

Editorial

AtlanChim Pharma turns 14 this year. 14 beautiful years during which we collaborated together on various projects where we bring our expertise on chemical synthesis and stable isotope labeling.

In order to answer your future challenges, we have recently developed a Know-how in the so-called « Food Grade » synthesis. Therefore, we have increased AtlanChim Pharma's traceability while we are controlling our lab environment as well as reagents and solvents used. Hazard Analysis and Critical Control Point (HACCP) is an internationally recognized system for Food Industry that required that potential hazards are identified and controlled as specific points as our compounds will be used for olfactory and taste purposes.

As part of our scientific monitoring work, Professor **Jacques LEBRETON** would like to share with you an article dealing with pyrrole skeleton construction mainly from work in organic chemistry developped in the last few years.

Strengthening our chemistry team, we are pleased tointroduce you to Flavie JANVIER, chemistry technician, who joined our team recently.

Have a good reading and do not hesitate to contact us for any synthesis request !

What's new in pyrrole skeleton construction?

Jacques Lebreton
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Pyridines[1] and pyrroles are important nitrogen-containing heterocycles found in crucial compounds in the chemistry of living organisms. Pyrrole forms the nucleus of widely various bioactive natural products[2], such as chlorophyll or marinopyrrole A[3], an interesting biological active compound isolated from marine sources, as shown in **Figure 1**. Pyrrole skeleton is also present in many important drugs (see in **Figure 1**)[4]. Furthermore, pyrroles have found large applications in organic synthesis as key building blocks, in particular in the preparation of more complex heterocyclic compounds, as well as in materials science[5] and supramolecular[6] chemistry. In this regard, new routes to build polysubstituted pyrrole frameworks are still a challenging task of current interest to provide efficient access to various diversified building blocks from readily available starting materials.[7]

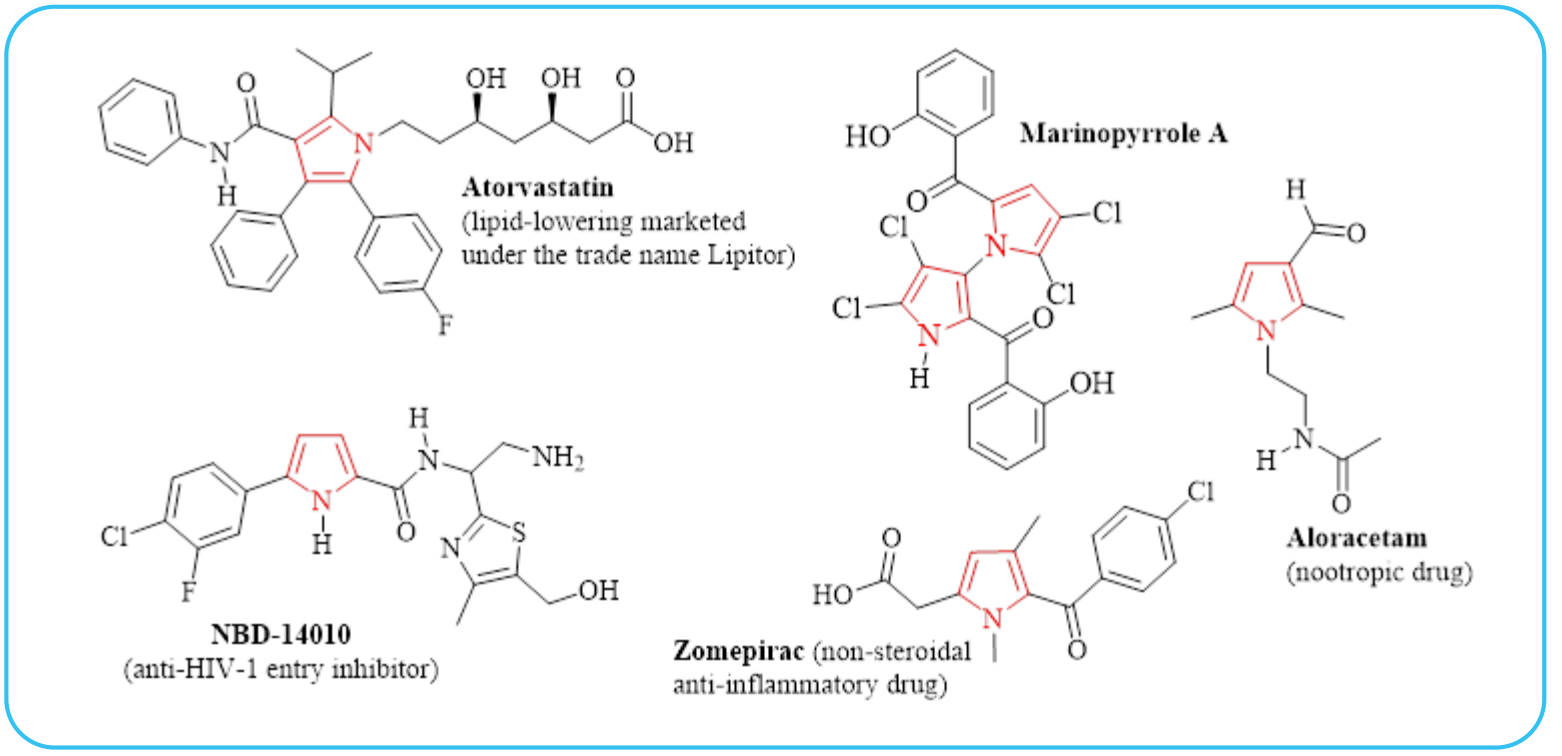


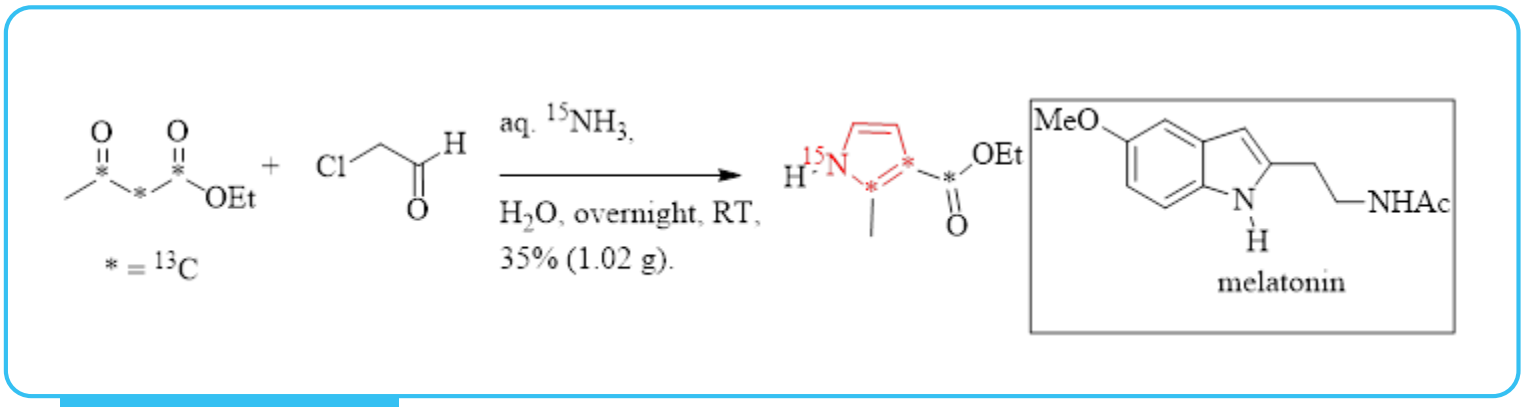
Figure 1 Some presentative pyrrole natural products and bioactive compounds.

[1] J. Lebreton. Synthesis of pyridine derivatives through recent examples of pharmaceuticals. *AtlanChim Pharma Scientific Letter* (http://www.atlanchimpharma.com/our-scientific-letters/) 10, Nov. **2016**.
[2] I. S. Young, P. D. Thornton, A. Thompson, *Nat. Prod. Rep*. **2010**, *27*, 1801-1839, and cited literature.
[3] P. Gomez-Bougie, C. Dousset, G. Descamps, A. Schnitzler, L. Audiger, A. Tessier, D. Dubreuil, J. Lebreton, C. Pellat-Deceunynck, M. Amiot, *Br. J. Haematol*. **2018**, *180*, 157-159.
[4] For an excellent reviews on this field, see: (a) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman, P. Sharma, *RSC Adv.* **2015**, *5*, 15233-15266. (b) S. S. Gholap, *Eur. J. Med. Chem*. **2016**, *110*, 13-31.
[5] H. Maeda, Y. Bando, *Chem. Commun.* **2013**, *49*, 4100-4113.
[6] P. Ballester, *Isr. J. Chem*. **2011**, *51*, 710-724.
[7] For recent reviews on the synthesis of pyrroles, see: (a) V. Estévez, M. Villacampa, J. C. Menéndez, *Chem. Soc. Rev*. **2010**, *39*, 4402-4421. (b) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev*. **2013**, *113*, 3084-3213. (c) V. Estévez, M. Villacampa, J. C. Menéndez, *Chem. Soc. Rev*. **2014**, *43*, 4633-4657.

The aim of this letter is to present the most significant recent contributions in this field. It is organized according to the various synthetic methods including cycloaddition reactions, multicomponent condensation reactions, and metal-catalyzed reactions used to construct the pyrrole core.

The Knorr[8], the Hantzsch[9] and the Paal-Knorr[10] reactions are one of the oldest and still popular methods for the preparation of polysubstituted pyrroles. However, these classical methodologies have significant limitations, such as tedious preparation of the correctly substituted precursors prior to cyclization.

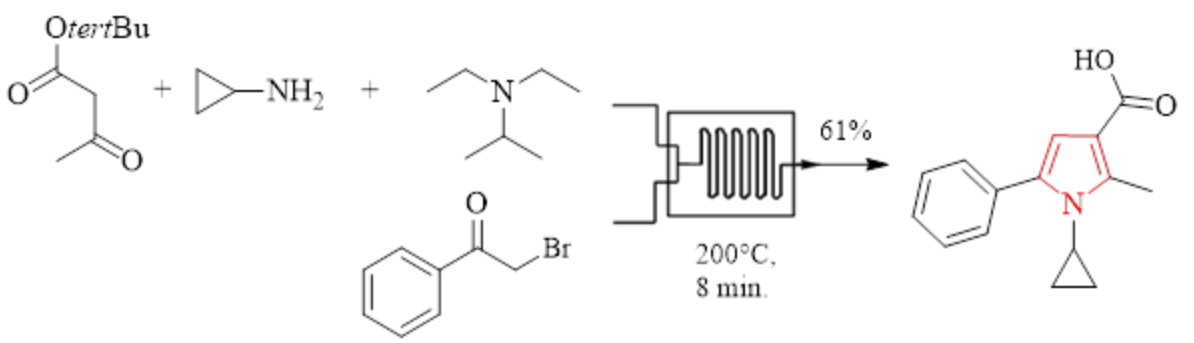
The **Hantzsch pyrrole synthesis** is the condensation of α-haloketones with 1,3- dicarbonyl compounds in the presence of ammonia. This multicomponent pyrrole synthesis has been used with success by Skaddan[11] to efficiently prepare from inexpensive readily available labeled precursors, the $^{13}C_4$,^{15}N-Ethyl 2-methyl-1H-pyrrole-3-carboxylate, a key intermediate to study melatonin metabolism, as reported in **Scheme 1**.



SCHEME 1

[8] L. Knorr, *Chem. Ber.* **1884**, *17*, 1635-1642.
[9] A. Hantzsch, *Ber*. **1890**, *23*, 1474-1476.
[10] C. Paal, *Ber*. **1885**, *18*, 367-371.
[11] M. B. Skaddan, *J. Label Compd. Radiopharm* **2010**, *53*, 73-77.

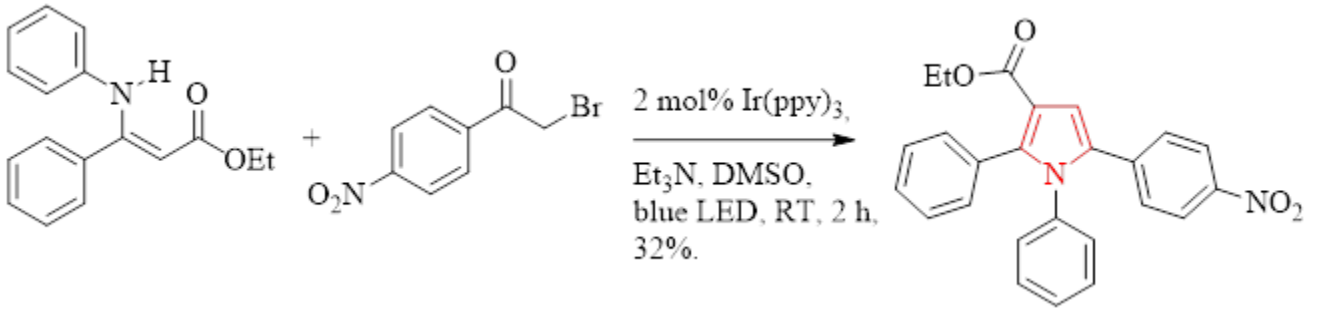
An efficient continuous flow procedure for the synthesis of pyrrole-3-carboxylic acid derivatives directly from *tert*-butyl acetoacetates, using various amines and α-bromoketones has been reported by Herath and Cosford.[12] In this elegant protocol, HBr formed during the Hantzsch reaction served to cleave the *tert*-butyl ester, *in situ* under continuous flow, to provide directly the corresponding acid as outlined in **Scheme 2**.



SCHEME 2

Mechanistic investigations have proposed that 1,3-dicarbonyl compounds reacted with ammonia or amines to provide presumably the corresponding β-enaminone as the first step in this reaction.[13] So, variant of this classical method has been reported using directly the condensation of α-haloketones with β-enaminones in various conditions.

For example, visible light initiated Hantzsch reaction by irradiation of a mixture of various enaminones and α-bromo ketones, with a catalytic amount of Ir(ppy)3 at λ = 450 nm and ambient temperature provided a broad range of 2,5-diaryl-substituted pyrroles as reported by Wu and Coll.[14] This photocatalytic methodology is illustrated in **Scheme 3**.

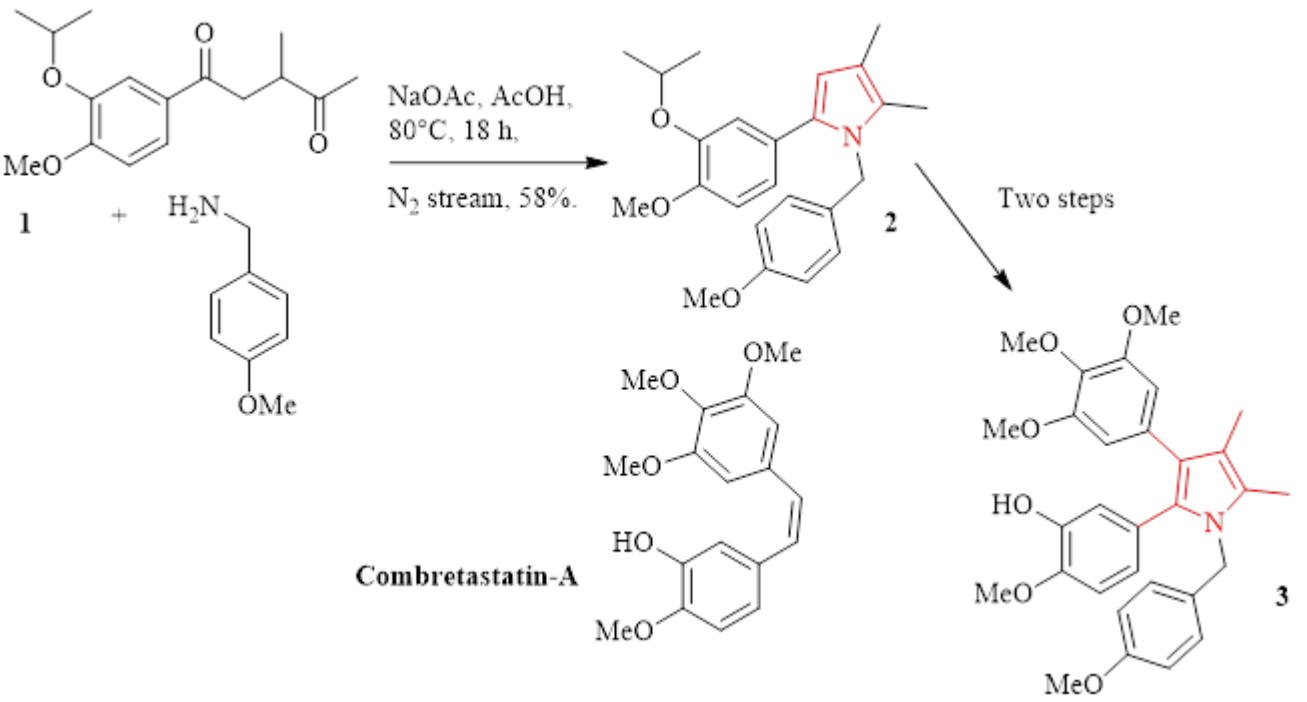


SCHEME 3

[12] A. Herath, N. D. P. Cosford, *Org. Lett.* **2010**, *12*, 5182-5185.
[13] M. W. Roomi, S. F. MacDonald, *Can. J. Chem*. **1970**, *48*, 1689.
[14] T. Lei, W.-Q. Liu, J. Li, M.-Y. Huang, B. Yang, Q.-Y. Meng, B. Chen, C.-H. Tung, L.-Z. Wu, *Org. Lett.* **2016**, *18*, 2479-2482.

The **Paal-Knorr pyrrole synthesis** is the condensation of a 1,4-dicarbonyl compound with an excess of a primary amine or ammonia to provide the corresponding substituted pyrrole.

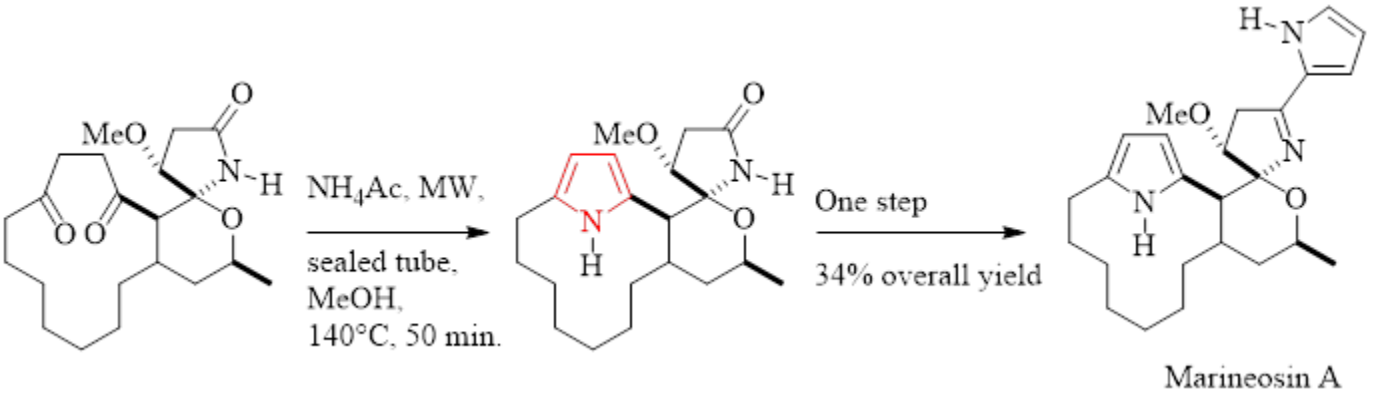
A set of 2,3-diaryl-1*H*-pyrrole derivatives structurally similar to Combretastatin A-4, a potent antimitotic natural product isolated from the bark of the South African bush willow *Combretum caffrum*, has been synthetized and evaluated.[15] As reported in **Scheme 4**, Paal-Knorr condensation of diketone **1** with 4-methoxybenzylamine provided in correct yield the desired adduct **2** which was then engaged in the next two steps to provide the targeted Combretastatin A-4 analogue **3**. This latter compound **3** exhibited the most potent activity, against MDA-MB-231, a highly aggressive, invasive and poorly differentiated triple-negative breast cancer cell line, and was only twice less active than Combretastatin A-4. This work demonstrated that the replacement of a (*Z*) double bond by a pyrrole moiety led to a novel generation of Combretastatin A-4 analogues.



SCHEME 4

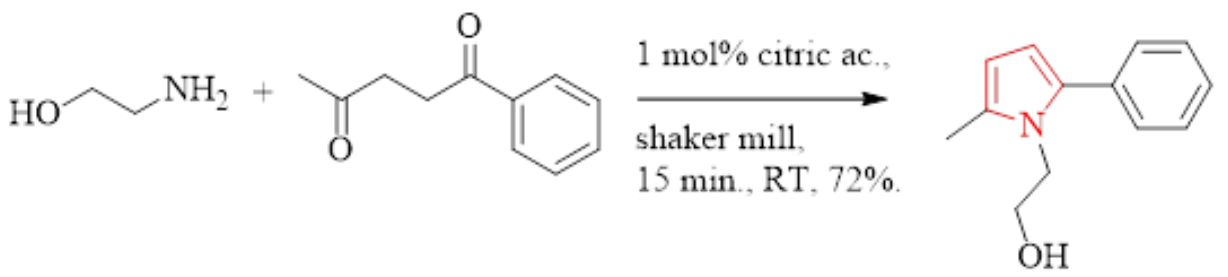
[15] E.-K. Jung, E. Leung, D. Barker, *Bioorg. Med. Chem. Lett*. **2016**, *26*, 3001-3005.

A total synthesis of the proposed structure for Marineosin A isolated from a marine sediment-derived actinomycete, having an unique skeleton with a *trans*-fused macrocyclic ring, a spiro tetrahydropyran-dihydropyrrole iminal moiety, and two pyrroles, has been recently reported by Shi and Coll. (see **Scheme 5**).[16] Marineosin A displays significant inhibition against human colon carcinoma (HCT-116) cell growth. The formation of one of both pyrrole units was achieved from the requisite diketone using a microwave-assisted Paal-Knorr reaction in a sealed tube at 140°C in the presence of a large excess of ammonium acetate.



SCHEME 5

A solventless Paal-Knorr pyrrole synthesis using mechanochemical activation and citric acid as biosourced catalyst has been reported by Rousseau and Coll. (see **Scheme 6**).[17] Under these mild reaction conditions more than 40 1,2,5-trisubstituted pyrrole derivatives have been obtained.

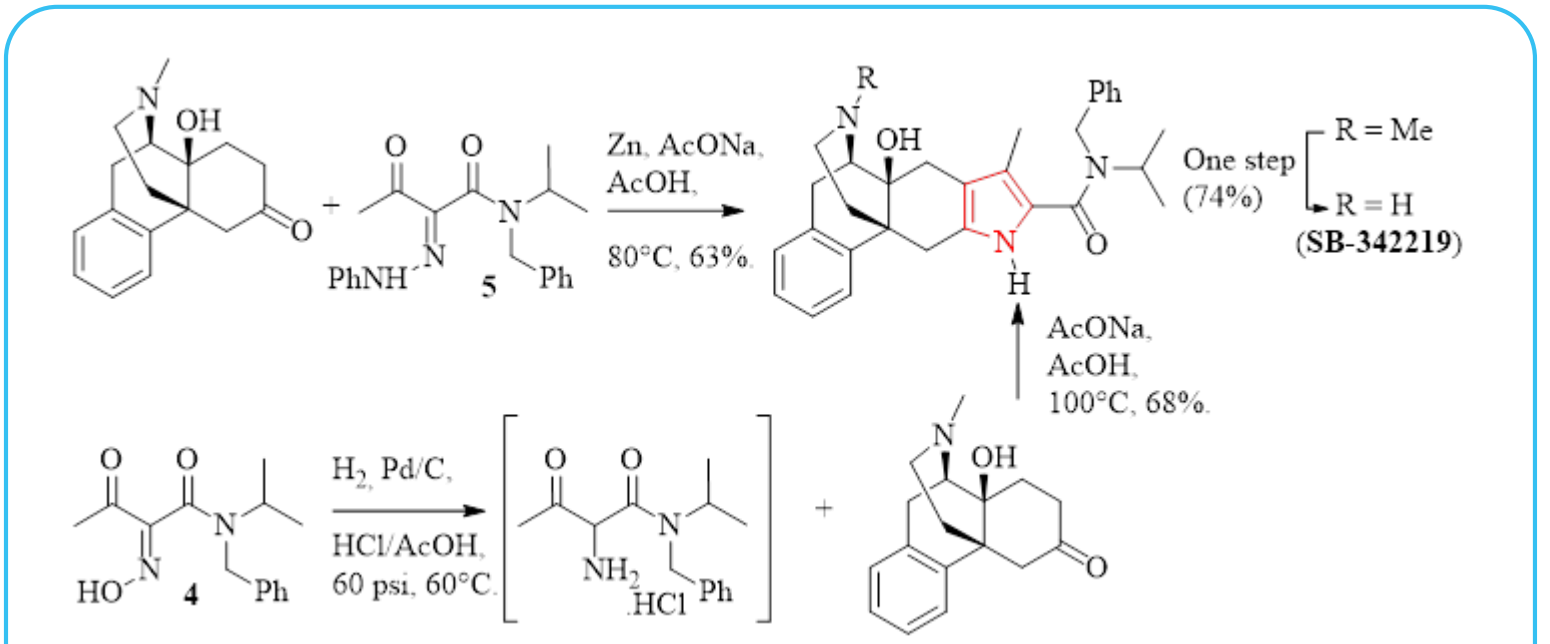


SCHEME 6

[16] B. Xu, G. Li, J. Li, Y. Shi, *Org. Lett.* **2016**, *18*, 2028-2031.
[17] L. Akelis, J. Rousseau, R. Juskenas, J. Dodonova, C. Rousseau, S. Menuel, D. Prevost, S. Tumkevičius, E. Monflier, F. Hapiot, *Eur. J. Org. Chem*. **2016**, 31-35.

The reaction between an α-amino ketone and a second carbonyl partner containing a reactive α-methylene group is known as **Knorr pyrrole synthesis**. In this highly regioselective reaction, the α-amino ketone is generally formed *in situ* by reduction of the corresponding oxime.

During the optimization study of large-scale synthesis of **SB-342219** a selective d-opioid receptor agonist, a Knorr pyrrole reaction was investigated to construct the heterocyclic core. In this work, the authors found that the hydrogenation of the oxime α-amino ketone **4** was more efficient compared to zinc reduction of the corresponding phenylhydrazone **5** as outlined in **Scheme 7**.[18] The use of finely divided zinc powder, to reduce the phenylhydrazone **5**, was problematic for scale-up as it required portion wise addition to the hot and flammable solvent to maintain a low concentration of the intermediate α-aminoketone. Furthermore, zinc reduction of phenylhydrazone **5** led to the formation of aniline which greatly complicated the purification process.



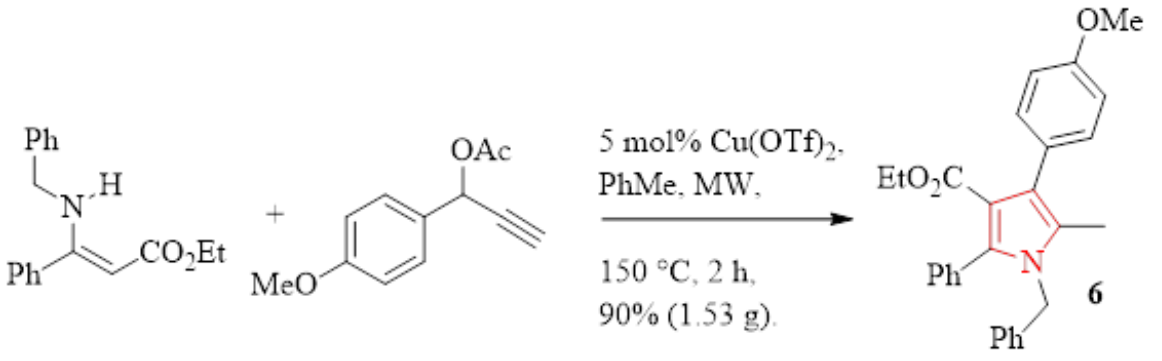
SCHEME 7

Since the pioneering works of Hantzsch, Paal and Knorr, various strategies for the construction of pyrrole skeleton have been explored, developed and reported in the literature. In this regard, metal-catalyzed reactions from a broad range of starting materials have attracted much attention.

[18] R. K. Bellingham, J. S. Carey, N. Hussain, D. O. Morgan, P. Oxley, L. C. Powling, *Org. Process Res. Dev.* **2004**, *8*, 279-282.

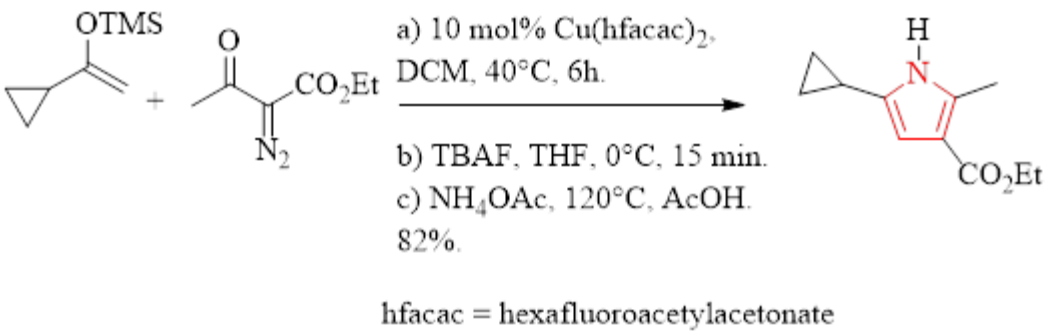
Metal-catalyzed synthesis of pyrroles

Cui, Zhang and Coll. developed a one-step tandem Cu(II)-catalyzed propargylation/alkyne azacyclization/isomerization sequence under microwave irradiation from readily available starting materials to provide efficiently fully substituted pyrroles.[19] This methodology (27 examples 0.2 mmol scale, 40-90%) is outlined in **Scheme 8** through the gram-scale preparation of the pentasubstituted pyrrole **6**. A reaction mechanism has also been proposed for this copper-catalyzed process.



SCHEME 8

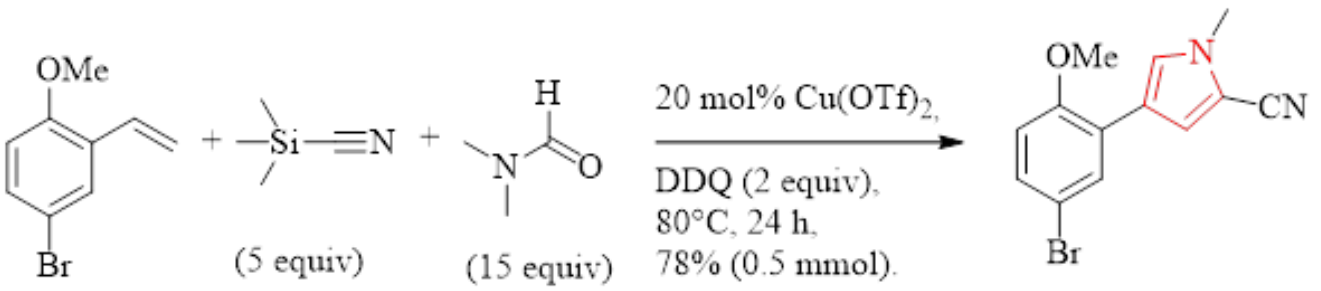
A Cu(II)-catalyzed cyclization reaction between silyl enol ethers, derived from methyl ketones, with α-diazo-β-ketoesters provided the 1,4-diketone surrogates which were subsequently treated with TBAF followed by ammonium acetate in acetic acid under reflux to give 2,3,5-trisubstituted pyrroles in good yields (6 examples 0.2 mmole scale, 42-92%) (see **Scheme 9**).[20] This methodology originally devoted to furan preparation, was extended with success to thiophenes using Lawesson's reagent instead of ammonium acetate, an example is presented in pyrroles series.



SCHEME 9

[19] X.-Y. Zhang, Z.-W. Yang, Z. Chen, J. Wang, D.-L. Yang, Z. Shen, L.-L. Hu, J.-W. Xie, J. Zhang, H.-L. Cui, *J. Org. Chem.* **2016**, *81*, 1778-1785.
[20] W. Tan, N. Yoshikai, *J. Org. Chem.* **2016**, *81*, 5566-5573.

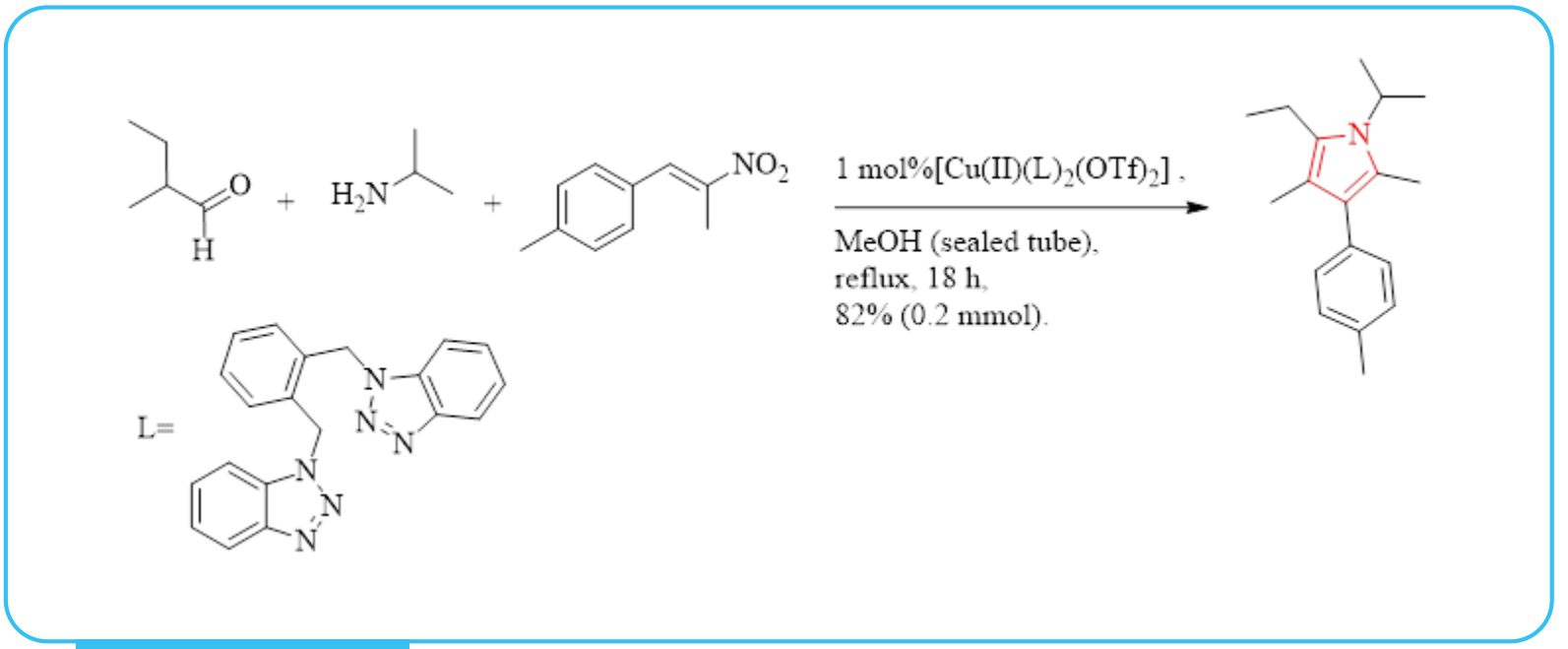
Wang and Coll. reported an original access to 2-cyanopyrrole derivatives by Cu(II)-catalyzed dicyanation of *N*,*N*-substituted formamides in the presence of an excess of TMSCN to provide the corresponding azomethine ylides, by elimination of HCN, which subsequently reacted following a regioselective [3+2] cycloaddition with alkene partners.[21] Then, the latter cycloadducts formed *in situ* was submitted to a first DDQ dehydrogenation leading to the corresponding dihydropyrroles which was then subjected to a second DDQ dehydrogenation to provide the desired 2-cyanopyrrole derivatives. As pointed out by the authors, the addition of DDQ is crucial, also as described in the general experimental procedure, the first equivalent of DDQ was introduced through a batchwise mode (0.2 equiv/2 h for 5 times) and, the second equivalent was added all at once. This Cu(II)-catalyzed tandem three-component reaction (29 examples 0.5 mmol scale, ~40-90%) is presented in **Scheme 10**.



SCHEME 10

[21] X.-Q. Mou, Z.-L. Xu, L. Xu, S.-H. Wang, B.-H. Zhang, D. Zhang, J. Wang, W.-T. Liu, W. Bao, *Org. Lett*. **2016**, *18*, 4032-4035.

Very recently, Kostakis, Lykakis and Coll. reported a new and elegant Cu(II)-catalyzed regioselective synthesis of polysubstituted pyrroles from aldehydes, amines, and β-nitroalkenes as outlined in **Scheme 11**.[22] This full study (around 40 examples) open a new avenue to a wide range of tri-, tetra-, or pentasubstituted pyrroles under catalytic conditions with low catalyst loading (0.3-1 mol%). One of the most intriguing part of this nice work is the reactivity of the α-aryl - or α-alkyl-substituted aliphatic aldehydes which proceeded with a 1,2-aryl/alkyl migration.

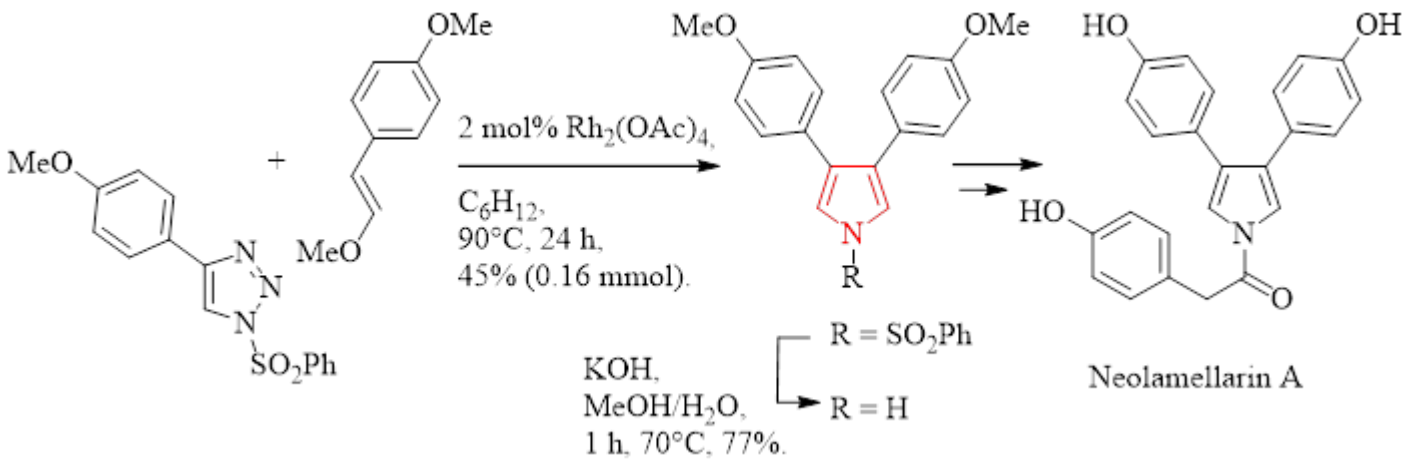


SCHEME 11

Preliminary mechanistic studies pointed out the plausible formation of a nitrogen radical intermediate which by addition to the β-nitroalkene led to the pyrrole ring formation.

Various 1,3-disubstituted pyrroles (35 examples 0.17 mmol scale, 42-92%) have been obtained with high regioselectivity from 1,2,3-triazoles and substituted enol ethers under Rh(II)-catalyzed transannulation conditions.[23] In particular with *N*-Sulfonyl 1,2,3-triazoles, the corresponding pyrrole intermediates were treated with KOH in MeOH/THF to provide the desired polysubstituted pyrroles, as exemplified in **Scheme 12** through the formal synthesis of Neolamellarin A (inhibitor of hypoxiainducible factor-1 isolated from the sponge *Dendrilla nigra*).

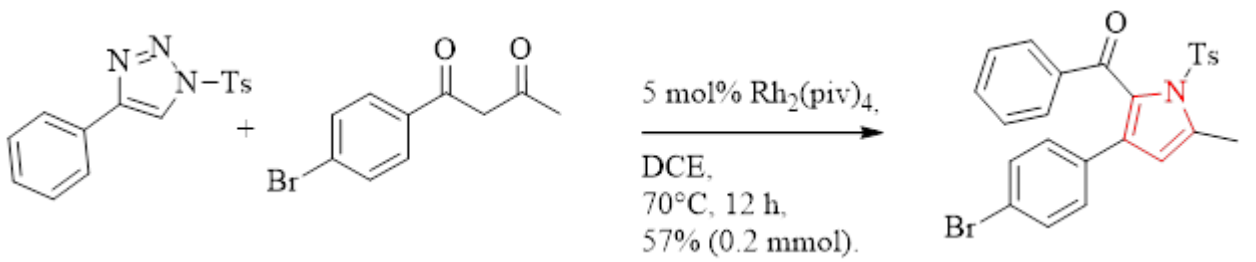
[22] D. Andreou, M. G. Kallitsakis, E. Loukopoulos, C. Gabriel, G. E. Kostakis, I. N. Lykakis, *J. Org. Chem*. **2018**, *83*, 2104-2113.
[23] S. Rajasekar, P. Anbarasan, *J. Org. Chem.* **2014**, *79*, 8428-8434.



SCHEME 12

The use of cyclic enol ethers was also investigated with success and 5 polycyclic 2,3,5 tri-substituted pyrroles have been obtained in good yields. Also, a plausible mechanism for this Rh(II)-catalyzed transannulation is discussed involving the formation of a reactive rhodium(II) carbenoid species.

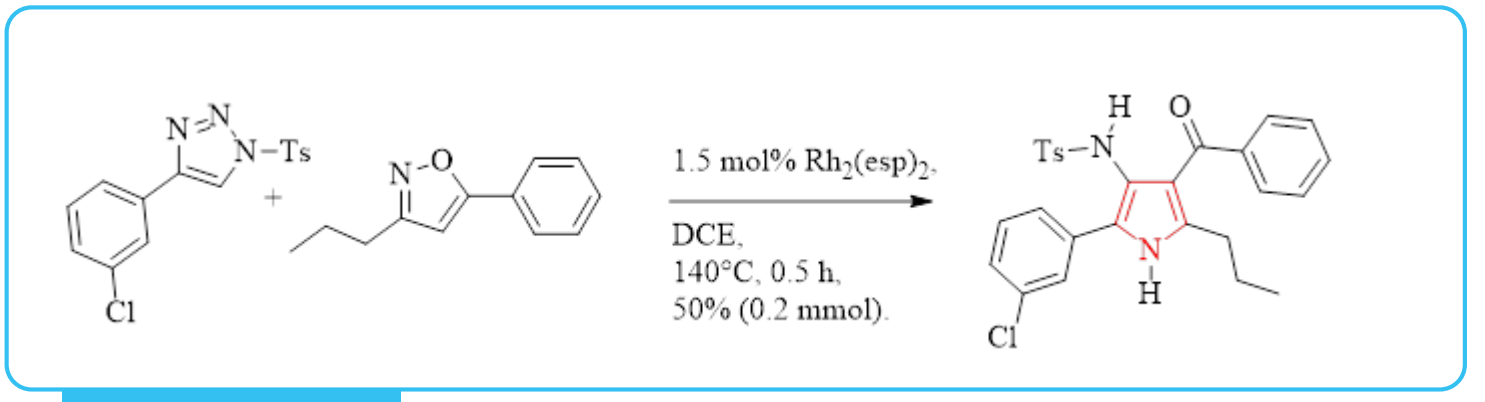
In a close context, Li, Xu and Coll. used a set of β-diketones which reacted under their enol forms, as the previous enol ethers, to provide in an efficient manner multisubstituted 2-carbonylpyrroles (20 examples 0.2 mmol scale, 50-92%) (see **Scheme 13**).[24]



SCHEME 13

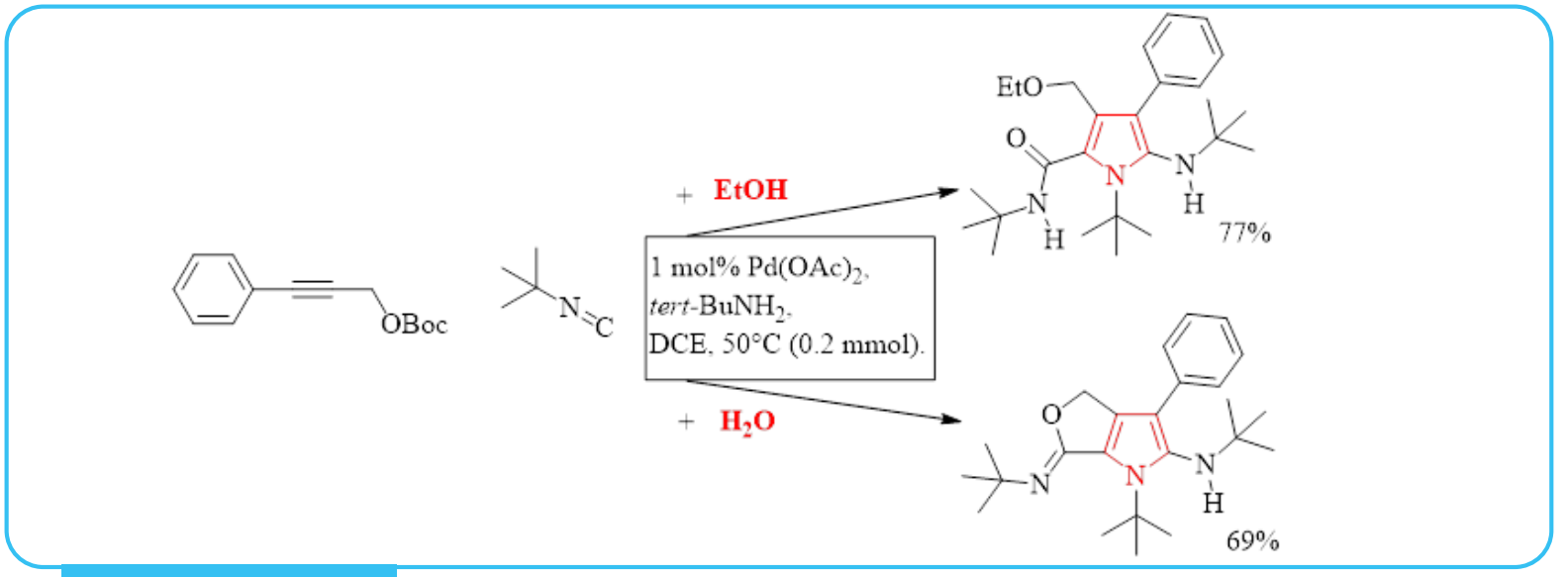
[24] W. Cheng, Y. Tang, Z.-F. Xu, C.-Y. Li, *Org. Lett.* **2016**, *18*, 6168-6171.

In a novel Rh(II)-catalyzed formal [3+2] cycloaddition with isoxazoles, He, Tang and Coll. have shown that *N*-Sulfonyl 1,2,3-triazoles could serve as precursors of polysubstituted 3-aminopyrroles.[25] In this one-pot sequence, *N*-Sulfonyl 1,2,3-triazoles, prepared from various electron-rich or -poor (hetero)aromatic terminal alkynes and tosyl azide, reacted with isoxazoles in the presence of catalytic amounts of $Rh_2(esp)_2$ which was found as the most efficient Rh(II) source. This methodology (26 examples 0.2 mmol scale, 35-87%) is outlined in **Scheme 14**. A mechanism of this Rh(II)-catalyzed formal [3+2] cycloaddition involving a Rh(II)-azavinylcarbene is also proposed.



SCHEME 14

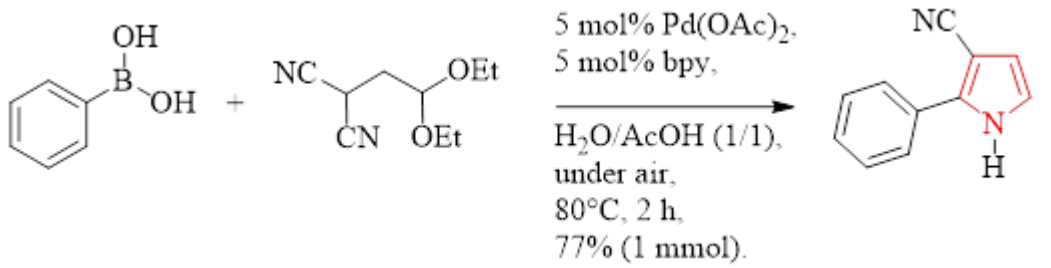
A Pd-catalyzed multicomponent synthesis of 2-aminopyrroles starting from propargyl carbonates, isocyanides and alcohols was recently published by Zhu and Coll.[26] Interestingly, this three-component reaction using water instead of alcohols, as nucleophile, provided the bicyclic analogues. The flexibility of this methodology (35 examples 0.2 mmol scale, 42-77%) is highlighted in **Scheme 15**. A possible reaction pathway involving from the propargyl carbonate, the formation of (σ-allenyl)Pd(II) species with concomitant release of CO_2 is discussed.



SCHEME 15

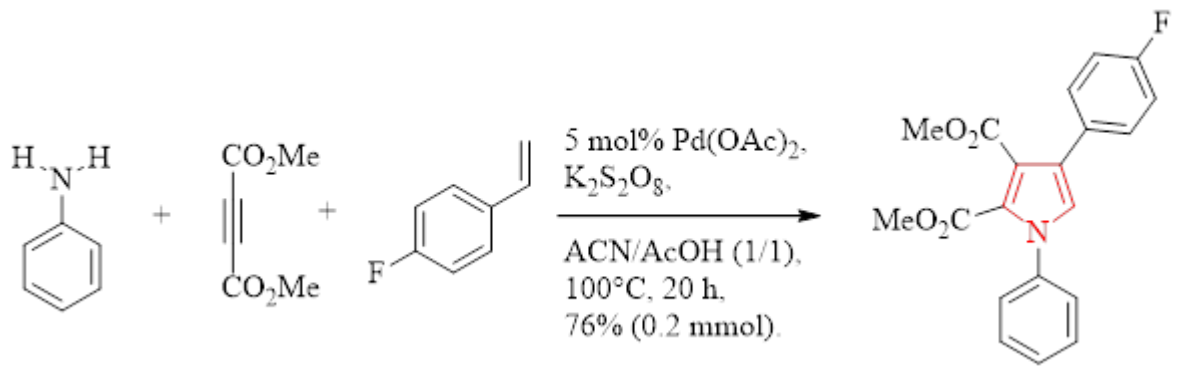
[25] X. Lei, L. Li, Y.-P. He, Y. Tang, *Org. Lett*. **2015**, *17*, 5224-5227.
[26] G. Qiu, Q. Wang, J. Zhu, *Org. Lett*. **2017**, *19*, 270-273.

An original access to various 3-substituted 2-aryl-1*H*-pyrroles has been reported by Yousuf and Adhikari using a Pd(II)-catalyzed C−C coupling reactions between substituted aliphatic nitriles and arylboronic acids followed by *in situ* cyclodehydration in aqueous acetic acid.[27] An example of this one-pot reaction protocol is described in **Scheme 16** (20 examples 1.0 mmol scale, 51-84%) starting with malononitrile to provide the corresponding 3-cyano substituted 2-arylpyrrole. It should be pointed out that under the same reaction conditions with ethyl cyanoacetate moiety, instead of malononitrile moiety, the 3-carbethoxy substituted 2-arylpyrrole was isolated in 81% yield. This one-pot synthesis of 3-substituted 2-arylpyrrole in aqueous media *via* a domino addition-annulation process is supported by a mechanistic study.



SCHEME 16

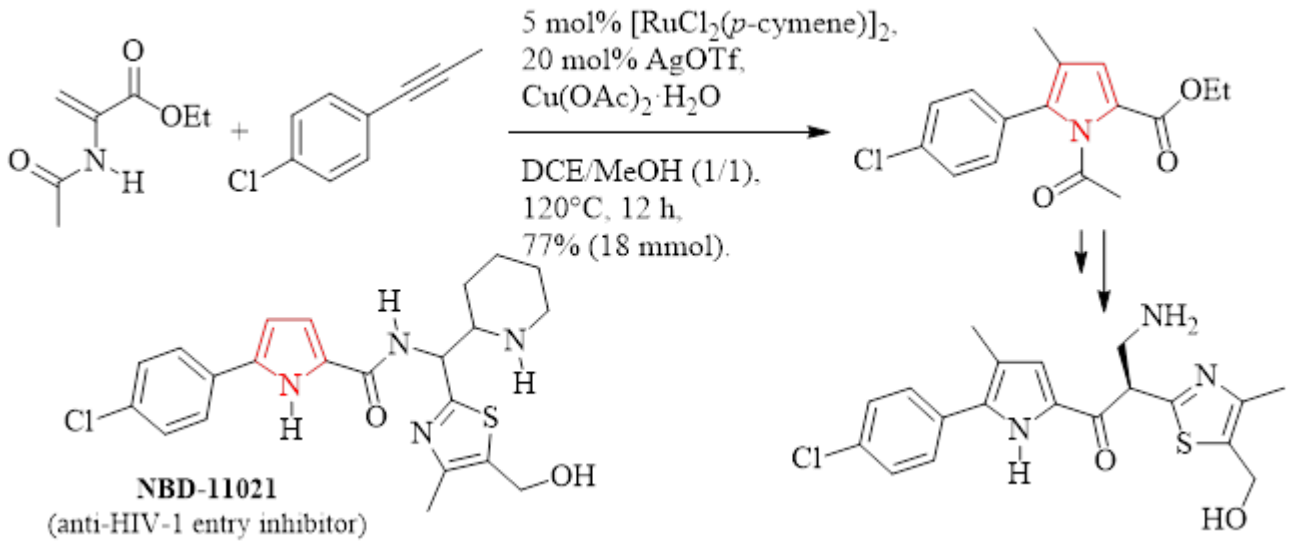
Yi and Coll. published an efficient oxidative three-component cascade reactions of amines, alkyne esters, and styrenes under Pd(II)-catalyzed conditions to provide wide variety of 2,3,4-trisubstituted pyrroles (44 examples 1.0 mmol scale, 63-95%) as outlined in **Scheme 17**.[28] A catalytic cycle involving a cascade formation of $C(sp_2)$-$C(sp_2)$ and $C(sp_2)$-N bonds *via* Pd(II)-catalyzed regioselective alkene migratory insertion, intramolecular radical addition, and oxidation sequential processes has been proposed by the authors. It was also pointed out that $K_2S_2O_8$ played a key role as oxidant and radical-generating reagent.



SCHEME 17

[27] M. Yousuf, S. Adhikari, *Org. Lett*. **2017**, *19*, 2214-2217.
[28] X. Zhang, X. Xu, G. Chen, W. Yi, *Org. Lett*. **2016**, *18*, 4864-4867.

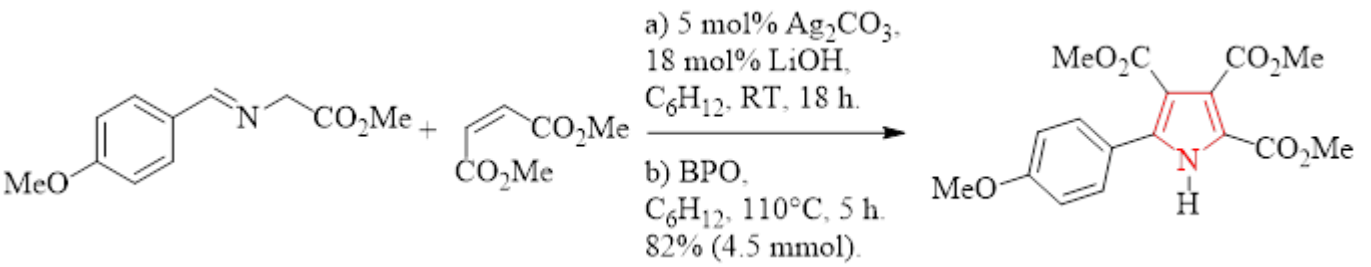
A regioselective Ru(II)-catalyzed oxidative annulation of enamides with alkynes to prepare substituted pyrroles *via* the cleavage of C(sp_2)-H/N-H bonds, previously reported by Li, Wang and Coll.,[29] has been recently used with success[30] to optimize the lead HIV-1 entry antagonist, **NBD-11021**. The required pyrrole core was efficiently prepared as presented in **Scheme 18**, on multigram scale (18 mmol) with the less-expensive and readily available ruthenium complex [{$RuCl_2$(*p*-cymene)}$_2$] as the catalyst and $Cu(OAc)_2$ as the oxidant to generate active Ru(II) species from Ru(0) in the catalytic cycle.



SCHEME 18

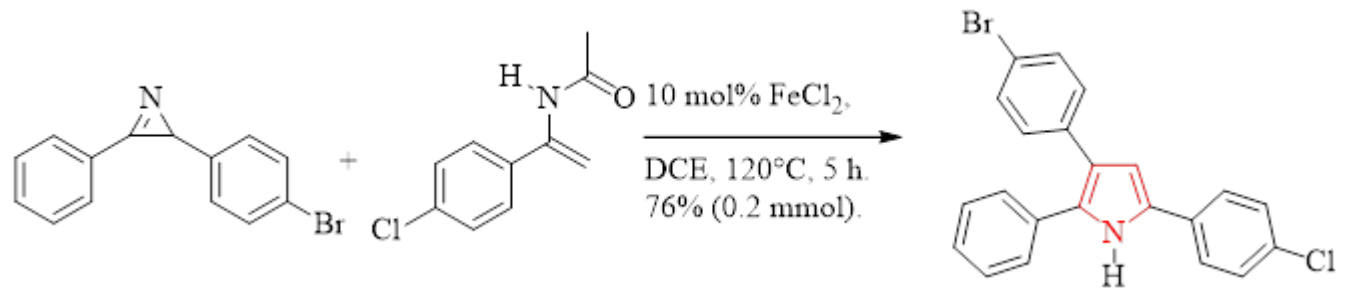
For the synthesis of heterocycles, inexpensive silver has proven to be an efficient catalyst, under ligand-free conditions. In this way, a synthesis of polysubstituted pyrroles based on a one-pot Ag-catalyzed 1,3-dipolar cycloaddition of imines with alkenes bearing various electron-withdrawing groups has been developed by Hu, Wang and Coll.[31] The formation of the pyrrole core involved a new benzoyl peroxide (BPO)-mediated oxidative dehydrogenative aromatization process. The broad substrate scope of this methodology has been studied, as well as the mechanism of the second step from which the pyrrolidine intermediate involved a hydrogen-atom transfer reaction initiated by thermal decomposition of BPO. One example of this methodology (25 examples 10.0 or 0.3 mmol scale, 40-89%) is presented in **Scheme 19**.

[29] B. Li, N. Wang, Y. Liang, S. Xu, B. Wang, *Org. Lett*. **2013**, *15*, 136-139.
[30] F. Curreli, Y. D. Kwon, D. Belov, R. R. Ramesh, A. Kurkin, A. Altieri, P. Kwong, A. K. Debnath, *J. Med. Chem*. **2017**, *60*, 3124-3153.
[31] Y. Liu, H. Hu, X. Wang, S. Zhi, Y. Kan, C. Wang, *J. Org. Chem*. **2017**, *82*, 4194-4202.



SCHEME 19

A preparation of triaryl-substituted pyrroles (see **Scheme 20**) using a new Fe(II)-catalyzed radical ring opening of mainly 2,3-diphenyl-2*H*-azirine followed by sequential cycloaddition with α-aryl-*N*-acyl enamides has been reported by Guan and Coll.[32] 2*H*-Azirines, readily accessible through the Neber reaction in two steps from the corresponding ketones, are excellent reagents for nitrene transfer[33] and they have been largely used as valuable three-atom building blocks[34] in preparation of various nitrogen-containing heterocycles.



SCHEME 20

Gold-catalyzed intermolecular reactions by electrophilic activation of π-systems such as alkynes with organic azides reacting by nitrene transfer have been largely used to prepare pyrroles from simple building blocks in an atom- and step-economic way.[35]

In this context, Huang and Coll. published a gold-catalyzed intermolecular nitrene transfer from 2*H*-azirines to ynamides leading to the formation of various substituted 2-aminopyrroles (see **Scheme 21**, 38 examples 0.3 mmol scale, 60-99%).[36]

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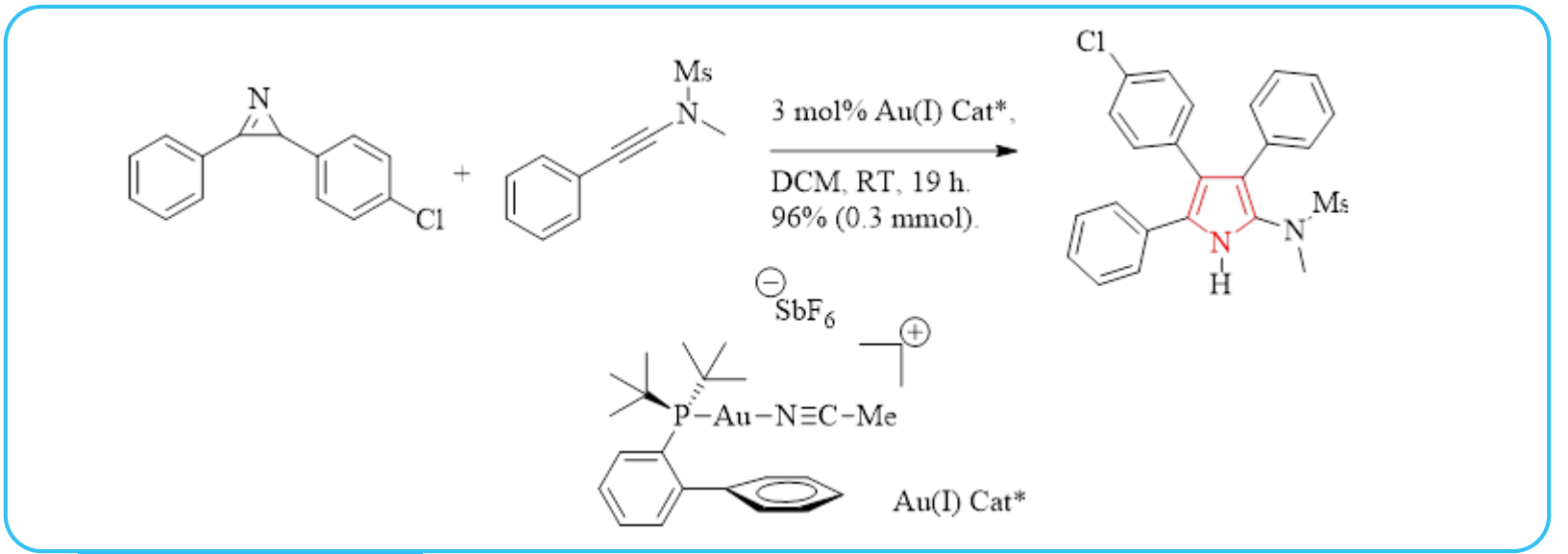
[32] M.-N. Zhao, Z.-H. Ren, D.-S. Yang, Z.-H. Guan, *Org. Lett*. **2018**, *20*, 1287-1290.

[33] For a recent review on this topic, see: C.-Y. Huang, A. G. Doyle, *Chem. Rev.*, **2014**, *114*, 8153-8198.

[34] For a recent example of pyrroles synthesis using Ru(II)-catalyzed [3+2] cycloaddition of 2H-azirines with alkynes, see: T. Li, H. Yan, X. Li, C. Wang, B. Wan, *J. Org. Chem*. **2016**, *81*, 12031-12037.

[35] For a recent review on this field, see: R. Dorel, A. M. Echavarren, *Chem. Rev*. **2015**, *115*, 9028-9072.

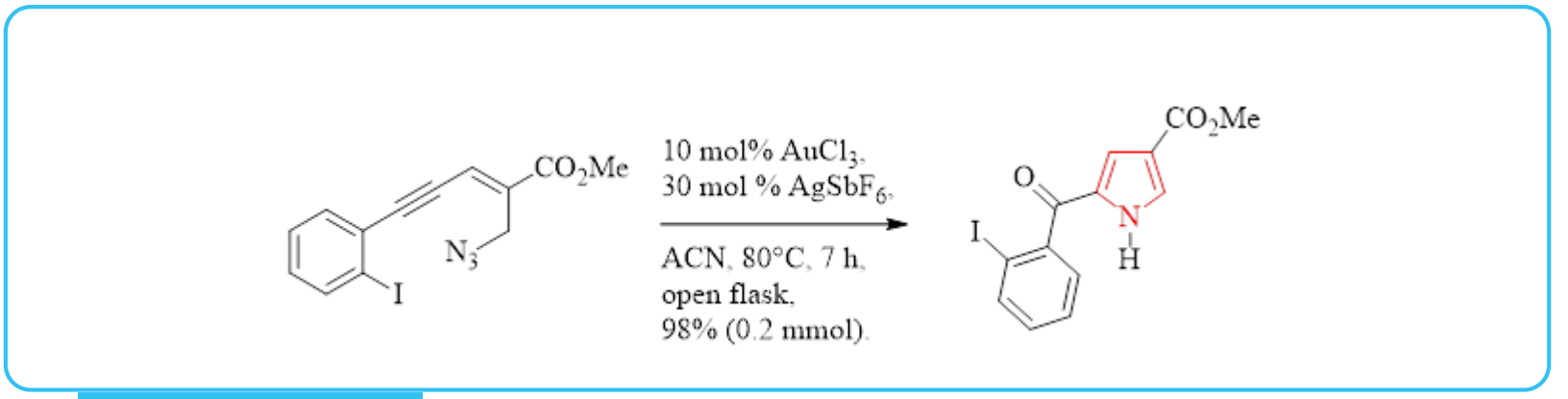
[36] L. Zhu, Y. Yu, Z. Mao, X. Huang, *Org. Lett*. **2015**, *17*, 30-33.



SCHEME 21

Preliminary mechanistic investigations are also presented.

An intramolecular gold-catalyzed intramolecular oxidative aza-annulation has been optimized by Redy and Coll. to provide substituted 2-keto- and 2-formyl-pyrroles from enyne azide precursors.[37] A representative example of this methodology is outlined in **Scheme 22** (17 examples 0.3 mmol scale, 50-98%).[38] The starting enyne azides are prepared from the Morita-Baylis-Hillman acetates of propargyl aldehydes with sodium azide.[39]



SCHEME 22

Mechanism studies of this gold-catalyzed oxidative cyclization suggested that water was the source of oxygen-atom for the carbonyl group.

A gold-catalyzed intermolecular ynamide amination-initiated aza-Nazarov cyclization has been reported by Lu, Ye and Coll. starting from benzyl azides and 3-en-1-ynamides to provide 2-amino-pyrroles.[40] This formal [4+1] cycloaddition is presented in **Scheme 23** (17 examples 0.3 mmol scale, 50-76%).

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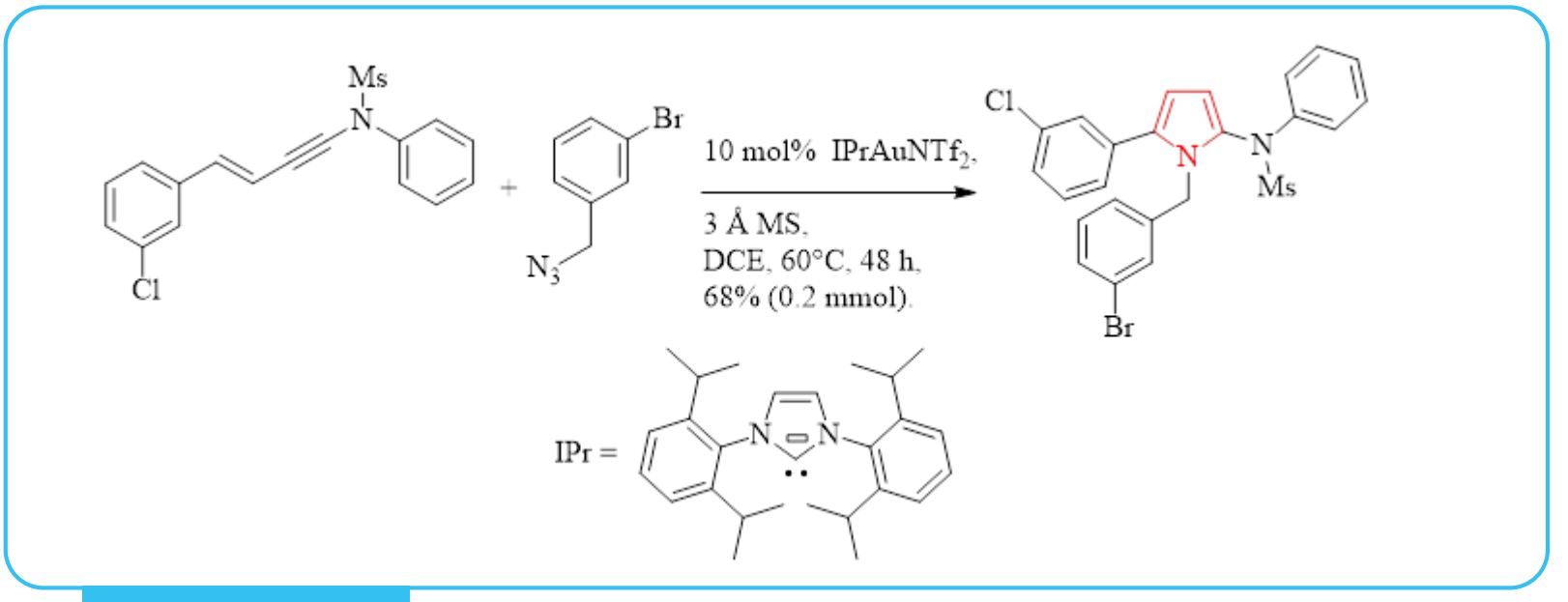
[37] C. R. Reddy, S. A. Panda, A. Ramaraju, *J. Org. Chem*. **2017**, *82*, 944-949.

[38] For previous investigations from the same authors in this area, see. C. R. Reddy, M. D. Reddy, B. Srikanth, *Org. Biomol. Chem*. **2012**, *10*, 4280-4288. C. R. Reddy, S. A. Panda, M. D. Reddy, *Org. Lett*. **2015**, *17*, 896-899.

[39] S. P. Park, S.-H. Ahn, K.-J. Lee, *Tetrahedron* **2010**, *66*, 3490-3498.

[40] C. Shu, Y.-H. Wang, C.-H. Shen, P.-P. Ruan, X. Lu, L.-W. Ye, *Org. Lett*. **2016**, *18*, 3254-3257.



SCHEME 23

The mechanistic rational of this transformation has been investigated by DFT (density functional theory) calculations which supported the formation of a key imine-containing gold-carbene intermediate. This latter intermediate could be regarded as an aza-analogue of the oxypentadienyl cationic species formed in the classical Nazarov reaction.[41]

Metathesis in the preparation of pyrroles

In less than two decades, ruthenium catalyzed olefin metathesis has become one of the most powerful tool in organic synthesis. More recently, this technology has emerged as an attractive solution for the preparation of aromatic and heteroaromatic compounds.[42] Following pioneering works of Donohoe[43] and Rutjes,[44] many syntheses of pyrroles using a ring closing metathesis (RCM)-aromatization sequence have been reported in the literature.

A recent example by Kotha and Coll. described an efficient and direct preparation of the pyrrole-based C3-symmetric compound **7** from the corresponding *N*,*N*'-diallyl precursor **8** using a RCM-aromatization one-pot sequence with Grubbs first generation catalyst (G-I) as outlined in **Scheme 24**.[45]

---

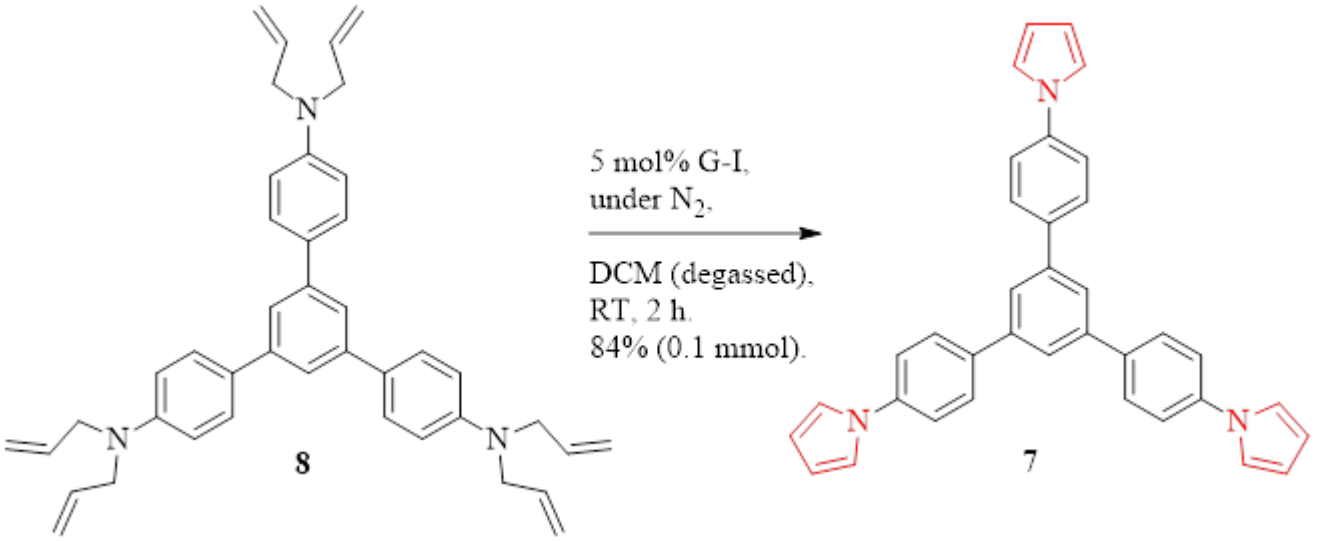
[41] For a recent review on Nazarov reaction, see: M. G. Vinogradov, O. V. Turova, S. G. Zlotin, *Org. Biomol. Chem.*, **2017**, *15*, 8245-8269.

[42] For a recent review on metathesis in the synthesis of aromatic compounds, see: W. A. L. van Otterlo, C. B. de Koning, *Chem. Rev.* **2009**, *109*, 3743-3782.

[43] T. J. Donohoe, J. F. Bower, *Proc. Nat. Acad. Sci*. **2010**, *107*, 3373-3376, and cited literature.

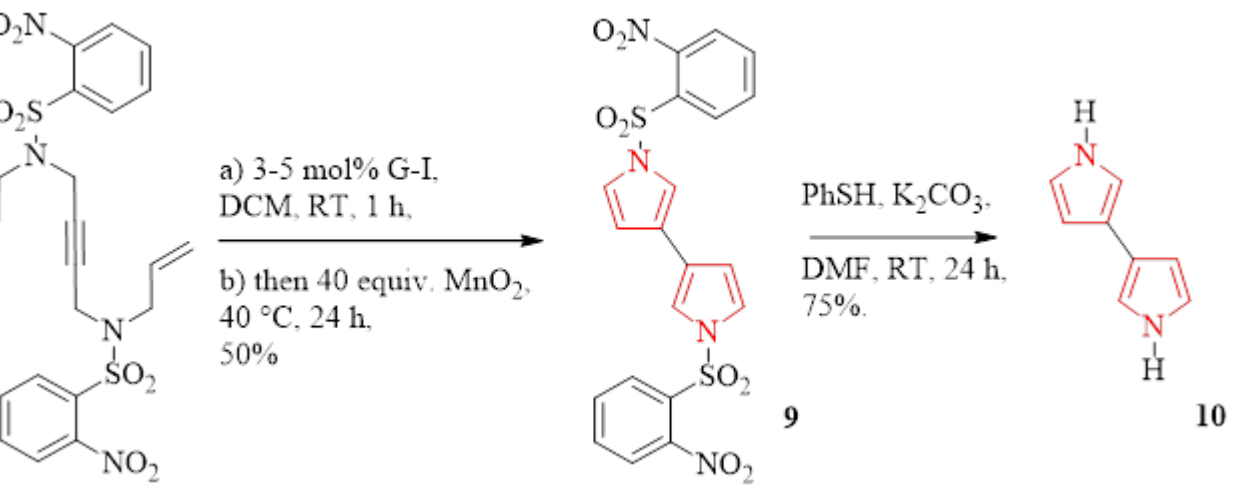
[44] V. De Matteis, O. Dufay, D. C. J. Waalboer, F. L. van Delft, J. Tiebes, F. P. J. T. Rutjes, *Eur. J. Org. Chem.* **2007**, 2667-2675.

[45] S. Kotha, S. Todeti, T. Das, A. Datta, *Tetrahedron Lett.* **2018**, *59*, 1023-1027.



SCHEME 24

In this field, Evans and Coll. reported an elegant telescoping reaction sequence involving an enyne metathesis[46] in the presence of G-I followed by consecutive addition of large excess of MnO_2 to give the *bis*-*N*-sulfonyl pyrrole **9** in 50% yield (see **Scheme 25**).[47] In the following step, standard nosyl protecting group cleavage conditions were applied to furnish the desired *bis*-pyrrole parent **10** in 75% yield. In contrast to the previous example, an aromatization mediated by MnO_2 was necessary to provide the pyrrole core.

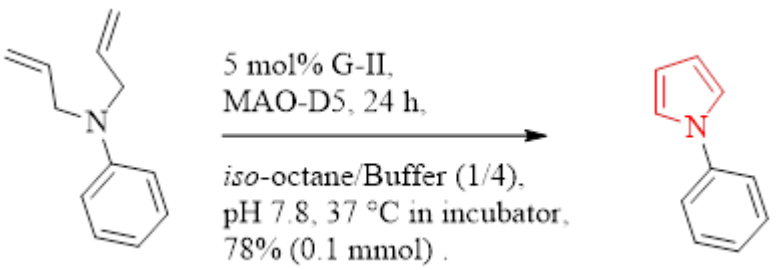


SCHEME 25

[46] For a recent review on enyne metathesis see: C. Fischmeister, C. Bruneau, *Beilstein J. Org.Chem*. **2011**, *7*, 156-166.

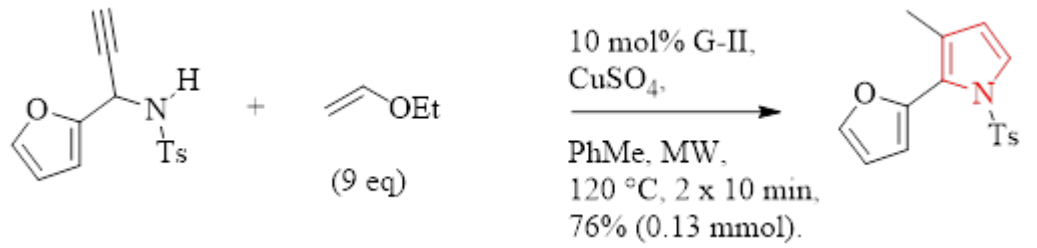
[47] A. Keeley, S. McCauley, P. Evans, *Tetrahedron* **2016**, *72*, 2552-2559.

A tandem RCM reaction-monoamine oxidase (MAO) chemoenzymatic cascade was developed by Castagnolo and Coll. This one-pot sequence combining chemical and enzymatic (whole cells of *E. coli* expressing recombinant monoamine oxidase D5) catalysts is illustrated in **Scheme 26**.[48] This elegant contribution to pyrroles synthesis described for the first time a one-pot RCM reaction-enzymatic aromatization sequence.



SCHEME 26

As a new input in this field of pyrroles synthesis, the same group reported the first one-pot tandem enyne cross metathesis (CM)-cyclization.[49] Under microwave irradiation in the presence of Grubbs'catalyst second generation (G-II), CM reaction between *N*-protected propargyl amine and excess of ethyl vinyl ether afforded *in situ* formation of the corresponding crotonaldehyde equivalent which in the presence of $CuSO_4$ led to cyclization to provide the *N*-protected 2,3-substituted pyrrole (see **Scheme 27**). As pointed out by the authors, two equivalents of this weak Lewis acid, presumably acting by coordinating the OEt group, was necessary to promote the cyclization step.



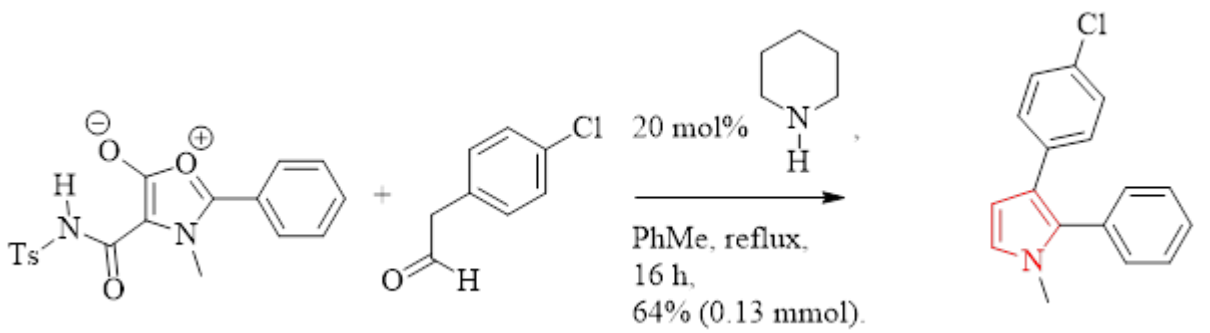
SCHEME 27

[48] N. Scalacci, G. W. Black, G. Mattedi, N. L. Brown, N. J. Turner, D. Castagnolo, *ACS Catal*. **2017**, *7*, 1295-1300.

[49] H. Chachignon, N. Scalacci, E. Petricci, D. Castagnolo, *J. Org. Chem*. **2015**, *80*, 5287-5295.

Metal-free catalyzed synthesis of substituted pyrroles

An amine-catalyzed preparation of pyrroles by cycloaddition of 1,3-oxazolium-5-olates and aldehydes has been reported by Harrity and Kakaawla.[50] 1,3-Oxazolium-5-olates, so-called "münchnones", represent one of the most prominent classes of five-membered mesoionic compounds, and have been largely used as key intermediates in 1,3-dipolar cycloaddition reactions to provide heterocyclic products. One example of this methodology is highlighted in **Scheme 28**. As discussed by the authors, under these optimized conditions, the enamines were formed *in situ* from the corresponding aldehydes and catalytic amounts of piperidine.



SCHEME 28

Conclusion

As presented in this letter, polysubstituted pyrrole cores could be constructed *via* numerous methodologies, nevertheless it is still a challenging area of research to develop, from readily accessible substrates, straightforward protocols leading to the desired polyfunctionalized pyrrole skeletons.

I would like to thank Johann Leblanc and Professor François-Xavier Felpin for fruitful discussions and comments. I also thank my colleagues, Dr. Sylvie Archambaud, Dr. Aude Vibert and Dr. Julien Farard from Atlanchim Pharma for their valuable suggestions during the preparation of this manuscript.

[50] T. K. K. Kakaawla, J. P. A. Harrity, *Org. Lett*. **2018**, *20*, 201-203.

PORTRAIT

Flavie JANVIER, technicienne chimiste chez AtlanChim Pharma est venue renforcer l'équipe courant 2017. Elle est titulaire d'un DUT chimie et d'une Licence professionnelle Chimie fine et synthèse (réalisée en alternance) obtenus au Mans.

Flavie a intégré pendant plusieurs mois l'équipe du Dr FERRARI sur la synthèse et la séparation via HPLC/ flash chromatographie des diastéréoisomères des "Prodrug nucleotides" à visée anticancéreuse et antivirale à *« School of Pharmacy and Pharmaceutical Sciences, Cardiff University,* **CARDIFF***, CF10 3NB »*

Actuellement, Flavie travaille sous la responsabilité d'un chef de projet ce qui lui permet de réaliser des synthèses de l'échelle du milligramme à plusieurs dizaines de grammes d'intermédiaires ou de molécules finales.

Flavie JANVIER, chemistry technician at AtlanChim Pharma, joined our team in 2017. She holds a DipHE in Chemistry obtained at the University of Le Mans as well as BSC degree in Fine Chemistry and synthesis with a work placement.

Flavie has been part of Dr FERRARI's team working on the synthesis and separation via HPLC / flash chromatography of the diastereoisomers of "Prodrug nucleotides" for anticancer and antiviral purposes at "*School of Pharmacy and Pharmaceutical Sciences, CARDIFF University,* **CARDIFF**, *CF10 3NB* »

Flavie works under the reponsability of a Project manager which allows her to perform syntheses on a lab scale of intermediates or final molecules.