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Transition metal catalyzed cyclizations and C-H couplings of heterocyclic scaffolds

Presented by

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Dedicated to my grandparents,

to be always with me.

Table of contents

List of Abbreviations

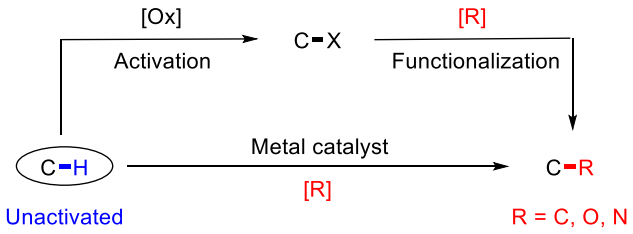
Ar	Aryl
$BArF_4$	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2´-bis-1,1´-binaftile
Bn	Benzyl
Boc	*t*-Butycarboxylate
COD	(1*Z*,5*Z*)-1,5-Cyclooctadiene
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density Funtional Theory
DMF	*N*,*N*-Dimethylformamide
DMAP	*N*,*N*-Dimethyaminopyridine
dr	Diasteromeric ratio
ee	Enantiomeric excess
equiv.	Equivalents
FF	Furfural
HMF	5-Hydroxymethyl furfural
HRMS	High Resolution Mass Spectrometry
i-Pr	Isopropyl
IR	Infrared Spectroscopy
J	Coupling costant
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
KHMDS	Potassium *bis*-diisopropylsilylamine
m-CPBA	3-Chloroperoxybenzoic acid
MeCN	Acetonitrile
MeOD	Deuterated Methanol
MeOH	Methanol
MHz	Mega Hertz
M.p.	Melting Point
MS	Molecular Sieves
MW	Microwaves
NMR	Nuclear Magnetic Resonance
NXS	*N*-halosuccinamide
PhMe	Toluene
PMP	*p*-methoxyphenyl
PTSA	*p*-Toluenesulphonic acid
r.t.	Room Temperature
t-Bu	*tert*-Butyl
TBSCl	*t*-Butyldimethylsilyl chloride
Tf	Triflate
TFA	Trifluoroacetic acid
Ts	Tosyl
THF	Tetrahydrofuran
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

General Introduction

Heteroatom-containing (poly)cyclic structures are molecules of the utmost importance found in natural compounds and in bioorganic molecules. They are also widely used nowadays in chemistry as ligands for transition metal-catalyzed processes or as organocatalysts. Consequently, the search for selective and atom/step-economical ways to synthetize or functionalize heterocyclic systems is a topic of continuous interest.

In this contest, the use of transition metals in catalysis is certainly one of the most popular widespread methods in organic synthesis whether in academia or in industry.[1] Transition metals allow the formation of new bonds in mild conditions starting from easily synthesizable substrates, often not pre-functionalized, operating selectively even in presence of high complex molecules. The role of transition metal-catalyzed reactions in contemporary chemistry is indeed absolute, as demonstrated by the frontier research works in organic field: from Wilkinson (Nobel Price 1973) to Sharpless and Noyori (Nobel Price 2001), passing through Grubbs (Nobel Price 2005) until, last but not least, the pioneering works of Heck, Suzuki and Negishi (Nobel Price 2010) for "palladium-catalyzed cross couplings in organic synthesis".

In addition, with the emergence of the concept of green chemistry and atom economy, C–H bond activation reactions catalyzed by transition-metals have gained in importance. Since C–H bonds are strong and not very polarized, their activation represents an even greater challenge for chemists. This technique reduces the number of steps generally required for the introduction and removal of functional groups, and thus allows C–C or C–X bonds to be formed by direct C–H bond functionalization with a clear economy of steps and atoms (Scheme 1).[2]



Scheme 1. *General example of C–H activation/functionalization* via *transition-metal catalysis.*

As reported in Figure 1, this trend continues to grow up due to the increasing use of transition-metals for C–H activation, as underlined by the explosive growth, both in quality and quantity, of articles published on this this topic up to 2015.[3] Among them, the undisputed predominant role is covered by palladium, followed by rhodium, copper and ruthenium.

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1 Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis, 2nd ed.,* Wiley-VCH, Weinheim, **2004**.
2 Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Catal. A: Chem,* **2017**, *426,* 275-296.
3 Wu, Y.; Wan, Y.; Zhang, F. *Curr. Org. Synth.I,* **2018**, *15*, 781-792.

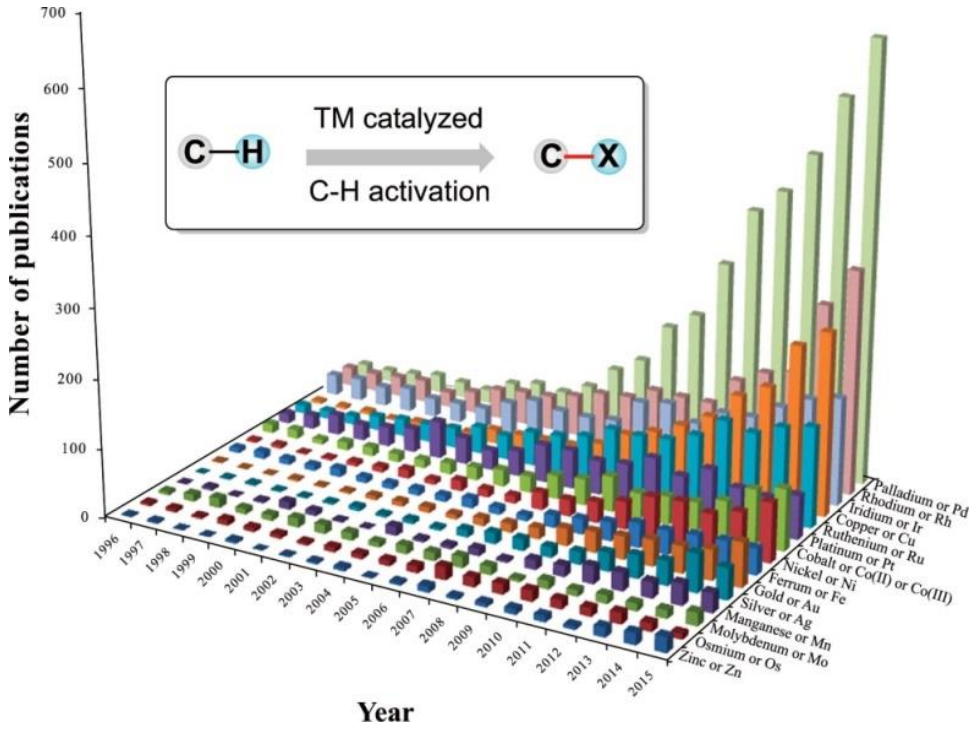


Figure 1. *Number of publications on "C–H activation" according to the transition metal employed.*

In view of the importance of the above-mentioned considerations, the subjects of this manuscript are divided into three main parts. In the first chapter, we will present divergent palladium- or platinum-catalyzed strategies for heterocycles synthesis by hydroamination or hydroarylation processes from *O*-propargyl-2-aminophenols. Then, in second chapter, the use of ruthenium-catalyzed C–H activation will be investigated for the C3-carbonylation of 5-membered-heteroaromatic rings, as revision of well-known Murai reaction. Finally, in chapter three, a new oxidant-free variant of Fujiwara-Moritani reaction for the C3-alkenylation of 5-membered-heterocycles, exploiting as well the same type of ruthenium-catalyzed C–H activation, will be presented.

Chapter 1: Pd- and Pt-Catalyzed Divergent Hydroamination/Hydroarylation Cyclization

1. Introduction – Divergent Synthesis

With the discovery of the transition-metal catalysis in organic synthesis, a wide range of reactions have been identified and are now widely used in total synthesis. As a consequence, the synthetic potentials of numerous compounds have become more important, as has the concept of divergent synthesis.

The term "Divergent Synthesis" commonly refers to different reaction pathways, which occur on a same precursor and under controlled conditions. Typically changing catalyst source or modifying the reaction parameters, it allows versatile reactivity according to the functional groups or of scaffolds involved (Figure 2).

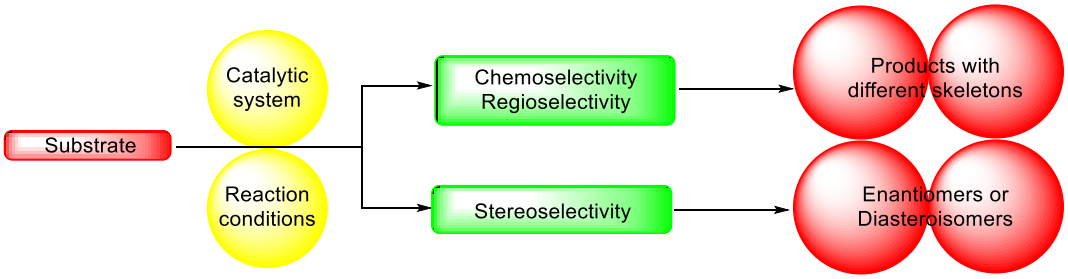
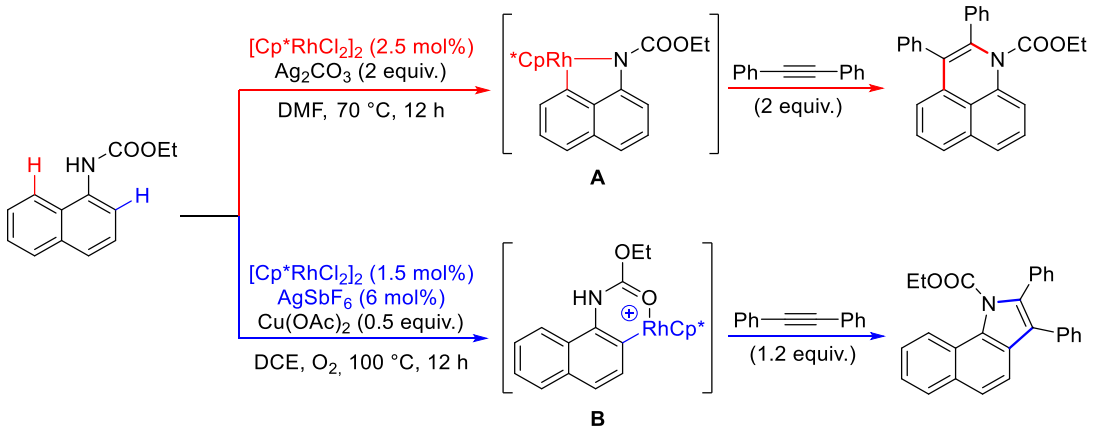


***Figure 2**. General principles of divergent catalysis.*

Considering the high potentiality in synthetic flexibility and in complete control of the product formed according to the catalyst structure, the divergent synthesis is considered a highly attractive tool for the discovery of new drugs and for the preparation of functional materials.[4] In order to develop efficient strategies for the synthesis of many structural frameworks, and taking in account the link between structural complexity, diversity, and bioactivity of organic compounds, like in case of natural products, a large number of divergent syntheses have been developed.[5] Depending to the structure of the starting material and consequently of the products formed, the type of divergent synthesis can be summarily divided in: 1) regioselective divergence and 2) chemoselective divergence, which allows to easily obtain different scaffolds, but also 3) stereoselective divergence, favoring the formation of one or more enantio- or diastereomers working on prochiral substrate and/or with chiral reagents/ligands.

[4] Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. *Angew. Chem., Int. Ed.*, **2012**, *51*, 10954-10990.
[5] Garcia-Castro, M.; Zimmermann, S.; Sankar, M. G.; Kumar, K. *Angew. Chem., Int. Ed.*, **2016**, *55*, 7586-7605.

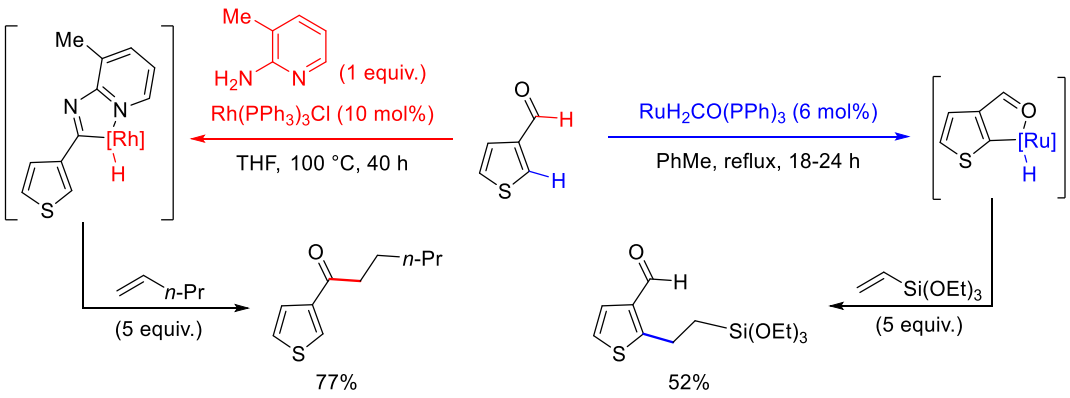
Focusing on transition metals catalyzed C–H activation processes, the regioselective control of the functionalized position is the most interesting challenge for chemist and that one in which the greatest efforts have been made. A versatile and reliable strategy for regioselective C–H bond functionalization is obviously the use of directing groups, which through coordination to the transition metal catalyst, deploy the proximity effect and dictate the regioselective functionalization of a specific C–H bond. An interesting example in this sense was reported by Jin and coworkers, who worked on naphthyl carbamates.[6] The use of a neutral Rh(III) catalyst leads to the activation of the *peri* C–H bond to form a Rh–N rhodacycle intermediate **A**, that later evolves in the final benzoquinoline working in DMF and with Ag_2CO_3 as oxidant. In contrast, the cationic Rh(III) species generated *in situ* in presence of $AgSbF_6$ activates the *ortho* C–H bond in DCE to furnish the benzo-fused indole product. In this case, the cationic Rh complex more electrophilic gives the *O*-coordination, favoring a 6-membered rhodacycle **B** (Scheme 2).



Scheme 2. *Regioselective alkynylation/cyclization of naphthyl carbamates.*

The presence of functional groups for directing a catalyzed process can be sometimes a source for a new type of reactivity. This is the case of the chemoselective divergence obtained from C3-thiophene aldehyde by Jun[7] and Murai[8] respectively in 1997 and 2001. On the one hand, the formation of an aldimine between the aldehyde function and a primary amine is a suitable way for the hydroacylation. This process takes place in presence of Wilkinson's Rh catalyst and 2-amino-3-picoline and involves a Rh(I) complex chelate with the picoline imine intermediate **A**. On the other hand, the same aldehyde reacted with triethoxyvinylsilane in the presence of a formal Ru(0) source generated *in-situ*. These conditions afforded the C2-hydroarylation through a 5-membered ring intermediate **B**, in which the ruthenium coordinates the oxygen of the aldehyde function (Scheme 3).

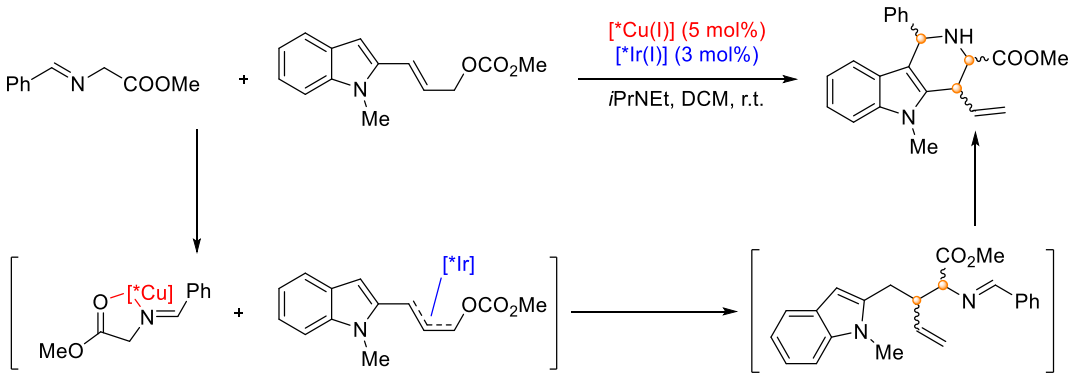
6 Zhang, X.; Si, W.; Bao, M.; Asao, N.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2014**, *16*, 4830-4833.
7 Jun, C. -H.; Lee,D. -Y; Hong, J. -B. *Tetrahedron Lett*. **1997**, *38*, 6673-6676.
8 Kakiuchi, F.; Sato, T.; Igi, K.; Chatani N.; Murai, S. *Chem. Lett.* **2001**, *30*, 386-387.



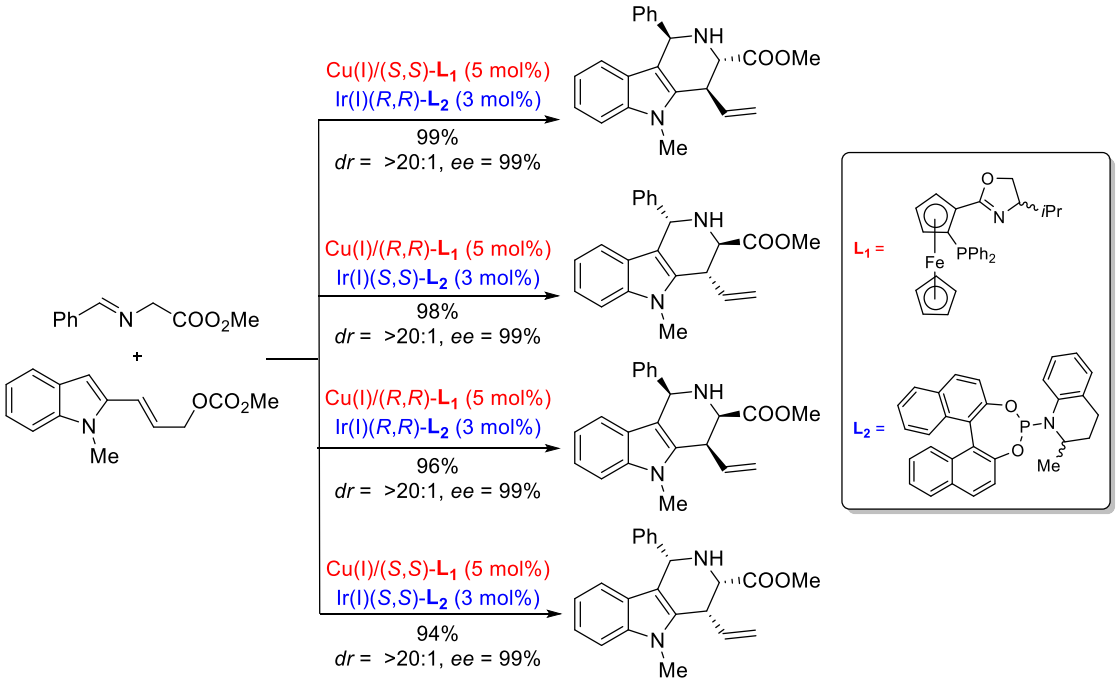
Scheme 3. *Chemodivergence with C3-thiophene aldehyde.*

The last category of divergence refers to the possibility of a total control in the formation of one or more sterocentres. In this panorama, metal-catalyzed or organocatalyzed processes are the main strategies in stereodivergent catalysis. The challenge of providing different enantiopure compounds while avoiding the use of opposite sources of chirality is crucial and has found its main response in the use of structural modifications of chiral ligand of metal complexes or in the organocatalysts. In metal catalysis, besides the employment of the ligand, also the metallic precursor used to form the catalytic species is considered an important strategy, as well as chiral or achiral counter anions which can play an important role in the case of cationic metal complexes.

A suggestive example is the work reported by Wang's group for the synthesis of tetrahydro-γ-carbolines.[9] The authors showed how a dual metallic catalytic system, with independently *in situ* formation of Cu(I)-ylide and Ir(III)-π-ally species, allows the stereoselective control of three stereocenters through a catalyzed asymmetric cascade allylation/cyclization reaction starting from aldimine esters and indolyl allylic carbonates. The reaction pathway involves to catalytic cycle in which the chiral information is bring by the two enantiopure ligands of Cu(I) and Ir(I) salts, which determine the configuration of two stereocenters and consequently, after the cyclization step, the stereochemistry of the last one (Scheme 4).



[9] Xu, S.; M.; Wei, L.; Shen, S.; Xiao, L.; Tao, H. -Y.; Wang, C. -J. *Nat. Commun.* **2019**, *10*, 5553-5564.



Scheme 4. *Stereodivergent synthesis of tetrahydro-γ-carbolines.*

Although the number of publications and the works of many research teams focusing on or referring to examples of divergent catalysis are gradually increasing,[10] research efforts on the development of this type of process are still rare in the literature.

In this context, our team aimed to develop a divergent cyclization process of *O*-propargyl-2-aminophenols from Pd or Pt catalysts. Before presenting our results on these reactions, we will first look at the literature on differences between Pd- and Pt-catalyzed either hydroamination or hydroarylation reactions.

2. Transition metals for hydroamination or hydroarylation of alkynes: Pd *vs* Pt

A distinctive reactivity feature of transition metal compounds is their propensity towards electrophilic activation of unsaturated C–C bonds. Among them, palladium (above all) and platinum complexes are very versatile and continue nowadays to be largely employed in catalytic processes. Although these metals are intrinsically different from one another, it is common that their catalysis of alkenes or alkynes activation can lead to similar products, as well significant different behaviors, due to their capacity to coordinate functional groups, can be recorded. In addition palladium and platinum salts in +II state are square planar and can have two independent coordination sites, but their salts also often act as Lewis acids and they can form σ-complexes with heteroatoms. Last but not least, palladium and platinum complexes undergo oxidation state changes far more readily than other transition metal centers.

[10] For other examples see: [a] Ping, L.; Chung, D. -S.; Bouffard, J.; Lee, S. *Chem. Soc. Rev.* **2017**, *46*, 4299-4328; [b] Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2017**, *139*, 5627-5639; [c] Beletskaya, I. P.; Nájera, C.; Yus, M.; *Chem. Rev*. **2018**, *118*, 10, 5080-5200.

2.1. Palladium catalysis in hydroarylation or hydroamination of alkynes

Palladium is a transition metal of group 10, located in the second row of the periodic table. Considering the all possible forms, palladium complexes exist in the three main oxidation states: Pd(0), Pd(II), Pd(IV), each oxidation state with its own different electronic and chemical properties. All the Pd-catalyzed reactions involved a combination of steps concerning one or more of the three states in metal complexes. Among them there are: a) dative ligand coordination or ligand exchange, b) oxidative addition/reductive elimination [Pd(0)/Pd(II) or Pd(II)/Pd(IV)], c) π-system (alkene/alkyne/allene) coordination/*cis*- or *trans*-palladation (migratory insertion) and d) dative ligand 1,1-insertion. According to the oxidation state of the palladium, the starting elementary step of the catalytic cycle can be the oxidative addition, the ligand coordination, or the ligand exchange, while the closing elementary step may be the reductive elimination or the depalladation step (usually dehydropalladation). Mainly due to its versatility, palladium-catalyzed couplings have proven to be powerful and key reactions for the synthesis of a great number of scaffolds, including carbo- and heterocycles.[11] In this section, it is reviewed a selection of published works dedicated to Pd-catalyzed hydroarylation or hydroamination of unsatured alkyne systems.

Regarding the hydroarylation of alkynes systems with aryl and/or heteroaryl scaffolds, several works exploiting the use of Pd(0) or Pd(II) sources have been published. The great versatility of this metal allows a high control in regio- and stereoselectivity of the final product, according to the inner features of the catalyst and the presence of directing groups on the substrate. In addition, the starting aryl compound can present activating groups on the ring, which allow the insertion of the palladium center in the C-X bond and then the following migration of the aryl on the alkyne moiety. However, a wide range of examples show that simply unfunctionalized aryl system can be attack by alkynes, previously activated by the palladium catalyst.

Among the activated aryl reagents, particularly appealing are the arenediazonium salts and the arylsodium sulphinates, for example employed by Cacchi and Deng respectively.[12] In both cases, the reaction tolerate a wide variety of substituents on the aromatic rings, functional groups and crowded substrates. Independently by the original substrates form, the mechanism can be summarized through three key intermediates: an initial stereoselective addition of the formed σ-arylpalladium complex to the alkyne, followed by reaction of the carbopalladated adducts **A** with a proton donor to give the intermediate **B**. In the end the final reductive elimination step furnishes the desired product. The active form of the catalyst, a Pd(0) species, is in both cases obtained by *in situ* ligand exchange (Scheme 5).

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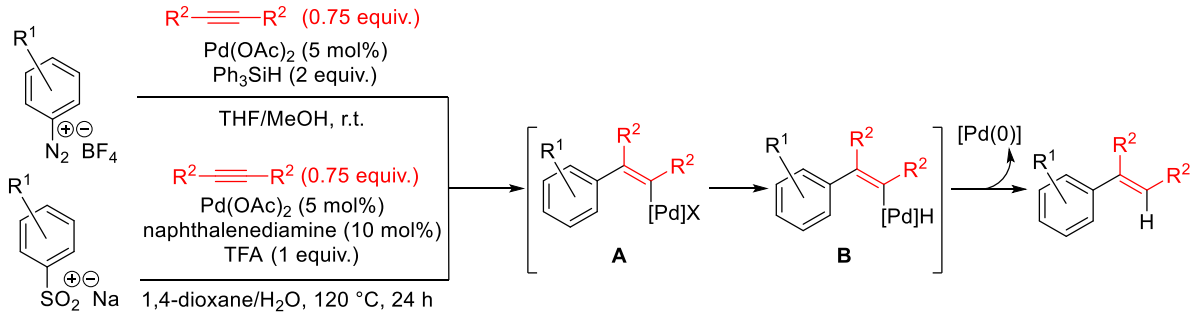
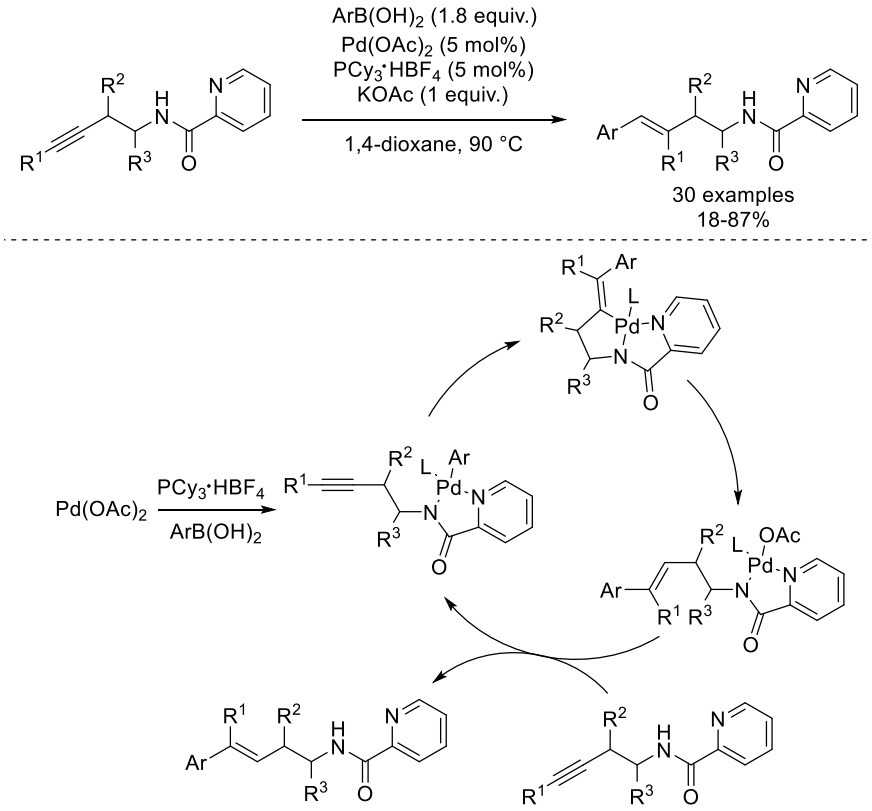
[11] For some example see: [a] *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, **2002**; [b] *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed*.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**; [c] Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011,** *111***,** 1417-1492; [d] Tsuji, J. Ed. *Palladium in Organic Synthesis*, Springer, **2005**.

[12] [a] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Persiani, D. *Org. Lett.*, **2008**, *10*, 1597-1600; [b] Liu, S.; Bai, Y.; Cao, X.; Xiaoa, F.; Deng, G.-J. *Chem. Commun*. **2013**, *49*, 7501-7503.



Scheme 5. *Arenediazonium salts and arylsodium sulphinates in alkyne hydroarylation.*

The use of boronic acids as aryl partners for the hydroarylation of alkynes has been widely investigated.[13] Among them, a Pd(II)-catalyzed regioselective *syn*-hydroarylation reaction of homopropargyl amines was developed by Deng and coworkers.[14] The stereoselective control employing nonsymmetrical disubstituted alkyne substrates was obtained using a cleavable bidentate directing group such as picolinamide (Scheme 6).



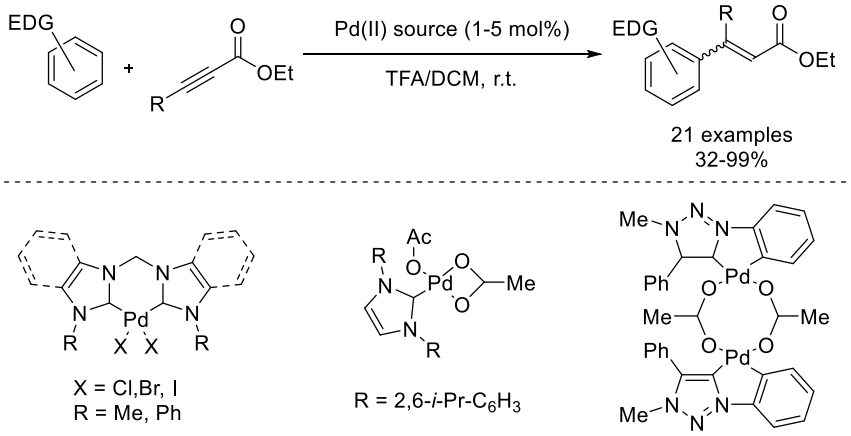
Scheme 6. *Aryl boronic acids and arenediazonium salts in alkyne hydroarylation.*

On the other hand, also methodologies based on nonfunctionalized aryl systems have been largely studied, in the perspective to realize double aryl/alkynyl C-H functionalization processes. One of the

[13] [a] Xu, X.; Chen, J:; Gao, W.; Wu, H.; Ding, J.; Su, W. Tetrahedron 2010, 66, 2433-2438; [b] Gupta, A. K.; Kim, K. S.; Oh, C. H.*Synlett* **2005**, *3*, 457-460.

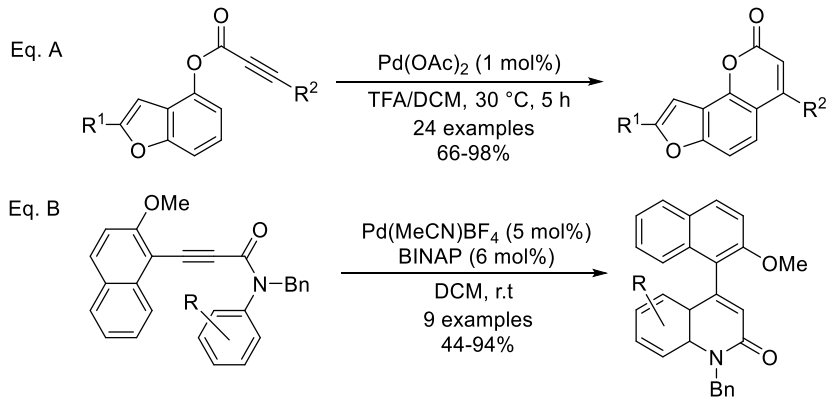
[14] Liu, Z.; Derosa, J.; Engle, K. M. *J. Am. Chem. Soc.***2016**, *138*, 13076-13081.

simplest and largely investigated intermolecular alkynes hydroarylation is the reaction of high electrondonor substituted aryl scaffolds with ethyl propiolate, in presence of a Pd(II) source, a variant of the well-known Fuijiwara-Moritani reaction.[15] It is interesting to note that, as reported in Scheme 7, different types of ligands for palladium catalyst, such as carbenes and triazolydenes resulted to be suitable to perform the reaction, enlarging the possible structures of these complexes.



Scheme 7. *Pd(II)-catalyzed hydroarylation of ethyl propiolate with electron-rich aryl systems.*

Additionally, Pd-catalyzed hydroarylation of alkynes was also developed at intramolecular level in the synthesis of more complex structures. For example the use of Pd(II) allows to synthesize 4-benzofuranyl lactones as useful precursors of angelicin derivatives (Scheme 8, Eq. A). Otherwise, the synthesis of axially chiral 4-aryl 2-quinolinones was achieved starting from aryl alkynes in presence of Pd(II) catalyst and chiral bisphosphine ligands (Scheme 8, Eq. B).[16]

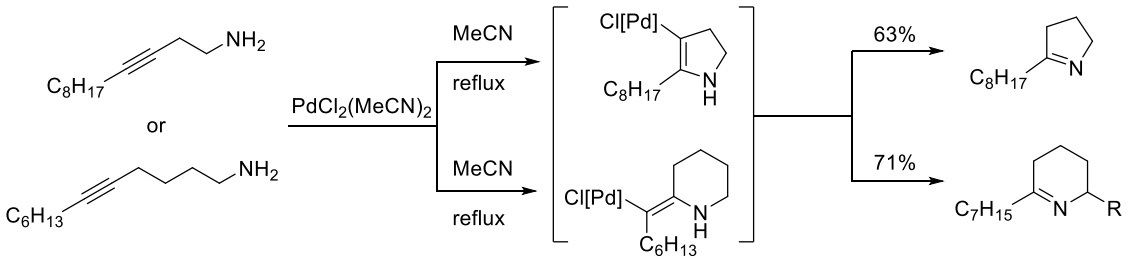


Scheme 8. *Intramolecular Pd(II)-hydroarylation of inner alkynes.*

[15] [a] Buscemi, G.; Cristina, A. B.; Basato, T. M. *Catalysis Today* **2009**, *140*, 84-89; [b] Viciu, M. S.; Stevens, E. D.; Petersen, J. L.; Nolan S. P. *Organometallics* **2004**, *23*, 3752-3755; [c] Saravanakumar, R.; Ramkumar, V.; Sankararaman S. *Organometallics* **2011**, *30*, 1689-1694.

[16] [a] Kitamura, T.; Otsubo, K. *J. Org. Chem*. **2012**, *77*, 2978-2982; [b] Shibuya, T.; Shibata, Y.; Noguchi, K.; Tanaka, K. *Angew. Chem*. **2011**, *123*, 4049-4053

Moving on C-N bond formation, one of the first example employing catalytic amounts of $PdCl_2$ for the hydroamination of an alkyne moiety was reported by Utimoto in 1983.[17] Later in time, the same group showed that treatment of internal 3-alkynylamines with a catalytic amount of $PdCl_2(MeCN)_2$ in refluxing acetonitrile containing a few percent of water gave exclusively 1-pyrrolines in good yields, whereas 5-alkynylamines afforded 2,3,4,5-tetrahydropyridines. In each case, intramolecular 5-endo-dig or 6-*exo-dig* aminopalladation of alkynylamines gave an alkenylpalladium intermediates that hydrolyzed and isomerized to thermodynamically stable cyclic imines (Scheme 9).[18]



Scheme 9. *First example of palladium-catalyzed hydroamination of alkynes.*

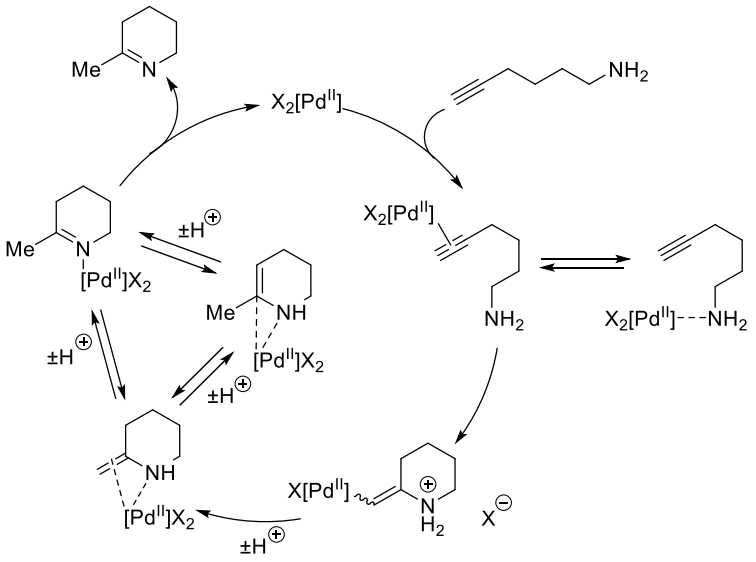
A few years later, after identifying the most active transition metal catalysts for the hydroamination of alkynes, Muller and Yan proposed a general mechanism with transition metals belonging to 7^{th}-12^{th} groups.[19] In contrast to the old mechanism based on oxidative addition of an amine to the metal centre, which was previously suggested for catalysis with Rh(I) and Pd(II),[20] only the coordination of the catalyst with the unsaturated alkyne (in equilibrium with the complexation with the amine function) can explain the hydroamination of alkynes with various transition metals from the 7^{th}-10^{th} groups (*i.e.* Pd(II), Rh(I)…), as well as with metal catalysts of 11^{th} and 12^{th} groups (*i.e.* Zn(II) and Cu(I), which have no oxidation state available). The key step involves then the nucleophilic attack of the nitrogen lone pair on a coordinated alkyne moiety to furnish, after deprotonation of the ammonium moiety and protonation of alkenylpalladium intermediate, the final metal coordinated cyclic compound. The authors suggested also the participation of the catalyst in the double bond isomerization, through a three centre mechanism, before the decoordination step (Scheme 10, example with Pd(II) catalyst).

17 Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845-1852.

18 Fukada, Y.; Matsubara, S.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 5812-5816.

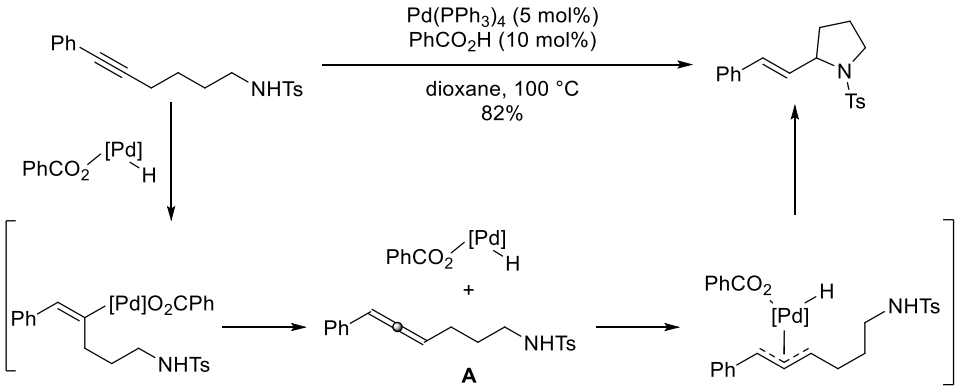
19 Muller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A. -K.; Walter, E.; Yan, Y. -K. *Organometallics* **2000**, *19*, 170-183.

20 [a] Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.***2002,** *67*, 5977-5980. [b] Hong, S. Marks, T. J. *J. Am. Soc. Chem.* **2002,** *124*, 7886-7887. [c] Heutling and, A.; Doye, S. *J. Org. Chem* **2002,** *67*, 1961-1964.



Scheme 10. *Reaction mechanism for alkyne hydroamination with Pd(II) catalyst.*

Another interesting example was recorded by Yamamoto and coworkers in 1999.[21] Developed both to inter- and intramolecular level, the reaction occurs with high regio- and stereoselectivity working with catalytic amounts of $Pd(PPh_3)_4$ and benzoic acid (10 mol%), which are required for the formation of an hydropalladium species. As shown in Scheme 11, properly this species is required in a first catalytic cycle for the *in situ* formation of the allene system **A**. Later, the same allene is involved in a second mechanism where the hydropalladation of the allene leads to a π-allylpalladium species that reacts with the amine to give the desired allylic amine as product and regenerates the active hydridopalladium species.



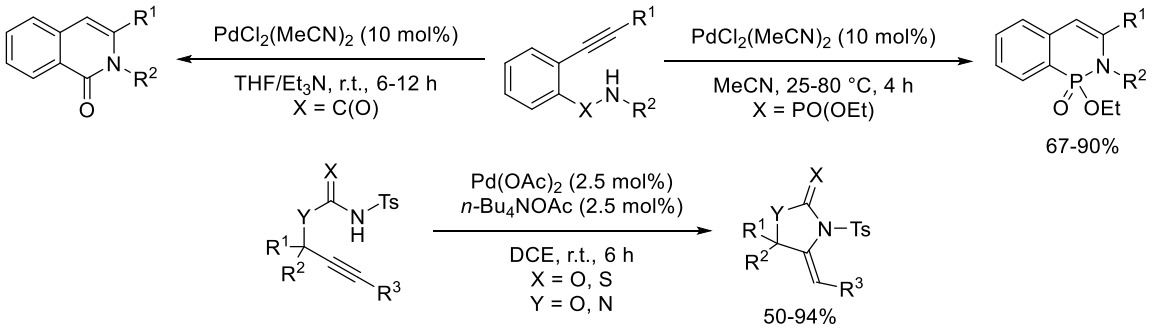
Scheme 11. *Pd(0) catalytic hydroamination via allene formation.*

Problems of regioselectivity were instead recorded during the hydroamination reaction on amidoalkynes, which was function to the scaffold used and the distance between the alkynyl function and the amino group involved. Thus, while *N*-alkyl-*o*-ethynylbenzamides and phosphonamides preferably undergoes a 6-endo-dig cyclization in presence of $PdCl_2(MeCN)_2$ as catalyst,[22] propargylic (thioureas) and

[21] Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570-4571.

[22] [a] Sashida, H. *Synthesis* **1999**, *7*, 1145-1148; [b] Tang, W.; Ding, Y.-X. *J. Org. Chem.* **2006**, *71*, 8489-8492; [c] Zhou, J.; Tang, W.; Guo, Y.; Ding, Y. Chin. J. Chem. 2009, 27, 1733-1740.

(thio)carbamates with an analogous Pd(II) source prefer a 5-*exo*-selective intramolecular hydroamidation process for the synthesis of five-membered ring cyclic compounds (Scheme 12).[23]

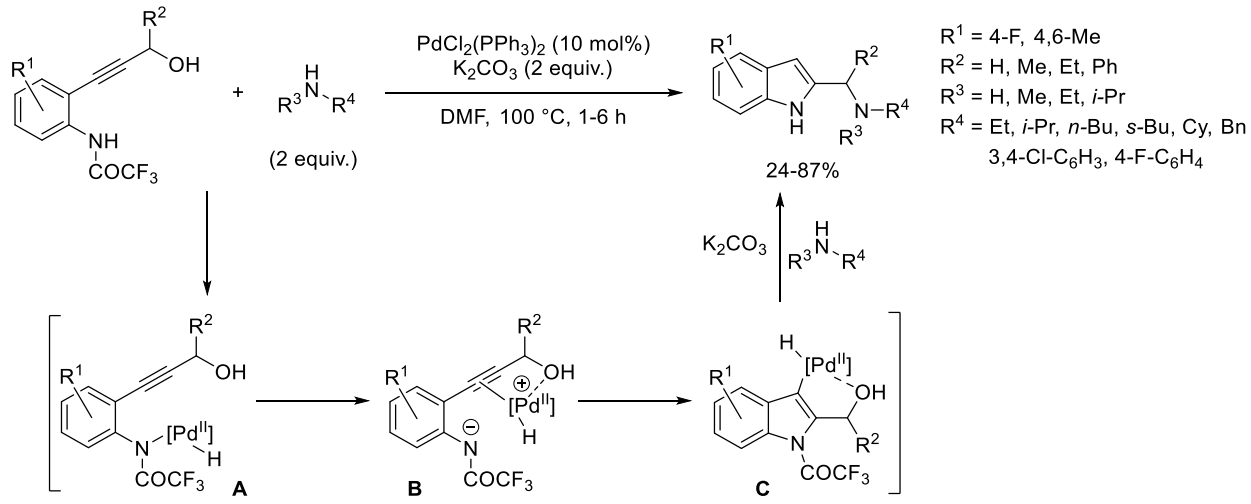


Scheme 12. *5-endo-dig vs 6-endo-dig cyclization of alkynyl amides.*

The use of hydroamination protocols in sequential hydroamination/nucleophilic substitution reactions were more recently investigated by Goggiamani group for preparations of indole derivatives starting from 2-alkynyl-hydroxybenzenes (Scheme 13).[24] The proposed mechanism consists, in the first step, in an oxidative addition of the N-H bond to Pd(0) species (generated *via* reduction by the secondary amine of Pd(II) pre-catalyst) to afford compound **A**. In this context the nature of the nitrogen influencing the acidity of the N-H bond plays a crucial role in the oxidative addition. The subsequent coordination of the cationic palladium hydride fragment to the alkyne bond generates intermediate **B**, which is followed by intramolecular nucleophilic attack of the anionic nitrogen on the activated triple bond to give the σ-indolylpalladium intermediate **C**. In addition to exploit the role for coordinating group to the metal centre, the hydroxyl group is in the end replaced *via* direct nucleophilic substitution with the amino group assisted by the coordination of the palladium. After two reductive elimination steps, the final 2-hydroxymethylindole is obtained beside the regenerated the active palladium catalyst. Finally, the role of the base K_2CO_3 is limited to the based-catalyzed hydrolysis of nitrogen protecting group.

[23] [a] Alamsetti, S. K.; Persson, A. K. Å.; Backvall, J.-E. *Org. Lett*. **2014**, *16*, 1434-1437; [b] Alamsetti, S. K.; Persson, A. K. Å.; Jiang, T.; Backvall, J.-E. *Angew. Chem., Int. Ed.* **2013**, *52*, 13745-13750.

[24] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Molinaro, C.; Verdiglione, R.; *J. Org. Chem.* **2014**, *79*, 401-407.



***Scheme 13**. Palladium-catalyzed indole derivatives synthesis of 2-(aminomethyl)indoles.*

Globally, hydroarylation and hydroamination reactions and among them palladium-catalyzed processes have evolved into broadly range of applicable methodologies that permit to access to various classes of considerable synthetic useful compounds. These reactions often proceed with high chemo-, regio-, and stereoselectivity and although many examples of such protocols have already been developed,[25] this research area is in continuous evolution, and numerous cascades reaction will surely be investigated in future.

2.2. Platinum catalysis in hydroamination or hydroarylation of alkynes

Platinum, for its properties, belongs to the so-called "Noble metals", located in the group 10 and in the period 6 of the periodic table. Resistant to acidic attack and corrosion, but sensitive to halogen attack, from a chemical point of view it is mainly found in complexes in the two most common oxidation state of Pt(II) and Pt(IV). In the oxidation state of Pt(II) the complex to assume a planar-square geometry, because of the electronic configuration of the metal. In addition Pt(II) is a soft acid and preferably coordinates soft bases with donor atoms such as S and P, although complexes with *N*-donor ligands or with halogens are more numerous.

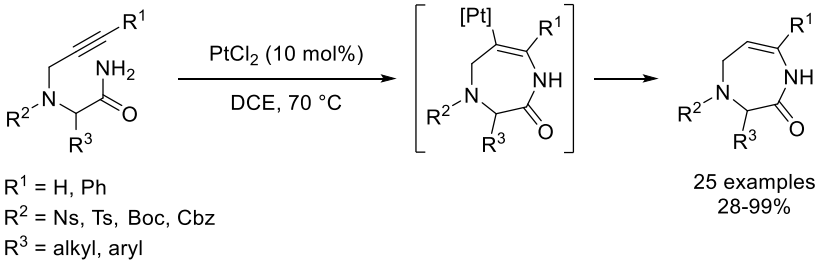
Platinum has played a central role in the activation of various unsaturated bonds over the last half century, in both fundamental understanding and approaches to actual functionalization. However, nowadays its application in these fields is continuing to fall off. The two main reasons for this behaviour are first of all the high prices of platinum catalysts compared with first row transition metals and secondary the trend to considered third row transition metal catalysts mainly suitable for mechanistic investigations in

[25] For other example see: [a] Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen¨, L. J. *Chem. Rev.* **2015**, *115*, 2596-2697; [b] Alonso, F.; Beletskaya, I. P.; Yus M. *Chem. Rev.* **2004**, *104*, 3079-3159.

stoichiometric amount rather than for catalysis.[26] Despite this, platinum-based catalysts have found use in organic synthesis especially by coupling reaction between (hetero)aryl systems and partners containing unsaturated bonds, such as alkenes and alkynes. In this paragraph, it is considered the role covered by platinum catalysis in functionalization process of unsatured bonds, with particular regard to the hydroamination and hydroarylation/cyclization of alkyne systems.

Even if in literature a lower number of publications, compared to the Pd-catalyzed version are reported, Pt-catalyzed hydroamination of alkynes is a fruitful methodology for the synthesis of five to seven membered rings *N*-containing heterocycles, as well for the preparation of nitrogen containing function.

For example, Takomoto's group reported the synthesis of 1,4-diazepanones exploiting the attack of an amido group on an unactivated alkyne system.[27] Through the regioselective 7-*endo*-*dig* reaction pathway, the use of a catalytic amount of $PtCl_2$ in mild reaction conditions allows the coordination to the unsatured function and promotes the intramolecular attack of the amido nitrogen on the alkyne (Scheme 14). Interestingly, the developed conditions are tolerant for the protecting groups for the amine and for several substituents at the α-position, such as alkyl or aryl substituents, which tend to stabilize the transition state.



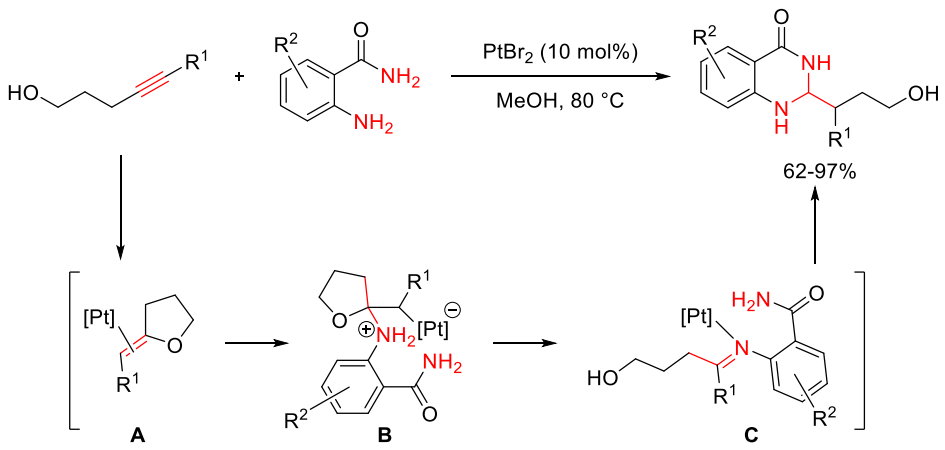
Scheme 14. *Pt(II)-catalyzed 7-*endo-dig *hydroamination of terminal and inner alkynes.*

Similarly, the synthesis of tetrahydroquinazolinones can be achieved *via* double hydroamination step of alkynyl alcohols, as reported by Sridhar and Reddy groups.[28] In this case, the coordination of the Pt(II) catalyst to the alkynes promotes an initial metal-olefin intermediate **A** after an intramolecular attack by the hydroxy function, which rapidly evolves into the imino intermediates **C** after intermolecular attack by the an aniline group into intermediate **B**. In the end, the remaining amido function attacks the electrophilic imino carbon with formation of the final product. The reaction was also applied for the synthesis pyrrolfused quinoxalines (Scheme 15).

[26] Labinger J. A. *Chem. Rev.* **2017**, *117*, 8483-8496.

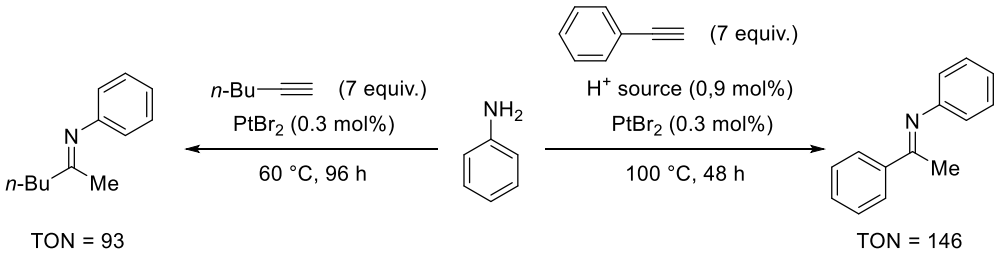
[27] [a] Girard, A. -L., Enomoto, T.; Yokouchi, S.; Tsukano, C.; Takemoto, Y. *Chem. Asian J.* **2011**, *6*, 1321-1324; [b] Girard, A. -L; Enomoto, T.; Yokouchi, S.; Tsukano, C.; Kuribayashi, T., Sakamoto, S. Takemoto, Y. *Org. Biomol. Chem.* **2012**, *10*, 6074-6086.

[28] [a] Patil, N. T.; Kavthe, R. D.; Raut, V. S.; Shinde, V. S.; Sridhar, B. *J. Org. Chem*. **2010**, *75*, 1277-1280; [b] Patil, N. T.; Kavthe, R. D.; Raut, V. S.; Reddy V. V. N. *J. Org. Chem.* **2009**, *74*, 6315-6318.



Scheme 15. *Pt(II)-catalyzed double intermolecular hydroamination of alkynyl alcohols.*

Examples of Pt(II)-catalyzed hydroamination of alkynes have been reported also at intermolecular level, by condensation of alkyl or aryl amines with the unsatured system. One of the first works was reported by Vincendeau for the coupling between substituted anilines and alkyl/aryl acetylenes.[29] As shown in Scheme 16, the authors reported how the process, in presence of Pt(II) salts, resulted to be fully regioselective according to a Markovnikov type addition to the alkyne system. The high catalytic turnover number in the preparation of the imine derivative can be further increased in presence o f a proton source (anilinium sulphate) from TON = 93 up to 146.



Scheme 16. *Intermolecular imines synthesis* via *hydroamination of alkynes with Pt(II) salts.*

Many other examples have been recently reported about the use of platinum in alkynes hydroamination, focusing on regio- and stereoselectivity,[30] even if greater efforts in this branch of platinum catalysis still need to be done.

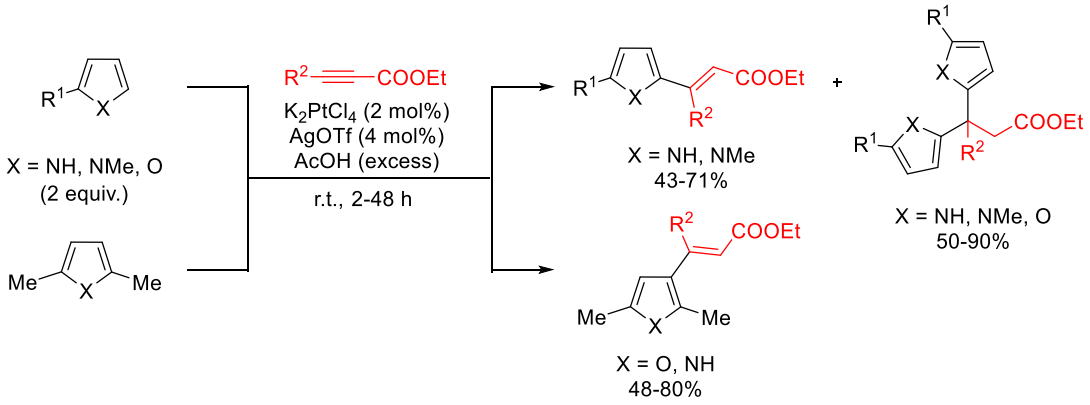
In the same way, Pt(II)-catalyzed hydroarylation of alkynes furnishes a valid alternative to the first methodologies developed with Pd(II) catalysts for the alkenylation of (hetero)arenes with alkynes.[31] Properly basing on these works, Kitamura group reported a more selective hydro-heteroarylation of

[29] Brunet, J. J.; Chu, N. C.; Diallo, O; Vincendeau, S. *J. Mol. Catal. A: Chem.* **2005**, *240*, 245-248.

[30] For some examples see: [a] Liu, X. Y.; Che, C. M. *Angew. Chem. Int. Ed.*, **2009**, *48*, 2367-2371; [b] Costello, J. P.; Ferreira, E. M. *Org. Lett*. **2019**, *21*, 9934-9939.

[31] [a] Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc*. **2000**, *122*, 7252–7263; [b] Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995.

internal and terminal alkynes with 5-membered ring heteroarenes (pyrroles and furans) in presence of Pt(II) catalyst, such as K_2PtCl_4/AgOTf, in acetic acid.[32] In the absence of a directing group, the difunctionalization of alkyl alkynoates is directed towards the more reactive C5 position of the ring, while in case of C2,C5-substituted pentatomic heterocycles with terminal alkyne the monohydroarylation involves the C3 position (Scheme 17). The key intermediate step are the activation of the alkynoic ester by Pt(II) cationic catalyst and the following attack by the heteroarene electrophilically to form a Wheland intermediate.

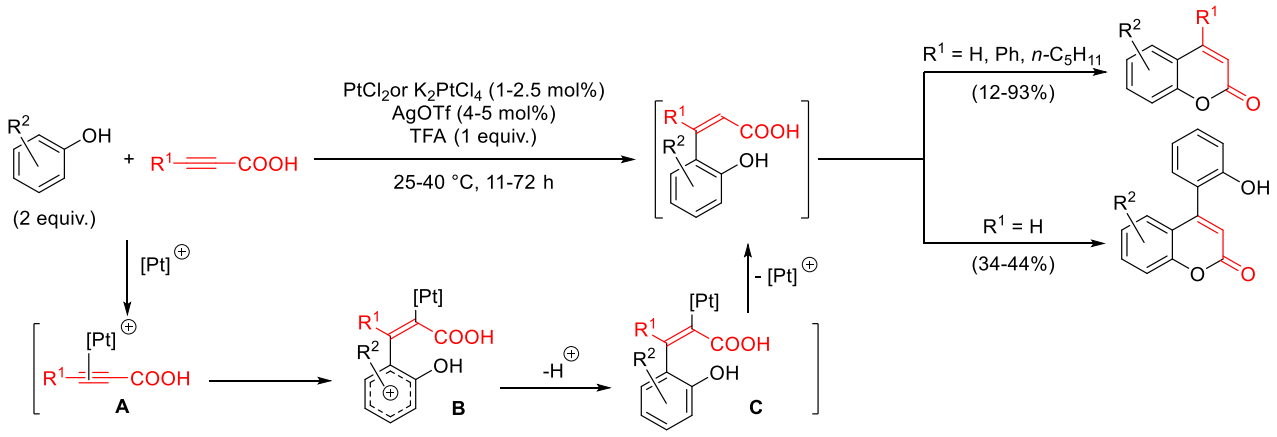


Scheme 17. *Hydroarylation of inner and terminal alkynes with heteroarenes.*

The catalytic cycle was already confirmed by a previous work of the same authors about the synthesis of coumarins, through reaction between acetylene carboxylic acids with substituted phenols using K_2PtCl_4/AgOTf or $PtCl_2$/AgOAc catalyst in trifluoroacetic acid.[33] These reactions proceed *via* directed alkenylation of the phenols followed by the intramolecular cyclization of *ortho*-hydroxysubstituted cinnamic acids (Scheme 18). The reaction mechanism starts with the i*n situ* generated cationic species from AgOTf and Pt(II) salt which coordinates to the alkyne moiety into intermediate **A**. The following attack of the arene proceeds *via* aromatic electrophilic substitution (Wheland intermediates **B**). Proton release followed by protonation of the resulting intermediate **C** affords a heteroarylalkene. In general, hydroamination reaction gives *anti*-addition products of hydrogen and aryl group to the triple bond.

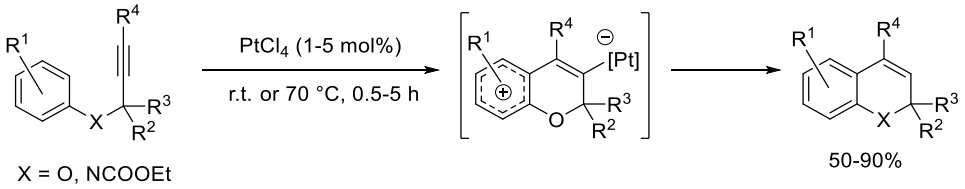
[32] [a] Oyamada, J.; Kitamura, T. *Tetrahedron* **2007**, *63*, 12754-12762; [b] Oyamada, J.; Kitamura, T. *Tetrahedron* **2009**, *65*, 3842-3847.

[33] Oyamada, J.; Kitamura, T. *Tetrahedron* **2006**, *62*, 6918-6925.



Scheme 18. *Synthesis of coumarins through Pt(II)-catalyzed hydroamination reaction.*

Similarly to Kitamura's work, an intramolecular hydroamination version for the synthesis of benzopyranes was developed in 2003 by Sames group.[34] The best results are obtained using $PtCl_4$, which exhibited an higher activity compared to other Pt(II) sources, probably because of the higher electrophilicity and the greater solubility (Scheme 19). The great tolerance to functional groups and electron-donor or electron-withdrawing substituents, as well the use of internal/terminal alkynes extended the functionalization to a series of possible scaffolds, as phenols, protected amines,[35] halides and esters. The work was also extended to alkyl heterocycles, even if in case of pyrrole and furan nucleus a mixture of *endo*/*exo*-cycled products was detected.

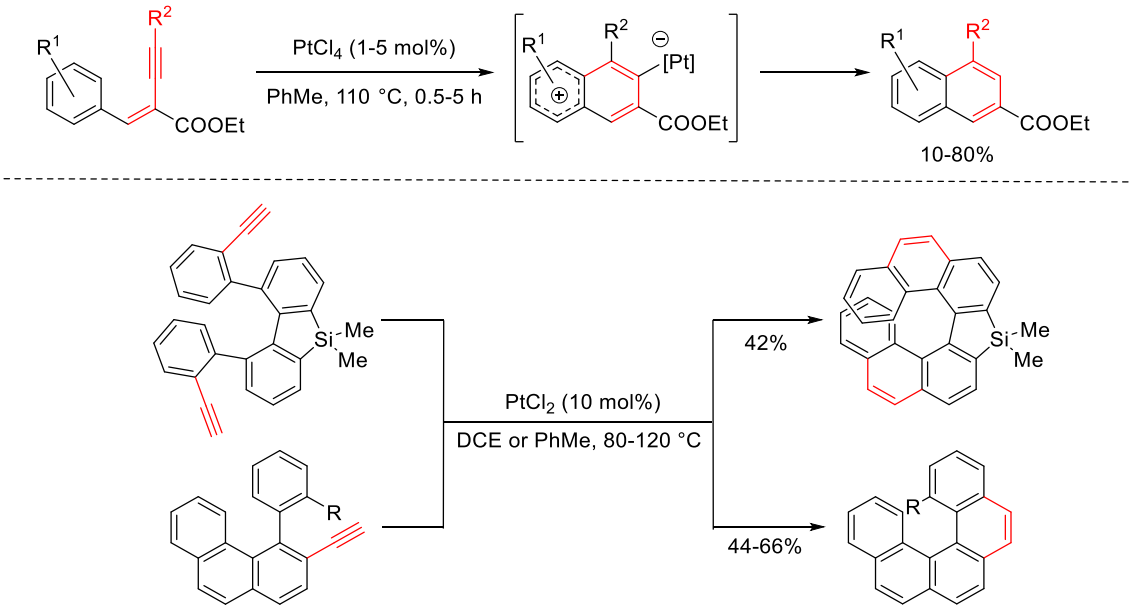


Scheme 19. *Pt(IV)-catalyzed synthesis of dihydrobenzopyranes.*

Platinum-catalyzed intramolecular hydroarylation were also employed in the synthesis of benzo-condensed 6-membered carbocycles. The use, for the same reasons as in the previous case, of platinum chloride salts in the Pt(II) and Pt(IV) oxidation state has been particularly efficient compared to the activity of other transition metal catalysts. This is the case of naphthalenes synthesis proposed by Lee and co-workers starting from the ethyl (*E*)-2-ethynyl/alkynyl cinnamates under Pt(II)-catalysis.[36] The 6-*endo*-cyclization step goes through a zwitterionic arylplatinum intermediate, which in the end aromatizes in the final product (Scheme 20, top). The same Pt-catalyzed carbocyclization on terminal alkynes was applied in

[34] Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett*. **2003**, *5*, 1055-1058.
[35] Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859-8868.
[36] Kang, D.; Kim, J.; Oh, S.; Lee *Org. Lett*. **2012**, *14*, 5636-5639.

the synthesis of dimethylsila[7]helicene and substituted[5]helicenes exploiting $PtCl_2$ as catalyst according to a 6-*endo* process (Scheme 20 ,bottom).[37]



Scheme 20. *Pt(IV)-catalyzed hydroarylation for the synthesis of naphthalenes and helicenes derivatives.*

Even if some interesting contributions in the field of Pt-catalyzed functionalization of unsaturated bonds are known[38] and effectively could offer a valid alternative to other transition metal catalysis, the research interest for platinum is still low. This fact is mainly due to the higher cost of platinum catalysts and to the lower efficiency and versatility of the same catalysts compared to other compounds containing transition metals, *in primis* palladium, gold and ruthenium.

According to the above mentioned examples, both Pd and Pt catalysts permit to access to hydroaminated or hydroarylated cycled products. So our efforts were directed towards the development of reaction conditions which permit to have a divergent behaviour according to the catalysts employed.

3. Results and Discussion

3.1. Purpose of the project

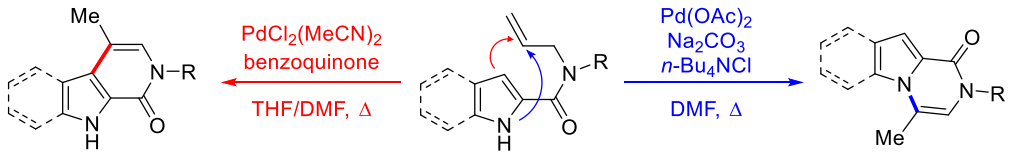
In the previous section, we presented some examples of palladium and platinum catalysis which allowed the formation of cyclic systems and we investigated the role of palladium and platinum in activation of unsatured bonds, and in particular alkynes. In this context, the development of synthetic approach based on activation/functionalization processes, catalyzed by these transition metals, would

[37] Oyama, H.; Nakano, K.; Harada, T.; Kuroda, R.; Naito, M.; Nobusawa, K.; Nozaki, K. *Org. Lett.* **2013**, *15*, 2104-2107.

[38] For other example see [a] Boyarskiy, V. P.; Ryabukhin, D. S.; Bokach, N. A.; Vasilyev, A. V. *Chem. Rev.* **2016**, *116*, 5894-5986; [b] Kitamura T. *Eur. J. Org. Chem.* **2009**, 1111-1125; [c] Yamamoto, Y. *Chem. Soc. Rev.* **2014**, *43*, 1575-1600.

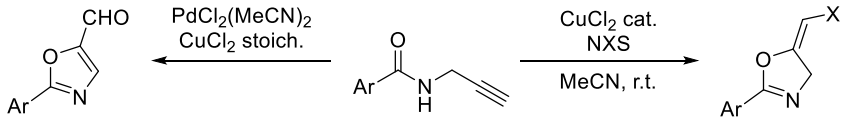
allow the access to a wide plethora of heterocyclic scaffolds depending on the types of substrate and the transition metal used.

Our research team had already been interested in previous works in the possibility of divergent synthesis for the formation of heterocyclic rings. For example, we reported two divergent Pd-catalyzed reactivities for *N*-containing heterocycles (indole and pyrrole nucleus) bearing an alkene pendant.[39] The use of two different Pd(II) pre-catalysts, as well as different reaction conditions results in formation of polycyclic structures in complete regioselective pathways, through a C–C or C–N bonds formation respectively with the C3-position or the nitrogen atom of the ring (Scheme 21).



Scheme 21. *Pd-catalyzed divergent reactivity of indole and pyrrole allyl amides.*

The same potentiality was obtained by our group working on alkynyl amides. In particular, a catalytic amount of $PdCl_2(MeCN)_2$ in the presence of a stoichiometric amount of $CuCl_2$ as reoxidant agent and traces of water, allowed us to access to substituted oxazoles through an alkoxylation process, followed by a dehydrogenation (Scheme 22, left).[40] Instead, a Cu(II)-catalyzed process, in presence of an halogens source like halosuccinamide (NXS) permitted to realize an alkoxyhalogenation process to prepare 2,5-substituted oxazolidines (Scheme 22, right).[41]



Scheme 22. *Divergent reactivity of N-propargyl amides with Pd(II) or Cu(II) catalysis.*

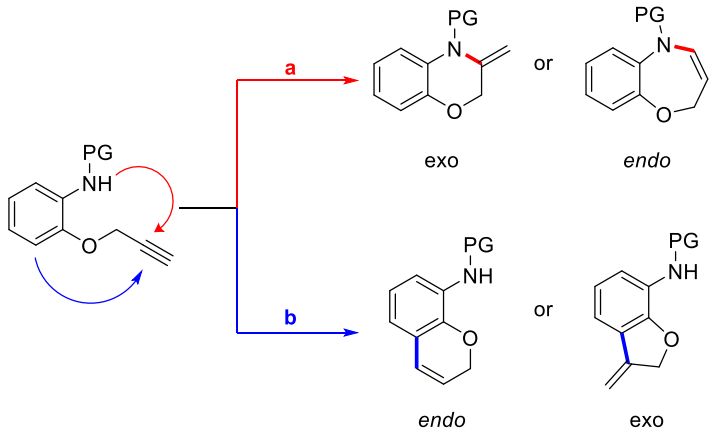
Combining the concepts of these past works, we decided to continue to focus on exploring the intramolecular coupling of unsaturated non-activated systems. We have thus envisaged a possible chemoselective divergent reactivity of the *O*-propargyl-2-aminophenols with different transition-metal catalysts, in order to identify reaction conditions able of giving a hydroamination process (path a) or a hydroarylation one (path b) as shown in Scheme 23. In addition, we also wanted to evaluate also the regioselective control of *endo*/*exo* products during the C–C or C–N bonds formation.

---

[39] [a] Abbiati,G.; Beccalli, E. M.; Broggini, G.; Zoni, C. *J. Org. Chem.* **2003**, *68*, 7625-7628; [b] Beccalli, E. M.; Broggini, G.; Martinelli, M.; Paladino, G.*Tetrahedron* **2005**, *61*, 1077-1082.

[40] Beccalli, E. M.; Borsini, E.; Broggini, G.; Palmisano, G.; Sottocornola, S. *J. Org. Chem.* **2008**, *73*, 4746-4749.

[41] Gazzola, S.; Beccalli, E. M.; Borelli, T.; Castellano, C.; Chiacchio, M. A.; Diamante, D.; Broggini, G. *J. Org. Chem.* **2015**, *80*, 7226-7235.

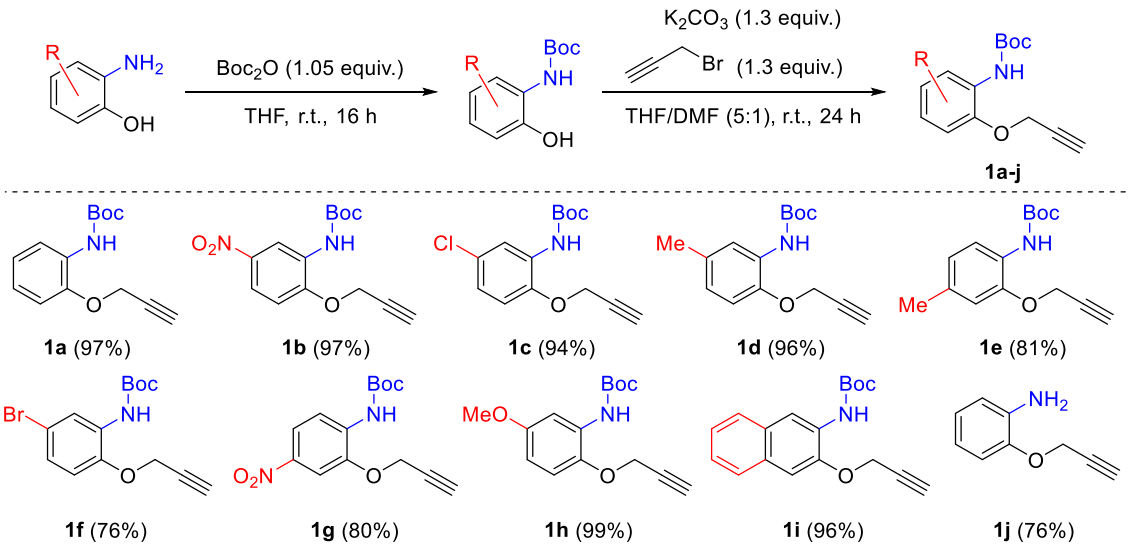


Scheme 23. *Divergent catalyzed cyclization: hydroamination vs hydroarylation of O-propargyl-2-aminophenols.*

3.2. Substrates preparation and optimization tests

The work began with the preparation of the substrates necessary for the study of intramolecular coupling with different transition metal catalysts. For this purpose, a series of diversely substituted *o*-hydroxy anilines were identified as the main structure for our type of substrate.

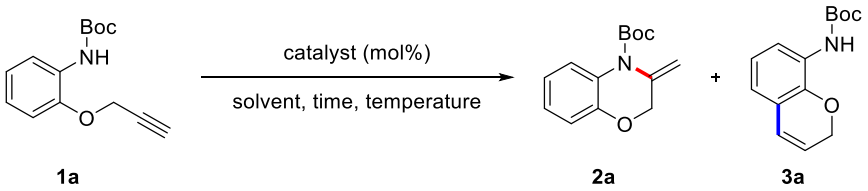
As reported in Scheme 24, the amino function was initially protected in presence of Boc_2O in THF. Then the hydroxyl group was alkylated in the presence of propargyl bromide and K_2CO_3 to furnish the desired *O*-propargyl-2-aminophenols **1a-i** with high yields. Boc as a protective group was chosen in order to increase the acidity of the N–H bond and thus potentially to favor cyclisation. In addition, we decided to prepare substrate **1j** avoiding the initial protection with the Boc group in order to confirm the importance of acid amino hydrogen. This compound was obtained by alkylation of 2-nitrophenol, followed by a hydrogenation step.



Scheme 24. *Preparation of substituted O-propargyl-2-aminophenols **1a-j**.*

At this point we started to investigate which transition metal catalysts can be suitable for the C–N or C–C intramolecular coupling. In these preliminary tests, we opted for the most simple 2-(propargyloxy)aniline **1a** as reaction benchmark (Table 1).

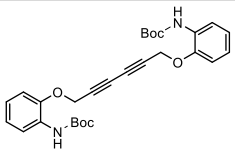
Table 1. *Catalyst screening for **2a** and **3a** synthesis.*



1a **2a** **3a**

Entry	Catalyst (mol%)	Base (equiv.)	Solvent	Temperature	Time	Product	Yields
1	$AuCl_3$ (8%)	-	MeCN	r.t.	16 h	-	-
2	$AuCl_3$ (8%)	-	MeCN	reflux	6 h	-	-
3	$AuCl_3$ (8%) AgOTf (4%)	-	DMF	120 °C	4 h	-	-
4	$AgNO_3$ (5%)	-	PhMe	80 °C	10 h	-	-
5	$AgNO_3$ (10%)	-	PhMe	100 °C (MW)	15 min	-	-
6	CuI (10%)	$CaCO_3$ (1.2)	DMF	120 °C	4.5 h	dimer[a]	-
7	$Ni(acac)_2$(10%) PPh_3 (40%)	*t*-BuONa (1.2)	PhMe	110 °C	6 h	-	-
8	$[Ir(COD)_2]BArF_4$ (5%) BINAP (10%)	-	dioxane	100 °C	16 h	mixture	
9	$Pd(PPh_3)_4$ (10%)	-	PhMe	100 °C	24 h	-	-
10	$Pd(PPh_3)_4$ (15%) PPh_3 (10%)	-	PhMe	100 °C	4 h	**2a**	83%
11	$PtCl_2(MeCN)_2$ (5%)	-	PhMe	90 °C	6 h	**3a**	40%

a: Di-*tert*-butyl [hexa-2,4-diyne-1,6-diylbis(oxy)]bis(2,1-phenylene)-dicarbamate



Catalyst screening has first shown that gold salts, already used for the hydroarylation of alkynes,[42] are ineffective to catalyze the reaction in the absence of a guiding group (entries 1 and 2), even in the presence of Ag(I) salts as a co-catalyst (entry 3). On the other hand, the only use of silver salts has also proved to be totally ineffective by simple heating or microwave irradiation (entries 4 and 5). Furthermore, CuI led to the conversion of the substrate into a dimer resulting from a Glaser-type process (entry 6). We also tested nickel catalysis, already used for the hydroamination process.[43] Unfortunately, no cyclisation

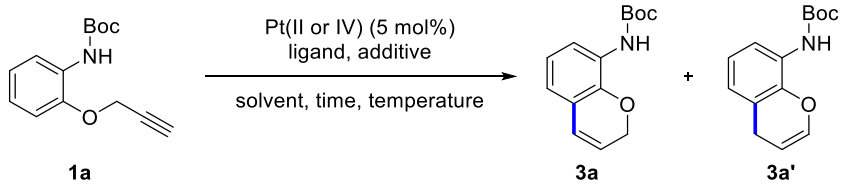
[42] Curtis, N. R.; Prodger, J. C.; Rassias, G.; Walker, A. J. *Tetrahedron Lett.* **2008**, *49*, 6279-6281.
[43] Ackermann, L.; Song, W.; Sandmann, R. *J. Organomet. Chem.* **2011**, *696*, 195-201.

product could be observed (entry 7). Similarly, a cationic complex of Ir(I), also described for hydroamination reactions,[44] gave instead a mixture of degradation products, and the deprotection of the amine (entry 8).

Subsequently, the switch to transition metal catalysts from the 10th group produced the expected results. Although the use of the $Pd(PPh_3)_4$ catalyst in toluene under thermal heating did not give any coupling products (entry 9),[45] the addition of triphenylphosphine (10 mol%) allowed the cyclization, affording 3-methylene benzoxazine **2a** in a good yield through a hydroamination process (entry 10). Likewise, the use of $PtCl_2(MeCN)_2$ as catalyst in toluene, provided the formation of the dihydrobenzopyran **3a** with 40% yield arose from a hydroarylation process (entry 11).

Considering the Pt-catalyzed hydroarylation process, besides the dihydrobenzopyran **3a** it was observed the formation of compound **3a'**, deriving from the double bond isomerization. In order to avoid the generation of side products and to increase the efficiency, an optimization work of the hydroarylation reaction with platinum catalysts was realized as reported in Table 2.

Table 2. *Pt catalysts screening for hydroarylation pathway.*



1a **3a** **3a'**

Entry	Catalyst (5 mol%)	Ligand (10 mol%)	Solvent	Temperature	Time	3a	3a'
1	$PtCl_2(MeCN)_2$	-	PhMe	90 °C	6 h	40%	10%
2	$PtCl_2(MeCN)_2$	PPh_3	dioxane	90 °C	3 h	30%	-
3	$PtCl_2$	-	PhMe	90 °C	3 h	55%	10%
4	**$PtCl_2$**	**-**	**PhMe/H_2O: 10/1**	**90 °C**	**5 h**	**60%**	**-**
5	$PtCl_2$	Xantphos	MeCN	70 °C	5 h	30%	-
6	$PtCl_2$	-	dioxane	90 °C	2 h	33%	23%
7	$PtCl_2$	JohnPhos	dioxane	70 °C	2 h	23%	10%
8	$PtCl_2$	JohnPhos + $AgBF_4$	Dioxane	70 °C	24 h	5%	-
9	$PtCl_2$	-	MeCN	70 °C	3 h	40%	-
10	$PtCl_2$	-	MeOH	50 °C	3 h	20%	-
11	$PtCl_4$	-	PhMe	80 °C	8 h	-	-
12	$PtCl_4$	-	DCE	r.t.	2 h	35%	5%

First of all, it is interesting to note that the best results are obtained when the catalyst is a source of Pt(II) and the reaction is carried out at 90 °C, whereas a species of Pt(IV) and low temperatures leads to a

[44] Burling, S.; Leslie, L. D.; Messerle, B. A.; Rumble, S. L. *Organometallics* **2007**, *26*, 4335-4343.
[45] Kundu, N. G.; Chaudhuri, G.; Upadhyay, A. *J. Org. Chem.* **2001**, *66*, 20-29.

drastic or total drop in yields (entries 11 and 12). The use of a phosphine ligand (entries 2, 5 and 7) did not seem effective to improve the reaction, as well the addition of a silver salt which drastically inhibits the catalytic cycle (entry 8). After testing several solvents (entries 5, 9 and 10), the best reaction conditions were found using $PtCl_2$ as a catalyst in wet toluene at 90 °C for 5 hours, leading to an isolated yield of 60% for the compound **3a** (entry 4). This trick of adding water, based on literature,[46] also avoided the formation of the side product **3a'**, already observed in dry solvents (entries 1, 3, 6, 7 and 12).

3.3. Pd-hydroamination *vs* Pt-hydroarylation

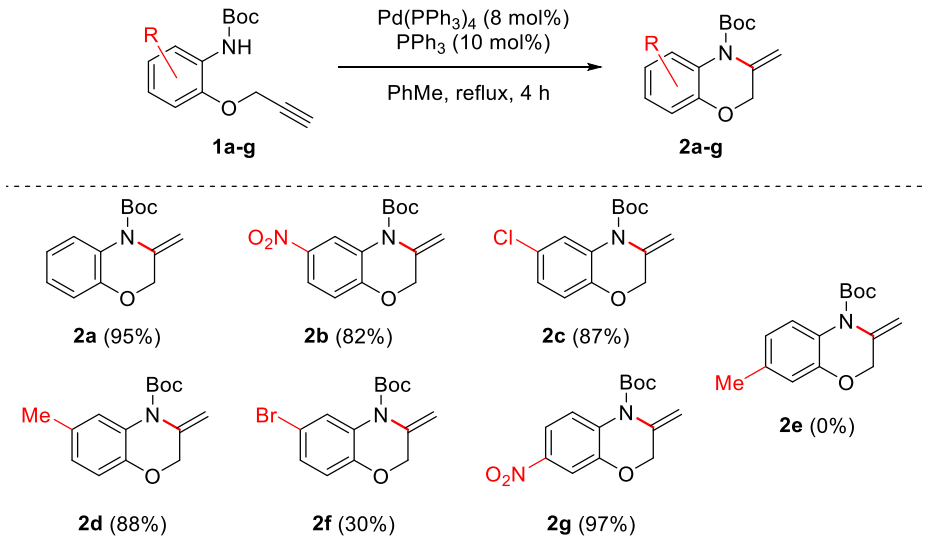
Once the most suitable transition metal catalysts for each process were identified, we started the substrate scope for the divergent synthesis. Primarily we focused our attention on the hydroamination step. In order to evaluate if it was possible to further increase the reaction yields, we optimized the reaction parameters for the cyclization of propargyloxy aniline **1a**. After some trials, we opted for a reduction in the amount of $Pd(PPh_3)_4$ to 8 mol% and an increase of reaction temperature (reflux in toluene), always in presence of 10 mol% of PPh_3. These changes permit to increase the global yield to 95% for compound **2a**.

As reported in Scheme 25, the work was extended to the others synthetized 2-propargyloxy anilines **1b-g**. First of all, it can be noted that in all cases considered, the 6-*exo*-dig cyclization was entirely selective, while the possible alternative 7-*endo*-dig was never recorded Consequently, the process led to the formation of only compounds **2b-g**, bearing the *exo*-methylene pendant. The purification of the products was performed on alluminium oxide column chromatography, in order to avoid the possible isomerization of the exocyclic double bond to the internal double bond.

The reaction was proven to be effective on substrates bearing both electron-donor and electron-withdrawing functional groups, even if some considerations have to be made. In particular, if excellent results were obtained with chlorine atom and NO_2 group in compounds **2b**, **2c** and **2g**, the same cannot be true for benzoxazine with bromine atom **2f**. The possible explanation is the behavior of bromo aryl compounds, which in presence of a Pd(0) catalyst, tend to lead to an oxidative addition step.

Similarly, a discrepancy of results was observed for propargyloxy amines **1d** and **1e**, respectively having a methyl group in *meta* or *para* position respect to the amino group. While in the first case the corresponding benzoxazine product **2d** was isolated with high yields, in the second one it was not possible to observe any trace of the desired product **2e**. A possible explanation can be found in the donor effect of the methyl group in *para* position, which tend to low the acidity of the carbamate function and to prevent the cyclization step.

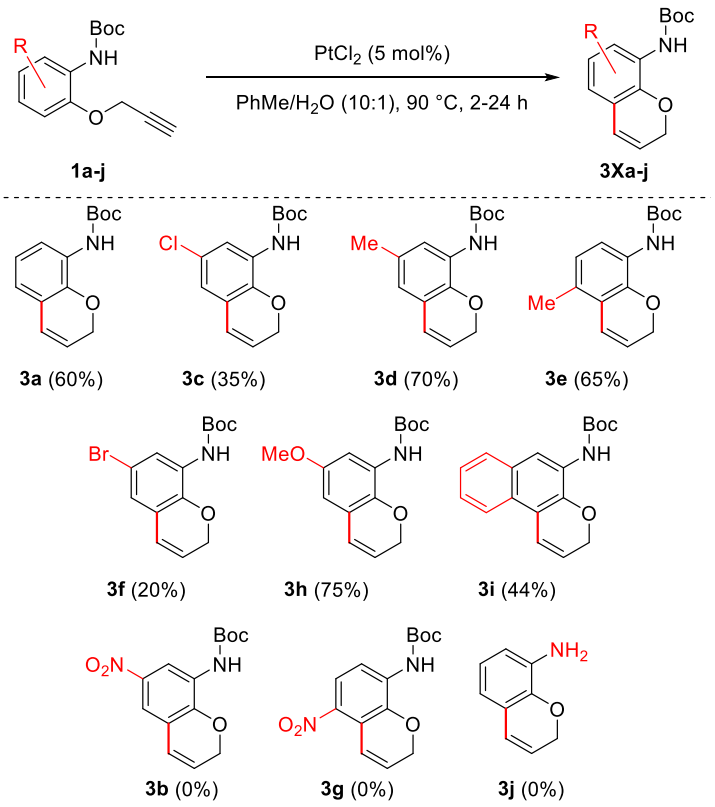
[46] Nevado, C.; Echavarren, A. M.; *Synth.* **2005**, 167-182.



Scheme 25. *Pd(0)-catalyzed hydroamination for preparation of benzoxazines* ***2a-g****.*

The optimized condition mentioned above were extended to all the prepared 2-(propargyloxy)anilines **2a-j** in order to evaluate the influence of electronic properties of the substituents in the various positions of the aromatic ring during the cyclization. Subsequently, we studied the synthetic scope of platinum-catalyzed hydroarylation. It is important to underline that no isomerization of the double bond in benzopyranes products was observed by the crude mixture or after the purification step.

In Scheme 26 are resumed the main results. According to experimental evidences, the presence of Boc group is fundamental for the reaction outcomes. The free amino function does not allow to access to the desired product **3j**. In addition, the electronic properties of the aromatic ring strongly influence the hydroarylation process. The presence of activating electron-donor moieties like Me or OMe in *meta* or *para* to propargyloxy function favored the reaction, as shown by yields of **3d**, **3e** and **3h** (65% to 75%). As expected, the conjugation of the aromatic system like in benzopyrane **3i** and the presence of halides on the ring (**3c** and **3f**), which are deactivating groups, causes a decrease in yields, while the presence of a stronger electron-withdrawing group like NO_2 in *meta* as well in *para* position of the propargyloxy anilines **1b** and **1g** totally inhibits the process.



Scheme 26. *Pt(II)-catalyzed hydroarylation for* the synthesis of *benzopyranes* ***3a-j***.

3.4. Proposed mechanisms and post-synthetical applications

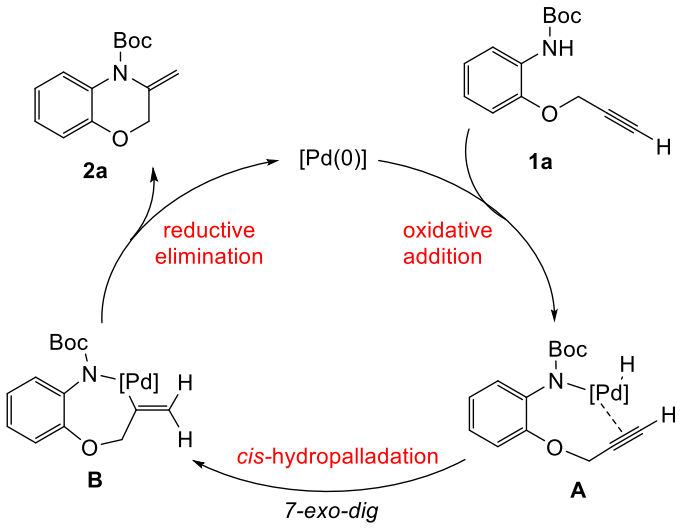
The next step was to compare the reaction mechanisms of the Pd(0)-catalyzed and the Pt(II)-catalyzed process, in order to explain both the regiocontrol in the formation of *endo*/*exo* products and in the divergent hydroamination/hydroarylation catalysis.

We first focused on the hydroamination process catalysed by a Pd(0) complex. We first anticipated the passage through an inner sphere mechanism, with a step of oxidative addition of the Pd(0) complex into the N-H bond. This mechanism is generally speculated in the case of amines possessing acidic hydrogen due to the presence of an attracting protective group.[25b,47]

Building on the reported literature and our results, the mechanism of this reaction is believed to entail first oxidative addition of the carbamate **1a** N-H bond to the Pd(0) complex,[48] to generate the palladium hydride complex **A**. Subsequent *cis*-hydropalladation is supposed to generate the 7-membered vinylidene amidopalladium complex **B**, which, after reductive elimination, affords the final product regenerating the starting Pd(0) complex (Scheme 27).

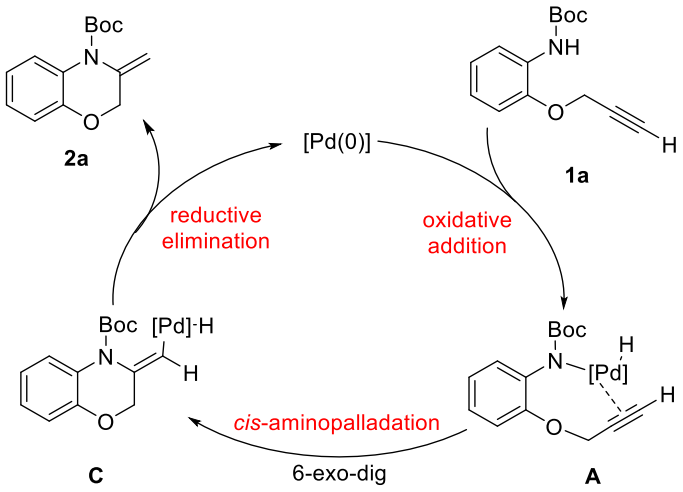
[47] [a] Patil, N. T.; Kavthe, R. D.; Shinde, V. S. *Tetrahedron* **2012**, *68*, 8079-8146; [b] Stokes, B. J., Driver, T. G. *Eur. J. Org. Chem.* **2011**, 4071-4088.

[48] Grunwald, A.; Heinemann, F. W.; Munz, D. *Angew. Chem. Int. Ed.* **2020**, *59*, doi.org/10.1002/anie.202008350.



Scheme 27. *Supposed mechanism* via *a 7*-exo-dig *hydropalladation step.*

An alternative mechanism may entail, after oxidative addition, an aminopalladation step, to generate the 6-membered vinylpalladium hydride complex **C**. Again, a reductive elimination is expected to close the catalytic cycle.



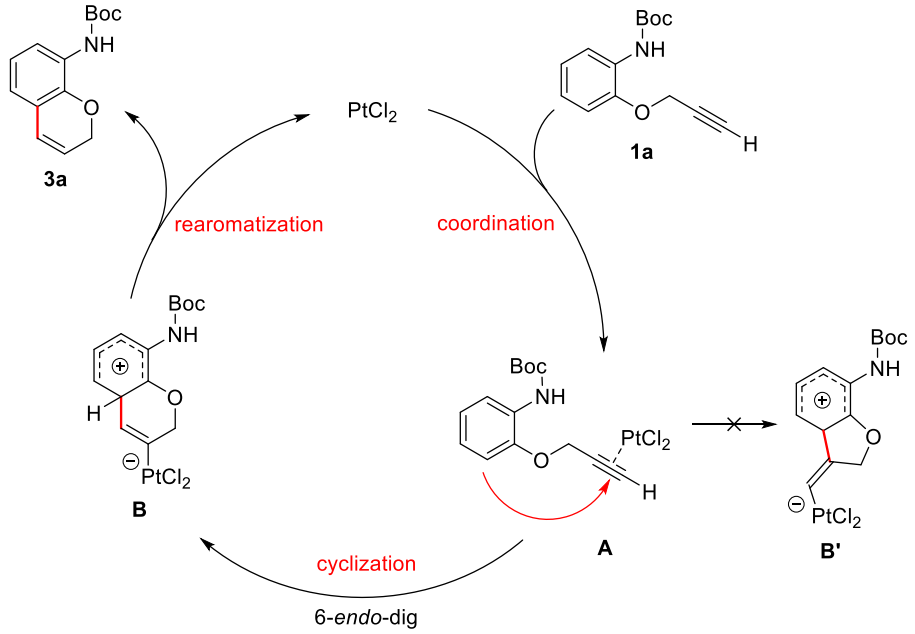
Scheme 28. *Alternative catalytic cycle through a 6*-exo-dig *aminopalladation step.*

In view of the low pKa value of PPh_3,[49] a further possible reaction mechanism based on deprotonation of the carbamate by PPh_3, as evoked by Yamamoto et al., seems improbable.[50]

For the platinum-catalyzed intramolecular hydroarylation of *O*-propargyl-2-aminophenol **1a**, we based our hypothesis on the well-known mechanisms reported in the literature (Scheme 29).[51] The catalytic cycle starts with the coordination of the Pt(II) catalyst at the alkyne leading to the intermediate **A**. Then, the attack of the activated alkyne is carried out by aromatic electrophilic substitution. The reaction can take

[49] Allman, T.; Goel, R. G., *Can. J. Chem.* **1982**, *60*, 716-722.
[50] Bajracharya, G. B.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4883-4886.
[51] Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155-3164.

place through two different Wheland intermediates. However, experimental evidence only shows the formation of the cyclization product *via* 6-*endo-dig* cyclization (Wheland intermediate **B**). Rearomatization followed by protonation of the alkenyl-platinum intermediate gives the benzopyrane **3a** and regeneration of the Pt(II) complex.



Scheme 29. *Mechanism for Pt-catalyzed hydroarylation of propargyloxy anilines.*

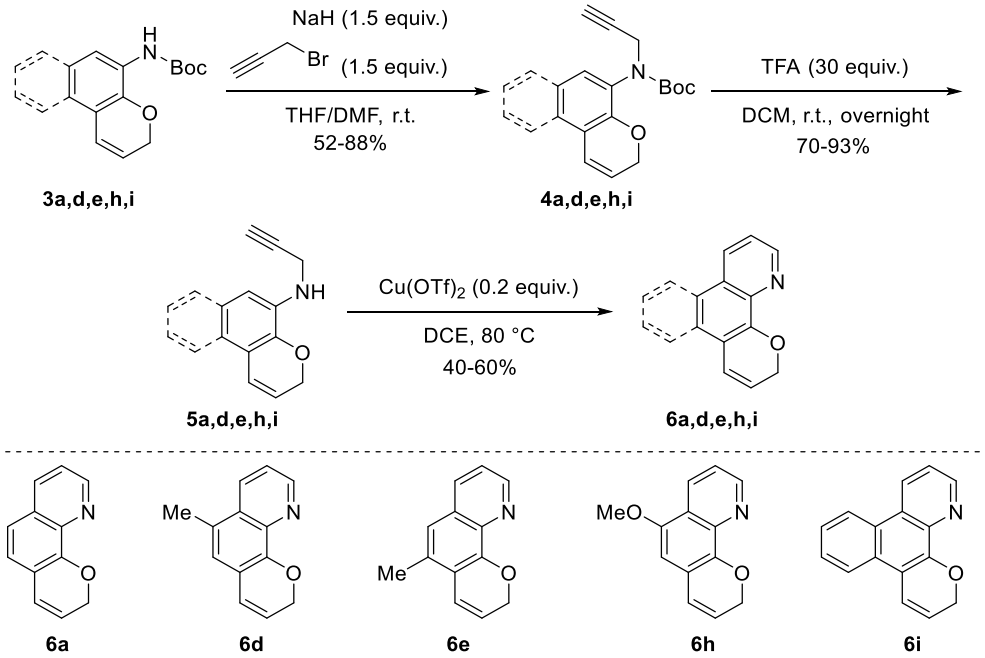
Finally, we tested the synthesized compounds in a new functionalization step, which allowed us to show the potentiality of these scaffolds as intermediates for more complex molecules. In particular, our attention was drawn to the benzopyrans prepared by platinum catalysis, which still contain the functionalizable aniline nitrogen. The propargylation of the unreacted nitrogen paved the way for a second hydroarylation step, this time in the *ortho* position of the amino function. In this way, it was possible to gain easy access to a series of pyrano[3,2-*h*]quinolines, targets with antiproliferative[52] and antioxidant[53] properties useful in the treatment of Alzheimer's disease.

The electron rich benzopyranes **3a,d,e,h,i**, which furnished the better yields, were chosen as substrate model. In Scheme 30 is reported the synthetic plan followed. First of all the amino function was propargylated in standard conditions to give compounds **4a-i** and subsequently the Boc protecting group was removed in strong acidic conditions employing TFA at room temperature to give the secondary anilines **5a-i**. The last step was the hydroarylation step, which was achieved under copper catalysis in DCE, due to

[52] [a] Fouda, A. M. *Med. Chem. Res.* **2017**, *26*, 302-313; [b] El-Agrody, A. M.; Abd-Rabboh, H. S. M.; Al-Ghamdi, A. M. *Med. Chem. Res.* **2013**, *22*, 1339-1355; [c] Hosny, M. A.; Radwan, H. A.; El-sawi, E. A.*E-J. Chem.* **2012**, *9*, 1737-1745.

[53] [a] Dgachi, Y.; Sokolov, O.; Luzet, V.; Godyn, J.; Panek, D.; Bonet, A.; Martin, H.; Iriepa, I.; Moraleda, I.; Garcìa-iriepa, C.; Janockova, J.; Richert, L.; Soukup, O.; Malawska, B.; Chabchoub, F.; Marco-Contelles, J.; Ismaili, I. *Eur. J. Med. Chem.* **2017**, *126*, 576-589; [b] Boulebd, H.; Ismaili, L.; Bartolini, M.; Bouraiou, A.; Andrisano, V.; Martin, H.; Bonet, A.; Moraleda, I.; Iriepa, I.; Chioua, M.; Belfaitah, A.; Marco-Contelles, J. *Molecules* **2016**, *21*, 400-416.

the unproductive platinum catalysis. Thus, after an in-situ oxidation, the pyrano[3,2-*h*]quinolines **6a-i** were isolated in good yields.



Scheme 30. *Three steps post-functionnalization of pyrano[3,2-*h*]quinolines **6a-i**.*

Unlucky, it was not possible to perform the synthesis of quinoline derivatives starting from the *N*,*O*-dipropargyl-2-aminophenol in an one pot reaction, employing both the reaction conditions tested nor other different metal catalysts.

4. Conclusions

In this chapter we presented two successful divergent regioselective cyclizations of propargyloxy anilines depending on the transition metal catalyst used.

We began to clarify what divergent catalysis is, presenting some significant examples and focusing on the usefulness of this methodology which has not yet been fully explored. Subsequently, we focused our attention on palladium and platinum catalysts, two metals that are extremely versatile for their chemical properties. More specifically, we reported various examples of intermolecular and intramolecular hydroamination and hydroarylation reactions of unsaturated bonds catalyzed by palladium or platinum.

We then presented the study on optimization of the reaction conditions for the hydroamination and hydroarylation methodology. In particular, the formation of the C–N bond was achieved using a $Pd(PPh_3)_4$ catalysis, while the C–C bond required the use of $PtCl_2$ as catalyst.

We observed that the hydroamination reaction worked well in the presence of electron-withdrawing substituents on the aromatic ring, allowing the desired benzoxazines to be isolated with good yields. On the

other hand, the hydroarylation process requires electron-rich arenes, which gives access to substituted benzopyrans with moderate or good yields.

We have also proposed two reaction mechanisms. The divergent pathway hypothesis is based on the fact that, while the Pd(0) catalyst first performs the oxidative addition in the N-H bond (co-catalyzed by the addition of triphenylphosphine) and therefore promotes coupling with the unsaturated fraction, platinum catalysis starts with the coordination of the catalyst at the alkyne, followed with a S_EAr.

The last phase was the clarification of both the reaction mechanisms. The hypothesis for the divergent pathways is based on the fact that, while palladium catalyst first fulfills oxidative addition on the aniline nitrogen and consequently promotes the coupling with the unsatured moiety, platinum catalysis starts with the coordination of the catalyst to the alkyne and only later carries on with the attack on the aromatic ring.

In the end, we demonstrated the benefit of benzopyranes synthesized via Pt-catalyzed hydroarylation reaction as intermediate in a new efficient synthesis for the preparation of pyrano[3,2-*h*]quinolones.

Chapter 2: Carbonylative Murai reaction on heterocyclic systems

1. Introduction

Five-membered heterocyclic compounds are common structural units present in different types of structures, as in natural compounds and biological molecules, like enzymes and active principles for drugs. Among them, heteroaromatics functionalized in various positions with a carbonyl/carboxyl group can be of particular interest (Figure 3).[54] Just for example, we can mention "Prazosin", an antihypertensive agent used in combination with other drugs in the therapy of patients with chronic hypertension.

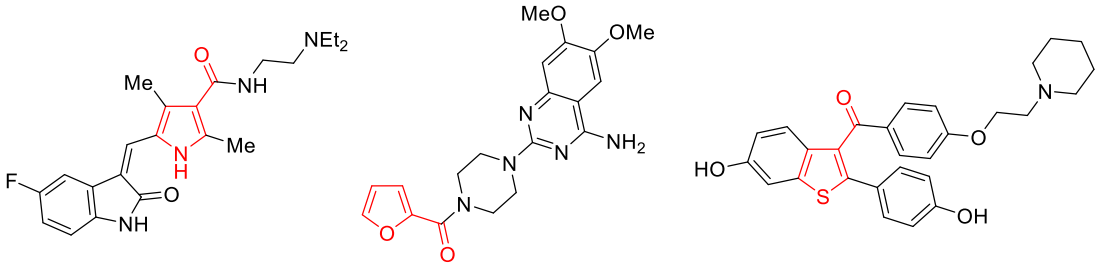
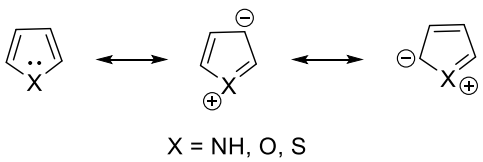


Figure 3. *Structures of biologically interesting carbonylated heterocycles.*

Due to their wide use in the pharmaceutical field, strategies for the functionalization of heteroaromatic motifs are usually of great interest in organic synthesis. In addition, the employment of transition metal catalysts for the functionalization allows a high degree of selectivity, high functional group tolerance, and a possible variation of the usual electronic properties.

Pyrrole, furan and thiophene are aromatic heterocyclopentadienes wherein the heteroatom lone pair participates to the aromaticity. As a consequence, the 6π-electron system of these heterocycle is rich and prone to undergo electrophilic aromatic substitutions (Scheme 31).[55]



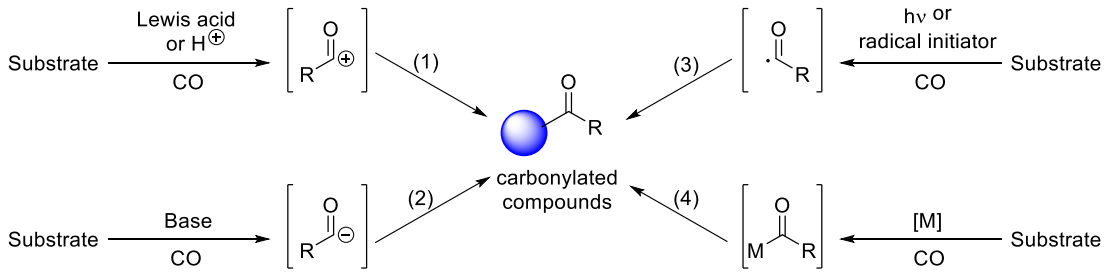
Scheme 31. *Possible resonance forms of five-membered heteroarenes.*

[54] [a] Papaetis, G. S.; Syrigos, K. N.; *BioDrugs*, **2009**, *23*, 377-389; [b] Graham, R. M.; Pettinger, W. A. *N. Engl. J. Med.* **1979**, *300*, 232-236; [c] Dadiboyena, S. *Eur. J. Med. Chem.*, **2012**, *51*, 17-34.

[55] Pratihar, S; Roy. S. *J. Org. Chem.* **2010**, *75*, 4957-4963.

1.1. Traditional carbonylative methods *vs* C–H activation

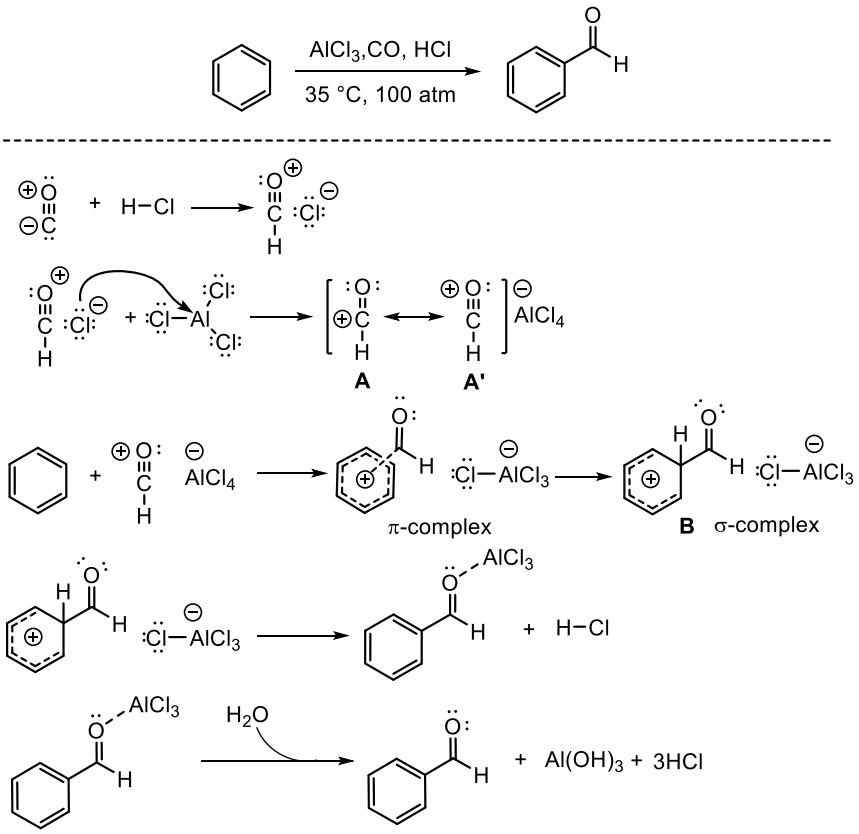
The general definition of "carbonylation" usually refers to organic reactions that insert carbon monoxide (CO) into a substrate.[56] Initially used in the synthesis of aldehydes, carboxylic acids and esters, the term has recently been extended to a range of organic processes. From a synthetic point of view, carbonylation reactions can be historically divided into four groups, depending on the reaction intermediates involved: 1) cationic carbonylations using strong Lewis or Brønsted acids; 2) anionic carbonylations with strong bases; 3) carbonylation *via* radical processes and 4) transition metal-mediated carbonylation with CO insertion (Scheme 32).



Scheme 32. *Different reaction pathways in carbonylative processes.*

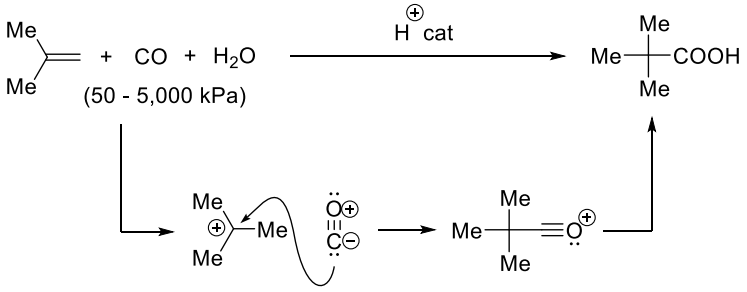
The oldest example of cationic carbonylation dates back to 1897, when Gattermann and Koch performed the formylation of toluene under CO and HCl atmosphere as acylating agents in Friedel-Crafts acylative conditions.[57] The formylation mechanism proceeds via the formyl cation, represented by the two resonance contributors **A** and **A'**, which is formed in situ by the reaction between CO and HCl. The formyl cation is then attacked by the aromatic ring to form the Wheland σ-complex intermediate **B**, which gives the aromatic aldehyde after deprotonation and hydrolysis. This reaction, known as the Gattermann-Koch reaction, is the major process for the synthesis of aromatic aldehydes in industry. Two protocols: at atmospheric pressure of CO with Cu_2Cl_2 present and at high-pressure in absence of Cu_2Cl_2, in which the optimal temperature for high-pressure synthesis of benzaldehyde is 35 °C (Scheme 33).

[56] For a review on carbonylation history see: Peng, J.- B.; Geng, H.- Q.; Wu, X.- F. *Chem* **2019,** *5*, 526–552.
[57] Gattermann, L.; Koch, J.A. *Ber. Dtsch. Chem. Ges.,* **1897***, 30*, 1622-1624.



Scheme 33. *Gattermann-Koch process for benzaldehyde synthesis.*

Another possible way for cationic carbonylation exploits the use of strong mineral acids as catalysts, which are widely used industrially. One of the first examples is represented by the Koch process for the synthesis of tertiary carboxylic acids.[58] This acid-catalyzed carbonylation using carbon monoxide involves the initial formation of a carbocation by protonation of an alkene (or an alcohol, or by direct generation from alkane in a superacidic aqueous medium *via* a protolytic ionization process), followed by the addition of carbon monoxide and water addition to the resulting acylium cation intermediate (Scheme 34).



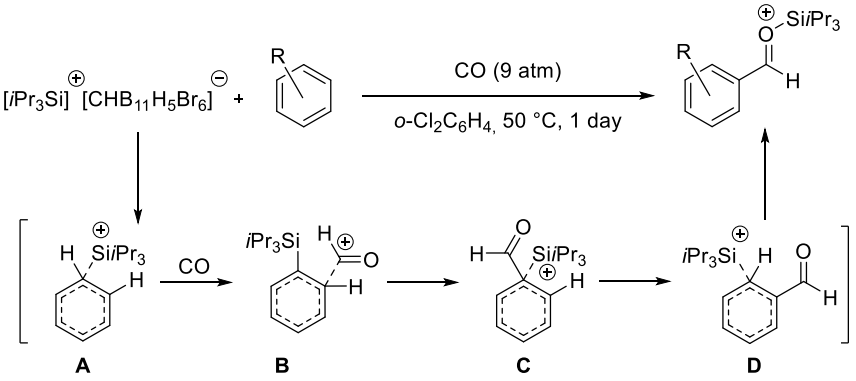
Scheme 34*. Koch process for the synthesis of pivalic acid.*

Very recently, Oestreich and his group reported a variant of carbonylative arene formylation mediated by a silylium ion.[59] The strong Lewis acidity of the silylium ion $[R_3Si]^+[WCA]$(WCA = weakly coordinating

[58] Koch, H.; Haaf, W. *Ann*. **1958**, *618*, 251-266.

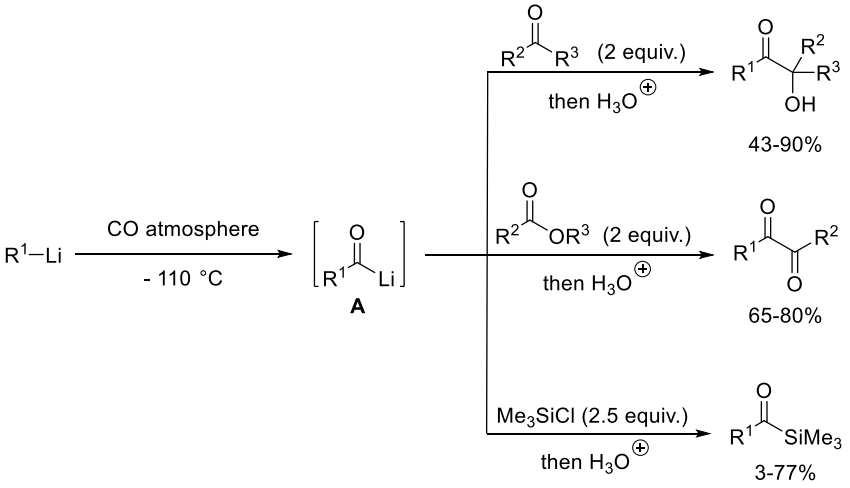
[59] Omann, L.; Qu, Z.-W.; Irran, E.; Klare, H.F.T.; Grimme, S.; Oestreich, M. *Angew. Chem. Int. Ed*. **2018**, *57*, 8301-8305.

anion) allows to carry out this S_EAr passing through the putative silyl intermediates **A**, **B**, **C** and **D**, whose possible structures have been determined by computation (Scheme 35). This procedure permitted to efficiently formylate sterically hindered as well as electron-poor arenes.



Scheme 35. *Arenes formylation* via *silylium-ion intermediates.*

Anionic carboxylation has been studied by several research groups, but has not been much exploited so far in organic synthesis. Examples in this field have been independently studied by Bose and Seyferth groups.[60] In particular, the carbonylation of alkyl compounds is based on the reaction between alkyllithium reagents and carbon monoxide. In presence of the suitable reaction partner, the authors demonstrated the possibility to synthetize α-hydroxy ketones, 1,2-diketones and acyltrimethylsilanes starting from the organolithium reagents and ketones, esters or chlorosilane respectively (Scheme 36). Although the mechanism of the organolithium/CO reaction is quite complex, the commonly accepted initial intermediate of these reactions is the acyllithium species **A**, which is *in situ* trapped by the electrophile partner. However, carefully controlled reaction conditions are required to obtain the highly reactive specie **A**.

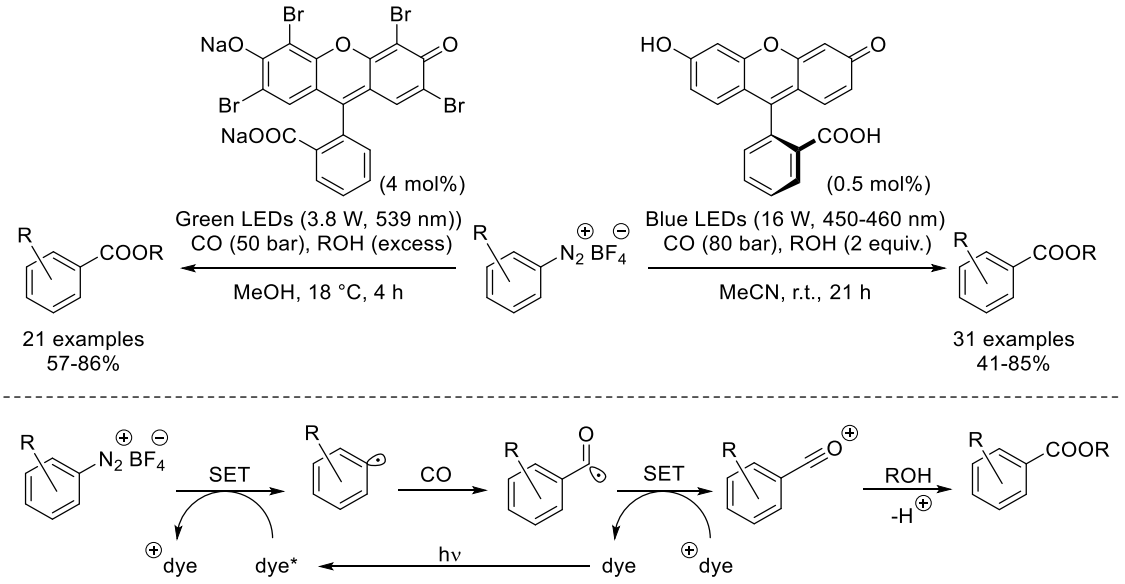


Scheme 36. *Anionic carbonylation through acyllithium intermediates*

[60] [a] Sahu, D. P.; Mashava, P.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1983**, *48*, 1144-1146; [b] Seyferth, D.; Weinstein R. M. *J. Am. Chem. Soc.* **1982**, *104*, 5534-5535.

Processes-based on a radical reaction are much more attractive from a synthetic point of view. Among the possible radical initiators, tin and peroxide compounds, as well as photochemistry are certainly the best known, although some oxidants and metals can also perform this step. Free radical-mediated carbonylation was first reported in 1952, when Brubaker, Coffman, and Hoehn described the copolymerization of ethylene with CO under high pressures and temperatures in presence of peroxide initiator.[61] However, these rather drastic reaction conditions initially limited the use of this technique. Another radical based example, reported by Ryu and co-workers, demonstrated the formylation of aromatic iodides in presence of carbon monoxide and a radical initiator.[62] The highly diluted reaction conditions are required in order to improve the yields of the reaction.

Recently, a great deal of interest has been devoted to the photo-induced reaction in visible light, both for the milder conditions used and for the green chemistry mindset. From the point of view of aromatic carbonylation, in 2015, the Xiao group on the one hand, and Wangelin and Majek on the other, independently reported an example of photo-induced carbonylation of arenes in the presence of aryl diazonium salts as a source of radicals.[63] Under irradiation with visible light (blue or green LEDs), the treatment of aryl diazonium salts with alcohols under CO pressure generated the corresponding esters with good to excellent yields. The addition of a photocatalyst [such as fluorescein (E^0_{red} = -1.21 V) or Yeosin (E^0_{red} = -1.11 V)] is necessary to promote a single electron transfer (SET) to the aryl diazonium to give the aryl radical. This is rapidly transformed into an acyl radical by trapping a CO molecule which is oxidized after another single electron transfer to give an acylium cation. Finally, the addition of alcohol to this acylium cation generates the final product (Scheme 37).



Scheme 37. *Radical alkoxycarbonylation of aryldiazonium salts through visible-light photoredox catalysis.*

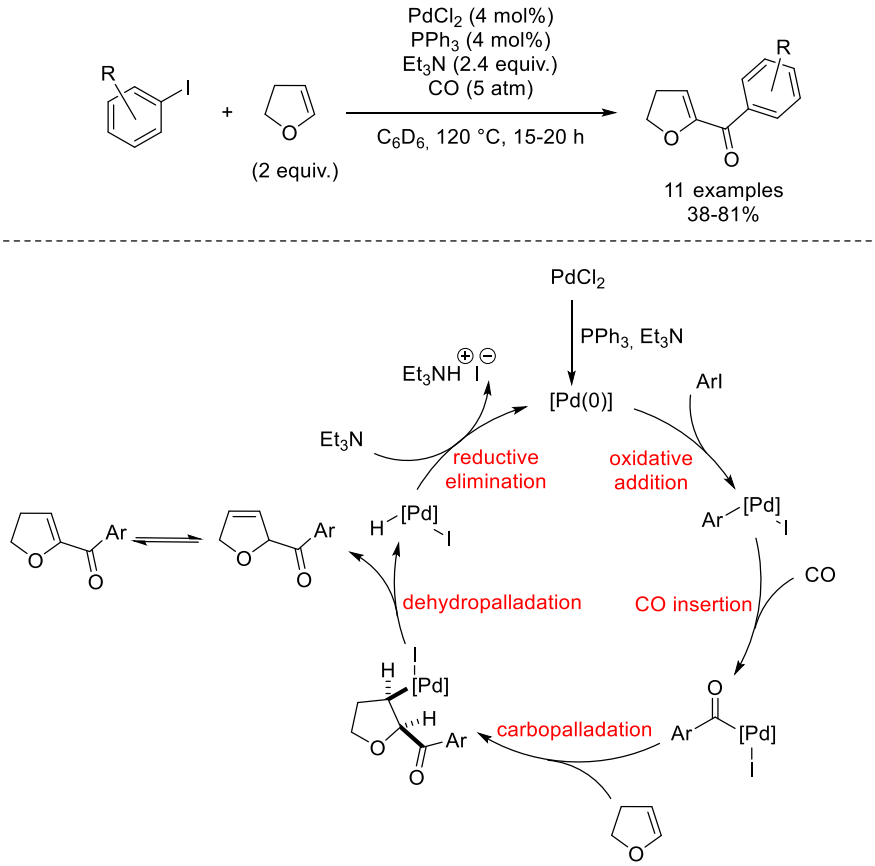
[61] Brubaker, M. M.; Coffman, D. D.; Hoehn, H. H. *J. Am. Chem. Soc.* **1952**, *74*, 1509-1515.

[62] Ryu, I.; Kusano, K.; Masumi, N.; Yamazaki, H. *Tetrahedron Lett.*, **1990**, *31*, 6887-6890.

[63] [a] Guo, W.; Lu, L.-Q.; Wang, Y.; Wang, Y.-N.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed*. **2015**, *54*, 2265-2269; [b] Majek, M.; Wangelin, A.J. *Angew. Chem. Int. Ed*. **2015**, *54*, 2270-2274.

Last but not least, transition metal-catalysis is the most employed way to perform carbonylative transformations. The main advantages of transition metal catalysis are the mild reaction conditions and the wide functional group tolerance. Several metal catalysts have been employed for the carbonylation of alkenes and arenes.[64]

For example, Miura and his colleagues reported in 1995 the first example of Pd(0)-catalyzed intermolecular carbonylative Mizoroki-Heck coupling.[65] The reaction between aryl iodides and five-membered alkenes, such as dihydrofuran, under CO pressure leads to 2-benzoyl-4,5-dihydrofuran, according to an α-regioselectivity of the carbopalladation step occurring between the ArCO[Pd]I complex and the double bond (Scheme 38).



Scheme 38. *Intermolecular Pd(0)-catalyzed carbonylation of dihydrofuran.*

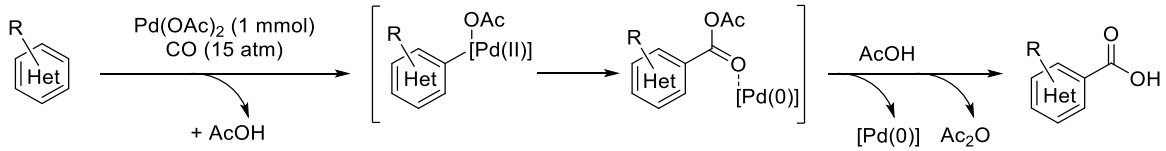
Compared with all the examples reported so far, the carbonylation by C–H activation presents clear advantages, including avoiding the pre-functionalization steps. The first example of arene carbonylation exploiting Pd(II) catalysis was reported by Fujiwara and co-workers in 1980.[66] The authors performed carbonylation reaction of (hetero)arenes with $Pd(OAc)_2$ as catalyst under CO pressure (15 atm) (Scheme 39). The initial C-H activation step leads to the formation of AcOH (see chapter 3), which, after the

[64] Beller, M;. Wu, X. -F. Transition Metal-Catalyzed Carbonylation Reactions, *Springer*, **2013**.

[65] Satoh, T; Itaya, T; Okuro, K; Miura, M.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 7267-7271.

[66] [a] Fujiwara, Y.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc. Chem. Commun*. **1980**, 220-221; [b] Fujiwara, Y.; Takaki, K.; Taniguchi, Y. *Synlett* **1996**, *7*, 591-599.

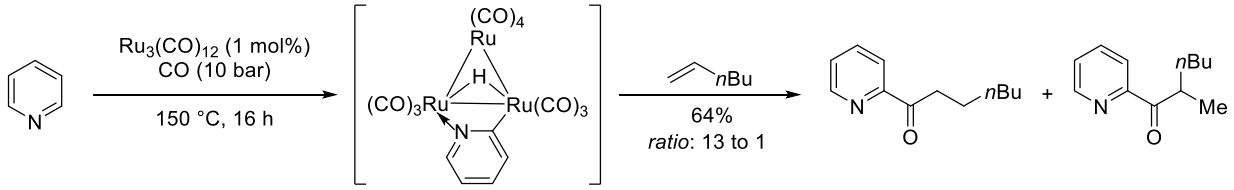
reductive elimination step, contributes to hydrolyse the anhydride intermediate to the final aromatic carboxylic acids.



Scheme 39. *First example of carbonylative C–H functionalization.*

However, other transition metal catalysts have been used in C-H activation/carbonylation methodologies. Among them, rhodium and ruthenium complexes proved to be particularly useful for the insertion of CO on (hetero)arenes scaffold.[67]

The first example exploiting ruthenium catalysis was reported by Moore and co-workers in 1992 at the Amoco Chemical Company, who performed the *ortho* acylation of pyridine in the presence of carbon monoxide atmosphere (10 bar) and using $Ru_3(CO)_{12}$ as catalyst.[68] Interestingly, other Ru(0) catalysts like $Ru_3(CO)_{11}(PPh_3)$ and other transition metal carbonyl complexes, such as $Rh_4(CO)_{12}$, $Os_3(CO)_{12}$ or $Fe_3(CO)_{12}$ resulted less or totally ineffective to promote the coupling. Worthy of note, pyridine is an electron-poor heterocycle that cannot be functionalized through a conventional Friedel-Craft acylation process, and other S_EAr functionalize the eta position. The reaction does not require the presence of a directing group, and provided good yields when terminal or di-substituted olefins were used, while tri and tetra-substituted alkenes were ineffective for the coupling. The authors suggested the involvement of a trimeric complex intermediate (Scheme 40).



Scheme 40. *Carbonylative Ru(0) catalyzed* ortho *C–H acylation of pyridine.*

Chatani and co-workers exploited the same $Ru_3(CO)_{12}$ catalyst for the aromatic C-H *ortho*-carbonylation of arylamides and the β-carbonylation of unactivated C(sp^3)-H bonds to obtain phthalimides and succinimides respectively (Scheme 41).[69] In both cases, the bidentate 2-pyridinylmethylamino directing group is crucial to the success of the transformation.

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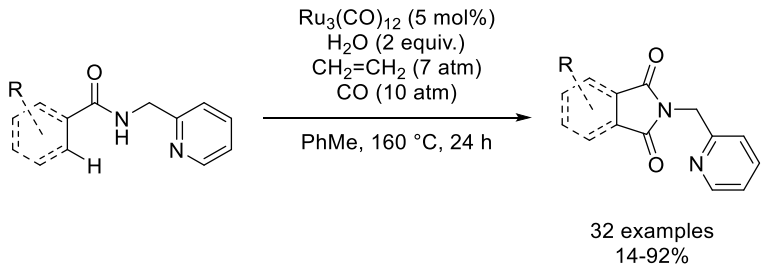
67 For a review on this topic see: Wu, X.- F.; Neumann, H. *ChemCatChem* **2012**, *4*, 447-458.

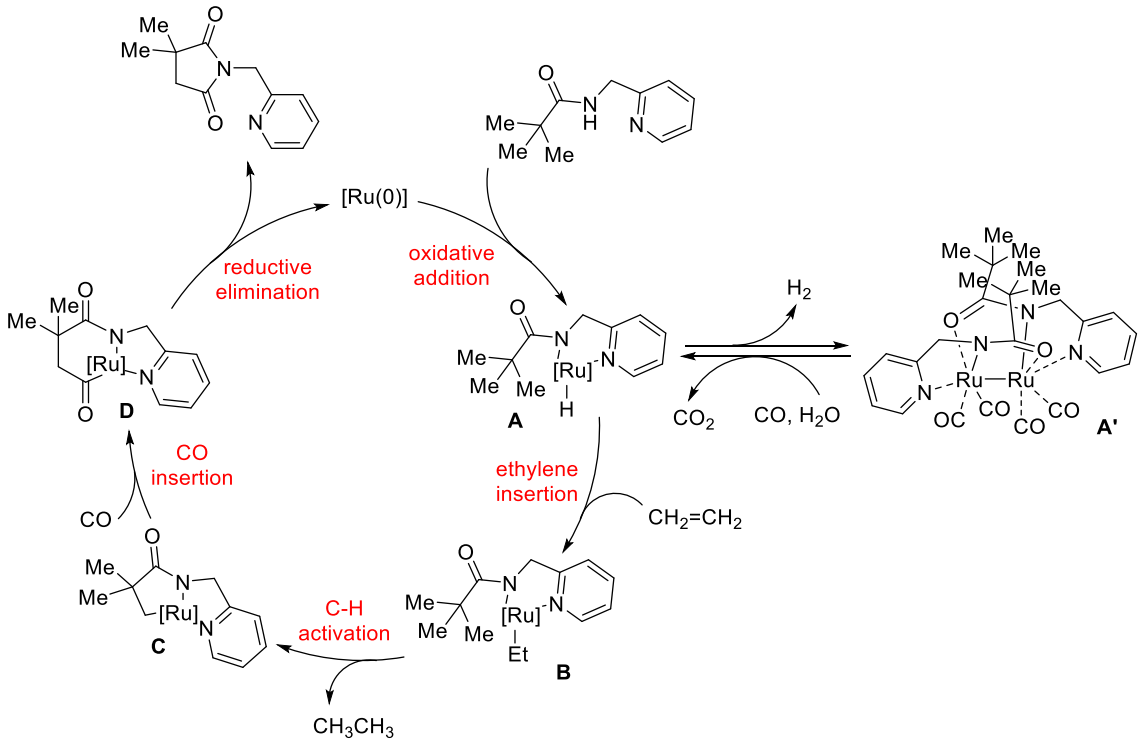
68 Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888-5890.

69 [a] Inoue, S.; Shiota, H.; Fukumoto, Y. ; Chatani, N. *J. Am. Chem. Soc*. **2009**, *131*, 6898-6899. [b] Hasegawa, N; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070-8073.



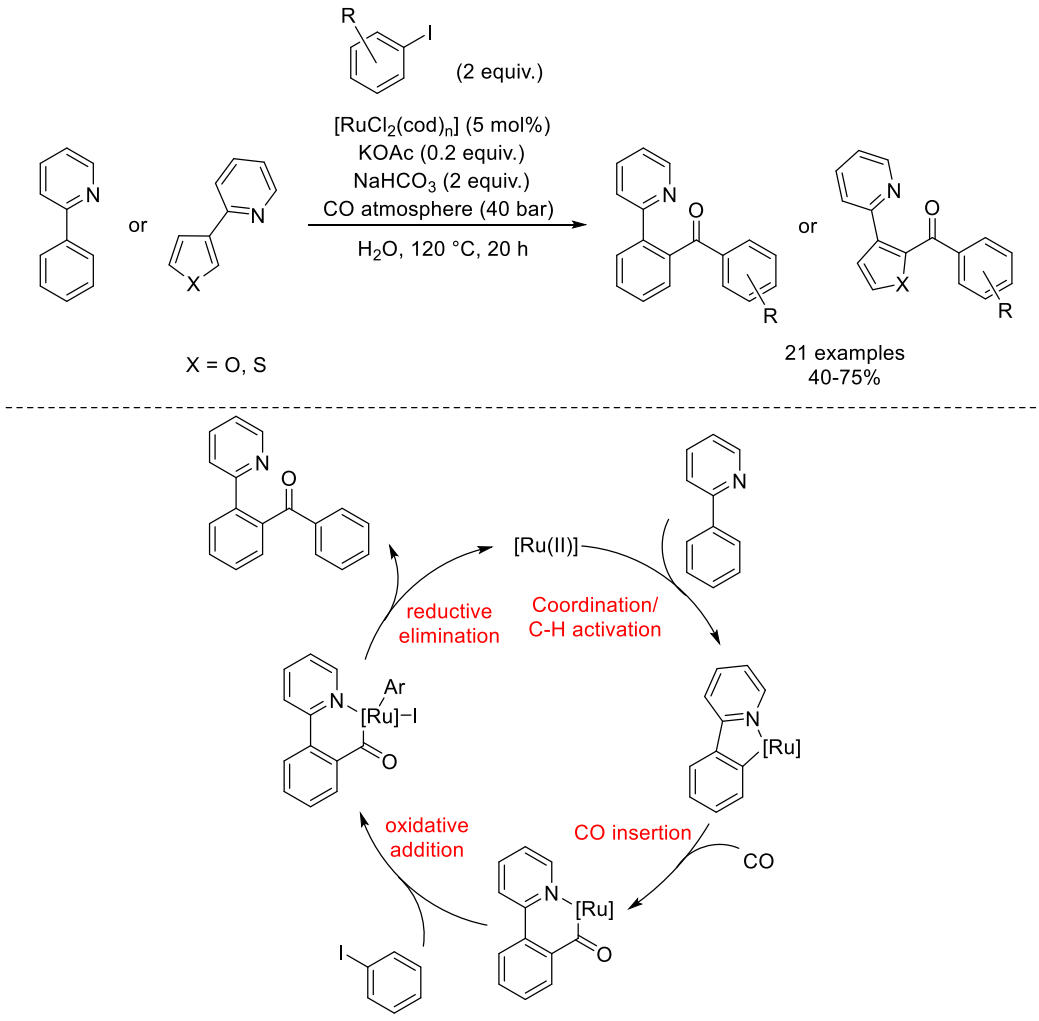
Scheme 41. *Ru-catalyzed carbonylation/cyclization sequence.*

As reported in Scheme 42, the mechanism proposed by the authors well accounts for the beneficial presence of water and ethylene. The catalytic cycle starts with the oxidative addition and coordination of Ru(0) complex to both the nitrogen atoms of the substrate, generating the intermediate **A**, also existing as dimeric form **A'** (inactive in the cycle). The insertion of ethylene leads to intermediate **B**, which through an irreversible C-H activation steps gives the metallacycle intermediate **C**. The key role of ethylene is confirmed by the lack of the final product when it cannot act as hydrogen acceptor. Subsequently the insertion of a CO molecule generates intermediate **D** and in the end, after the reductive elimination step, the final succinimide.



Scheme 42. *Reaction mechanism for Ru(0)-catalyzed succinimide synthesis.*

In 2013, Beller and co-workers reported a Ru(II) catalyzed carbonylative *ortho* acylation of 2-arylpyridines in the presence of iodoarenes and under carbon monoxide atmosphere (Scheme 43).[70] For the reaction mechanism, authors proposed the initial formation of the cyclometallated ruthenium complex by C–H activation, with subsequent carbonylation and oxidative addition of the aryl halide. In the end, the reductive elimination gives the product and regenerates the active catalyst.



Scheme 43. *Carbonylative* ortho *acylation of 2-arylpyridines.*

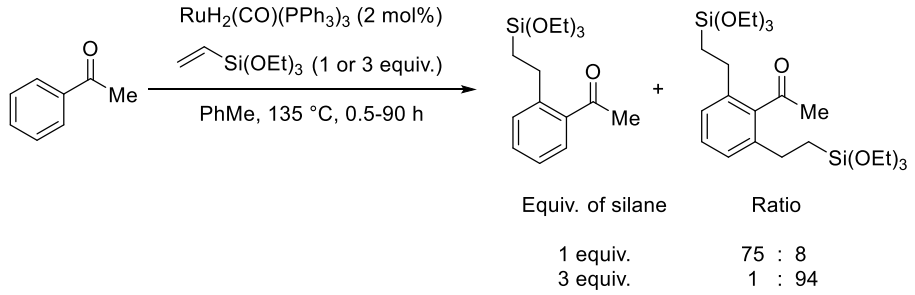
2. Murai Reaction: State of the Art

The Murai reaction consists in the Ru(0)-catalyzed *ortho* hydroarylation or hydrovinylation of alkenes or alkynes in the presence an arene carrying an appropriate directing group. Commonly used pre-catalysts for this process include $RuH_2(CO)(PPh_3)_3$ or $Ru_3(CO)_{12}$ as a source of Ru(0), and $[Ru(p\text{-cymene})Cl_2]_2$ as a Ru(II) catalyst. The Murai reaction is mainly described for the functionalization of aromatic ketones and imines, which act as directing groups for the C-H activation step.

[70] Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6293-6297.

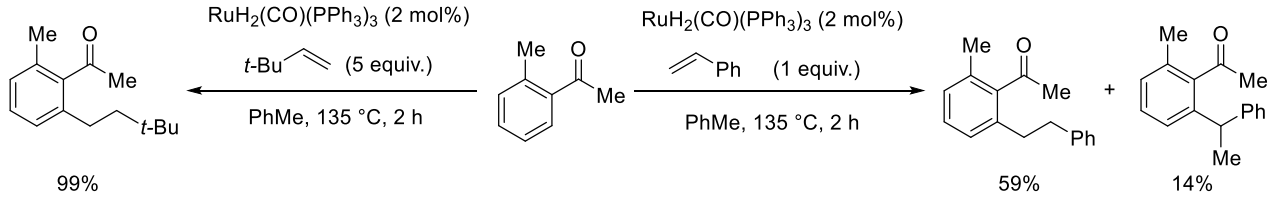
2.1. Pioneering works

In 1993, Murai and coworkers described the first Ru-catalyzed alkylation of aryl ketones in the presence of monosubstituted alkenes, later known as the "Murai reaction".[71] The ketone function acts as the steering group and allows exclusively the *ortho* coupling product to be obtained. The $RuH_2(CO)(PPh_3)_3$ precatalyst turned out to be the best one, and electron rich alkenes have been shown to be the most suitable coupling partners. First, various vinylsilanes were successfully employed to provide with good yields the coupling products with acetophenone and 2-methylacetophenone (Scheme 44).[72]



Scheme 44. *First example of Murai reaction.*

Aliphatic and cyclic olefins such as *tert*-butyl ethylene, norbornene and others could be also coupled with different aryl ketones. Styrene derivatives also produced the expected products with satisfactory yields, although as mixtures of linear and branched compounds (Scheme 45).

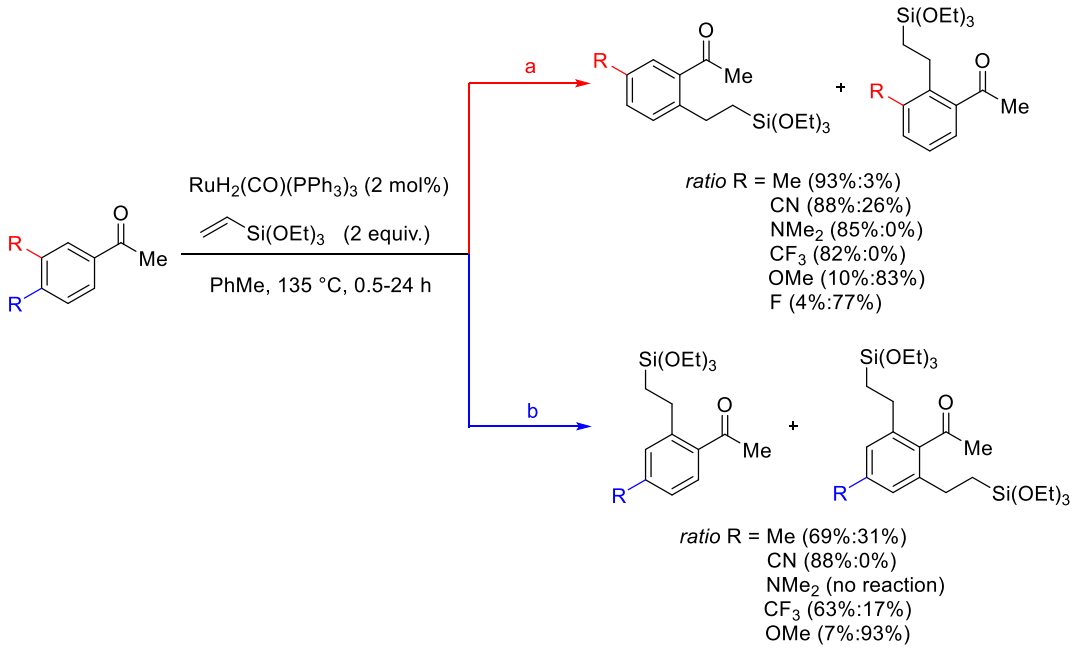


Scheme 45. *Alternative olefins for Murai coupling.*

The nature of the substituent placed at the *meta* position of the arene has also in influence on the reactive position. In particular, C-H activation takes place at the least hindered position in the case of methyl, nitrile, dimethylamino and CF_3 *meta* positioned groups, while a fluorine atom and a methoxy group direct functionalization at the most hindered position. This latter reactivity may be due to an extra interaction between ruthenium atom and the lone pair of oxygen and fluorine, and suggests that F and OMe groups behaved as a second directing group (Scheme 46, path. a).[73].

[71] Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529-531.
[72] Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 62-83.
[73] Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn*. **1997**, *70*, 3117-3128.

Weakly electron-donating or electron-withdrawing groups in the *para* position lead mainly to monoalkylation, while the presence of a strong donating methoxy group leads mostly to dialkylation. In this case, the ketone acting as directing group remains coordinated to ruthenium after the vinylsilane insertion, thus permitting to C-H activate/functionalize the remaining *ortho* position. However, no reactivity was observed in the case of a *para* dimethylamino group. Such an inhibition is likely due to the strong coordination to ruthenium by the ketone oxygen atom, due to the mesomeric effect of NMe_2, which enhances the Lewis basicity of the carbonyl oxygen (Scheme 46, path b).



Scheme 46. *Effect of substituents on acetophenone in Murai coupling.*

Bicyclic aromatic ketones, such as acetonaphthone or tetralone, and heterocyclopentadienes were also found to be ideal aromatic substrates for the Murai reaction.

2.2. Applications of the Murai reaction

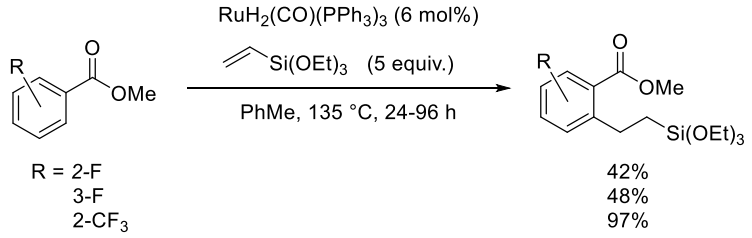
Over time, this type of coupling was studied and extended by other groups, including the Trost group.[74] Also, transition metal complexes other than ruthenium-based ones showed to be effective in promoting the coupling. In particular, the Jun group[75] developed the use of the Wilkinson complex [$RhCl(PPh_3)_3$], while Gao and Yokishai[76] made use of Co(II) complexes to accomplish this type of C-H couplings.

[74] Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371-5372.

[75] [a] Jun, C.-H.; Hong, J.-B.; Lim, S.-G.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 3440-3442; [b] Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-Y.; Kim, Y.-H. *Chem. Eur. J.* **2002**, *8*, 485-492.

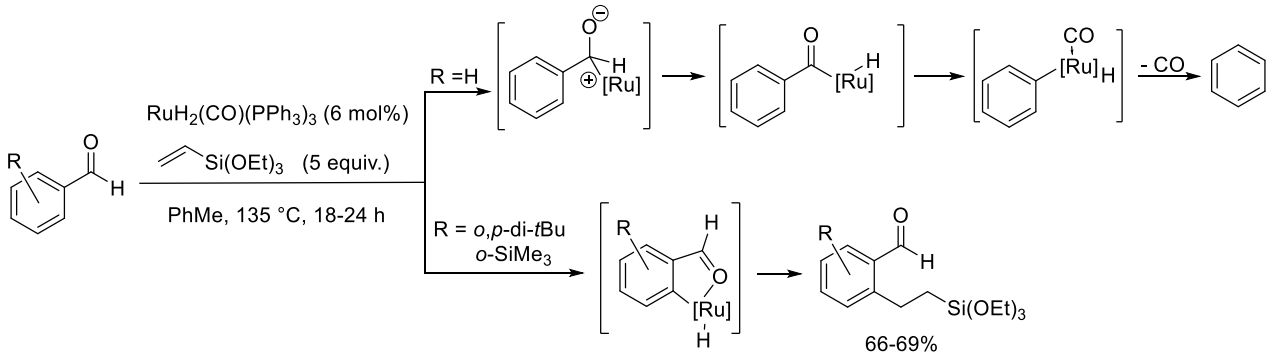
[76] Gao, K.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 6888-6892.

Murai also studied esters, aldehydes and imines as alternative potential directing groups for the arene substrates.[77] Esters led to the desired "Murai products" only if an electron withdrawing moiety, such as fluorine atom or CF_3 group, was also present in the aromatic nucleus.[78]



Scheme 47. *Esters as directing groups in Murai coupling.*

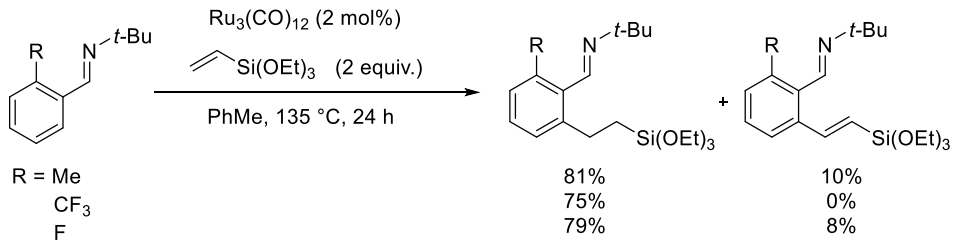
Furthermore, the replacement of a ketone by an aldehyde leads to decarbonylation of the starting benzaldehyde. In fact, the ruthenium center can realize nucleophilic attack, followed by hydrogen migration onto the ruthenium, in order to initiate the conventional course of decarbonylation. This is probably due to the more electrophilic nature of benzaldehyde compared to acetophenone. Nevertheless, the presence of large, electron-donating groups on the *ortho* positions of benzaldehyde, such as a trimethylsilyl group, prevents the formation of this Ru(0)-formyl complex, by making the formyl group less electrophilic and/or more hindered (Scheme 48)



Scheme 48. *Murai reaction on aromatic aldehydes.*

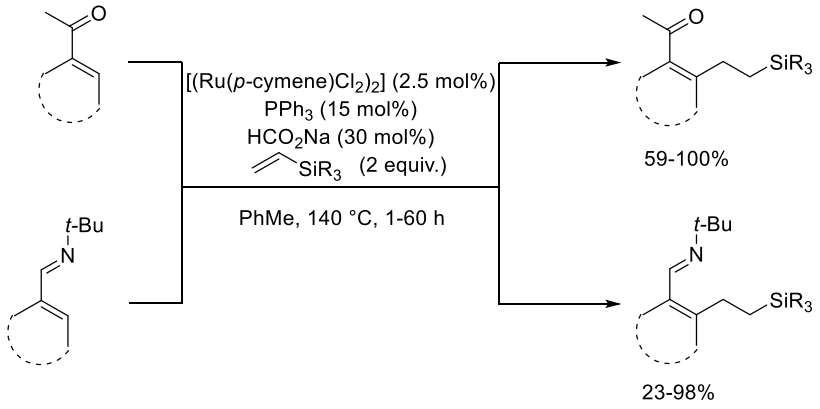
The Murai reaction was also developed with imines as steering groups, which proved to be much more efficient than the parent aldehydes. In particular, the reactivity could be improved by using $Ru_3(CO)_{12}$ instead of $Ru(H)_2(CO)(PPh_3)_3$, which turned out to be inactive for the functionalization of aromatic ketones. The reaction is selective for *ortho* positions with excellent yields, both with electron donating and withdrawing substituents (Scheme 49). However, in some case, the dehydrogenated coupling products were also observed.[79]

[77] Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, *24*, 679-680.
[78] Sonoda, M.; Kakiuchi, F.; Kamatani, A.; Chatani, N.; Murai, S. *Chem. Lett*. **1996**, *25*, 109-110.
[79] Kakiuchi, F.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, *25*, 111-112.



Scheme 49. *Aromatic imines for the Murai coupling.*

Different catalytic systems have also been developed by the group of Darses. In 2006, they reported the directed hydroarylation of aromatic ketones employing the dimer $[RuCl_2(p\text{-cymene})]_2$ as pre-catalyst in the presence of PPh_3 and sodium formate in toluene. Under these conditions, the catalytically active ruthenium dihydride complex is formed via decarboxylation of the corresponding diformate ruthenium complex. The latter can be reduced in the presence of an olefin as previously proposed by Murai, to form the active species of Ru(0). The authors then applied the system to several (hetero)aromatic ketones[80] and imines[81] with good results, using vinylsilanes and styrene derivatives as partners (Scheme 50).



Scheme 50*. In situ formation of ruthenium hydrides.*

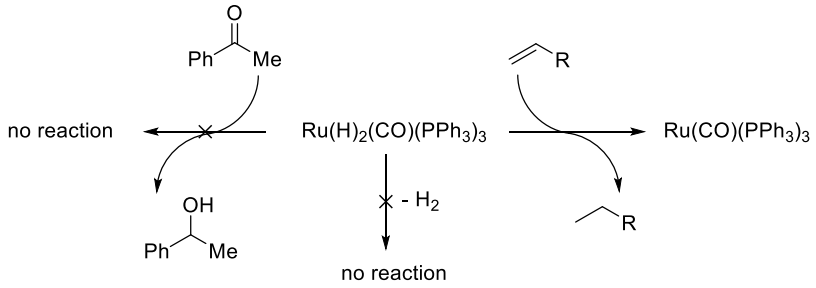
2.3. Mechanistic explanation

Several investigations have been carried out to understand the mechanism of the ruthenium-catalyzed hydroarylation of olefins. First of all, Murai deduced that the active species in the catalytic cycle is a mononuclear complex of Ru(0), generated *in situ*.[72] Three hypotheses were considered to account for the formation of the mononuclear $Ru(CO)(PPh_3)_3$ real catalyst. The first hypothesis involves H_2 de-coordination. However, such a deligandation is generally observed at very high temperature. The second hypothesis involves the reduction of a carbonyl compound by hydride transfer, to afford after protonation the corresponding alcohol. However, in the presence of a carbonyl compound such a reduction product has

[80] [a] Martinez, R.; Chevalier, R.; Darses, S.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2006**, *45*, 8232-8235; [b] Martinez, R.; Genêt, J.-P.; Darses, S. *Chem. Commun.* **2008**, 3855-3857.

[81] Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genêt, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887-7895.

never been observed. The last hypothesis involved alkene hydrogenation. Indeed, reacting $Ru(H)_2(CO)(PPh_3)_3$ with three equivalents of trimethoxyvinylsilane led to the disappearance of the Ru-H signal in ^{1}H-NMR and to the formation of the corresponding alkane. This last experiment demonstrated that that the conversion of the $Ru(H)_2(CO)(PPh_3)_3$ pre-catalyst into the active $Ru(CO)(PPh_3)_3$ species takes places through hydrogenation of the vinylsilane Scheme 51.



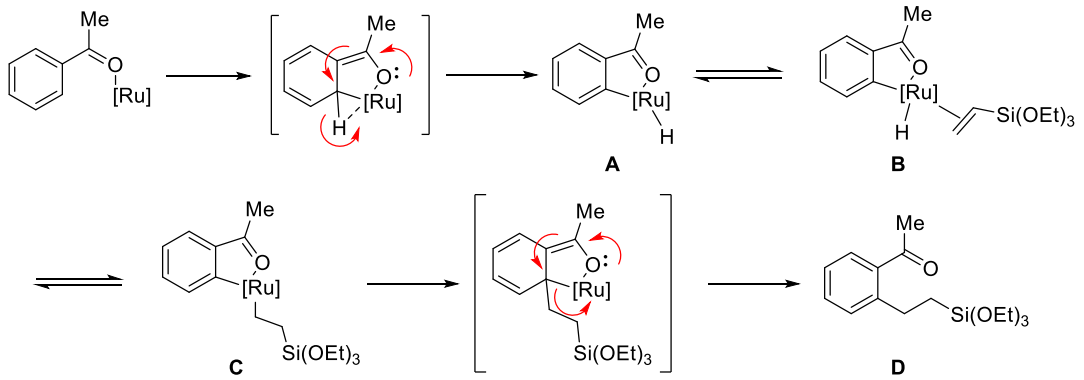
***Scheme 51**. Formation of the Ru(0) active species.*

A few years later, Matsubara and Morokuma studied the Murai reaction by DFT calculations.[82] According to these authors, the most favorable reaction path leading to the net oxidative addition step entails a first coordination of the metal by the carbonyl oxygen, followed by a 1,4-nucleophilic addition / 1,2-hydride migration sequence. The authors also showed that an agostic interaction between Ru and the *ortho* H helps stabilising intermediate **A** and promoting the subsequent migration. The computation also indicated that the C–H activation step is not the kinetically determining step.

The next step is the double bond coordination/insertion, which can in principle take place via carboruthenation or hydroruthenation. In the former case, the formation of the intermediate could be followed by a β-H elimination. However, the resulting alkene was never observed. On the other hand, after hydroruthenation, reductive elimination of **C** affords the actually observed coupling product **D**. The hydrometallation step could take place according to two different regioselectivities, providing after reductive elimination, a linear product (as shown), or a branched one (as additionally observed in the case of coupling with styrene). This allows to deduce that hydrometallation is the path followed (Scheme 52).

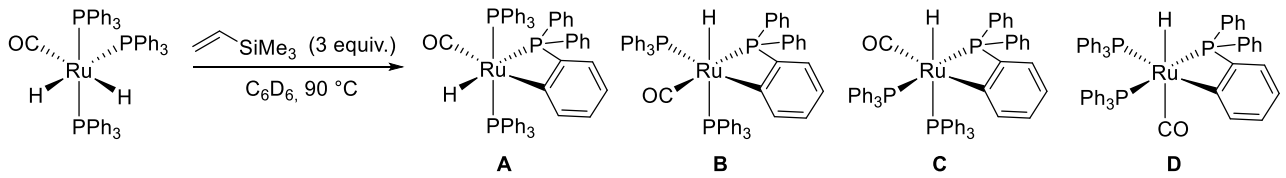
The last step of the catalytic cycle is the reductive elimination from intermediate **C**, with formation of the C–C bond and regenerates the Ru(0) complex. This step takes place through a rate determining 1,2-migration of the alkyl group on the aryl moiety through another 1,4-addition-like process.

[82] [a] Matsubara, T.; Koga, N.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **1998**, *120,* 12692-12693; [b]) Matsubara, T.; Koga, N.; Musaev, D. G.; Morokuma, K. *Organometallics* **2000**, *19,* 2318-2329.



Scheme 52. *Proposed C–H activation, alkene insertion and reductive elimination steps in Murai coupling.*

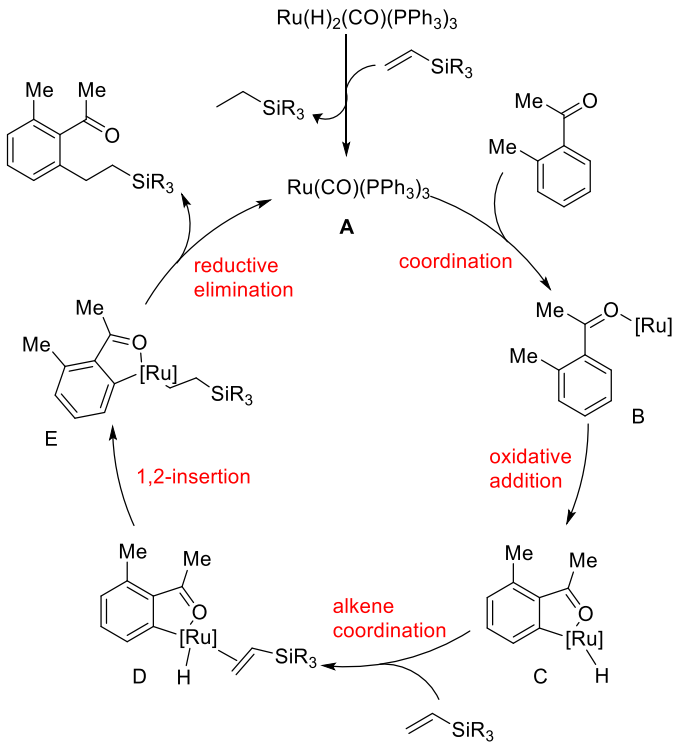
In 2010, Kakiuchi and Murai unveiled an important intermediate in the catalytic process.[83] By treating $Ru(H)_2(CO)(PPh_3)_3$ with trimethylvinylsilane in benzene, a series of cyclometallated complex involving one of the phosphine ligands were isolated (Scheme 53). One of these complexes **A-D**, tested as catalyst for the reaction between 2-methylacetophenone and trimethylvinylsilane, promoted the coupling in quantitative yield.



Scheme 53 *Isolated cyclometallated complexes with phosphine ligands in Murray reaction*

On the basis of all these considerations, a general reaction mechanism was proposed for the reaction of 2-methylacetophenone and vinylsilane, as shown in Scheme 54. The reaction begins with the conversion of the pre-catalyst into the active Ru(0) species **A** by hydrogenation of the vinylsilane. Coordination by the ketone group to the Ru center gives complex **B**. This step puts the Ru in close proximity to the *ortho* hydrogen bond on the ketone, making cyclometallation to ruthenacycle **C** easier. The vinylsilane can then π-coordinate the ruthenium atom to form complex **D**, in route for for the subsequent insertion into the Ru-H bond (hydroruthenation) to give species **E**. Finally, reductive elimination leads to the *ortho*-alkylated ketone and liberation of the Ru(0) catalyst.

[83] Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741-17750.



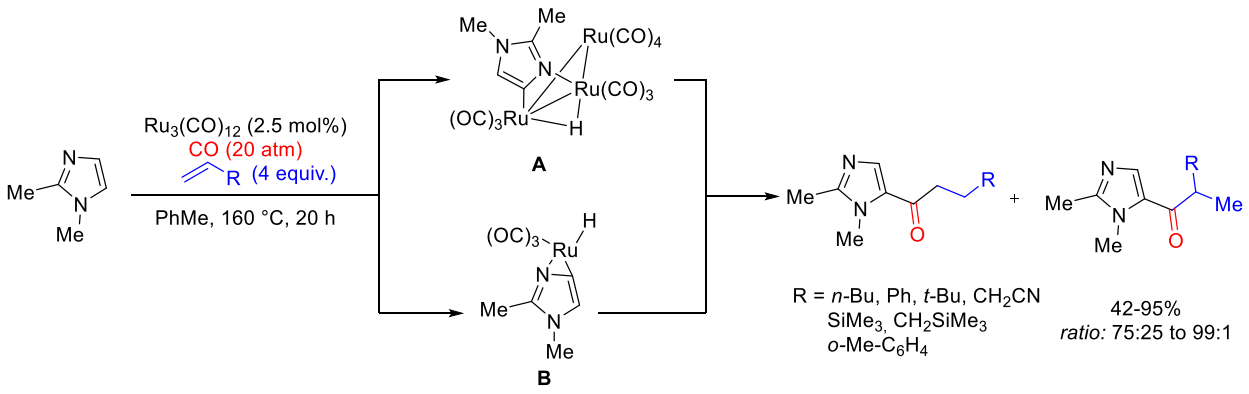
Scheme 54. *Plausible mechanism for the Murai coupling between acetophenone and vinylsilanes.*

2.4. The Carbonylative Murai reaction

Besides their studies on the alkylation of (hetero)aromatic systems with vinylsilanes or terminal olefins, Murai and co-workers developed a carbonylative version of the same reaction that allows to obtain the direct acylation of the aromatic substrate simply by working in the presence of a carbon monoxide source. In the perspective of organic synthesis, this reaction turns out to be a valid alternative to the well-known Friedel-Crafts acylation.

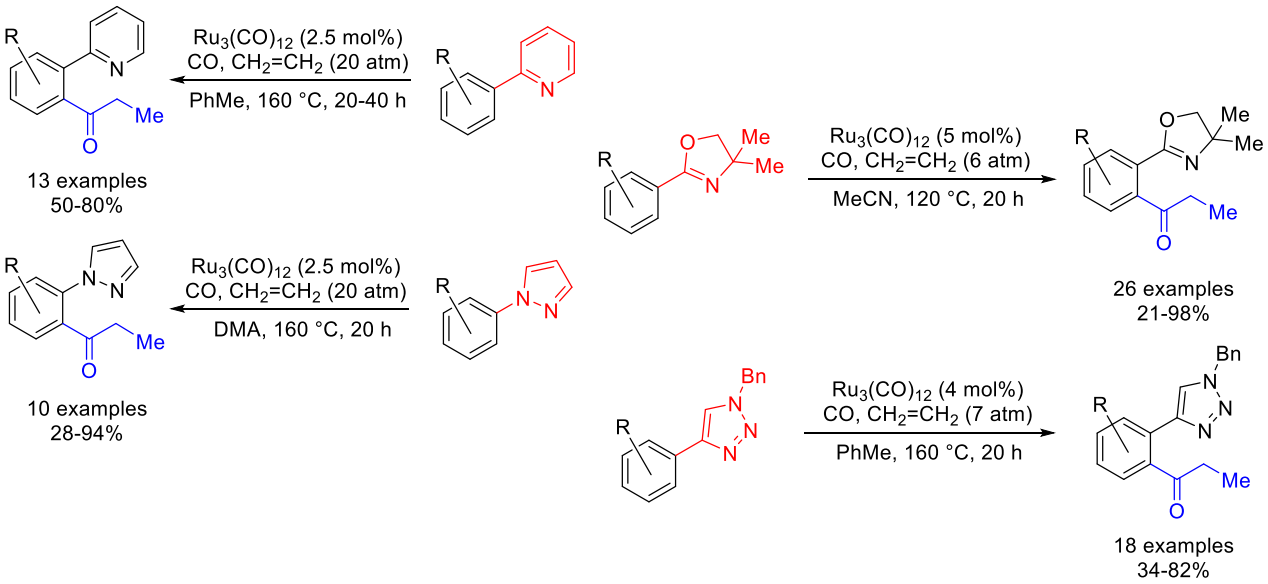
One of the first examples reported by the Murai team dealt with the regioselective acylation of imidazole in the presence of CO pressure and of $Ru_3(CO)_{12}$ as the ruthenium source.[84] The insertion of CO and of alkene following the C–H activation step permitted to obtain the desired acylation products with moderate yields. However, the regioselectivity in favor of linear products is not complete. In particular, the authors proposed two possible intermediates for the C–H activation step, one involving the trinuclear complex **A**, and the other involving the mononuclear complex **B**, similar to what reported by Moore[68] (Scheme 55).

[84] Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493-494.



Scheme 55. *First example of carbonylative Murai coupling.*

Subsequently, the authors applied this protocol to the regioselective acylation of other aromatic derivatives. As illustrated in Scheme 56, a number of directing groups containing at least one Lewis basic nitrogen atom could be used to selectively direct the *ortho* acylation. In particular pyridine,[85] as well as oxazolines,[86] pyrazoles[87] and triazoles[88] proved to be excellent directing groups, allowing to obtain the acylated products in good yields in the presence of both electron-withdrawing or electron-donating substituents on the aromatic scaffolds.

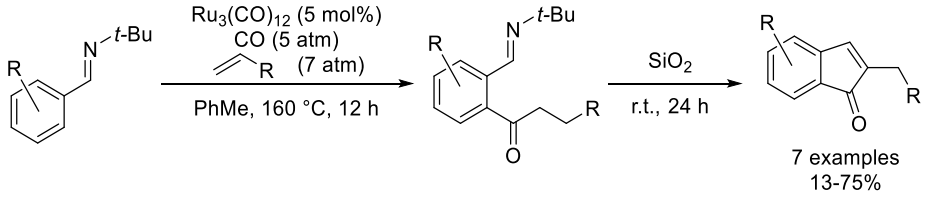


Scheme 56. *Nature of the directing group for carbonylative Murai reaction.*

The pyridine steering group enabled also the carbonylation at the C(sp^3)-H α-carbon of aliphatic amines, under Rh(I) catalysis.[89]

[85] Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997,** *62,* 2604-2610.
[86] Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000,** *65,* 1475-1488.
[87] Asaumi, T.; Chatani, N.; Matsuo, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2003**, *68*, 7538-7540.
[88] Haito, A.; Yamaguchi, M.; Chatani, N. *Asian J. Org. Chem.* **2018**, *7*, 1315-1318.
[89] Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000,** *122,* 12882-12883.

Another interesting development in this area is the use of benzaldehydes protected as imines to obtain the steering effect. Treatment with silica gel after the coupling reaction directly allowed to obtain the corresponding indenone in good yields, resulting from an intramolecular aldolization/dehydration sequence (Scheme 57).[90]



Scheme 57. *Imine functions as directing group in acylation reaction.*

Although the hydroarylation of alkenes has already reached a satisfactory degree of maturity in terms of scope and efficiency, the carbonylative version of the Murai reaction is still in its infancy. Indeed, it is limited to the use of a small number of aromatic rings and olefinic partners, and high quantities of carbon monoxide are required.

We will now present our work on the acylation of heterocyclic derivatives using an imine as a directing group for the C–H activation step.

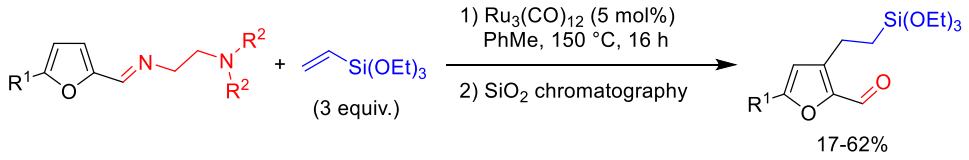
3. Results and Discussion

3.1. Aim of the work

In recent years, the functionalization by C-H activation of aromatic or heteroaromatic nuclei, especially of biomass derivation, has been a topic of interest for the IPCM's ROCS team. In 2017, the team reported the first application of the Murai reaction to the functionalization of furfural (FF) and hydroxymethylfurfural (HMF) derivatives,[91] which are platform molecules derived from agricultural waste.

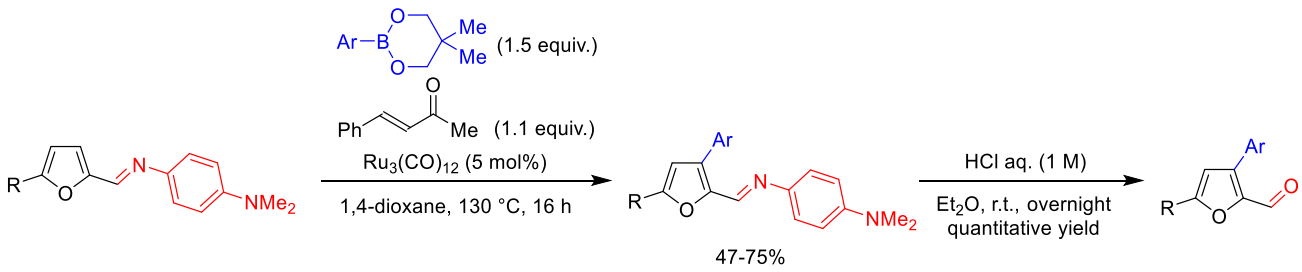
Thus, the use of a ruthenium catalyst and an imino-amine group to selectively direct the functionalization in the C3 position, allowed the development of the first furfurylation of alkenes. A mechanistic study by DFT confirmed the importance of this bidentate steering group throughout the transformation. After purification on silica gel, the corresponding alkylated aldehydes were obtained with good yields (Scheme 58).[92]

[90] Fukuyama, T.; Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997,** *62,* 5647-5650.
[91] Galkin, K. I.; Ananikov, V. P. *ChemSusChem* **2019**, *12*, 2976-2982.
[92] Pezzetta, C.; Veiros, L. F.; Oble, J.; Poli, G. *Chem. Eur. J.* **2017**, *23*, 8385-8389.



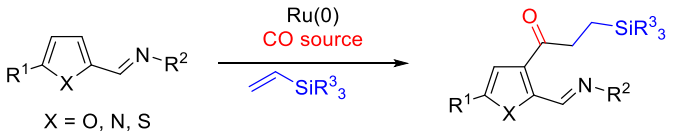
Scheme 58. *Alkylation of furfural imines in C3 position by Murai reaction.*

The team also described the arylation and olefination of furfural derivatives in the presence of boronic esters using a Ru(0) catalyst and benzylidene acetone as a hydride acceptor. In this case, an aromatic imine was used to achieve the best reactivity. Couplings with electron-withdrawing or electron-donating aryl groups as well as cinnamyl gave the functionalized products with good yields (Scheme 59).[93]



Scheme 59. *Ru(0) catatalyzed C3-arylation of aromatic furfural imines.*

These results led us to consider next the study of carbonylative versions of the Murai reaction on FF and HMF derivatives, and to extend this study to the corresponding nitrogen- and sulfur-based five-member heteroaromatic compounds (Scheme 60). This study is of great synthetic interest, as the acylation of furfural derivatives by the Friedel-Crafts reaction normally occurs in the C4 position of the formyl unit.[94]



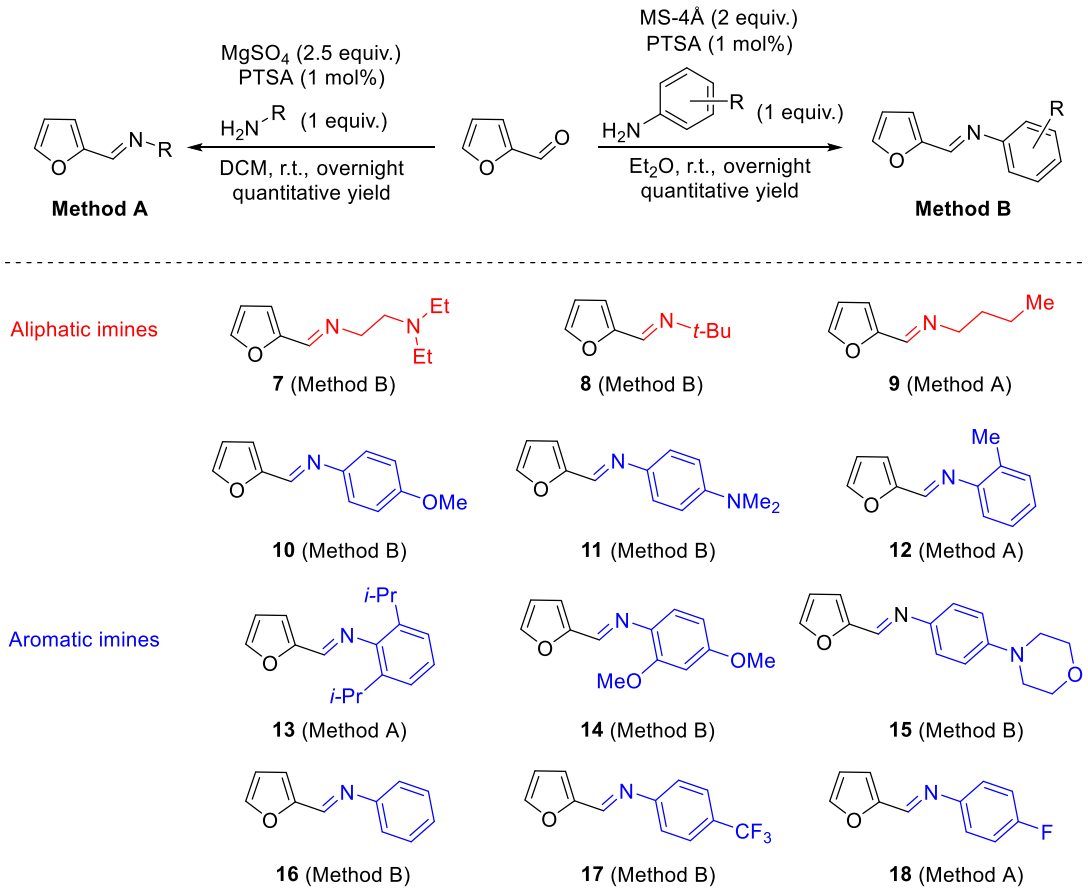
Scheme 60. *Ru(0)-catatalyzed C3-carbonylative Murai reaction of furfural imines.*

3.2. Furfural imines: preparation, optimization and substrate scope

The first step was the preparation of a variety of furfuryl imines from C5-substituted or unsubstituted furfural derivatives with aliphatic diamines and aromatic amines. Two procedures were adopted, both making use of catalytic amount of PTSA. One needed $MgSO_4$ as a drying agent in DCM solution (method A),[92] while the other molecular sieves MS-4Å in Et_2O solution (method B)[95] (Scheme 61). Thus,

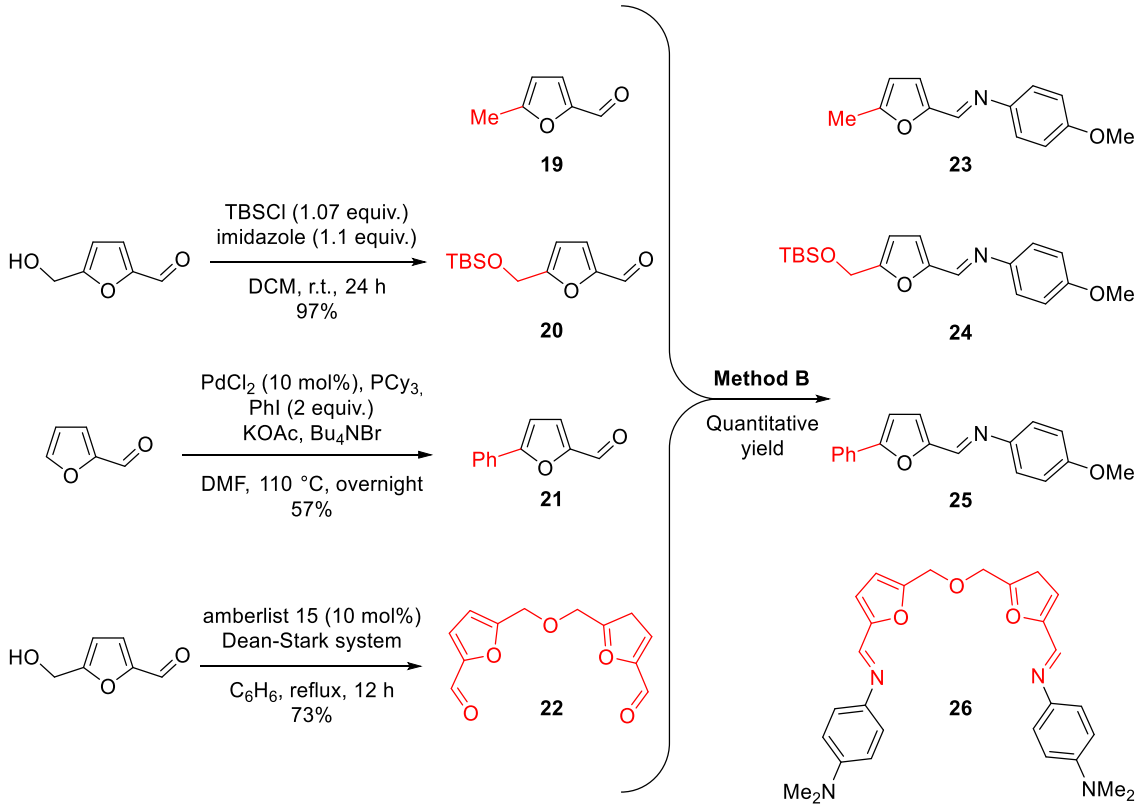
[93] Siopa, F.; Ramis Cladera, V.-A.; Afonso, C. A. M.; Oble, J.; Poli, G. *Eur. J. Org. Chem.* **2018**, *44,* 6101-6106.
[94] Brahmayya, M.; Wang, M. L. *Res. J. Pharm. Biol. Chem. Sci.* ***2014****, 5,* 751-755.
[95] Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570-1572.

furfurylimines **7-18** were obtained in quantitative yields. The two methods can be used alternatively, although method B is more suitable for the preparation of aromatic imines.



Scheme 61. *Synthesis of furfurylimines from furfural derivatives*

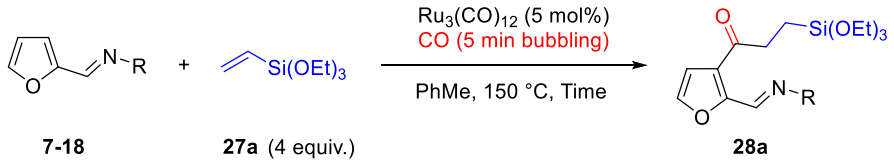
The same approach was then extended to 5-substituted furfuryl aldehydes. In particular, we chose the commercially available 5-Me-furfural and the HMF derived 5-CH_2OTBS-furfural. From these aldehydes the corresponding imines **23** and **24** were obtained. We also synthesized imines from 5-Ph-furfural and a dimer of furfural, leading to imines **25** and **26**, in order to evaluate the electronic and steric influence of the substituents. The choice of making the dimeric imine NMe_2 for compound **26** was essentially due to solubility problems (Scheme 62).



Scheme 62. *Synthesis of 5-substituted-furfural imines from corresponding aldehydes.*

We then began our optimization work adopting the same reaction conditions as described by the group for the alkylation of furfural derivatives,[92] with the additional presence of CO. From the outset of this study, the use of atmospheric pressure of CO was chosen in replacement of the use of high pressure, which requires special equipment. We therefore decided to bubble carbon monoxide directly into the solvent for 5 minutes in order to saturate the reaction medium. In contrast to the classical Murai reaction, the use of the bidentate imine **7** as well as the use of *tert*-butyl-furfurylimine **8** does not allow the formation of the desired compound. The long-chain aliphatic imine **9** allowed to isolate the desired acylated product, albeit in a very low yield. Satisfactory results were obtained with the electron-rich aromatic imines **10-15**, whereas it was not possible to observe the products when the electron-poor aromatic imines **16-18** were used (Table 3).

Table 3: *Ru-catalyzed direct C3-acylation of furfurylimines: screening of the imine directing groups.*



7-18 **27a** (4 equiv.) **28a**

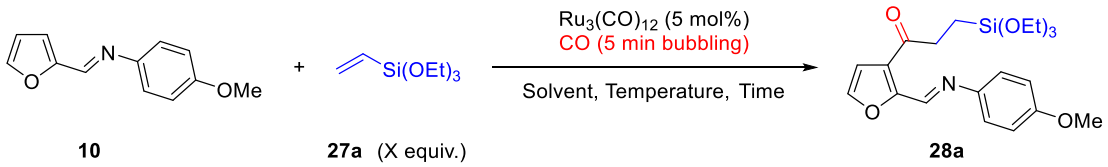
Entry	Substrate	Time	Conversion	Acylation Yield[a]
1	**7**	48 h	-	-
2	**8**	24 h	-	-
3	**9**	16 h	43%	26%
4	**10**	16 h	99%	44%
5	**11**	16 h	80%	38%
6	**12**	16 h	75%	27%
7	**13**	16 h	27%	16%
8	**14**	16 h	99%	23%
9	**15**	16 h	99%	34%
10	**16**	24 h	-	-
11	**17**	24 h	98%	(5%)
12	**18**	24 h	21%	(3%)

a: In brackets yields determined by ^{1}H-NMR spectroscopy, using 1,4-dinitrobenzene as internal standard.

These preliminary tests suggested that electron-rich aromatic imines where the imines of choice for the desired acylation reaction. In particular, PMP-imine **10** (Table 4, entry 4), which led to the best values of conversion and yield, was selected for the further optimizations.

Temperature, time, solvent, concentration and equivalents of silane **27a** were then optimized (Table 4). The decrease in reaction time below 16 h (entries 1-2) or of temperature, below 120 °C (entries 5-7) inhibits the conversion, while its increase (entries 4-9) causes partial degradation of the product. At the same time, use of an aromatic solvent as PhMe, and the concentration of 0.5 M (entries 8 and 14) resulted to be essential to obtain good conversion. Finally, we noted that the use of less of 4 equivalents of silane partner significantly affected the formation of acylated compound. In order to preserve the imine function from hydrolysis, the purification step was realized by silica gel deactivated with 1% of Et_3N. However, the considerable decrease from 85% of ^{1}H-NMR yield to 66% can be due to the intrinsic instability of the furfural ring.

Table 4. *Reaction parameters optimization on imine* ***7d.***



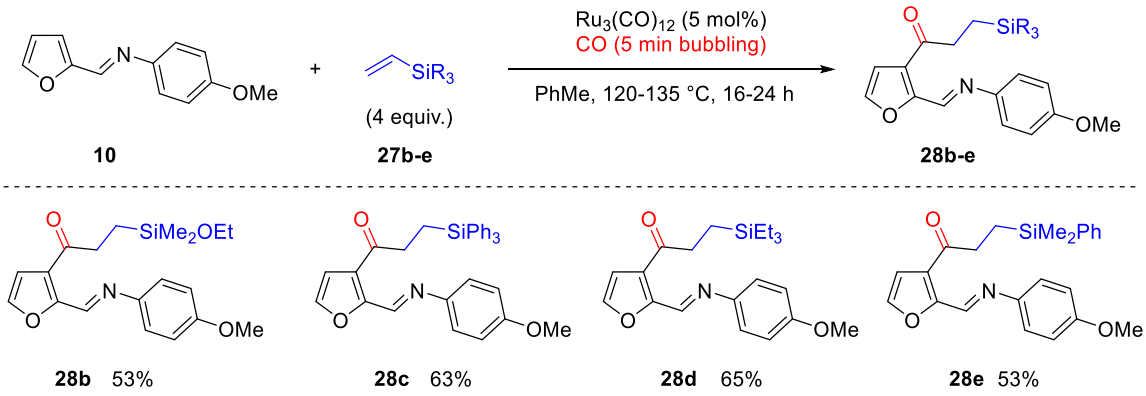
10 **27a** (X equiv.) **28a**

Entry	Time	Temperature	Solvent	[M]	Silane	Conversion	Yield[a,b]
1	8 h	135 °C	PhMe	0.5 M	4	59%	47%
2	12 h	135 °C	PhMe	0.5 M	4	66%	32%
3	16 h	135 °C	PhMe	0.5 M	4	99%	44%
4	24 h	135 °C	PhMe	0.5 M	4	99%	25%
5	16 h	80 °C	PhMe	0.5 M	4	-	-
6	16 h	100 °C	PhMe	0.5 M	4	9%	9%
7	16 h	110 °C	PhMe	0.5 M	4	95%	57%
8	**16 h**	**120 °C**	**PhMe**	**0.5 M**	**4**	**99%**	**85% (66%)**
9	16 h	150 °C	*p*-xylene	0.5 M	4	99%	26%
10	16 h	120 °C	Hexane	0.5 M	4	99%	51%
11	16 h	120 °C	MeCN	0.5 M	4	77%	48%
12	16 h	120 °C	THF	0.5 M	4	35%	23%
13	16 h	120 °C	Dioxane	0.5 M	4	99%	59%
14	16 h	120 °C	PhMe	0.25 M	4	99%	61%
15	16 h	120 °C	PhMe	1 M	4	77%	41%
16	16 h	120 °C	PhMe	2 M	4	76%	37%
17	16 h	120 °C	PhMe	0.5 M	1.1	99%	52%
18	16 h	120 °C	PhMe	0.5 M	2	99%	58%
19	16 h	120 °C	PhMe	0.5 M	3	99%	60%

a: Yield determined by ^{1}H-NMR spectroscopy of the crude extract using 1,4-dinitrobenzene as internal standard.
b: Between brackets yield by isolation on SiO_2 chromatography deactivated with 1% of Et_3N.

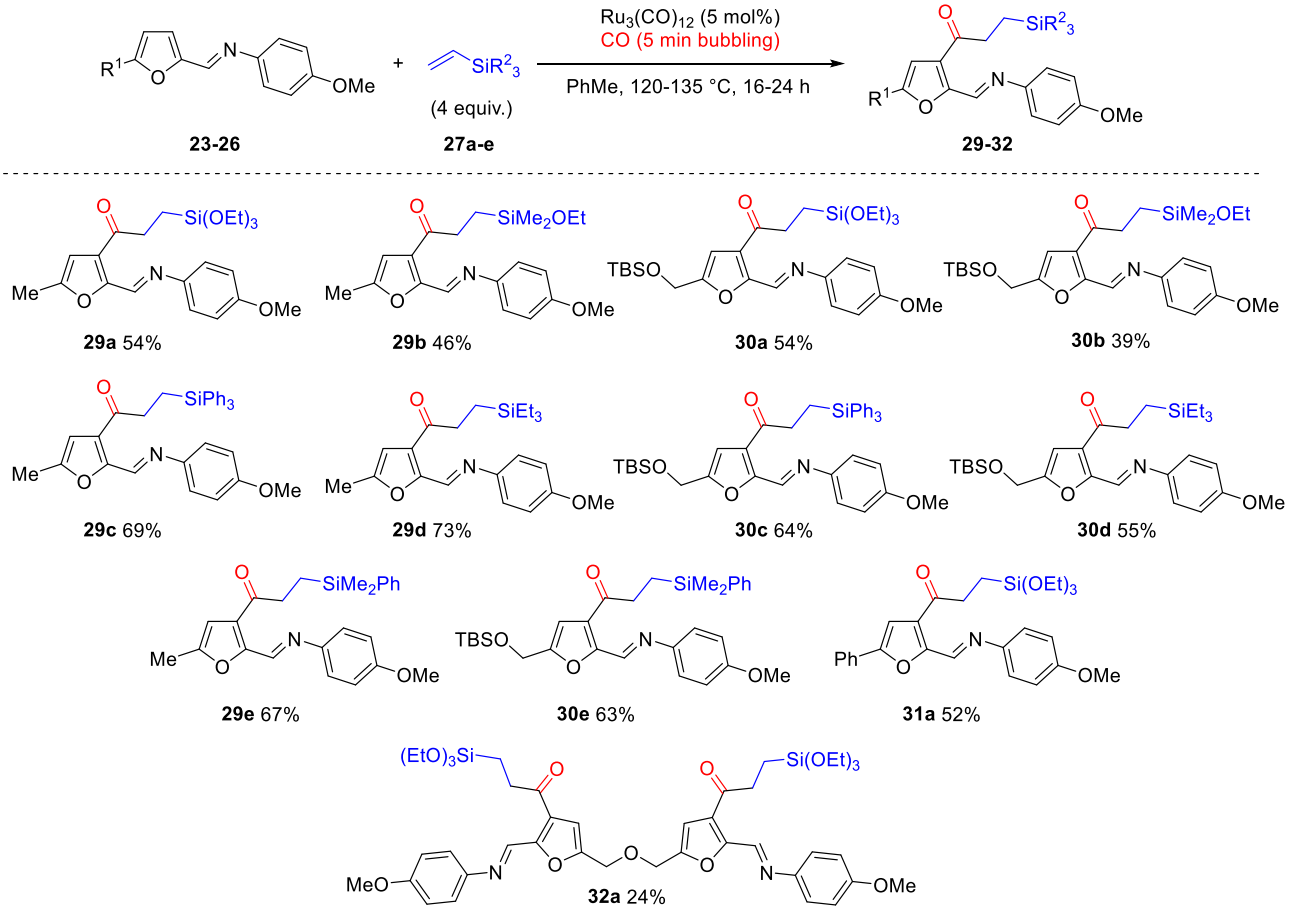
With these conditions in hand, we focused our attention on the scope of this C3-carbonylative Murai reaction with the PMP-imine **10** in the presence of a variety of trialkoxy-, trialkyl- and triaryl-vinylsilanes **27b-e** (4 equiv.) and $Ru_3(CO)_{12}$ (5 mol%), in toluene (0.5 M) at 120-135 °C during 16-24 h (Scheme 63).

A rapid chromatographic purification on deactivated silica gel allowed to obtain moderate to good yields of the corresponding C3-acylated imines **28b-e** (53-66% isolated yields). However, in the case of trialkyl- and triaryl-vinylsilanes, good yields were only obtained when the mixtures were heated at 135 °C. The reaction was also studied with styrenes, which unfortunately failed to react.



Scheme 63. *Scope of Ru-catalyzed direct C3-acylation of PMP-furfurylimines with silanes* ***16b-e****.*

Then, the scope was next extended to C5-substituted furfurals such as 5-Me-PMP-imine **23** and the TBS-O-protected HMF PMP-imine **24**. In the event, the corresponding C3-acyclated imines **29a-e** and **30a,c-e** could be isolated in reasonable to good yields. The 5-phenyl derivative **25** could also be acylated, but only through its *p*-dimethylaminophenyl-imine **31a**, whereas the PMP-imine led to complex results. Besides, a double coupling was successfully achieved with the HMF-dimer diimine **26** using eight equivalents of triethoxyvinylsilane, which gave the diacylated HMF imine dimer **32a** (Scheme 64).

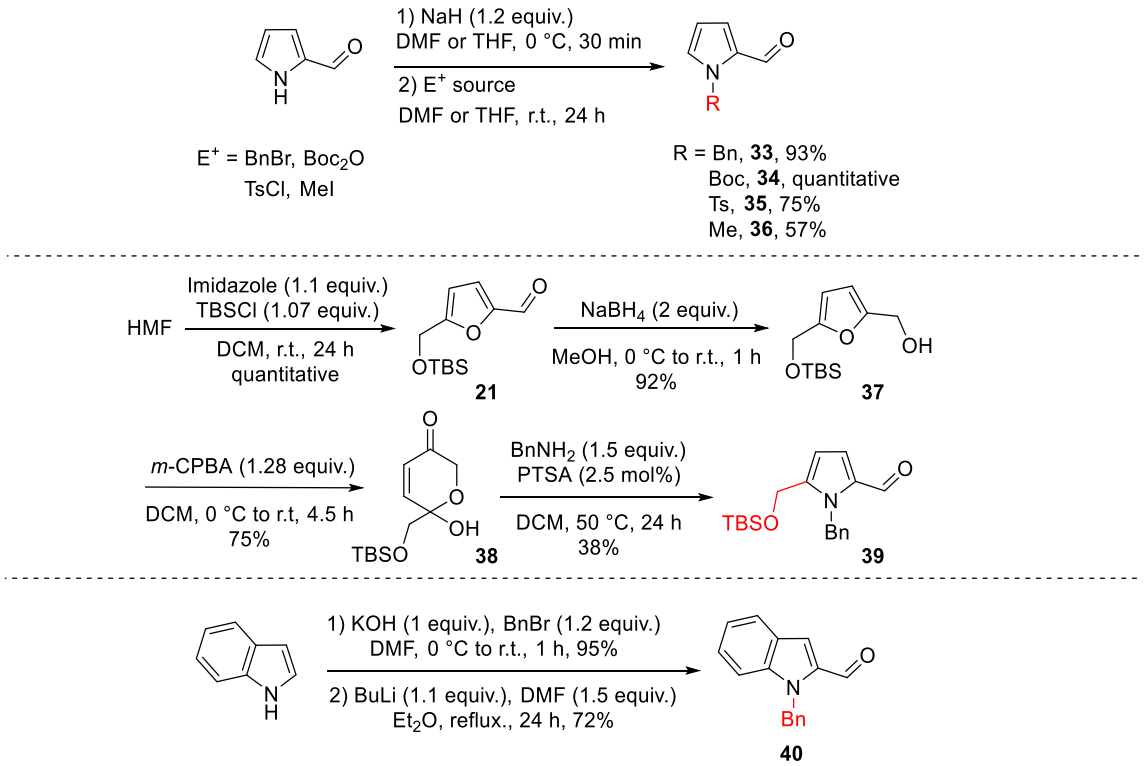


Scheme 64. *Carbonylative Murai reaction with C5-substituted furfural imines* ***23-26****.*

3.3. Studies on pyrrole, indole and thiophene nucleus

In light of the encouraging results obtained on FF and HMF imines, it was decided to extend our study to the remining *N*- and *S*-based 2-imino heterocyclopentadienes. Accordingly, pyrrole 2-carboxaldehyde was considered as an appropriate starting substrate for our study. Given its accessibility from furfural in one step, through a Paal-Knorr synthesis, or in three steps through a (carbonyl reduction/Achmatowicz rearrangement/Maillard condensation) sequence,[96] this substrate can be regarded as a biomass-derived building block, too. Extension to thiophene 2-carboxaldehyde has been also envisaged, to verify the generality of the heterocyclopentadiene family.

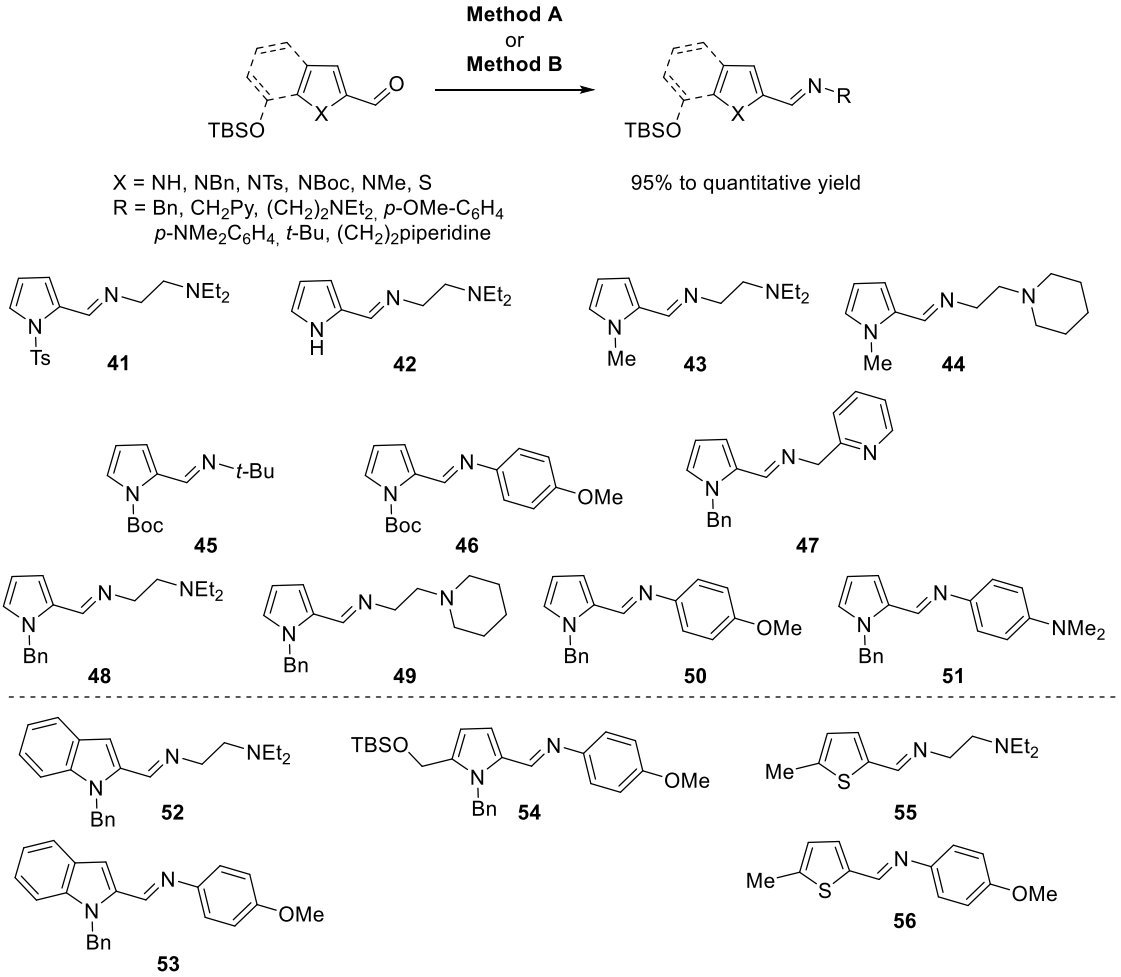
Standard *N*-protection of pyrrole 2-carboxaldehyde by NaH deprotonation in THF or DMF followed by trapping with a range of electrophiles gave access to the *N*-benzyl, *N*-Boc, *N*-Tosyl, and *N*-methyl derivatives **33**, **34**, **35**, and **36** in good to excellent yields. The 5-(TBS)oxymethyl pyrrole 2-carbaldehyde **39** was prepared from HMF in four steps: OH protection as TBS ether/carbonyl reduction/ Achmatowicz rearrangement/Maillard condensation. *N*-benzyl indole 2-carbaldehyde **40** was prepared from indole by standard N-benzylation followed by formylation at C2 by treatment with BuLi and DMF (Scheme 65).



Scheme 65. *Synthesis of 2-pyrrole carboxaldehydes and 2-indole carboxaldehyde*

[96] Yuen, T. –Y.; Eaton, S. E.; Woods, T. M.; Furkert, D. P.; Choi, K. W.; Brimble, M. A. *Eur. J. Org. Chem.* **2012**, *2014*, 1431-1437.

Imines **41-51**, **52-53**, **54** and **55-56** were prepared according to the above reported methods A or B, as previously shown (see Scheme 61) for the formation of furfural imines (Scheme 66). 5-methylthiophene-2-carbaldehyde was commercially available.[97]

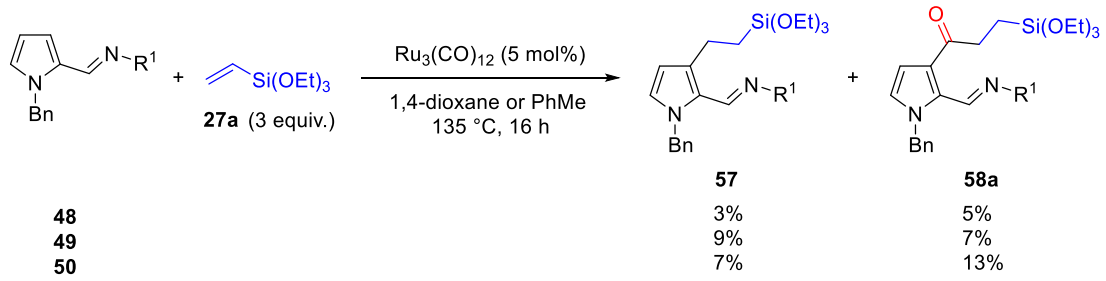


Scheme 66. *Preparation of-pyrrole, indole and thiophene imines.*

The drive to start a study of a carbonylative Murai reaction came from an intriguing result observed in the laboratory. In the course of preceding studies on the Murai reaction, Fares Roudesly[98] observed by ^{1}H-NMR yields that treatment of the bidentate imines **48** or **49** or PMP imine **50** in the presence of 3 equivalents of triethoxyvinylsilane **27a**, in toluene at 135 °C for 16 h gave rise to trace amounts of the desired C3-alkylated product **57** (classical Murai product) accompanied by trace amounts of the unexpected C3 acylation product **58a** (carbonylative Murai product). As the protocol did not contain an external source of CO, it was deduced that the unexpected acylation product had to come from a carbonyl ligand released from the catalyst, and, most notably, that the system was naturally biased toward CO insertion. We thus decided to start a study of carbonylative Murai reaction on our 2-imino heterocyclopentene.

[97] We opted for the use this substrate instead thiophene-2-carbaldehyde to avoid possible dimerization problems at C5 the position.

[98] Fares Roudesly, thesis Sorbonne Université 2018, «*Fonctionnalisation C-H dirigée d'hétérocycles azotés*».

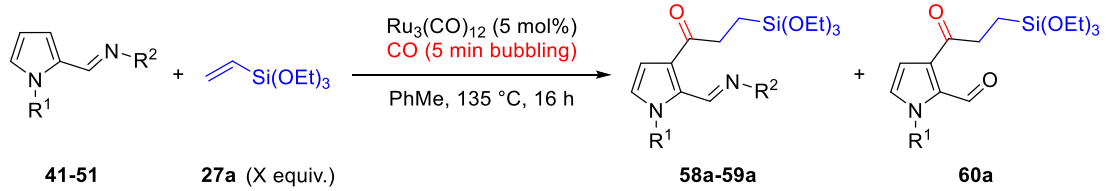


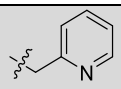
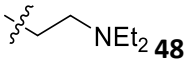
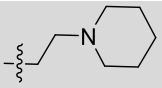
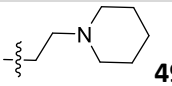
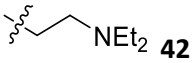
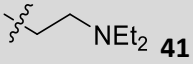
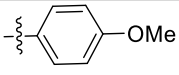
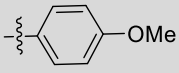
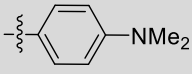
Scheme 67. *First tests on pyrrole imines: alkylation* vs *carbonylation.*

Our study was carried out by bubbling carbon monoxide in the reaction vessel prior dissolution of the imine and $Ru_3(CO)_{12}$ in PhMe and treating the substrates under the protocol previously optimized for the classical Murai reaction on the oxygen-based substrates.[92]

Table 5 summarizes the most important results. First, we assessed that 5 minutes of CO bubbling (average flow = 15 mL/min) was enough to obtain saturation of the reaction solvent.

Table 5. *Conditions optimization on pyrrole imines* ***41-51****.*

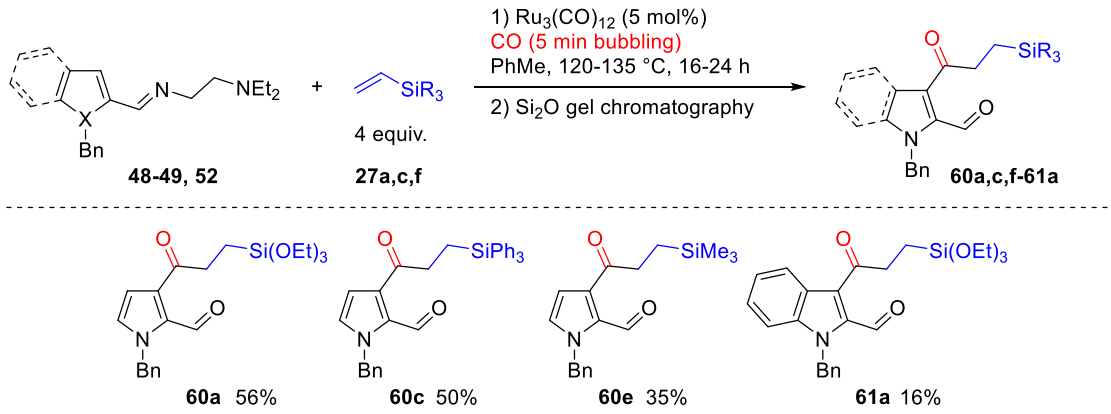


Entry	R^1	R^2	Conversion	Yield[a,b]
1	Bn	 **47**	88%	degradation
2	**Bn**	 **48**	**95%**	**72% (56%)**
3	Me	 **44**	71%	degradation
4	Bn	 **49**	96%	77% (59%)
5	Me	 **43**	37%	degradation
6	H	 **42**	88%	degradation
7	Ts	 **41**	90%	degradation
8	Boc	 **46**	99%	degradation
9	**Bn**	 **50**	**96%**	**80% (66%)**
10	Boc	*t*-Bu **45**	94%	degradation
11[c]	Bn	 **51**	96%	89% (62%)

a: Yield determined by ^{1}H-NMR spectroscopy of the crude extract using 1,4-dinitrobenzene as internal standard.
b: Between brackets yield by isolation on SiO_2 chromatography deactivated with 1% of Et_3N.
c: A co-solvent system PhMe/DCM (10/2) was used to avoid solubility problems.

The nature of the nitrogen protecting group was also considered. In particular, the replacement of the *N*-benzyl protecting group of pyrrole (entries 3, 5-8, **41-46**) for other groups such as H, Me, Ts, Boc is deleterious, and causes partial conversion or total degradation of the starting material. The *t*-Bu imine as directing group (entry 10, **45**) was also unsuitable. We therefore decided to stick to alkyl bidentate (iminoamino) **47-49** and aromatic imines **50-51**. With imine **51** a co-solvent system PhMe/DCM (10/2) was used in order to avoid solubility problems. The bidentate imines **50-51** allow excellent conversions in the acylation step and are readily hydrolyzed to the corresponding aldehydes **60a** after purification on silica gel chromatography (entries 2 and 4). However, with these imines, traces of hydrolyzed aldehydes can be already detected after the acylation step. Conversely, the aromatic imines **50-51** turned out to be much more robust, and products **58a-59a** could be isolated without problems by chromatography using deactivated (1% Et_3N) silica gel.

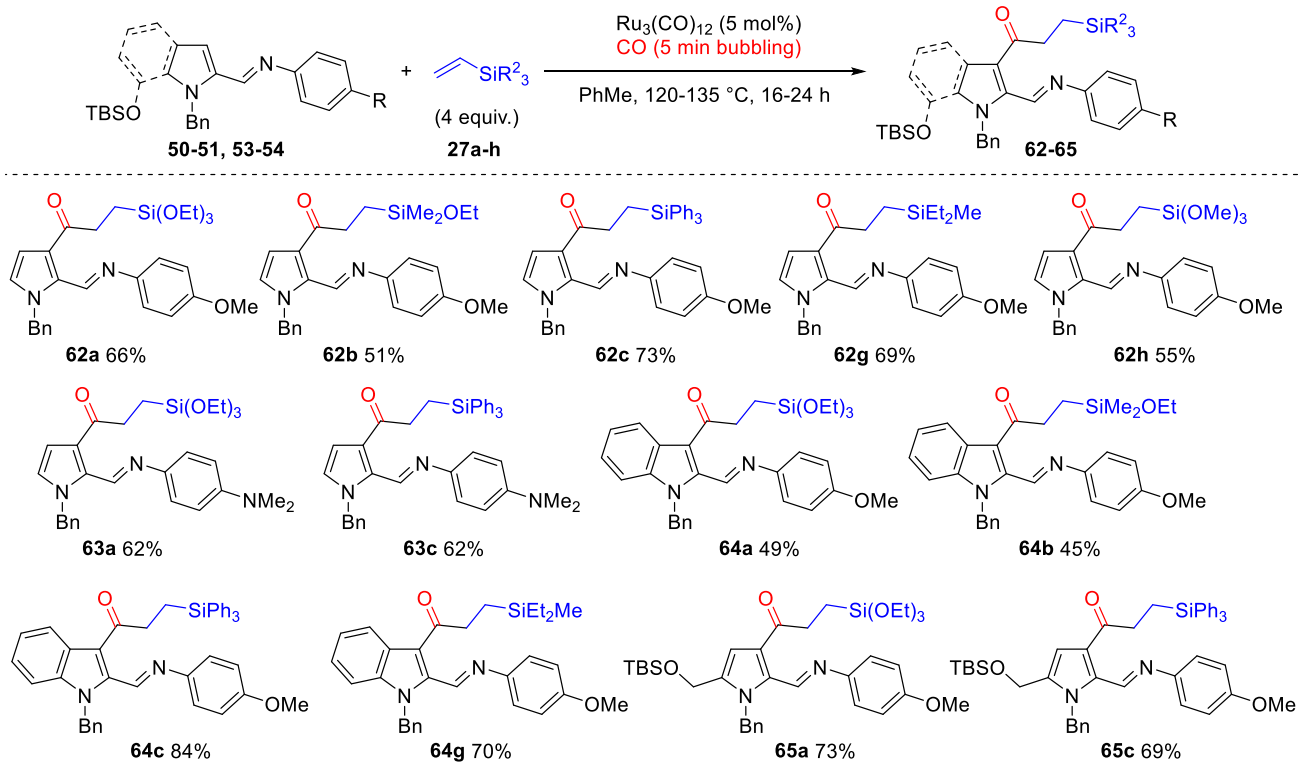
In view of the results of the previous screening, we passed to study the scope of the C3-carbonylative Murai reaction on pyrrole and indole derivatives using the *N,N'*-bidentate imine **48, 49** and **52**, using $Ru_3(CO)_{12}$ (5 mol%), and triethoxy-, triaryl-, trialkyl-vinylsilanes **27a-f** (4 equiv.) and performing the reaction in toluene (0.5 M) at 135 °C under CO atmosphere, during 16 h. As expected, in all case studied, the imines underwent spontaneous hydrolysis during the purification step, directly affording the C3-acylated aldehydes **60a,c,f** and **61a** (Scheme 68).



Scheme 68. *Carbonylative Murai reaction with vinylsilanes* ***27a,c,f.***

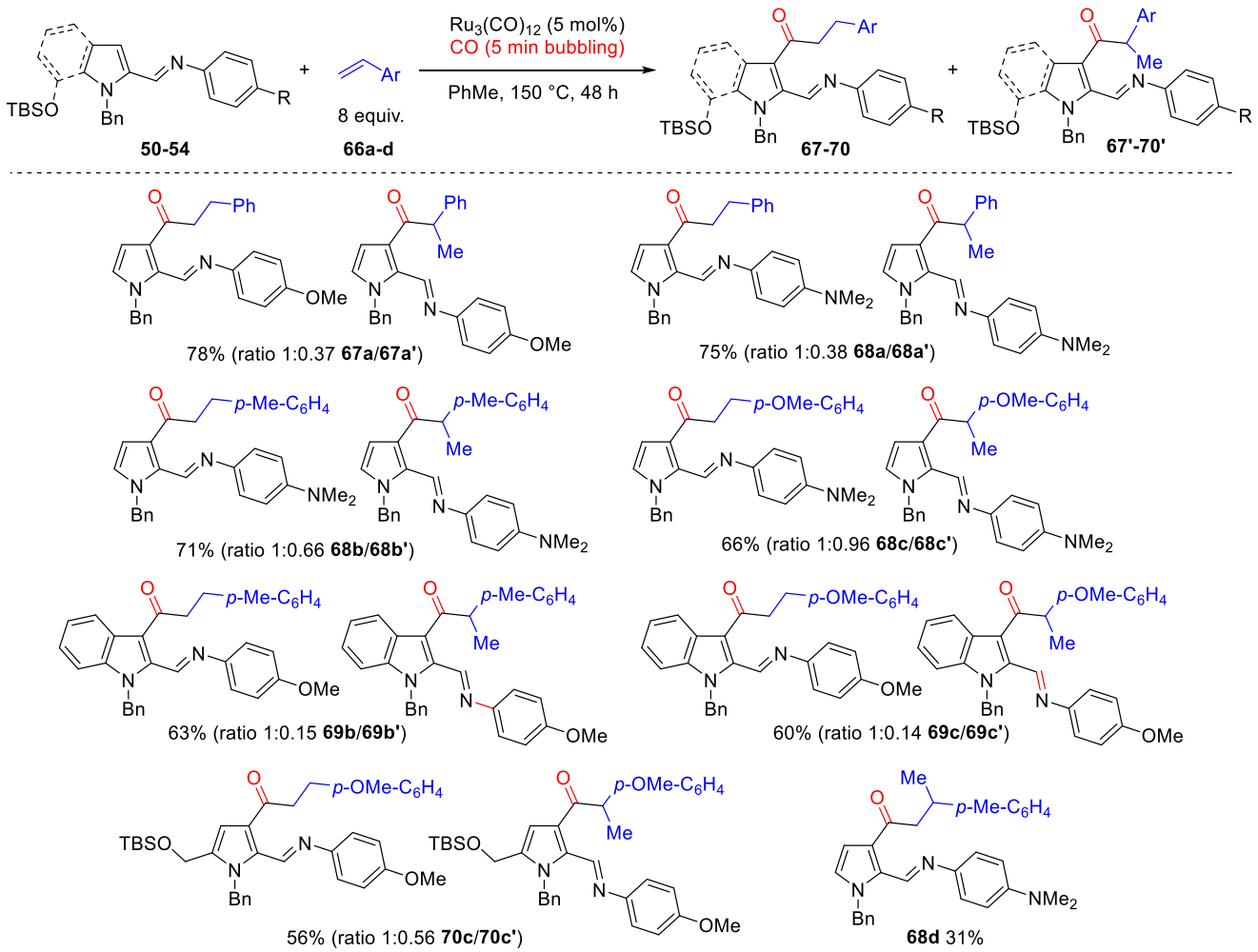
The reaction was additionally explored using the robust aromatic PMP **50** and *p*-NMe_2Ph **51** imines, which allowed the use of a larger variety of trialkoxyvinylsilanes.

In the event, these derivatives gave access to different C3-acylated imines from pyrrole **50-51** and indole **53** using the above mentioned alkoxy-, alkyl- and arylvinyl silanes **27a-e 27g-h** as olefinic partners. All the products were obtained in the monomeric form, even with triethoxy-**27a**, dimethylethoxy-**27b**, and trimethoxyvinylsilanes-**27h**, which tend to form the corresponding siloxanes. However, the best yields are obtained when using alkyl or aryl silanes as olefinic partners (Scheme 69).



Scheme 69. *Carbonylative Murai reaction with aromatic imines of pyrroles* ***50-51*** *and indole* ***53.***

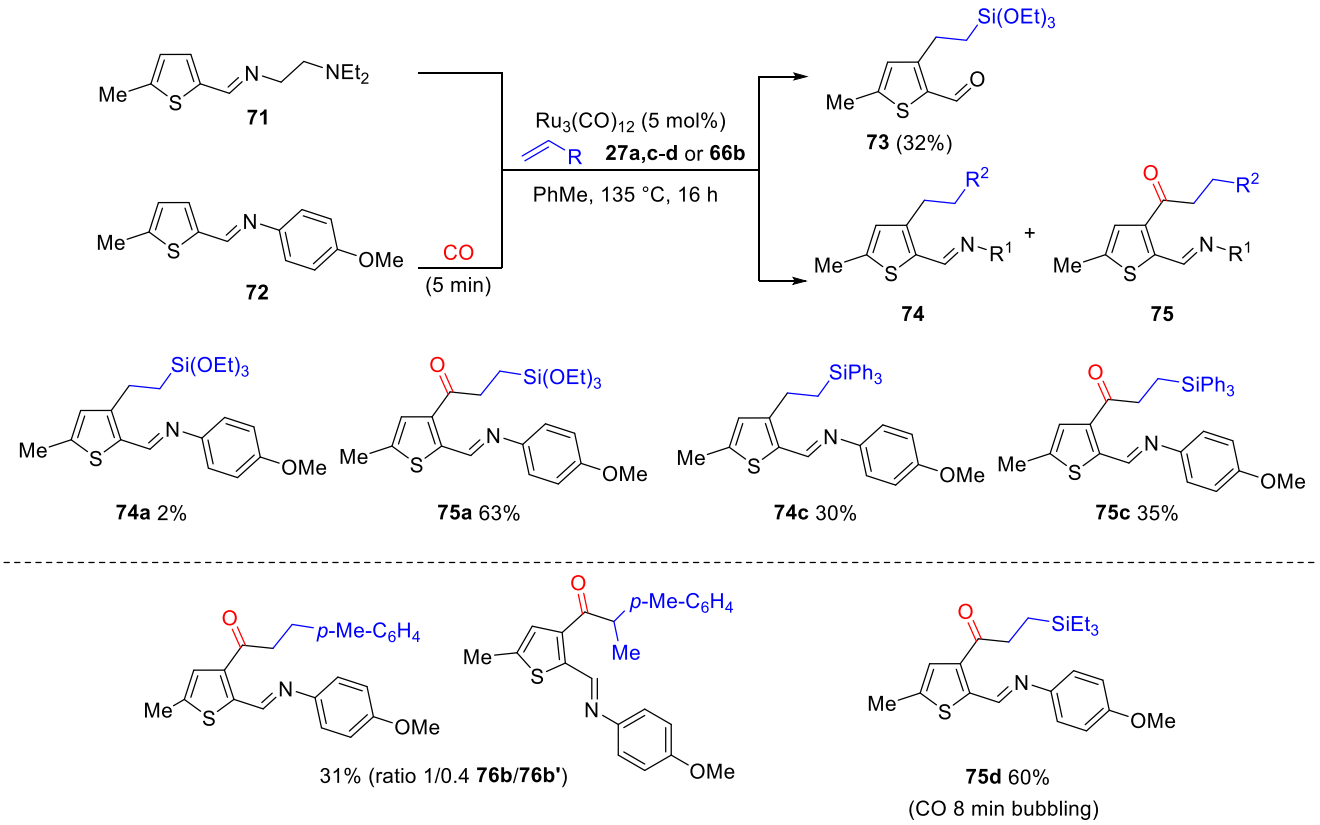
In the case of styrene derivatives as vinyl partners, best yields of the desired acylated products were obtained using the dimethylaminophenyl-imine for pyrrole **51**, and PMP-imine for indole **53**. Nevertheless, these reactions required higher temperatures (150 °C), longer reaction times (48 hours) and worked only with electron-rich styrene derivatives **66a-c**. In particular, *p*-Me **66b** and *p*-OMe **66c**, resulted to be suitable styrene partners, provided to use them in high excess (8 equiv.). Analogously to what observed in the classical Murai reaction, the carbonylative coupling of using the styrene derivatives always affords a mixture of linear and branched acylated product. This ratio, almost 1:1 in 5-substituted pyrrole **70**, is in favor of the linear compound for pyrrole **67a** and **68a-c** and even more for indole nucleus **69b-c** (Scheme 70). The only exception is the α-methyl styrene **66d**, which furnishes exclusively the linear compound **68d** with moderate yield.



Scheme 70. *Electron-rich styrenes for the carbonylative Murai reaction on aromatic imines of pyrroles* ***51-52*** *and indole* ***53****.*

To expand the scope of this new method, the Murai reactions were also performed on 5-methylthiophene 2-carboxaldimines, using the bidentate **71** or monodentate imines **72** (PMP-imine). Although the thienyl substrates proved to be less reactive than the corresponding furyl and pyrrolyl derivatives, a reactivity trend analogous to that of the *O*-based heterocyclopentadienes was detected. Indeed, the bidentate imine **71**, reacted as expected with triethoxyvinylsilane **27a**, but not with triethylvinylsilane and styrene, in presence of $Ru_3(CO)_{12}$ (5 mol%), in toluene (0.5 M) at 135 °C, leading to the corresponding C3-alkylated aldehyde **73**, in a moderate yield (Scheme 71), and the corresponding acylated products were never detected, even when working in the presence of CO atmosphere.

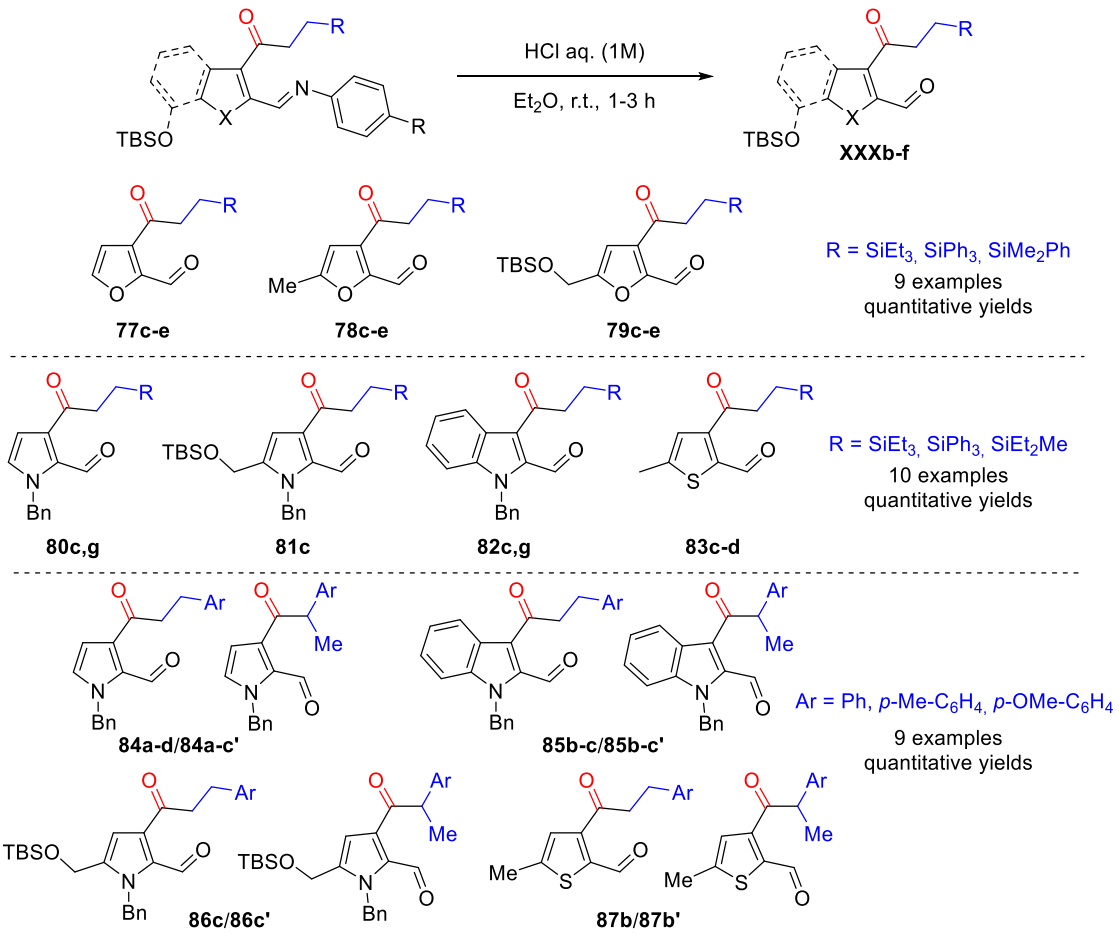
Conversely, treatment of PMP-imine **72** with triethoxy- **27a** or triethyl-vinylsilanes **27d** at 135 °C gave traces of the corresponding alkylated and acylated products in the absence of CO, and moderate yields of the corresponding C3-acylated products under CO atmosphere (Scheme 71). Noteworthy, these reactions required an increase of the CO bubbling time from 5 to 8 min to totally suppress the competing alkylated product, like in case of product **75d**. The reaction was also possible with a styrene derivative (8 equiv.) by increasing the temperature (150 °C) and the reaction time (48 h).



Scheme 71. *Thiophene imine **71-72** for carbonylative Murai reaction.*

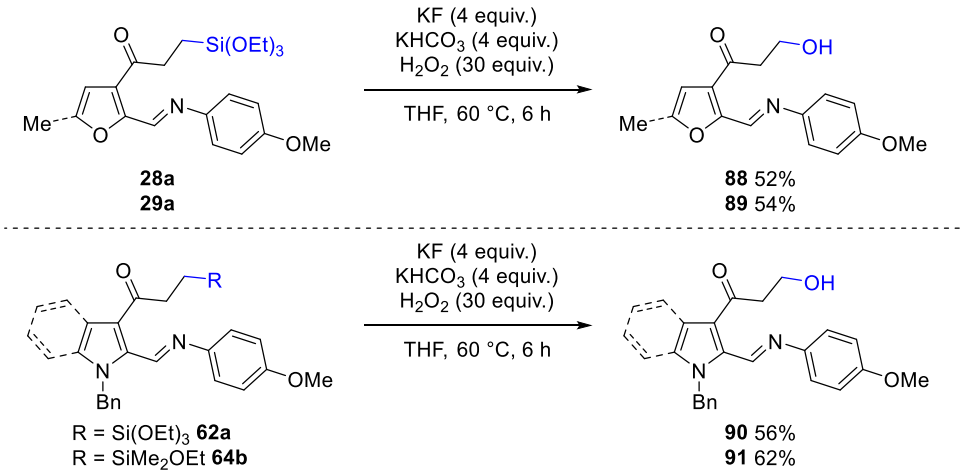
3.4. Imine hydrolysis and post functional transformations

Once concluded the scope of the substrates, some post-functional transformations of these products were considered, to enhance the synthetic value of the method. Accordingly, imine hydrolysis to the synthetically more attractive aldehyde was the first task considered (Scheme 72). In the event, treatment of the acylated products from the pyrrole, indole and thiophene series with aqueous HCl (1M) in ether at room temperature enabled access to the corresponding aldehydes in quantitative yields. However, this method is not suitable in the case of alkoxysilanes, which suffer from problems of polycondensation in acid medium.



Scheme 72. *Hydrolysis of C3-acylated compounds in aqueous acid conditions.*

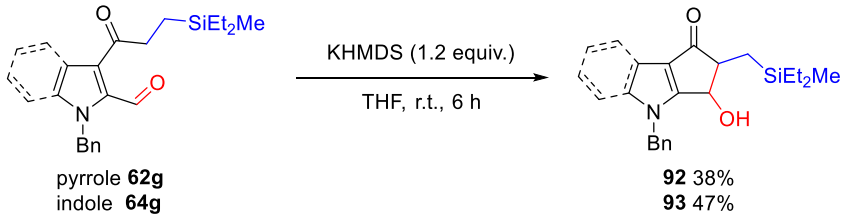
The reactivity of the silyl function was investigated next. In particular, we were interested to test the Tamao-Fleming oxidation, which allows the conversion of a C-Si bond into a C-O bond.[99] In the event, treatment of the C3-acylated furan-**28a**,**29a**, pyrrole- **62a** and indole-2-carboxaldimines **64b** with KF, $KHCO_3$ and H_2O_2 led to corresponding alcohols **88-91** in good yields, without further optimizations (Scheme 73).



Scheme 73. *Tamao-Fleming oxidation of alcoxy silanes derivatives.*

[99] Tamao, K.; Ishilda, N.; Tanaka, T.; Kumada, M.; *Organometallics*, **1983**, *2*, 1694-1696.

Additionally, treatment of pyrrole and indole aldehydes **62g** and **64g** with KHMDS (1.2 equiv.) in THF at room temperature brought about an intramolecular aldolization generating the aldols **92** an **93** in moderate yields as a 1:1 mixture of diasteroisomers (Scheme 74). Interestingly, these aldols were found to be refractory to dehydration, likely due to the antiaromatic character of the cyclopentadienone moiety.



Scheme 74. *Aldolization of C3-acylated five-membered heterocycles.*

3.5. DFT calculations and proposed mechanism

In order to have a more precise idea of the detailed mechanism of this reaction, a collaboration was established with Prof. Luis F. Veiros (University of Lisbon), who carried out a full density functional theory (DFT) study of this transformation. The DFT studies were realized on the PMP-imine of pyrrole **50**, using trimethoxyvinylsilane as the reaction partner. The essential results of this study are exposed here below.

The generally accepted mechanism of the Murai reaction and its carbonylative variant involves a mononuclear Ru(0) complex as the first active species.[100] Accordingly, and as previously done in the study of the classical Murai reaction with furan substrates,[92] we hypothesized the initial conversion of the $Ru_3(CO)_{12}$ pre-catalyst into a mononuclear ruthenium carbonyl by Ru-Ru breaking and CO release.

The initial species in the proposed mechanism has the imine substrate **50** coordinated to the $Ru(CO)_3$ fragment (intermediate **A**). From **A**, there is an oxidative addition of the C3–H bond in the pyrrole ring to the metal center with formation of a hydride intermediate, complex **B**, in the opening step of the mechanism. Thus, the metal is formally oxidized from Ru(0), in **A**, to Ru(II), in **B**. That is a fairly easy step with a barrier of 14 kcal/mol and a free energy balance of ΔG = 3 kcal/mol. The reaction proceeds with olefin coordination followed by insertion into the Ru–H bond. Alkene coordination occurs with simultaneous break of imine coordination (intermediate **C**) and the insertion process results in a high energy intermediate where coordination of the newly formed alkyl ligand is stabilized by a C–H agostic interaction (intermediate **D**). Recoordination by the N-imine lone pair breaks the agostic interaction and results in the alkyl intermediate **E**. That process overcomes a barrier of 23 kcal/mol associated with the transition state for olefin insertion ($\mathbf{TS_{CD}}$). This is the highest energy transition state along the path and corresponds to the determining transition state of the process (TDTS). Overall, alkene insertion into the hydride complex – from **B** to **E** – is a favorable process with ΔG = –11 kcal/mol.

[100] Helmstedt, U. & Clot, E. *Chem. Eur. J.* **2012**, *18*, 11449-11458.

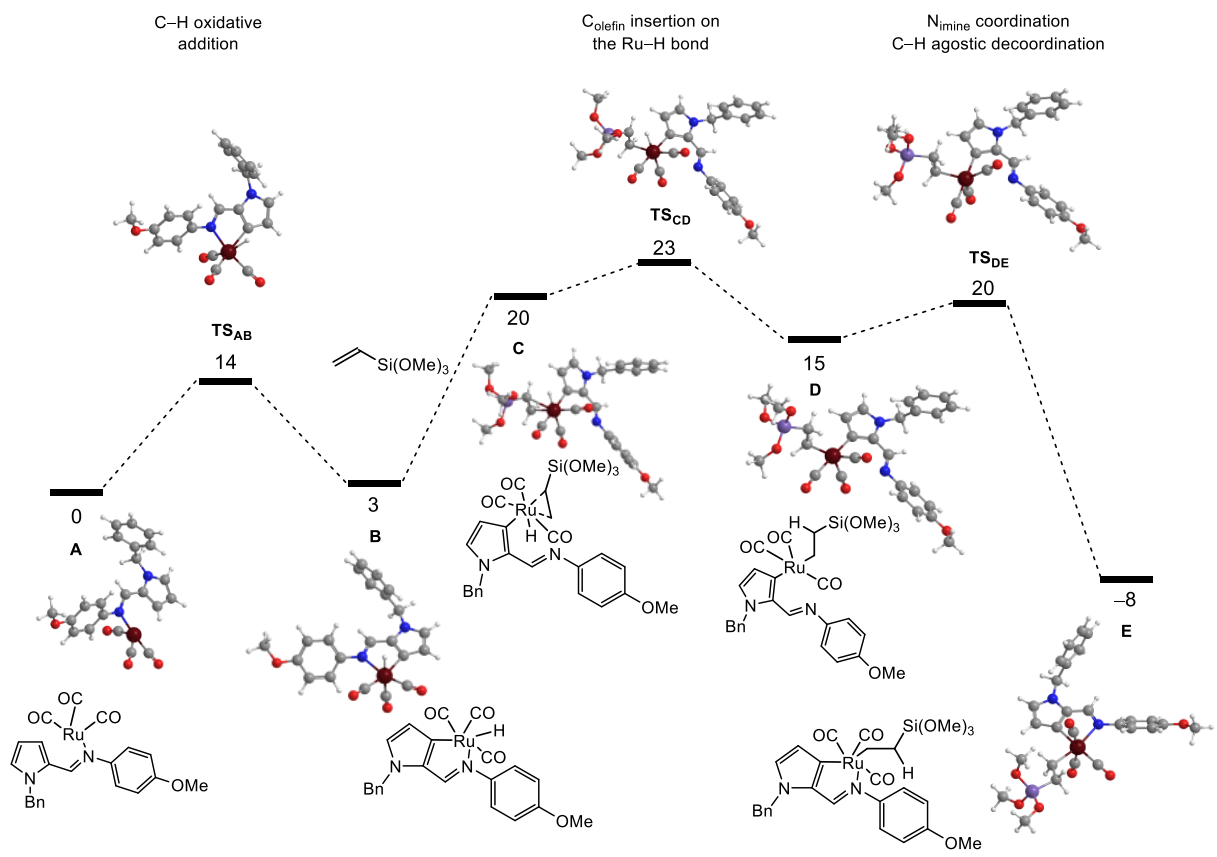


Figure 4. *Free energy profile (kcal/mol) calculated for the acylation of imine* ***50*** *(Part I).*

The mechanism proceeds with CO insertion into **E**, resulting in the acyl complex **F**. If compared with **A** energetic level, the transition state $\mathbf{TS_{EF}}$ has an energy of 13 kcal/mol, meaning that the CO insertion step is strongly endergonic (ΔG = 14 kcal/mol) and corresponding to a 21 kcal/mol barrier, measured from **E**. From intermediate **F** to **H**, the next step, is the coordination of a new CO molecule to the metal, in a very easy process with a transition state higher of only 3 kcal/mol. Checking the values of the different intermediates along the entire mechanism, the resulting acyl complex **H**, is the most stable species, being 22 kcal/mol more stable than **50**, the determining intermediate in the process (**TDI**). In the final step, the reductive elimination process between the acyl ligand and the Ru-C3 heteroaromatic carbon brings the metal back to its initial oxidation state, Ru(0). This last step endergonic (ΔG = 6 kcal/mol) overcomes a barrier of 21 kcal/mol, measured from the acyl intermediate **H**, to the following transition $\mathbf{TS_{HI}}$, just few kcal/mol more stable than **A** (Figure 5).

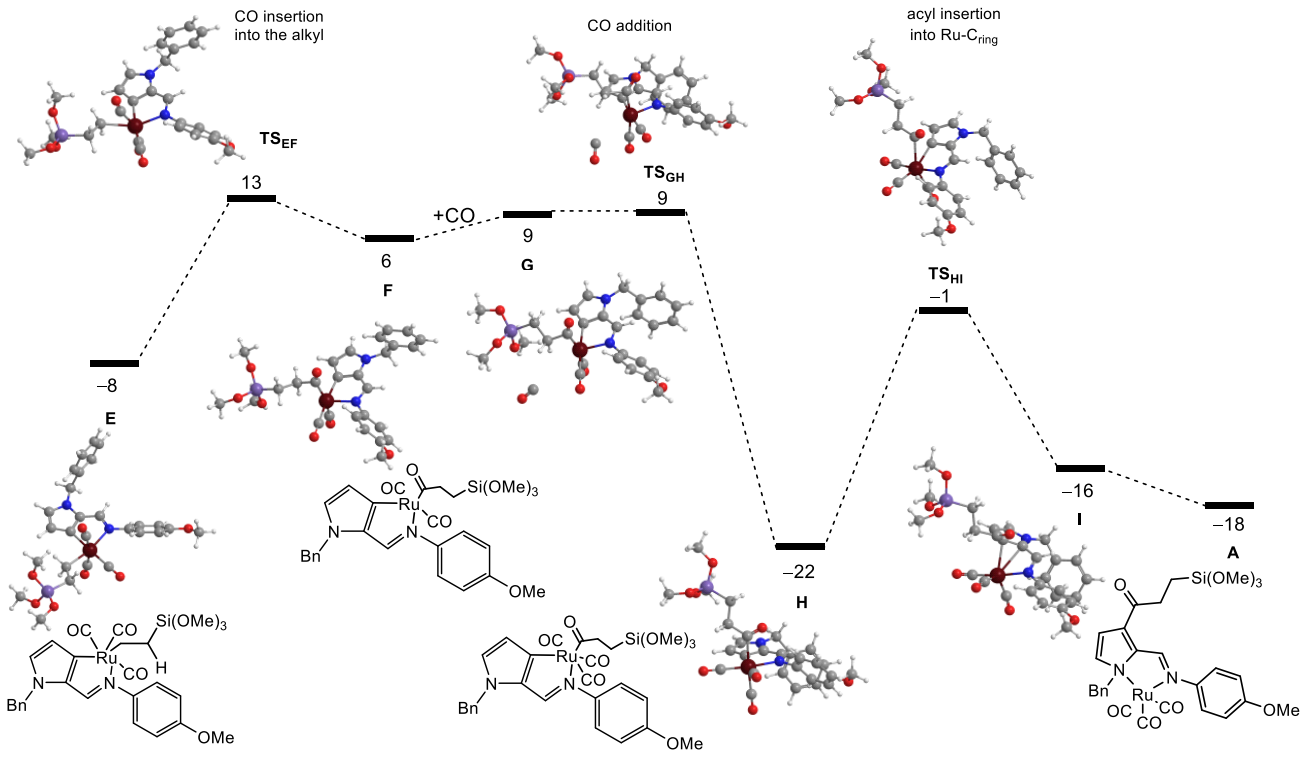
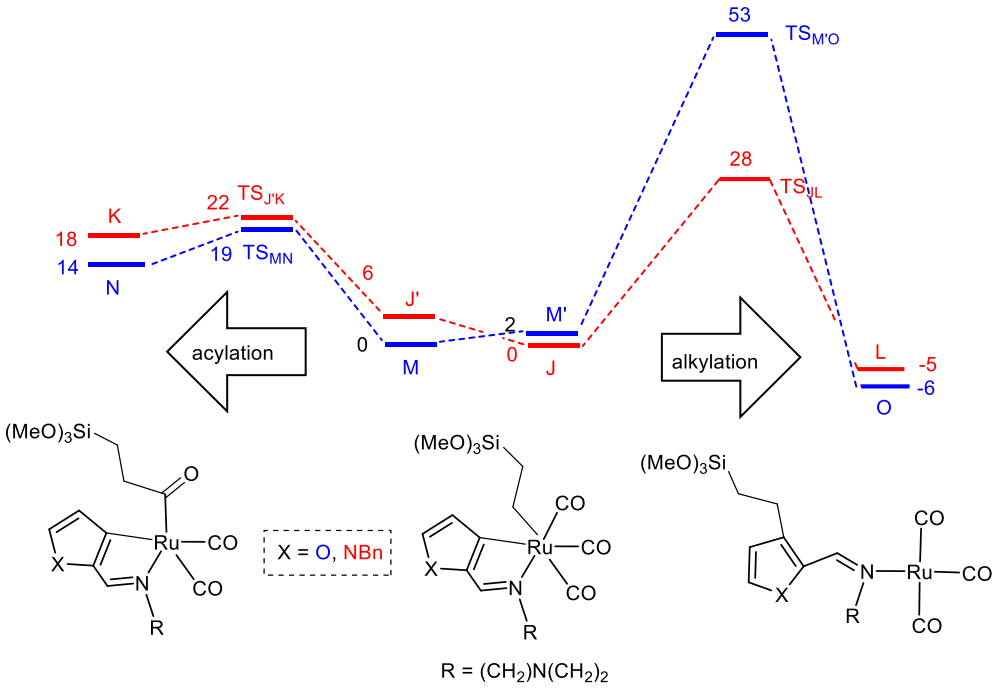


Figure 5. *Free energy profile (kcal/mol) calculated for the acylation of imine **50** (Part II).*

Considering the global energy values, the entire cycle is exergonic, being the final species **I** 16 kcal/mol more stable than **A** and has an overall barrier of 27 kcal/mol, measured from **H** to the transition state for olefin insertion of the following cycle $\mathbf{TS_{CD}}$. The closure of the cycle, with liberation of the acylated compound **62h** and coordination of a new imine **50**, from **I** back to **A**, has a favorable free energy balance of ΔG = –2 kcal/mol.

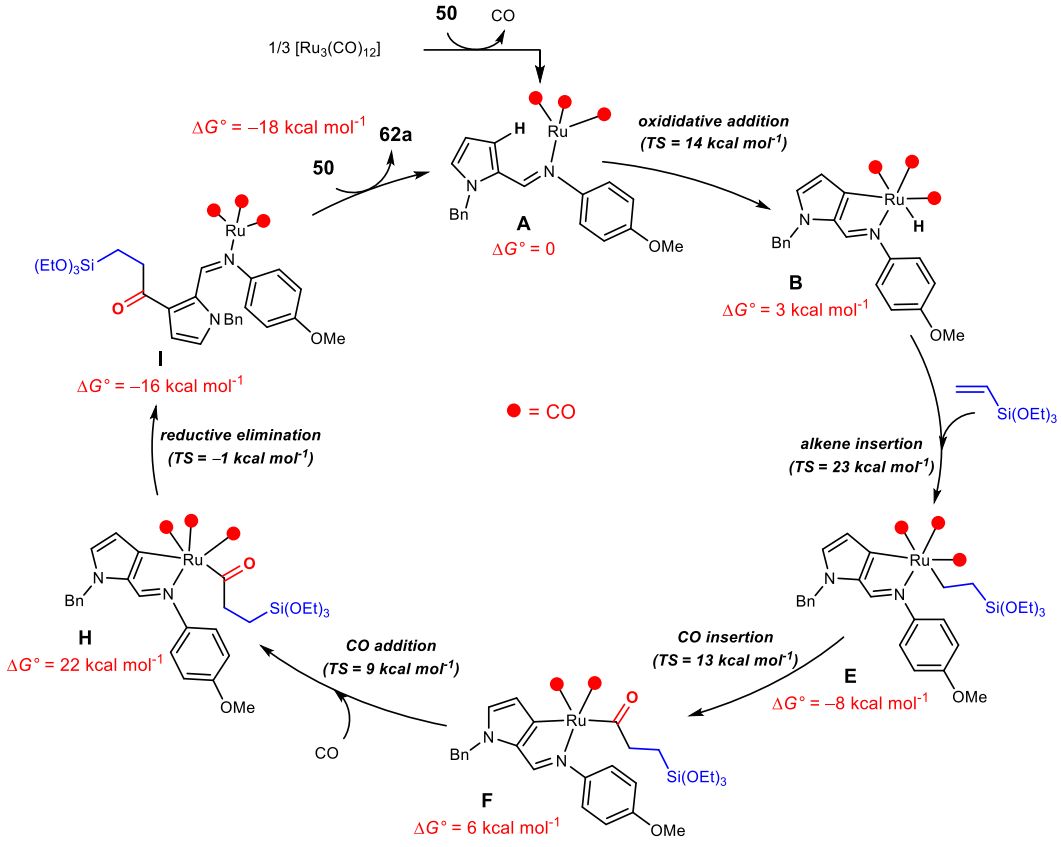
On the other hand, a comparison between the reductive elimination and the CO insertion steps starting from the common tricarbonyl intermediates deriving from furan imine and pyrrole imine **49** after olefin insertion, shows that the barrier associated with the reductive elimination is higher than the one associated with the CO insertion, by 34 kcal/mol in the case of the furan imine and by 6 kcal/mol in the case of the pyrrole imine. This confirms that in the presence of CO atmosphere the reductive elimination step is always intrinsically disfavored with respect to CO insertion (Scheme 75).[101]

[101] **J** and **J'**correspond to the same alkyl complex intermediate, considering the different conformation of the alkyl ligand.



Scheme 75. *Free energy profile (kcal/mol) for the comparison between carbonylation and alkylation.*

On the basis of the DFT calculation, we propose the following mechanism, taking the acylation of **50** with triethoxyvinylsilane as a model example (Scheme 76).



Scheme 76. *Proposed mechanism for the carbonylative Murai reaction.*

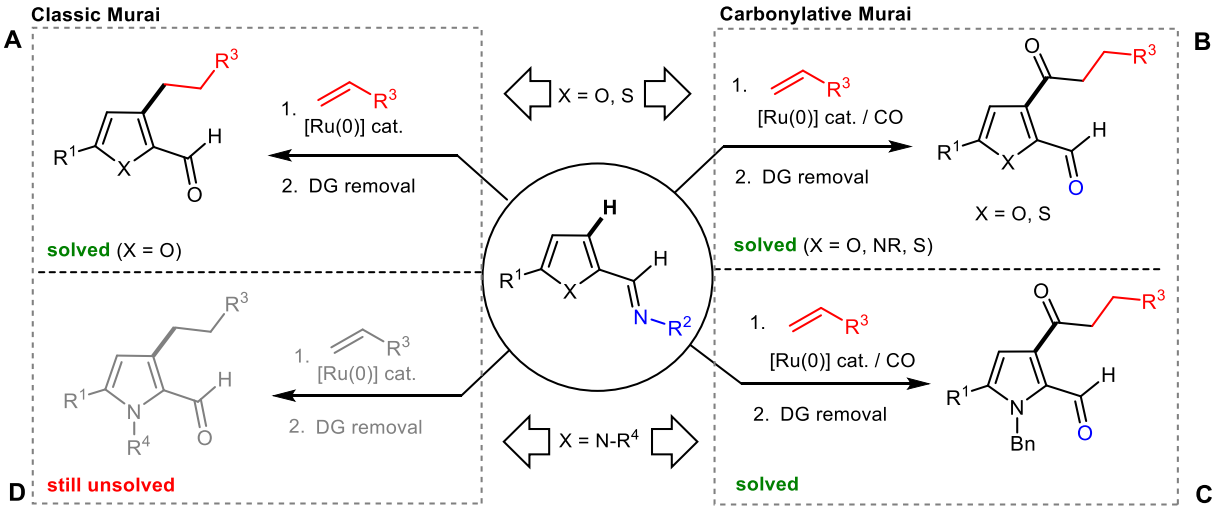
4. Conclusions

The chapter started with the presentation of carbonylative methods, with a special focus on the C-H carbonylation of aromatic compounds. Then, we presented the Murai reaction, its mechanism, a selection of significant examples and its carbonylative version.

Then, we described our first experiments of Ru(0)-catalyzed carbonylative acylation of 2-imino furfural derivatives, using a CO atmosphere. After optimization of the reaction conditions, the scope of the acylation was assessed by the use of different vinylsilanes. Then, we passed to study the corresponding C3-H carbonylative acylation of 2-imino pyrroles and 2-imino thiophenes, which turned out to be successful not only using vinylsilanes, but also with electron-rich styrenes (Scheme 77, squares B and C). Some post-functionalizations of the coupled products were also accomplished, which emphasize the new method.

Finally, a full DFT computation enabled us to propose a detailed reaction mechanism for this transformation. The carbonylative C–H activation couplings developed in this study largely expand the scope of the Murai reaction on the heteroarenes and combining with our previous work on furfural imine alkylation (Scheme 77, Square A) allow to extend the combination of alkylative and acylative version of Murai reaction.

Future studies will be directed towards the development of methods that allow the alkylation of 2-formyl-*N*-containing heterocycles, since some preliminary tests did not afford satisfying results (Scheme 77, square D). As well we are interested to develop more eco-friendly version with *in situ* release of carbon monoxide.[102]



***Scheme 77**. General resume on Murai reaction.*

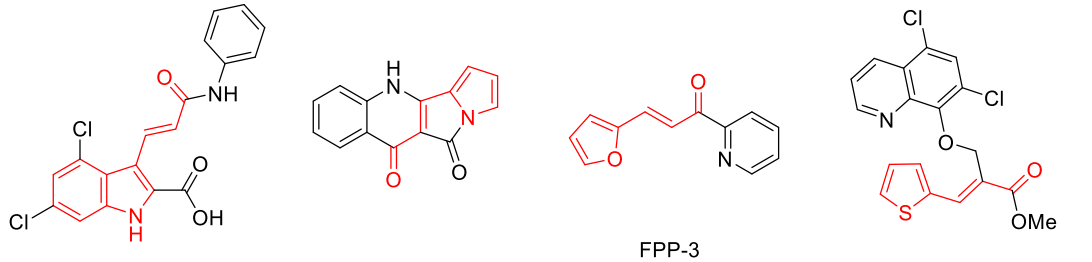
At the same time, our group is currently involved in the development of the above transformations under *flow conditions*, and/or *heterogeneous catalysis*, to improve yields and scale up.

[102] [a] Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc*. **2011**, *133*, 6061-6071; [b] Gockel, S. N.; Hull, K. L. *Org. Lett.* **2015**, *17*, 3236-3239.

Chapter 3: Ru-catalyzed Oxidant free Fujiwara-Moritani type reaction

1. Introduction

If heterocyclic nuclei play a predominant role in both organic and pharmaceutical chemistry, the nature and the position of their substituents in the ring are also key. More specifically, heterocyclic scaffolds conjugated to variously substituted alkenyl systems (and in particular acrylic motives) have been identified in numerous natural products. For example, the drug "Gavestinel" is an antagonist of the NMDA receptor complex in the treatment of acute intracerebral haemorrhages. Other examples of alkenyl heterocycles are described in Scheme 78.[103]



Scheme 78. *Conjugated heterocycles in drugs and natural products.*

Not unexpectedly, the development of methods for the synthesis of these scaffolds and their functionalization, to end up with more complex structures in the most efficient and eco-compatible way is a very topical subject. In particular, with the advent of the use of transition metals in organic synthesis, a great boost has been given in the coupling reaction between aryl (or heteroaryl) systems and alkenes.

Considering the increasing demand for protocols that minimize the formation of by-products (atom economy) and also allow a significant reduction in the number of reaction steps (step economy), the direct alkenylation reaction of aromatic systems through the cleavage of one or two C-H bonds is particularly attractive.

2. Alkenylation of heteroaromatic systems

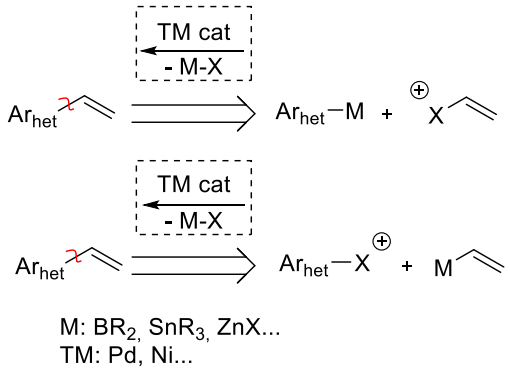
In the seventies, the advent of the use of transition metal catalysis in organic synthesis gave a huge acceleration to the development of coupling reactions involving aryl-C(sp^2) and aryl-C(sp) systems. In

[103] [a] Balsamini, C.; Bedini, A.; Diamantini, G.; Spadoni, G.; Tontini, A.; Tarzia G. *J. Med. Chem*. **1998**, *41*, 808-820; [b] Abe, M.; Imai, T.; Ishii, N.; Usui, M.; Okuda, T.; Oki, T. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 1202-1205; [c] Lee, E. S.; Park, B. C.; Paek, S. H.; Lee, Y. S.; Basnet, A; Jin, D. Q.; Choi, H. G.; Yong, C. S.; Kim, J. A. *Biol. Pharm. Bull.*, **2006**, *29*, 361-364; [d] Sivadasa, A.; Abdulmalika, N.; Subbarayab, N. ISSN: 2456-7949.

particular, the transition metal catalyzed alkenylation reaction of (hetero)aryl systems using alkene partners appeared as the most prominent strategy.

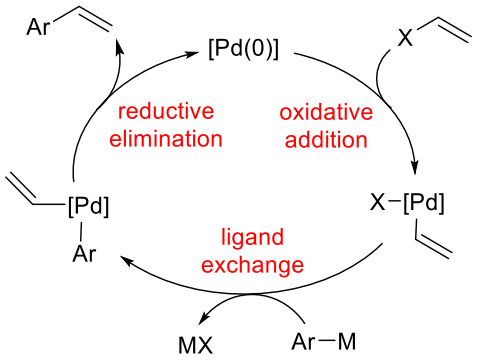
2.1. Transition metal-alkenylation methods in organic synthesis

The most popular method for obtaining alkenyl heteroaromatics relies on the classical transition metal catalyzed coupling between heteroaryl nucleophiles and alkenyl halides, or, inversely, between heteroaryl halides and alkenyl nucleophiles (Scheme 79).



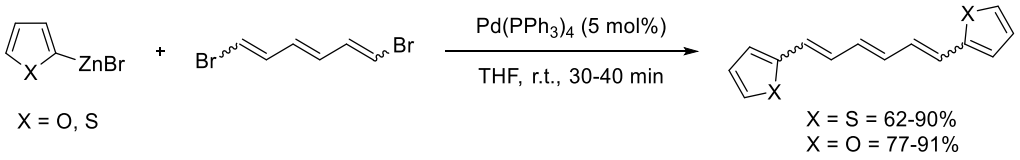
Scheme 79. *Alkenyl heteroaromatics through classical cross-coupling.*

These cross-coupling methods are classified and named according to the nature of the nucleophilic species used and the scientist that mainly contributed to their discovery: organoboron derivatives (Suzuki-Miyaura), organotin derivatives (Migita-Kosugi-Stille), organozinc (Negishi), or silanes (Hiyama-Denmark). These reactions typically need palladium catalysis, and rely on the following general sequence of elementary steps: oxidative addition/ligand exchange (transmetalation)/reductive elimination (Scheme 80).



Scheme 80. *General mechanism of a classical Pd-catalyzed cross-coupling reaction.*

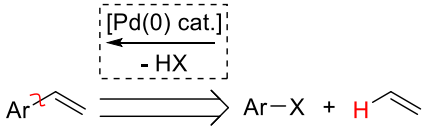
For example, the synthesis of disubstituted heteroaryl hexatrienes was achieved by Negishi coupling using the dibromohexatriene and the heteroaryl Zn(II) salt (Scheme 81).[104] These types of reactions, considering the excellent yields, are a powerful tool in the synthesis of biological active compounds



Scheme 81. *Example of Pd(0)-catalyzed Negishi coupling*

The cross-coupling reaction, which earned Suzuki and Negishi two thirds of the 2010 Nobel Prize,[105] is a very powerful transformation, endowed with a number of positive features, such as: high yields, total regioselectivity, high functional group tolerance, mild reaction conditions, adaptability to modular synthesis. Nevertheless, this approach is not without drawbacks. Indeed, stoichiometric amounts of the nucleophilic (usually organometallic) reagent are needed, and often require several synthetic steps. Furthermore, the halogen atom in the starting aryl or vinyl halide has to be positioned in the appropriate position through an had-hoc step, usually by halogenation of the corresponding arene or alkene precursor. Finally, the reaction forms stoichiometric amounts of a waste salt.

An alternative approach toward alkenyl heteroaromatics is based on the Pd-catalyzed interaction between a heteroaryl halide and an appropriate alkene as reported in Scheme 82.



Scheme 82. *Alkenyl heteroaromatics through the Mizoroki-Heck reaction.*

This type of reaction was pioneered by Mizoroki, [106]in Japan, and Heck,[107],[108] in USA, who reported independently and almost at the same time that heating an aryl iodide in the presence of an alkene and of catalytic amounts of $PdCl_2$ [or $Pd(OAc)_2$] and of a base gave rise to the desired alkenylated arene. This reaction was improved in the following years by Heck and others,[109] becoming an invaluable method of obtaining C-C couplings, and earned Heck the remaining third of the 2010 Nobel Prize in Chemistry.

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[104] Villiers, P.; Vicart, N.; Ramondenc, Y.; Plé, G. *Eur. J. Org. Chem.*, **2001**, 561-574

[105] Backvall, J. E. B. *Presentation of the Nobel Prize in Chemistry 2010.*

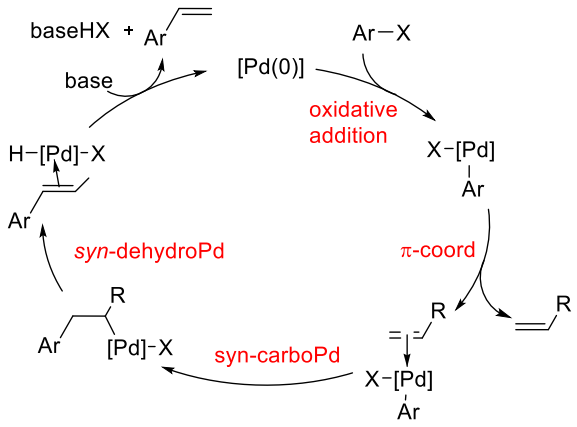
[106] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jap.*, **1971**, *44*, 581.

[107] Heck, R. F.; Nolley, J. P. *J. Org. Chem*., **1972**, *37*, 2320-2322.

[108] In 1969, Richard Heck showed that heating phenylmercuric acetate and styrene in the presence of one equivalent of $Pd(OAc)_2$ in MeCN gave rise to stilbene. Heck, R. F. *J. Am. Chem. Soc*. **1969**, *91*, 6707-6714.

[109] Oestreich, M. *The Mizoroki-Heck Reaction,* Wiley-VCH, **2009**.

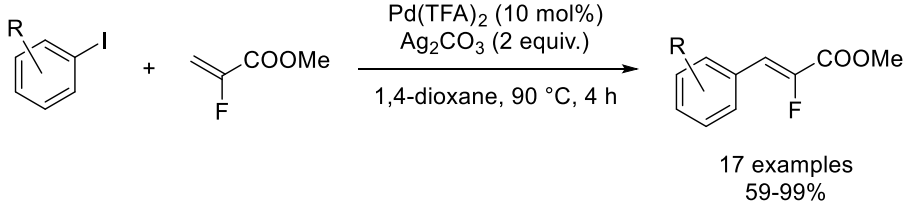
The mechanism of this reaction involves an initial oxidative addition of the aryl halide to Pd(0), followed by coordination of the alkene to the palladium atom of the resulting σ-arylpalladium(II) complex. Subsequent alkene syn-carbopalladation generates a σ-alkylpalladium(II) complex, which, after appropriate conformational change, undergoes a syn-dehydropalladation. Final reductive elimination forms the alkenylated arene target and regenerates the Pd(0) catalyst (Scheme 83).



***Scheme 83**. Simplified mechanism of the Mizoroki-Heck reaction.*

The Mizoroki-Heck approach shares some points in common with the previously discussed cross-coupling. Both the approaches are based on Pd(0) catalysis and the first elementary step is the same oxidative addition. However, this latter approach has the added bonus that does not require the organometallic nucleophile, whose preparation may be uneasy. On the other hand, the carbopalladation step of the Mizoroki-Heck protocol can be associated to regioselectivity issues that are not present in the classical cross-coupling.

Among the wide plethora of Mizoroki-Heck type processes, such as with aryl boronic acids,[110] one innovative example exploiting an arylhalide and a α-fluoro-acrylate was reported by Couve-Bonnaire in 2016 for the stereospecific preparation of substituted α-fluoroacrylates (Scheme 84).[111] The reaction, highly tolerant for various functional groups and very efficient in term of fluoroalkenes, does not require the presence of a neutral ligand and permit to access to high substituted olefin, generally low reactive in this type of coupling.



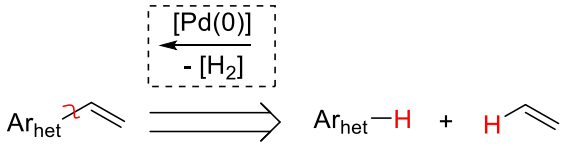
***Scheme 84** Mizoroki-Heck reaction for the synthesis of tri- and tetrasubstituted α-fluoroacrylates.*

[110] Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 2424-2425.

[111] Rousee, K.; Bouillon, J.-P.; Couve-Bonnaire, S.; Pannecoucke, X. *Org. Lett*. **2016**, *18*, 540-543.

2.2. The Fujiwara-Moritani reaction

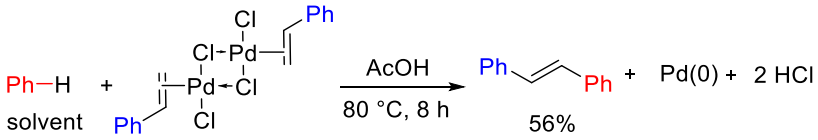
An even more atom-economical, although more challenging, alternative coupling to obtain the desired alkenyl heterocycles is based on the direct interaction between an unfunctionalized heteroaromatic and an unfunctionalized alkene (Scheme 85).



Scheme 85. *Alkenyl heteroaromatics through the Fujiwara-Moritani reaction.*

This oxidative cross dehydrogenative coupling (CDC) approach[112] is based on a double C-H activation and does not generate stoichiometric amounts of waste salt. Indeed, the only byproduct is dihydrogen, or the reduced form of a sacrificial (stoichiometric) oxidizing agent, if an H_2 acceptor is needed to drive the reaction.

This type of coupling reaction was first reported by Fujiwara and Moritani as early as 1967,[113] that is, five years before the publication of the Mizoroki-Heck reaction! In their first paper, these scientists reported that that heating the complex [styrene-$PdCl_2$] in the presence of a large excess of benzene and AcOH gave rise to stilbene, accompanied by Pd(0), HCl and some amounts of 1-phenylethyl acetate byproduct (Scheme 86).



Scheme 86. *First example of dehydrogenative alkenylation of aromatic system.*

Although the original reported method, as such, was rather uninteresting, due to the stoichiometric use of palladium and of one reaction component needed as a solvent, the discovery was groundbreaking.

In the following years, Fujiwara and his group refined the protocol, trying to understand its mechanism and improve the limitations. In a second paper, they reported the use of $Pd(OAc)_2$ to replace the stoichiometric Pd(II)-styrene complex, using AcOH and/or AcONa, which avoided the formation of the byproduct.[114] Subsequently, they were able to turn the reaction catalytic in palladium. This was obtained by

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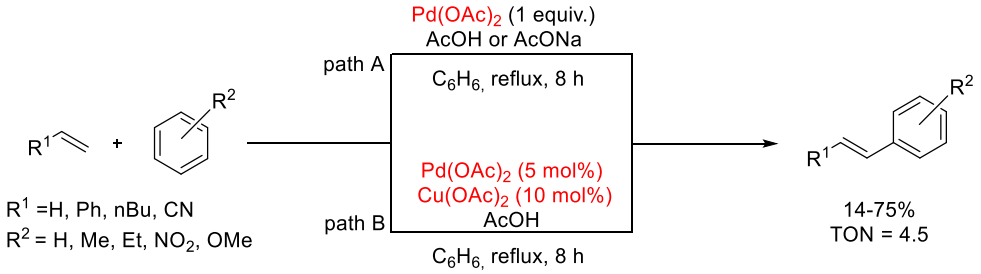
[112] For reviews see: [a] Yeung, C. S.; Dong, V. M.; *Chem. Rev.* **2011**, *111*, 1215-1292; [b] Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170-1214; [c] Srivastava, A; Jana, C. K.. *Heterocycles via Cross Dehydrogenative Coupling,* Springer, **2019**.

[113] [a] Moritani, I.; Fujiwara, Y. *Tetrahedron Letters* **1967**, *12*, 1119-1122; [b] Fujiwara, Y.; Moritani, I.; Matsuda, M. *Tetrahedron*, **1968**, *24*, 4819-4824.

[114] Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Letters* **1968**, *5*, 633-636.

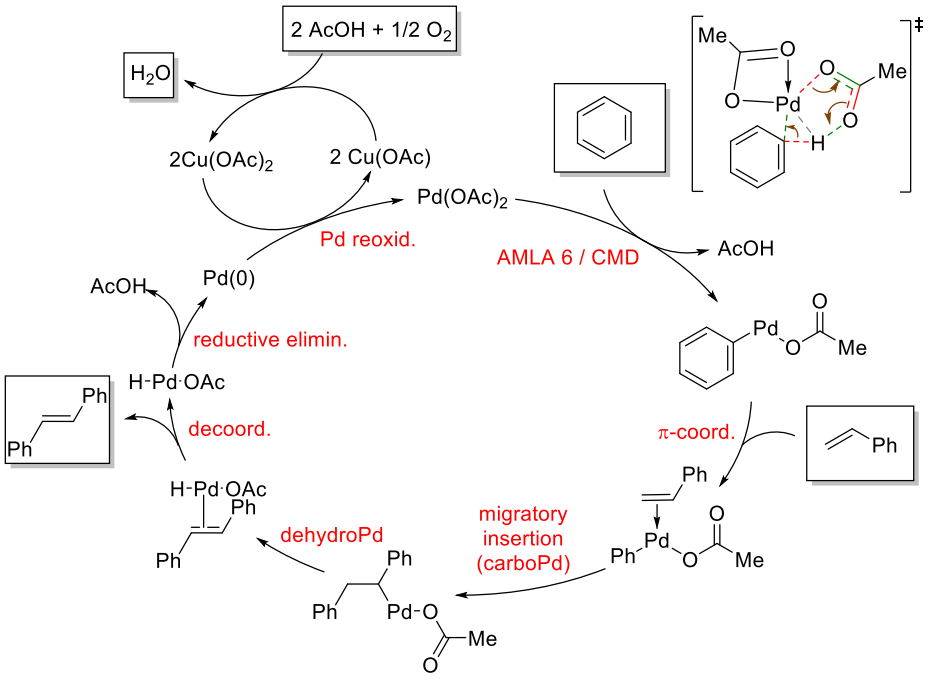
working in the presence of stoichiometric amounts of AgOAc[115] or under aerobic conditions (O_2) in the presence of catalytic amounts of AgOAc or $Cu(OAc)_2$ as co-oxidizing agents, [116] which allowed to obtain the desired alkenylated arenes in moderate to good yields, with turnover numbers (TON) of 4.5 (Scheme 87).



Scheme 87. *The Fujiwara-Moritani reaction.*

A plausible mechanism of the Fujiwara-Moritani reaction is described here below.[117] Benzene palladation is expected to take place *via* an AMLA 6[118]/CMD[119] path,[120] which releases arylpalladium acetate and acetic acid. This step has an electrophilic character, and has been often proposed to pass through an alternative Wheland-type intermediate.[121] After coordination of the alkene to the palladium atom of the σ-arylpalladium(II) complex, alkene *syn*-carbopalladation generates a σ-alkylpalladium(II) complex, which, after appropriate conformational change, undergoes a *syn*-dehydropalladation to generate the alkenylated arene and a palladium hydride. Deprotonation of the palladium hydride by acetate triggers reductive elimination and yields Pd(0), which, in the presence of the $Cu(OAc)_2$ co-catalyst and oxygen, can be re-oxidized to $Pd(OAc)_2$ and reenter the catalytic cycle.

[115] Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968**, 9, 3863-3865.
[116] Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.*, **1969**, *91*, 7166-7169.
[117] [a] Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, 19, 3895–3908; [b] Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754-13755; [c] Mulligan, C. J.; Parker, J. S.; Hii, K. K. *React. Chem. Eng.*, **2020**, *5*, 1104-1111.
[118] Boutadla, Y.; Davies, D.L.; Macgregor, S.A.; Poblador-Bahamonde, A.L. *Dalton Trans.* **2009**, 5820-5831
[119] Gorelsky, S.I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658-668.
[120] Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Cat. A. Chem.* **2017**, *426*, 275.
[121] [a] Shilov, A. E.; Shul'pin G. B. *Chem. Rev.* **1997**, *97*, 2879-2932; [b] Fuchita, Y.; Kawakami, M.; Shimoke, K. *Polyhedron* **1991**, *10*, 2037; [c] Fuchita, Y.; Taga, M.; Kawakami, M.; Kawachi, F. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1294.

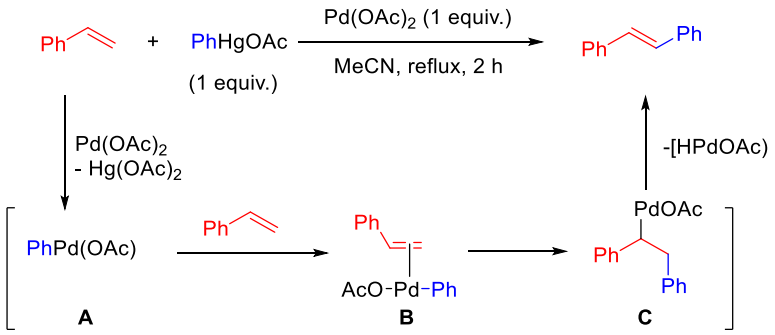


Scheme 88. *Simplified mechanism of the Fujiwara-Moritani reaction.*

Analysis of the elementary steps is very instructive, as it reveals that Fujiwara-Moritani reaction intermediates are found incorporated in other known name reactions, developed before or after the disclosure of this reaction.

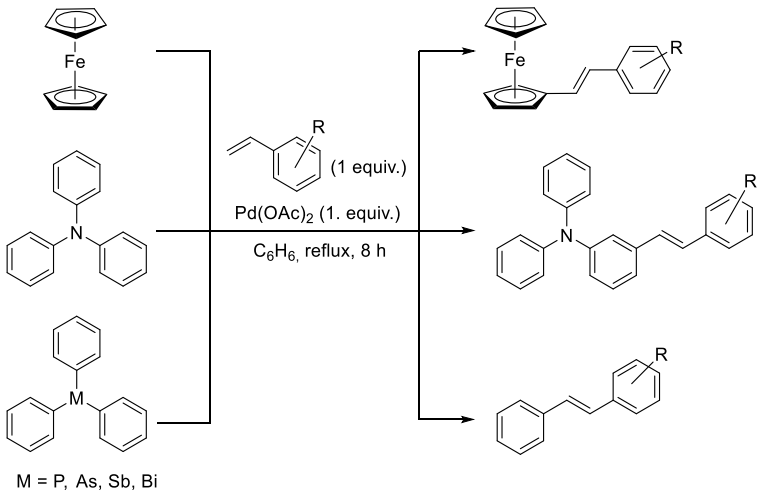
The first step is in common with the Van Helden reaction,[122] reported in 1965 (*i.e.* two years before the FM reaction), which refers to the oxidative coupling of aromatic compounds in the presence of Pd(II) salts. The subsequent steps, till to the formation of the final alkenylated product and Pd(0) are totally in common with the stoichiometric coupling between arylmercury reagents and alkenes to give the alkenylated arenes, pioneered by Heck in 1969,[123] (and later improved to the catalytic oxidative version, and known under the name of "oxidative Heck", by using a sacrificial oxidant and nucleophilic partners other than arylmercury compounds), as well as with the Mizoroki-Heck reaction, reported in 1971-1972, and discussed earlier. Finally, the eventual Pd(0)-to-Pd(II) reoxidation is clearly inspired by the Wacker process, reported in 1959 (Scheme 89).[124]

[122] Van Helden, R.; Verberg, G. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1263-1273.
[123] Heck, R. F. *J. Am. Chem. Soc*. **1969**, *91*, 6707-6714.
[124] Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Ruttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176-182.



***Scheme 89**. Palladium-promoted coupling between arylmercury reagents and alkenes.*

Coming back to the synthetic part, the Fujiwara group also extended the substrate scope of the alkenylation to various substituted aryl[125] and alkyl[126] olefins, but still employing stoichiometric amounts of $Pd(OAc)_2$. The method was also extended to the alkenylation of the aryl group of triarylamines and ferrocene. Triaryl phosphines, arsines, and other aryl semi-metals reacted with cleavage of the carbon-heteroatom bond to furnish the substituted stilbenes in different yields according to the semi-metal used (Scheme 90).[127]



***Scheme 90.** Tertiary aromatic amines and ferrocene undergo the Fujiwara-Moritani reaction.*

The alkenylation method could also be extended to 2-imino heterocyclopentadienes and their benzofused structures, which, not unexpectedly, proved to be much more reactive than benzenic systems.[128] The reaction resulted totally C2-selective, although constantly giving mixtures of mono- and dialkenylated compounds. Indole and benzofuran gave the corresponding 2,3-bis-alkenylated products,

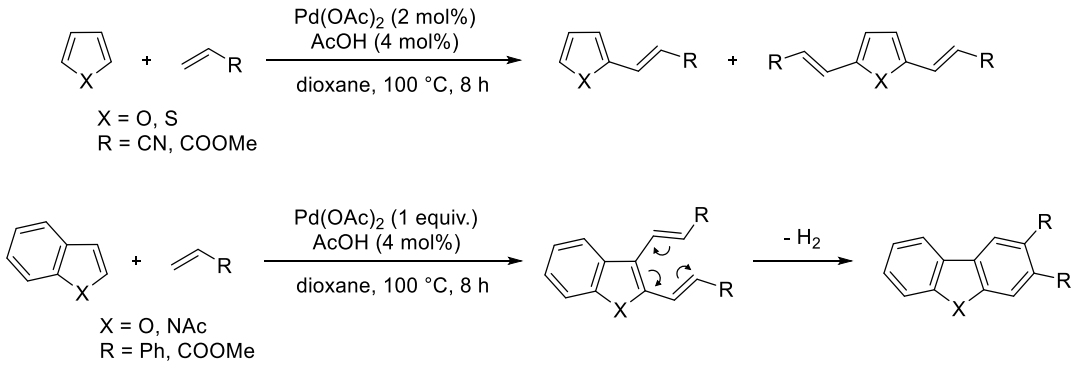
[125] [a] Danno, S.; Moritani, I.; Fujiwara, Y. *Tetrahedron*, **1969**, *25*, 4809-4813; [b] Danno, S.; Moritani, I.; Fujiwara, Y. *Tetrahedron*, **1969**, *25*, 4819-4823;

[126] [a] Fujiwara, Y.; Moritani, I.; S.; Asano, R.; Teranishi, S. *Tetrahedron Lett.*, **1968**, *9*, 6015-6017; [b] Yamamura, A.; Moritani, I.; Sonoda, A.; Teranishi, S. Fujiwara, Y. *J. Chem. Soc.* ***1973***, 203-205.

[127] [a] Asano, R.; Moritani, I.; Sonoda, A; Fujiwara, Y.; Teranishi, S. *J. Chem. Soc (C)*, **1971**, 3691-3692; [b] Asano, R.; Moritani, I.;Fujiwara, Y.; Teranishi, S. *Bull. Chem. Soc. Japan*, **1973**, *45*, 2910-2911.

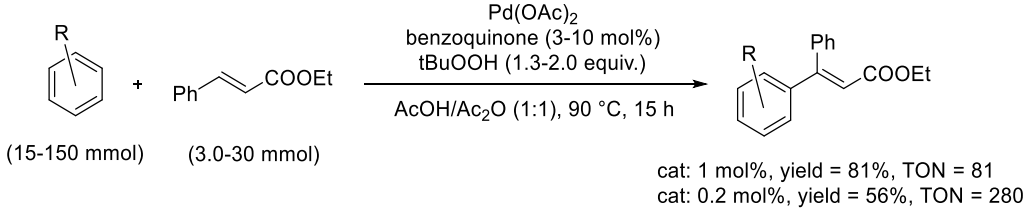
[128] Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851-855.

which evolved in situ into carbazole or dibenzo[*b, d*]furan via electrocyclic cyclization / dehydrogenation (Scheme 91).



Scheme 91. *First example of Fujiwara-Moritani reaction on heteroaromatic rings.*

More recent studies by the Fujiwara's group found that catalytic benzoquinone/stoichiometric *t*BuOOH was a good oxidizing system, which allowed to scale the substrate and decrease the catalyst loading, up to a TON of 280 (Scheme 92). Also, the alkenylation of arenes showed good tolerance for substituents on the conjugated olefin as well as on the aromatic ring.[129]



Scheme 92. *Highly efficient Fujiwara-Moritani reaction with peroxide as oxidant.*

2.3. Directed Pd-catalyzed Fujiwara-Moritani reaction

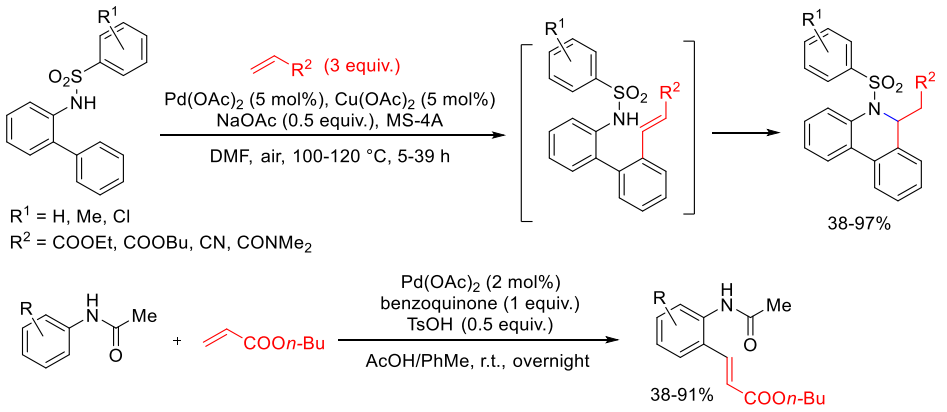
Building on the results obtained by the Fujiwara's team in this cross dehydrogenative coupling, several research groups developed improvements and variants of this groundbreaking reaction.

The most significant improvement of the Fujiwara-Moritani reaction is represented by the implementation of a substrate-control strategy, based on the use of directing Lewis bases covalently linked to the aromatic substrate, so as to induce approach of the transition metal in the vicinity of a specific aromatic C-H bond to activate.[130] The long known *ortho*-cyclometalation[131] of substituted aromatics is an example of such reactivity, which has been implemented in the Fujiwara-Moritani reaction.

[129] Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y.; *Org. Lett.*, **1999**, *1*, 2097-2100.

[130] Sambiagio, C., Schönbauer, D., Blieck, R., DaoHuy, T., Pototschnig, G., Schaaf, P., Wiesinger, T., Zia, M.F.,Wencel-Delord, J., Besset, T., Maes, B. U. W.; Schnürch. M. *Chem. Soc. Rev.* **2018**, *47*, 6603-6743.

Accordingly, and likely inspired by the above described Ru(0)-catalyzed Murai directed oxidative addition step, Satoh and Miura,[132] and soon after Van Leuween and de Vries, [133] developed the first directed Fujiwara-Moritani reactions. This was another big step forward with respect to the original protocol. Indeed, the directing group eased the metalation step, rendering no longer necessary the use the aromatic partner as a solvent. Furthermore, the directing group allowed the selective C-H activation of a specific aromatic C-H bond (Scheme 93). In the former study, the Fujiwara-Moritani reaction is followed by a spontaneous intramolecular aza-Michael reaction to provide a phenanthridine system.



Scheme 93. *First directed Fujiwara-Moritani reactions.*

The directing effect in the aromatic C-H activation has been extensively exploited in the last ten years.[134] For example, in 2010, J. Q. Yu reported that phenylpropionate acids allowed to perform efficient directed Fujiwara–Moritani couplings. Furthermore, the presence of a suitable amino acid derived ligand allowed to discriminate two different C-H *ortho* positions. For example, the employment of *N*-formyl isoleucine (Formyl-Ile-OH) as the ligand allowed to couple 5-Me-3-OMe benzyl carboxylic acid with ethyl acrylate with a 20:1 regioselectivity (Scheme 94).

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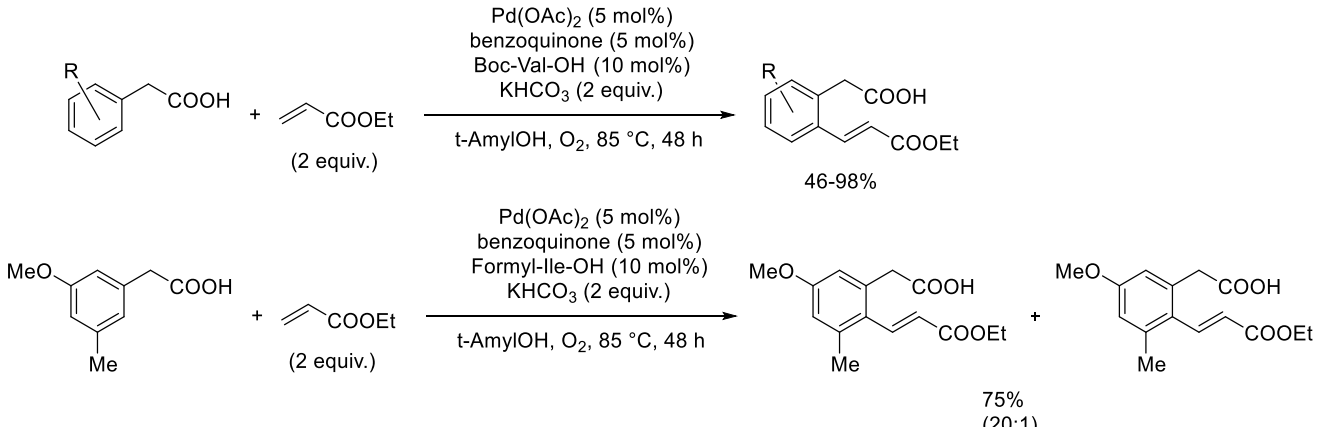
131 For seminal papers on transition metal promoted or catalysed directed *ortho* C-H activation, see: [a] Murahashi S. *J. Am. Chem. Soc.* **1955**, *77*, 6403-6404; [b] Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544-1545; [c] For a review, see: M. Albrecht, *Chem. Rev.* **2010**, *110*, 576-623.

132 [a] Miura, M.; Tsuda, T.; Satoh T., Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211-5215. [b] [a] Miura, M.; Tsuda, T.; Satoh, T.; Nomura, M. *Chem. Lett.* **1997**, 1103-1104.

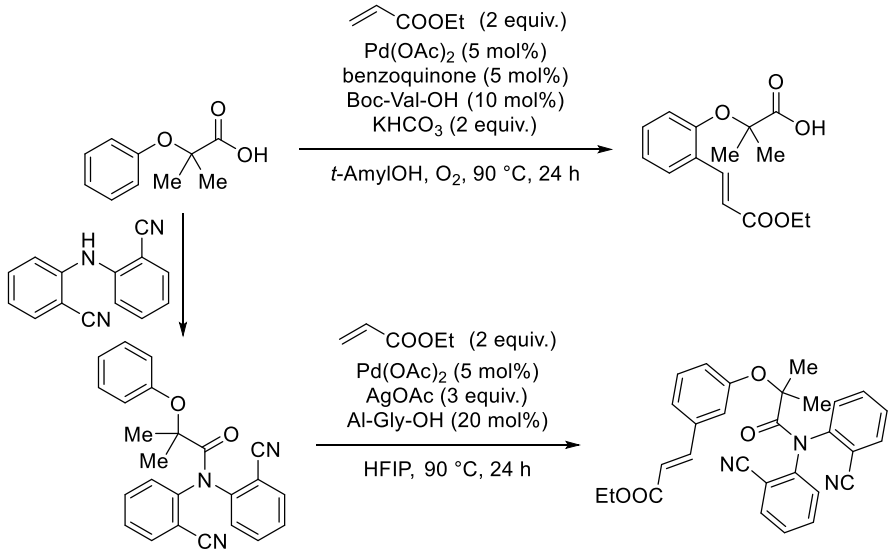
133 Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M *J. Am. Chem. Soc*. **2002**, *124*, 1586-1587.

134 [a] Engle, K. M.; Wang, D. -H.; Yu, J. -Q. *Angew. Chem*. **2010**, *122*, 6305 -6309; [b] Engle, K. M.; Wang, D. -H.; Yu, J. -Q. *Angew. Chem. Int. Ed*. **2010**, *49*, 6169 -6173; [c] Wang, D. -H.; Engle, K. M.; Shi, B. -F.; Yu, J. -Q. *Science* **2010**, *327*, 315 -319.



Scheme 94. *Carboxylic acids as directing groups in aryl alkenylation.*

The same team developed the *ortho* and *meta* functionalization of phenol derivatives through the use of the corresponding 2-methyl-2-aryloxypropanoic acids.[135] While *ortho* functionalization was obtained using directly the carboxylic acid, the more challenging *meta* functionalization was obtained through the use of an end-on coordinating nitrile incorporated into a 2,2'-bisnitrile-arylamide directing group (Scheme 95).



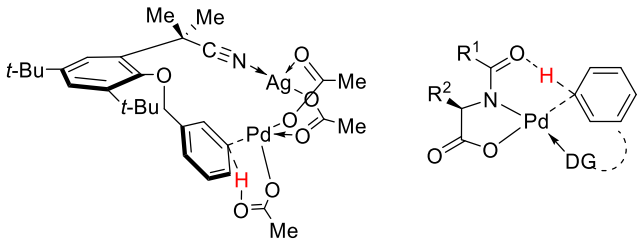
Scheme 95. Ortho *vs* meta *alkenylation of α-phenoxyacetic acids.*

Worthy of note in the *meta* functionalization protocol is the use of the silver salt, which has not the only role of oxidant, and of hexafluoroisopropanol (HFIP) as the solvent, which is known to increase the solubility of the reagents and catalysts, as well as stabilizing cationic intermediates.[136] Recent computations allowed to shed light on the crucial role played by the silver salt and the amino acid ligand (Scheme 96).[137]

[135] Dai, H.- X.; Li, G.; Zhang, X. –G.; Stepan, A. F.; Yu, J. –Q. *J. Am. Chem. Soc*. **2013**, *135*, 7567-7571.

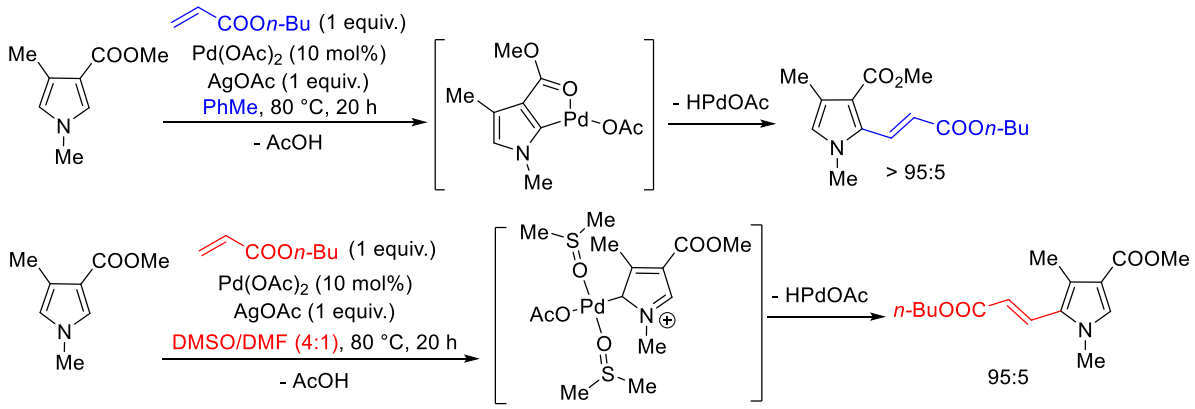
[136] [a] Wencel-Delord, J.; Colobert, F. *Org. Chem. Front.* **2016**, *3*, 394-400; [b] Colomer, I., Chamberlain, A., Haughey, M.; Donohoe, T. J. *Nat Rev Chem* **2017**, *1*, 0088.

[137] Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344-355.



Scheme 96. *Role of the silver salt and of the amino acid ligand in the meta directed Fujiwara-Moritani reaction.*

More recently, Yao's group demonstrated that the role of the directing group can be assisted and/or outclassed by other reaction parameters acting directly on the catalyst.[138] It is the case of the alkenylation of 3,4-disubstituted pyrroles, wherein simply switching the reaction medium from PhMe to a binary DMSO/DMF system, allowed to direct the alkenylation at the C2 or C5 position, respectively (Scheme 97). Indeed, in toluene as the solvent the ester directing group at C3 can effectively direct the alkenylation at C2. On the other hand, the DMSO/DMF system prevents such coordination by competitive solvation, which favors electrophilic reactivity at the more electron-rich C5 position.



Scheme 97. Solvent-controlled C2/C5-regiodivergent alkenylation of pyrroles

2.4. Rhodium and ruthenium catalyzed C-H-arene alkenylations

2.4.1. Non-directed alkenylations

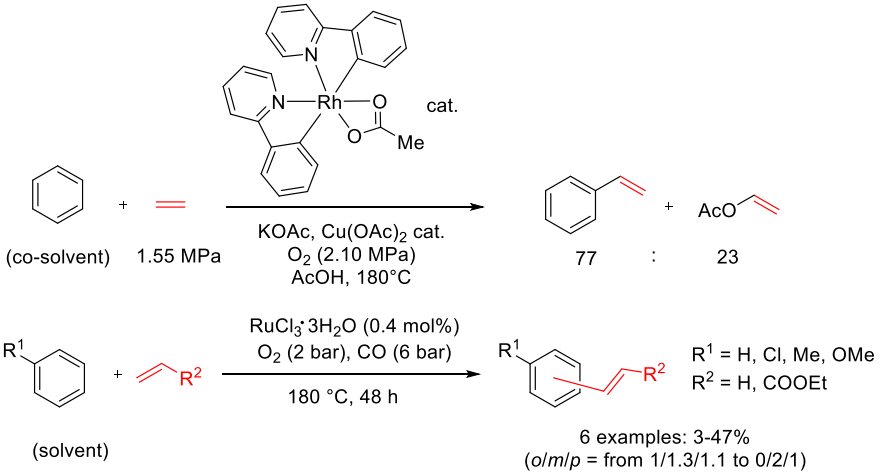
Transition metal complexes other than those based on palladium enable the direct oxidative coupling between alkenes and simple arenes.[139] In 2000, Matsumoto and Yoshida[140] reported that $Rh(ppy)_2(OAc)$ (ppyH = 2-phenylpyridine), in the presence of O_2/Cu oxidizing system, was able to catalyze the oxidative

[138] [a] Su, Y.; Zhou, H.; Chen, J;. Xu, J.; Wu, X.; Lin, A.; Yao, H. *Org. Lett.* **2014**, *16*, 4884-4887; [b] Su, Y; Gao, S.; Huang, Y.; Lin, A.; Yao, H. *Chem. Eur. J*. **2015**, *21*, 15820-15825.

[139] For an example of cobalt-catalyzed alkenylation see: Fallon, B. J.; Derat, E.; Amatore, M.; Aubert, C.; Chemla, F., Ferreira, F.; Perez-Luna, A.; Petit, M. *ORg. Lett.* , **2016**, *18*, 2292.2295.

[140] [a] Matsumoto, T.; Yoshida, H. *Chem. Lett.* 2000, 29, 1064-1066; [b] Matsumoto, T.; Periana, R. A.; Taube, D. J.; Yoshida, H. *J. Catal.* **2002**, *206,* 272-280.

arylation of ethylene with benzene to produce styrene. Soon after, Milstein[141] reported that $RuCl_3$ catalyzed the aerobic alkenylation of simple arenes with a series of Michael acceptors (Scheme 98). However, as the early palladium-catalyzed version, these methods suffer a number of problems, such as the use of huge excess of arene, high pressure conditions and rather low yields.

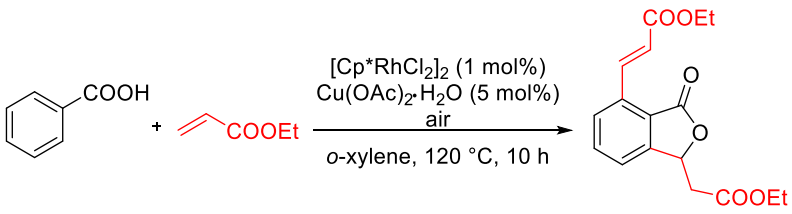


Scheme 98. *First examples of Rh(III) and Ru(III)-catalyzed aromatic alkenylation.*

As previously noted with palladium, the above issues could be solved by the use of covalently linked Lewis-basic functions (directing groups) which through pre-coordination eased the subsequent C–H bond functionalization.[130]

2.4.2 Directed alkenylations

More recently, Miura and Satoh reported the Rh-catalyzed directed vinylation of benzoic acids.[142] The aerobic coupling with acrylate partners takes place smoothly to produce isobenzofuranones derivatives *via* alkenylation and subsequent cyclization (Scheme 99).

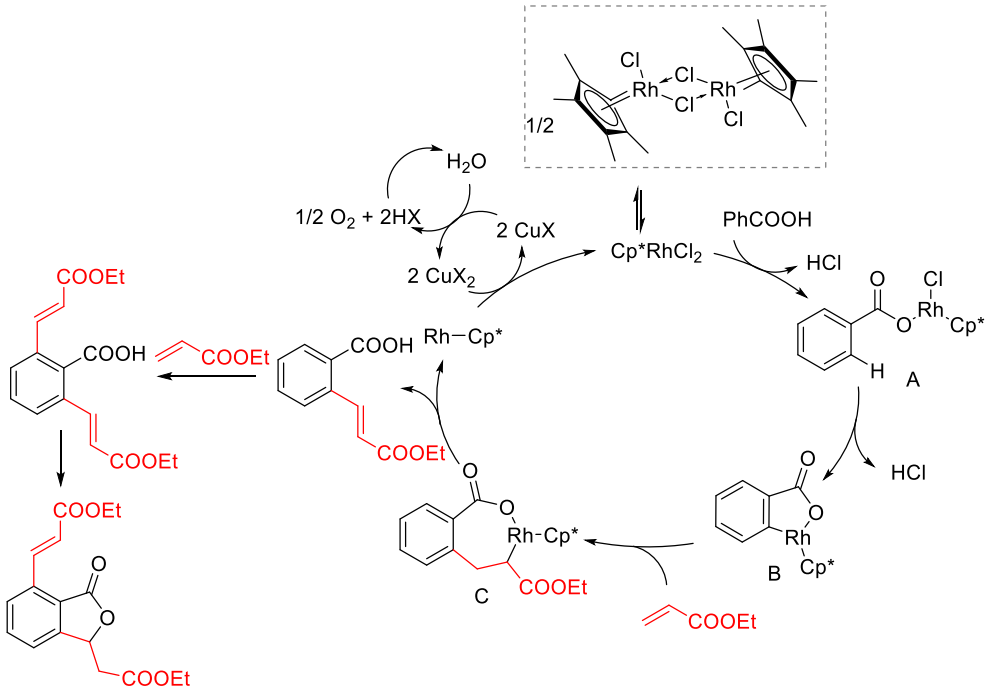


Scheme 99. *Rh/Cu-catalyzed reaction of benzoic acids with acrylates under air.*

The mechanism of this reaction is expected to involve the initial coordination of the carboxylate oxygen to $Rh(III)X_3$ to give a rhodium(III) benzoate **A**. Subsequent *ortho* rhodation forms the rhodacycle

[141] Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337-338.
[142] Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407-1409.

intermediate **B**. Subsequent coordination and migratory insertion of the first equivalent of the acrylate generates the 7-membered intermediate **C**, which undergoes dehydrorhodation to form the *ortho*-monovinylated benzoic acid and RhCp*, which is reoxidized by the system [$Cu(OAc)_2$ cat./air]. The second alkenylation takes place via an analogous mechanism, and a spontaneous intramolecular O-Michael addition generates the final isobenzofuranone (Scheme 100).

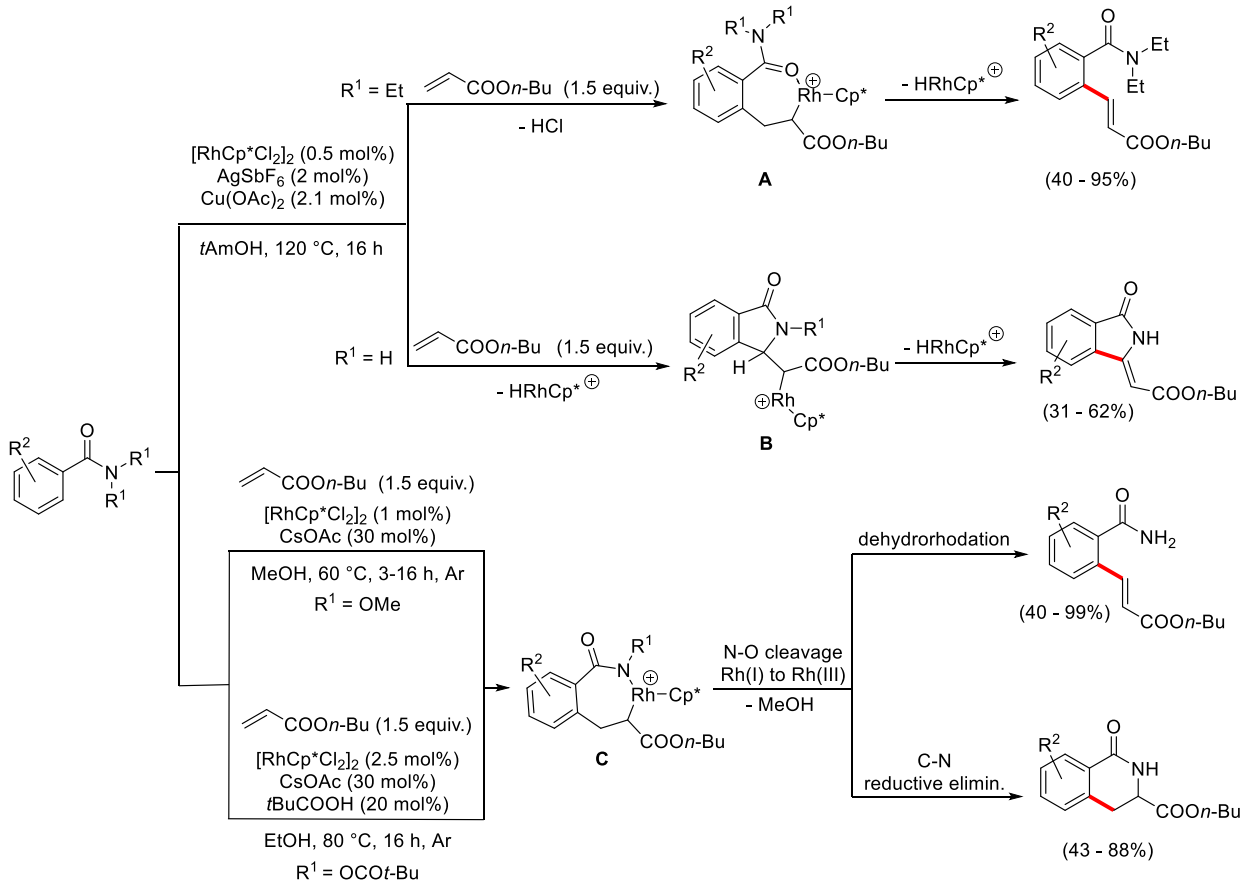


Scheme 100. *Mechanism of the Rh/Cu-catalyzed reaction of benzoic acids with acrylates under air.*

In 2011, Glorius' group studied the use of both amides[143] and *N*-alkoxy- and *N*-acyloxyamides[144] as directing groups for the Rh(III)-mediated alkenylation reaction. The use of tertiary benzamides leads to *ortho* olefination, passing through intermediate **A**, independently of the electronic richness of the ring. By contrast, primary benzamides generate γ-butyrolactams, as a result of a further [ClRh(III)Cp*]⊕-catalyzed oxidative intramolecular coupling passing through the *exo* benzolactams intermediate **B**. The main drawback of the protocol is the need of high reaction temperatures, which limit the range of substrates that can be employed, as well the long reaction times.

Interestingly, the *N*-methoxyamide group acts also as internal oxidant for the Rh(I) species, with generation of MeOH. In this case, depending on the nature of the selected *N*-alkoxy amide and on the reaction conditions, the protocol can give alkenylation with or without additional intramolecular C-N bond formation (Scheme 101).

[143] Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem. Int. Ed.,* **2011**, 50, 1064-1067.
[144] Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.*, **2011**, 133, 2350-2353.

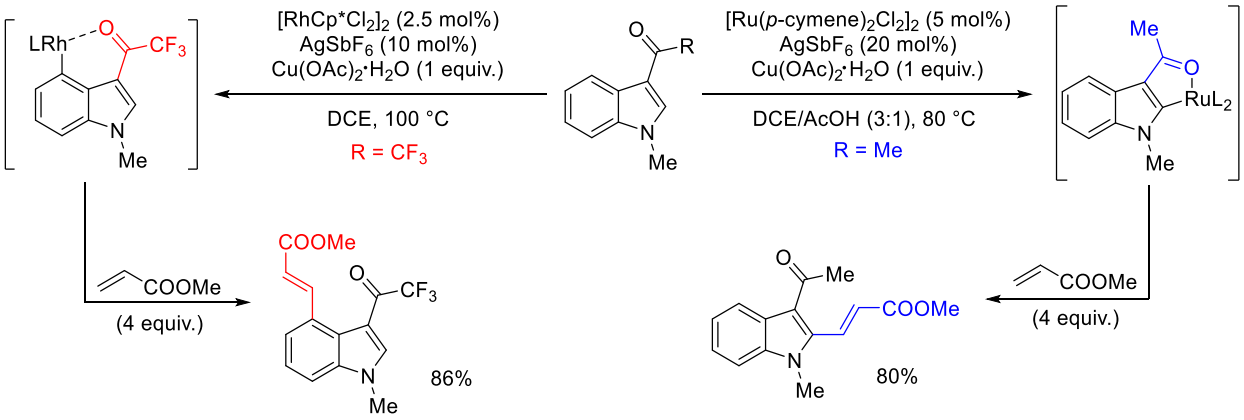


Scheme 101. *Rh(III)-catalyzed alkenylation of benzamides,* N*-methoxybenzamides and* N*-pivaloylamides*.

Shortly after, the same group reported a variant of the Rh(III)-catalyzed oxidative alkene-aryl cross-coupling to obtain *Z*-aryl tri- or-tetra-substituted olefins.[145] Key to obtain the *Z*-selectivity is the use of bromoarenes without chelate assisting-directing group and vinylic substrates bearing a directing group. In fact, the mechanism of this transformation is expected to involve a chelation-assisted Z-selective vinylic C–H bond activation prior of the bromoarene C–H activation.

More recently, Prabhu and coworkers reported on the use of Rh complexes for the regioselective functionalization of indole scaffolds bearing at C3 position a ketone function.[146] In particular, in the presence of a trifluoromethyl ketone, a weak directing group, and of a Rh(III) catalyst the C-H activation takes place at the more electron-rich C4 position, to generate a 6-membered rhodacycle. On the other hand, in the presence of a methyl ketone, which is a stronger directing group, in the presence of a Ru(II) catalyst the alkenylation takes place at C2, *via* pre-coordination (Scheme 102).

[145] Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Chem. Asian J*. **2012**, *7*, 1208-1212.
[146] Lanke, V.; Bettadapur, K. R.; Prabhu, K. R.; *Org. Lett*. **2016**, *18*, 5496-5499.

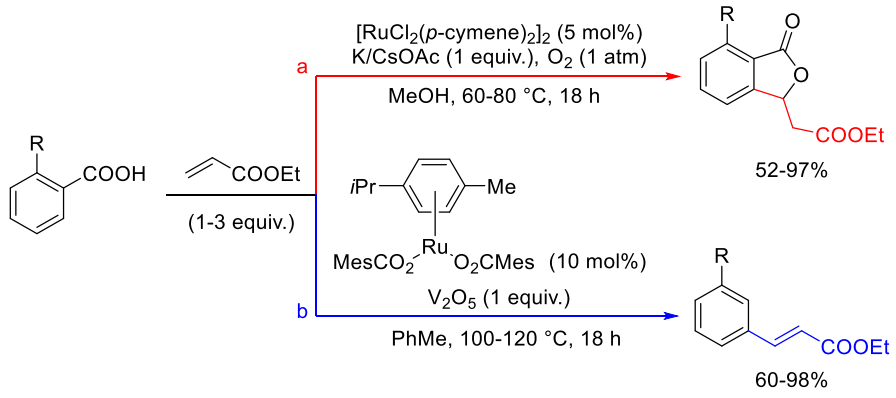


Scheme 102. *Rh(III)-catalyzed C4-functionalization vs Ru(II)-catalyzed C2-alkenylation of 3-ketoindoles.*

Ruthenium-based complexes, much cheaper than the rhodium and palladium ones, showed to be equally versatile as catalysts (or pre-catalysts) in the alkenylation of aryl and heteroaryl systems. These complexes are normally Ru(II) or Ru(III) complexes, such as $[RuCl_2(p\text{-cymene})]_2$, $RuHCl(CO)(PPh_3)_3$, and Ru(III), like $RuCl_3$. These Lewis acidic complexes, in the role of directing groups, have a high coordinating capacity toward the (oxygen- and nitrogen-based) Lewis bases.

The rapid development of directed Ru(II)-catalyzed oxidative C-H/C-H bond alkenylation of arenes and heteroarenes has been mainly developed by the group of Ackermann, who exploited the carboxylic function of benzoic acids as directing group.[147]

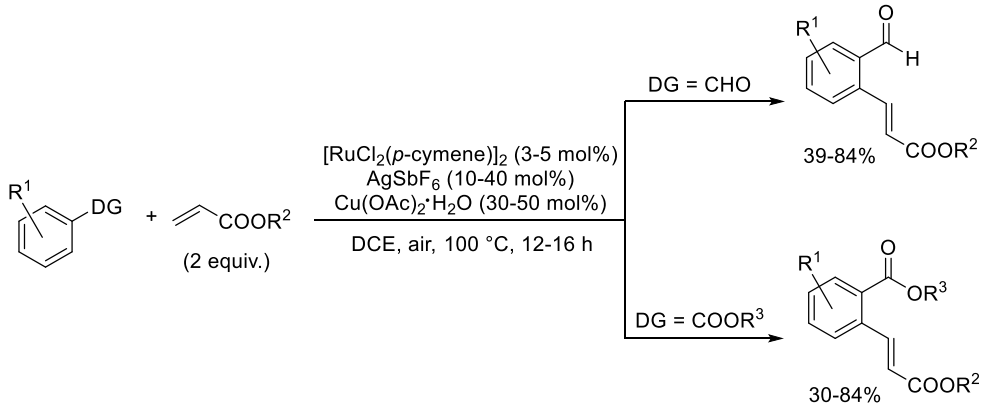
These authors reported the direct *ortho* alkenylative coupling between electron-rich arenes and electron-poor olefins. In particular, the use of $[RuCl_2(p\text{-cymene})]_2$ pre-catalyst under aerobic conditions gave the product of tandem alkenylation/cyclization sequence under mild conditions (Scheme 103, path a). On the other hand, an alkenylation/decarboxylation sequence can be obtained by employing the stronger V_2O_5 oxidant in the presence of a Ru(II) bis(carboxylate) catalyst (Scheme 103, path b).



Scheme 103. *Carboxylic acid as directing group in oxidative alkenylation.*

[147] [a] Ackermann, L. *Chem. Rev.***2011**, *111*, 1315–1345; [b] Bechtoldt, A.; Tirler, C.; Raghuvanshi, K.; Christoph Kornhaa, S. W.; Ackermann L. *Angew. Chem. Int. Ed*. **2016**, *55*, 264-267; [c] Phani Kumar, N. Y.; Bechtoldt, A.; Raghuvanshi, K.; Ackermann, L. *Angew. Chem. Int. Ed*. **2016**, *55*, 6929-6932.

Directing groups other than the carboxylic function can be used in Ru-catalyzed aromatic C-H activation. Thus, for example, the groups of Jeganmohan[148] and of Ackermann[149] independently reported *ortho*-directed alkenylative C-H couplings between aromatic esters and acrylates using the catalytic system {$[RuCl_2(p\text{-cymene})]_2/Cu(OAc)_2/AgSbF_6$} in air. Analogous results can be obtained using the aldehyde function as the directing group (Scheme 104).[150]



Scheme 104. *Ru(II)-catalyzed* ortho*-directed alkenylative C-H couplings*.

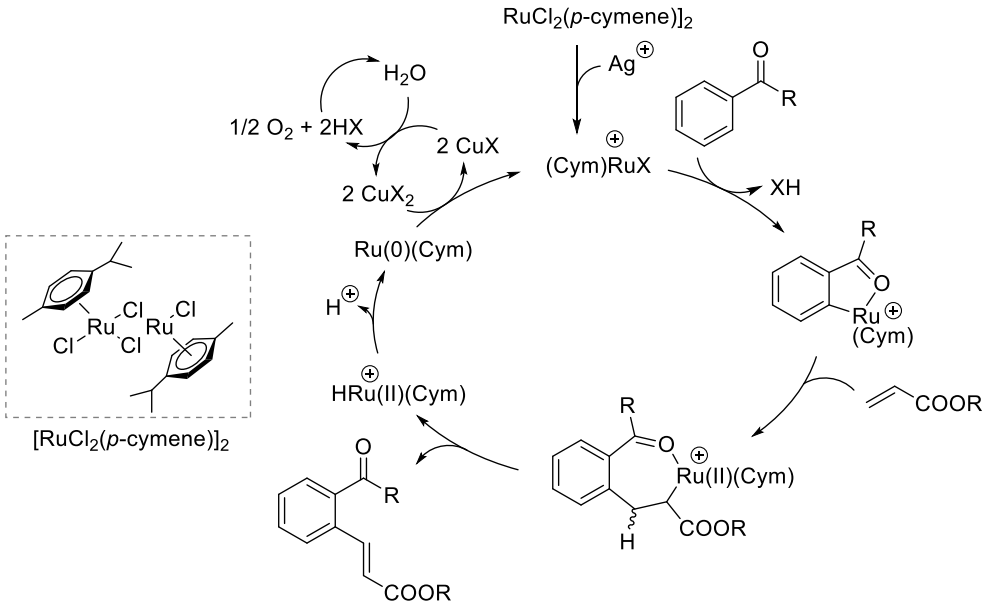
The mechanism is expected to start with the coordination at the cationic ruthenium complex by the directing group with concomitant *ortho* cycloruthenation (Scheme 105). Follow alkene insertion and dehydroruthenation, which releases the final coupled product and the cationic Ru(II) hydride complex. Reductive elimination generates a Ru(0) complex, which is oxidized to the starting catalytic species by the Cu(II)/O_2 system, as similarly reported in Sharada work for the synthesis of C5-substituted azaflavones.[151]

[148] [a] Padala, K.; Pimparkar, S.; Madasamy, P.; Jeganmohan, M. *Chem. Commun.*, **2012**, *48*, 7140-7142; [b] Manikandan, R.; Madasamy, P.; Jeganmohan, M. *ACS Catal.* **2016**, *6*, 1, 230-234.

[149] Graczyk, K.; Ma W.; Ackermann, L. *Org. Lett.,* **2012**, *14*, 4110-4113.

[150] Padala, K.; Jeganmohan, M.; *Org. Lett*., **2012**, *14*, 1134-1137.

[151] Bakthadoss, M.; Reddy, T. T.; Sharada, D. S. *RSC Adv.* **2020**, *10*, 31570-31574.



Scheme 105. *Plausible mechanism in the Ru(II)-catalyzed ortho-directed alkenylative C-H couplings.*

Analogous *ortho*-directed dehydrogenative alkenylations could be obtained from secondary benzamides, or anilides, and electron pour alkenes (Scheme 106).[152] In the case of secondary anilides, the mechanism is similar to the one previously described (Scheme 106, top). In the case of secondary benzamides, and in contrast to tertiary benzamides, which coordinate through the oxygen atom, the coordination at Ru atom takes place by the nitrogen atom, to generate an amido ligand, and the resulting complex may evolve in two different ways, depending on the nature of the secondary amide. On the one hand, a simple secondary benzamide (*i.e.* derived from a primary alkyl amine), after dehydroruthenation, will evolve releasing Ru(0). Therefore, as previously seen, the protocol will need the presence of a sacrificial external oxidant to be catalytic in Ru (Scheme 106, middle). On the other hand, an alkoxyamide[153] will evolve via N-O bond cleavage, releasing a Ru(II) complex. Thus, in this case, no sacrificial oxidant will be necessary for the catalysis (Scheme 106, bottom). A Weinreb amide (*i.e.* derived from the Weinreb amine Me(MeO)NH) as the directing group, behaves also as a in internal oxidant, although in this case the metal coordination will take place through the oxygen atom.[154] The use of a covalently linked directing group behaving as an *internal oxidant* in C-H activation was pioneered by the research groups of Cui and Wu,[155] Hartwig,[156] Yu,[157] and Guimond and Fagnou.[158]

[152] [a] Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V.*; Org. Lett.*, **2012**, *14*, 728-731; [b] Yuan, Y. -C.; Bruneau, C.; Roisnel, T.; Gramage-Doria, R. *Catal. Sci. Technol.*, **2019**, *9*, 4711-4717.

[153] Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.*, **2012**, *14*, 736-739.

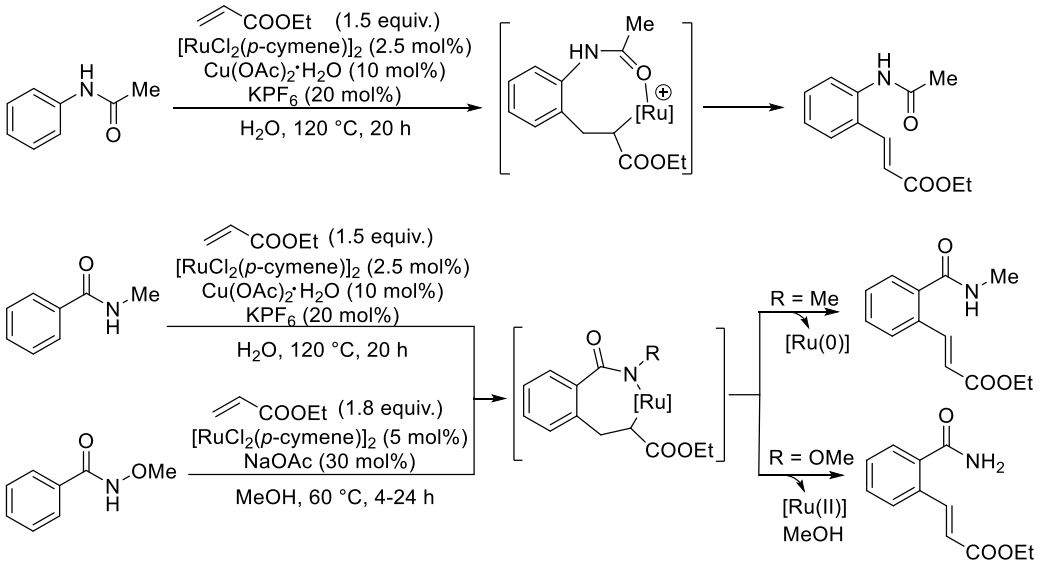
[154] [a] Kalepu, J.; Pilarski, L. T. *Molecules* **2019**, *24*, 830-852; [b] Das, R.; Kapur, M. *Chem. Asian J.*, **2015**, *10*, 1505-1512; [c] Das, R.; Kapur, M. *Chem. Eur. J.*, **2016**, *22*, 16984-16988.

[155] Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y.; *J. Am. Chem. Soc.* **2009**, *131*, 13888-13889.

[156] Tan, Y.; Hartwig, J. F.; *J. Am. Chem. Soc.* 2010, *132*, 3676-3677.

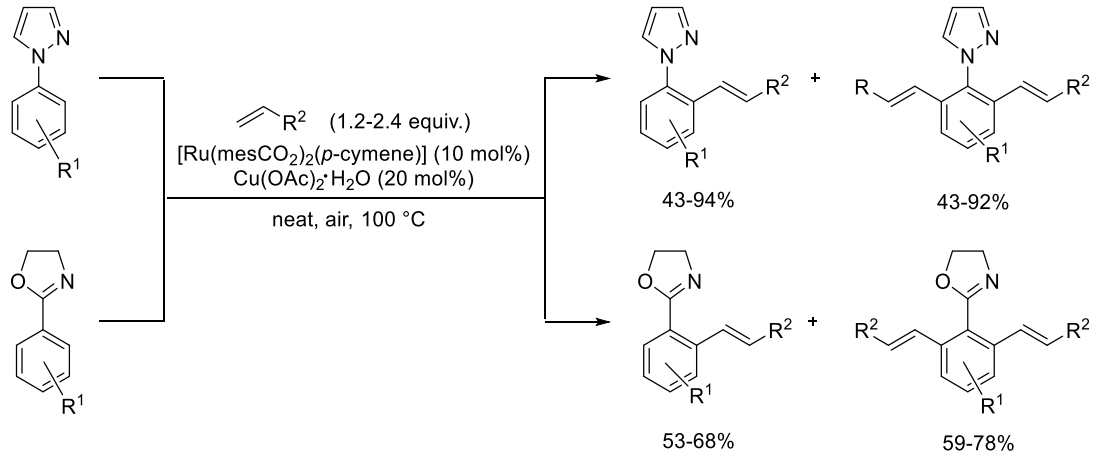
[157] Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862-12864.

[158] Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* 2010, *132*, 6908-6909.



Scheme 106. *Ru-catalyzed dehydrogenative couplings involving anilides and benzamides.*

Pyrazoles and oxazolines found also wide application as *ortho*-directing groups in Ru-catalyzed aromatic dehydrogenative couplings with electron-poor olefins. For example, inspired by the works of Dixneuf and Miura,[159] in 2015, Singh[160] reported the mono- or di- *ortho*-functionalization of *N*-aryl pyrazoles and 2-aryl oxazolines (Scheme 107).



Scheme 107. *Pyrazoles and oxazolines as directing groups in dehydrogenative* ortho*-alkenylations.*

Finally, considerable efforts have been devoted to the directed Ru-catalyzed dehydrogenative alkenylation of heterocyclic systems[161] or benzocondensed heterocycles.[162] Scheme 108 shows some examples.

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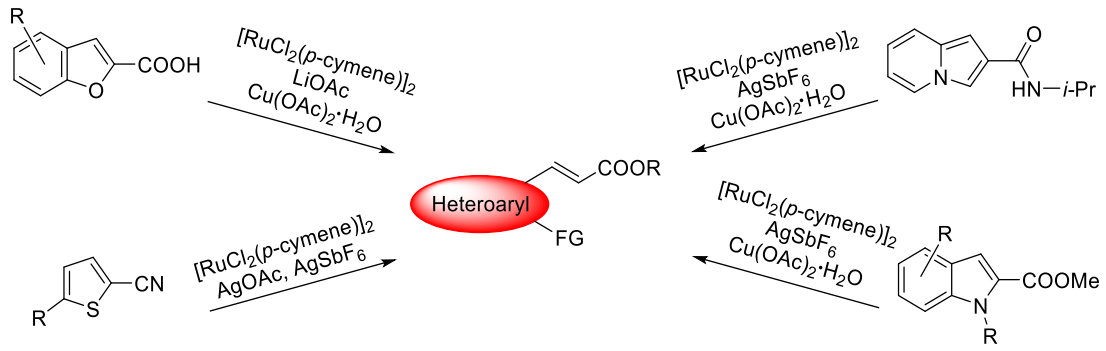
159 [a] Hashimoto, Y.; Ortloff, T.; Hirano, K.; Satoh, T.; Bolm, C.; Miura, M. *Chem. Lett*., **2012**, *41*, 151-153.; [b] Arockiam, P. B.; Fischmeister, C.; Bruneau C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 3075-3078.

160 Shome, S.; Singh, S. P.; *Eur. J. Org. Chem. 2015*, 6025-6032.

161 [a] Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett*., **2011**, *13*, 706–708; [b] Reddy, M. C.; Jeganmohan, M. *Chem. Commun.* **2015**, *51*, 10738-10741; [c] Jadhav, P. P.; Machhindra, N.; Dawande, S. D. *Eur. J. Org. Chem.* **2019**, 7831-7835.

162 Bakthadoss, M.; Reddya, T. T.; Sharada, D. S. *RSC Adv.*, **2020**, *10*, 31570-31574.



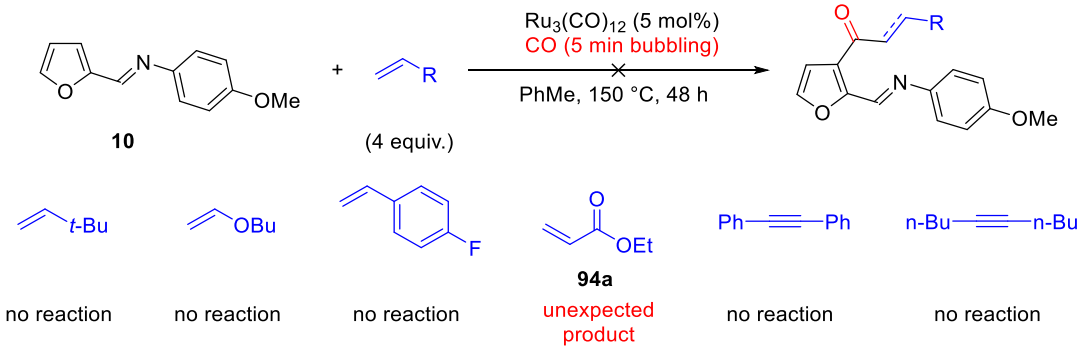
Scheme 108. *Ru-catalyzed dehydrogenative alkenylation of heterocyclic compounds.*

This introduction, far from being exhaustive, has tried to emphasize the importance of dehydrogenic alkylation in organic chemistry, in order to develop increasingly efficient protocols for the natural synthesis of products and the discovery of drugs. The following part of this chapter presents the work done during his doctoral thesis on this interesting topic.

3. Results and Discussion

3.1. The objective: a new oxidant-free methodology

In the course of our work on the carbonylative Murai reaction with aromatic imines (vide supra) we tested several types of unsaturated partners, in the hope to extend the scope of our coupling. Unfortunately, no reactivity was observed when electron-poor styrenes, hindered alkynes or terminal alkenes were employed. However, when we uses ethyl acrylate, an unexpected product was formed (Scheme 109).



Scheme 109. *Side reaction found when testing the carbonylative Murai reaction with acrylate.*

Figure 6 shows the comparison between the ^{1}H-NMR spectrum of product **28a**, coming from the carbonylative Murai reaction between imine **10** and triethoxyvinylsilane **27a** (top)**,** and that of the unexpected product **95a** (bottom). A strong upfield shift of the imine signal, from 9.0 ppm to 8.5 ppm (blue

frame), was immediately apparent, suggestive of the absence of CO insertion during the coupling. Additionally, the two aliphatic CH_2 at 0.9 and 2.9 ppm (red frame) of the carbonylative Murai product left the place to two doublets, at 6.2 and 7.9 ppm, in a typical zone of olefinic protons. In view of its ^{1}H-NMR spectrum, structure **95a** was assigned to the unexpected product, which thus corresponds to a surprising C3 dehydrogenative coupling between the imine and the acrylate. Further investigations and analyses confirmed the assigned structure and confirmed a synthetically interesting yield for this unexpected reaction (Figure 6).

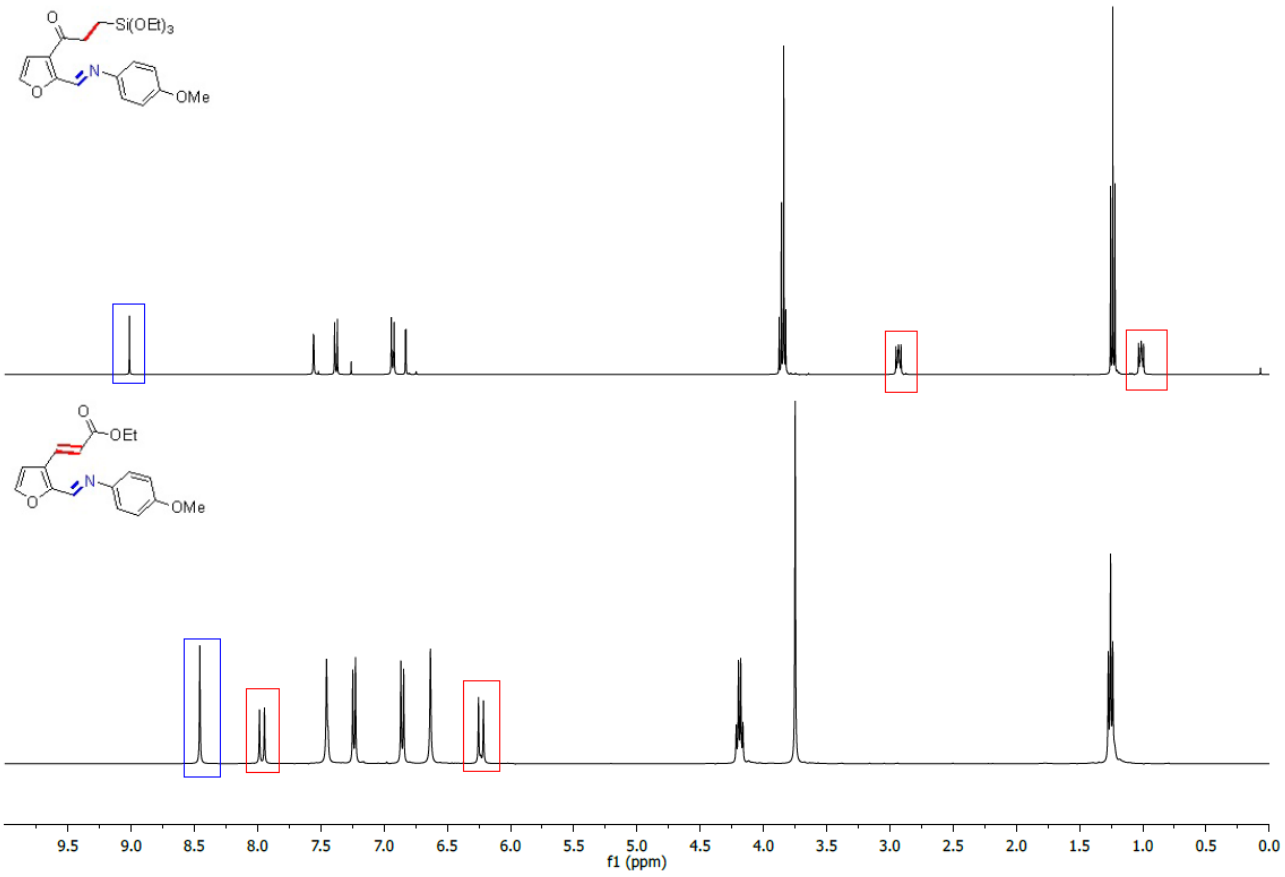
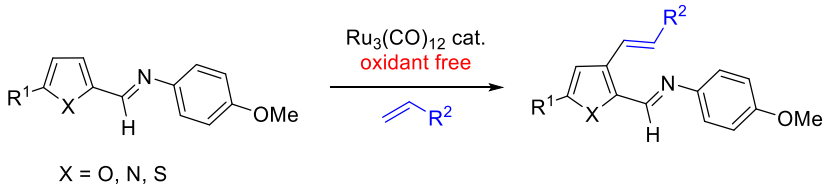


Figure 6. *Comparison between product* ***28a*** *(top) and the new compound* ***95a*** *(down).*

As mentioned at the beginning of this chapter, literature reports several examples of Fujiwara-Moritani reaction involving the functionalization of (hetero)arenes, and with transition metals other than palladium. Nevertheless, the C3 position of heterocyclopentadienes remains quite challenging to functionalize, especially in the case of furfural systems, whose C4 and C5 positions are the most electron rich, and thus the most reactive vis-à-vis of electrophilic reagents. However, the most striking feature of this newly discovered reaction is another. In a cross dehydrogenative coupling reaction, such as this newly discovered reaction, two hydrogen atoms are expulsed, which interact with the transition metal. Accordingly, to drive the reaction to completion, a stoichiometric amount of a sacrificial H_2 acceptor (oxidant) is needed to bring the oxidation state of the transition metal back to its original value. Although

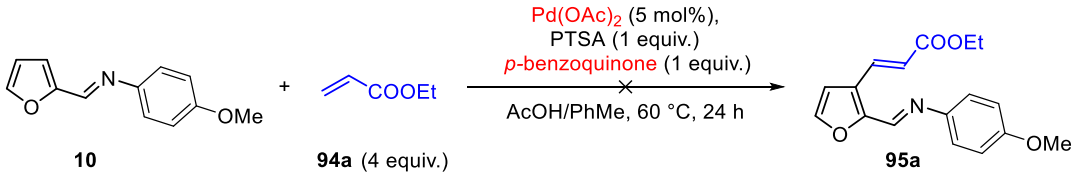
some acceptorless CDC have been recently reported,[163] to the best of our knowledge, all the reported aromatic alkenylations (vide supra), some of which concern Ru(II)-catalysis, need the use of a sacrificial oxidant. This is not the case for our newly discovered aromatic alkenylation. We thus decided to investigate in more detail this Ru(0)-catalyzed coupling between 2-imino heterocyclopentadienes and electron-poor alkenes (Scheme 110).



Scheme 110. *Oxidant free alkenylation of 2-imino heterocyclopentadienes.*

3.2. First tests and optimization of reaction conditions

In the perspective of developing an oxidant-free protocol for the C3-alkenylation of 2-imino heterocyclopentadienes, we first wished to test the behavior of our substrate in the presence of classical Fujiwara-Moritani reaction conditions. However, treatment of substrate **10** with ethyl acrylate, in the presence of $Pd(OAc)_2$ (5 mol%),PTSA (1 equiv.) and *p*-benzoquinone (1 equiv.)[164] in AcOH/Toluene at 60°C gave no trace of the product **95a** (Scheme 111).



Scheme 111. *Attempted Fujiwara-Moritani coupling on furfural PMP-imine **10**.*

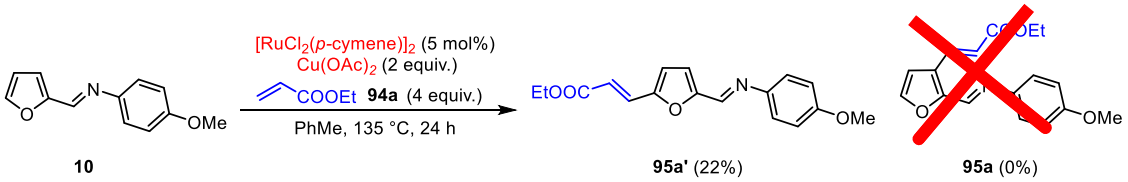
We subsequently submitted imine **10** to the Ru(II)-catalyzed reaction conditions used by Miura and co-workers for the C3 vinylation of thiophene-2-carboxylic acids, which needed $[RuCl_2(p\text{-cymene})]_2$ as the pre-catalyst and $Cu(OAc)_2$ as the sacrificial oxidant.[165] This experiment gave exclusively the C5 vinylation product **95a'**in a 22% NMR yield, with no evidence of the C3 vinylation product (Scheme 112). This result

[163] For a selection, see: [a] Li, F.; Lu, L.; Liu, P. *Org. Lett.* **2016**, *18*, 2580-2583. [b] Siddiki, S. M. A. H.; Toyao, T.; Shimizu. K.-i. *Green Chem.*, **2018**, *20*, 2933–2952. [c] Luque-Urrutia, J. A.; Solà, M.; Milstein, D.; Poater A. *J. Am. Chem. Soc.* **2019**, *141*, 2398−2403. [d] Manojveer, S.; Salahi, S.; Wendt, O. F.; Johnson, M. T. *J. Org. Chem.* **2018**, *83*, 10864−10870. [e] Zou, Y.-Q.; Zhou, Q.-Q.; Diskin-Posner, Y.; Ben-David, Y.; Milstein, D. *Chem. Sci.,* **2020**, *11*, 7188–7193; [f] Waiba, S.; Maji, B. *ChemCatChem* **2020**, *12*, 1891-1902; [g] Li, F.; Lu, L.; Liu, P. *Org. Lett.* **2016**, *18*, 2580-2583; [h] Putta, R. R.; Chun, S. Lee, S. B.; Oh, D. -C.; Hong, S. *Front. Chem.* **2020**, *8*, 1-8.

[164] Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Comm.*, **2009**, 3874-3876.

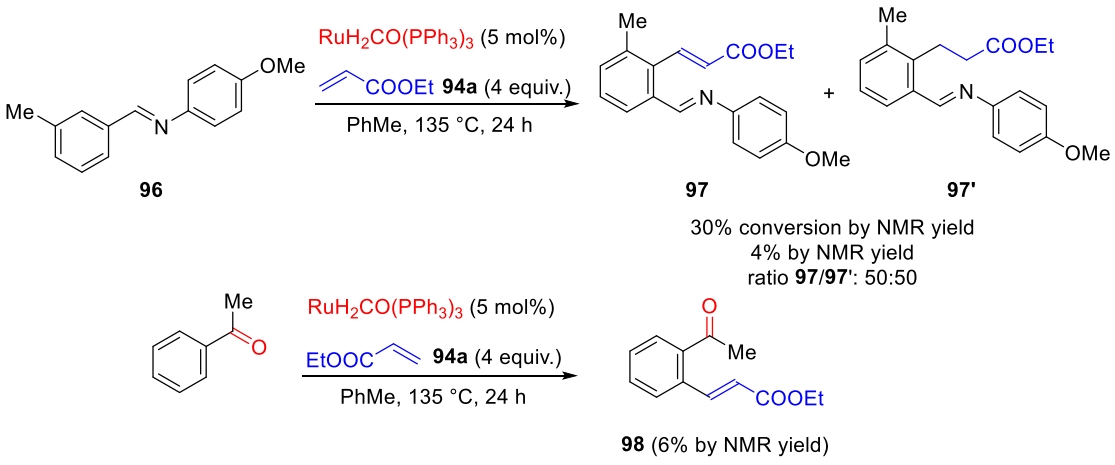
[165] Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.*, **2011**, *13*, 706-708.

suggests that under these reaction conditions, coordination of Ru(II) by the imine function does not take place, which allows alkenylation to take place at the most electron-rich position of the heterocycle. It thus appears that the nature and oxidation state of the Ru catalyst is crucial to obtain the desired imine-to-Ru coordination.



Scheme 112. *C5-alkenylation of furfural PMP-imine* ***10*** *via Ru(II)-catalysis.*

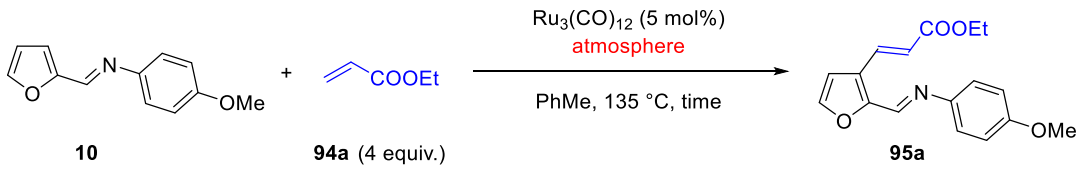
Two other coupling tests were subsequently carried out, one on the imine derived by the condensation between 3-methylbenzaldehyde and *p*-anisidine and the other on acetophenone, using $RuH_2CO(PPh_3)_3$ as pre-catalyst (which is supposed to liberate H_2 *in situ* and to become Ru(0)) and omitting the use of the copper salt, at reflux of toluene. In the event, the former experiment gave only 4% of the alkylated (Murai type) product, while the latter one gave only 6% of the alkenylated (Fujiwara-Moritani type) product (Scheme 113). These unsatisfactory results suggest that the previously observed reactivity is likely due to a combination of the electron richness of the heteropentadiene, the electron poorness of the acrylate, and to the use of a Ru(0) pre-catalyst.



Scheme 113. *Attempted $RuH_2CO(PPh_3)_3$-catalyzed alkenylations of a carbocyclic aryl PMP-mine and of acetophenone.*

After the above preliminary tests, we started the optimization of the reaction parameters on the model reaction, starting with the nature of the atmosphere used (Table 6). In the event, carrying out the coupling in CO, air, and argon atmosphere, gave comparable results in terms of yield of the final coupled product. These results suggest two important points: a) carbon monoxide does not intervene as ligand in the reaction mechanism; b) oxygen contained in the air does not act as an oxidizer for the ruthenium catalyst after the first cycle, actually making the system genuinely *oxidant free*.

Table 6. *Evaluation of atmosphere.*

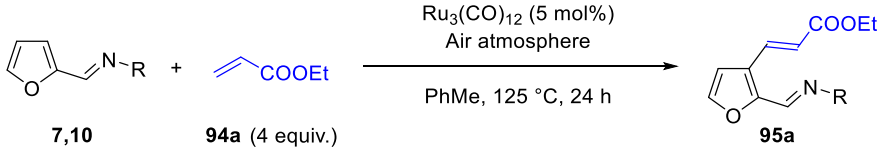


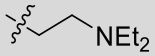
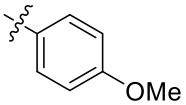
Entry	Time	Atmosphere	Conversion	Yield[a,b]
1	16	CO	98%	49% (44%)
2	24	Air	99%	50% (43%)
3	24	Argon	96%	47% (40%)

a: Yield determined by ^{1}H-NMR spectroscopy of the crude extract using *p*-dinitrobenzene as internal standard.
B: In brackets, isolated yields from silica gel chromatography deactivated with 1% Et_3N.

The nature of the imine directing group was next evaluated (Table 7). Accordingly, the coupling between PMP-imine **10** and ethyl acrylate was compared with that of *N,N*-diethylethylenimine **7,** previously used in our group to carry out the Murai reaction.[92] While the former reaction worked as expected, the latter one failed. The reason of this may be due either to the additional ligand possessed by the imine, which presumably prevents the subsequent coordination of the olefin, or by the intrinsic instability of this imine. Be what it may, since, the *p*-anisyl imine proved to be the best directing group in the carbonylative Murai studies with $Ru_3(CO)_{12}$, we decided to carry on our studies with this imine.

Table 7. *Evaluation of the nature of the imine.*



Entry	R	Compound	Conversion	Yield[a,b]
1		7	12%	-
2		10	95%	46% (41%)

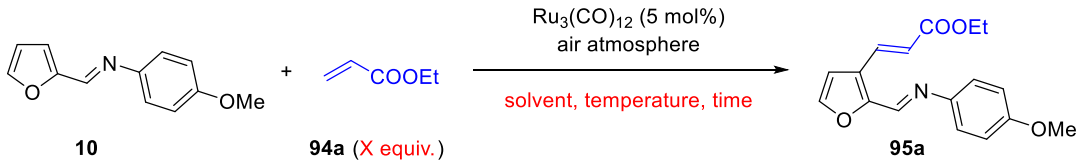
a: Yield determined by ^{1}H-NMR spectroscopy of the crude extract using *p*-dinitrobenzene as internal standard.
b: In brackets, isolated yields from silica gel chromatography deactivated with 1% Et_3N.

Considering the moderate isolated yields of product **95a** and the problems of partial hydrogenation in compound **97'** and reported in Scheme 113, we evaluated the insertion of a scavenger for hydrogen. However, neither the addition of alkyl olefins like *t*-butylethylene, nor the increase of acrylate equivalents permits to improve alkenylation yield. Furthermore, the use of other hydrogen acceptors, like

triethylorthoformate, completely inhibits the reaction. We speculate that coordination of the new olefin to the metal center prevents the catalytic cycle to proceed.

Optimization of the reaction conditions on the model reaction was then continued (Table 8). The decrease of reaction time (entries 1-3) or changes in temperature (entries 12-15) strongly affected the final yield. The same behavior was observed modifying the solvent concentration (entries 16-19), wherein higher conversion values correspond to a greater substrate degradation. As to the solvent (entries 5-11) shown that PhMe and 1,4-dioxane are the best solvents for this coupling. On the other hand, an unclear effect was shown when the amount of acrylate was varied (entries 18-20). In particular, as the alkene concentration decreases, greater substrate degradation is observed, without a considerable variation in the final yields.

Table 8. *Optimization of the Ru(0)-catalyzed alkenylation of furfural anisylimine*



10 **94a** (X equiv.) **95a**

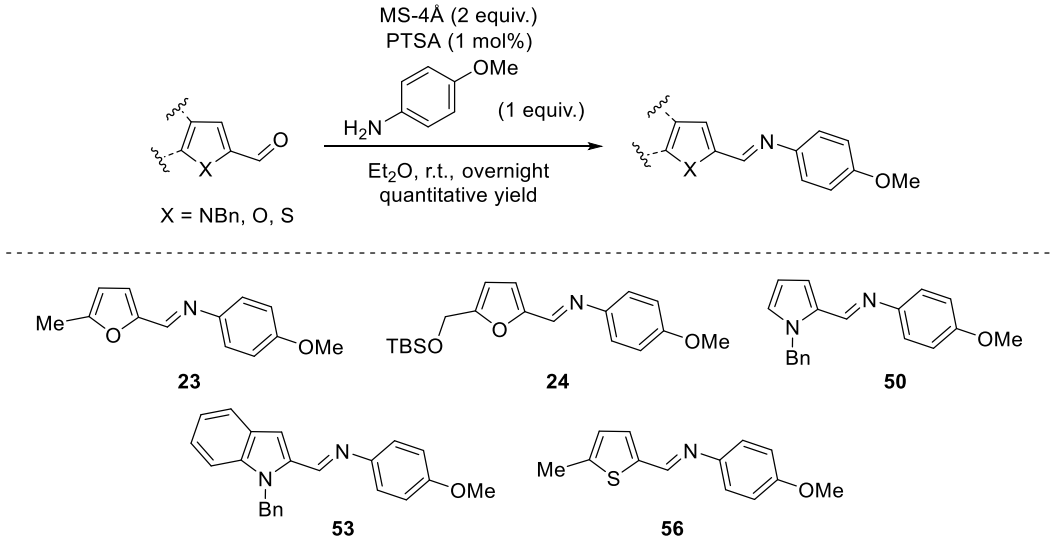
Entry	Time (h)	Solvent	Temperature	[M]	Acrylate **94a**	Conversion	Yield [a],[b]
1	4	PhMe	135 °C	0.5	4 equiv.	11%	5%
2	8	PhMe	135 °C	0.5	4 equiv.	46%	38%
3	16	PhMe	135 °C	0.5	4 equiv.	65%	41%
4	**24**	**PhMe**	**135 °C**	**0.5**	**4 equiv.**	**62%**	**50 (46%)%**
5	24	*p*-xylene	135 °C	0.5	4 equiv.	12%	2%
6	24	1,4-dioxane	135 °C	0.5	4 equiv.	77%	42%
7	24	THF	135 °C	0.5	4 equiv.	46%	25%
8	24	MeCN	135 °C	0.5	4 equiv.	17%	2%
9	24	Hexane	135 °C	0.5	4 equiv.	60%	26%
10	24	DMF	135 °C	0.5	4 equiv.	13%	8%
11	24	DCE	135 °C	0.5	4 equiv.	55%	35%
12	24	PhMe	80 °C	0.5	4 equiv.	9%	13%
13	24	PhMe	100 °C	0.5	4 equiv.	14%	12%
14	24	PhMe	120 °C	0.5	4 equiv.	19%	17%
15	24	PhMe	150 °C	0.5	4 equiv.	72%	44%
16	24	PhMe	135 °C	0.75	4 equiv.	71%	30%
17	24	PhMe	135 °C	1	4 equiv.	61%	16%
18	24	PhMe	135 °C	2	4 equiv.	93%	44%
19	24	PhMe	150 °C	2	1.1 equiv.	84%	34%
20	24	PhMe	150 °C	2	2 equiv.	64%	38%
21	24	PhMe	150 °C	2	3 equiv.	44%	31%

a: Yield determined by ^{1}H-NMR spectroscopy of the crude extract using *p*-dinitrobenzene as internal standard.
b: In brackets, isolated yields from silica gel chromatography deactivated with 1% Et_3N.

In conclusion, the following best reaction parameters (entry 4) are: reaction temperature of 135 °C, in PhMe (0.5 M), for 24 hours and using 4 equivalents of acrylate, which permits to isolate the coupling product **95a** in 46% yield after purification on silica gel chromatography deactivated with 1% of Et_3N to preserve the imine function.

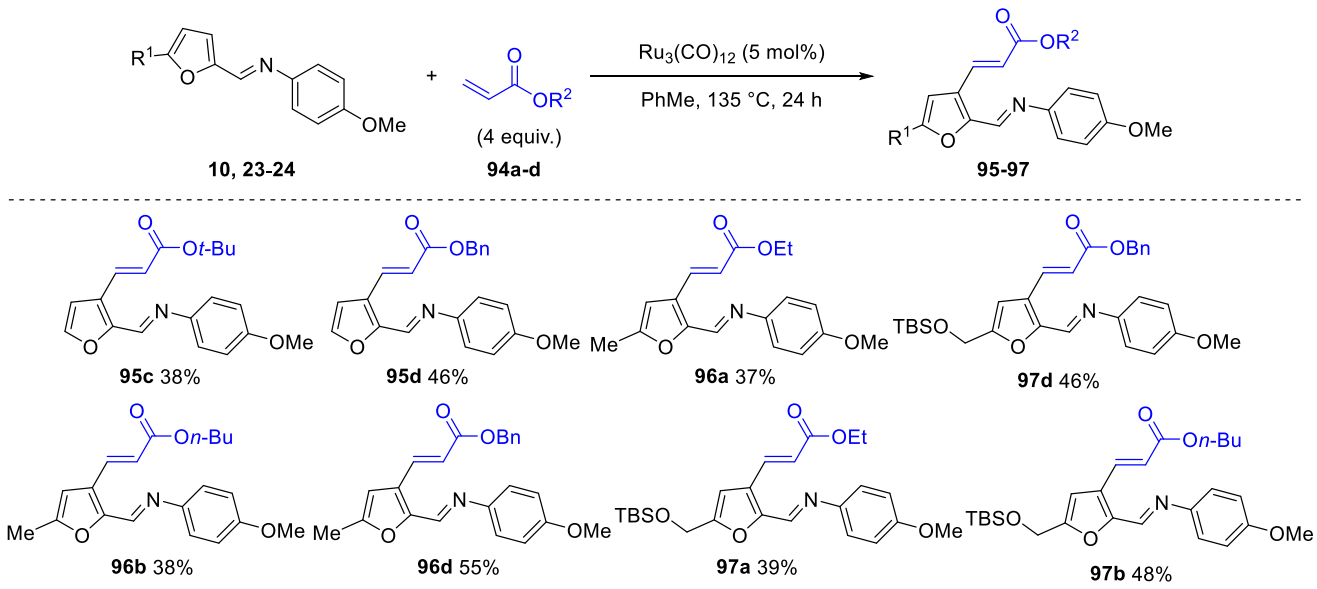
3.3. Scope on furfural imines and extension to other heteroaromatic rings

With the optimal reaction conditions in hand, we passed to study the scope of this new reactivity on other aromatic 2-imino heterocyclopentadiene. Condensation between five aldehydes and *p*-anisidine using the standard protocol allowed to obtain the corresponding imines derived from 5-methyl-furfural **23**, 5-TBSO-methylfurfural **24**, *N*-benzyl-2-formylpyrrole **50**, *N*-benzyl-2-formylindole **53**, and 5-methylthiophene **56** (Scheme 114).



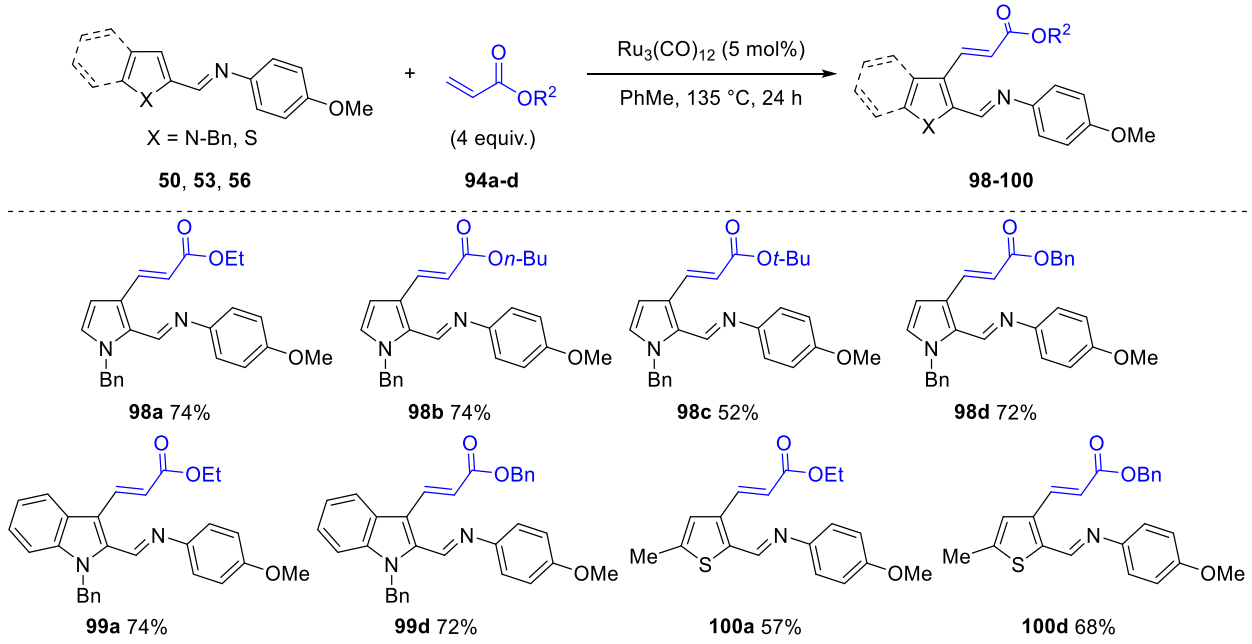
Scheme 114. *Preparation of furan-**20,22**, pyrrole-**50**, indole-**53** and thiophene-**56** based PMP-imines.*

The C5-substituted furfural imines were then tested in the alkenylative coupling with different acrylates partners. Ethyl **94a**, *n*-butyl **94b**, *t*-butyl **94c** and benzyl acrylate **94d** were reacted in the presence of 5 mol% of $Ru_3(CO)_{12}$ and without air removal. The nature of the substituent at C5 in the imine did not affect the coupling. On the other hand, an effect is played by the alcohol moiety of the acrylates: in particular benzyl acrylate **94d** resulting to be the best acrylic partner. It has to be noted that the alkenylated product is always found in the *E* geometry (Scheme 115).



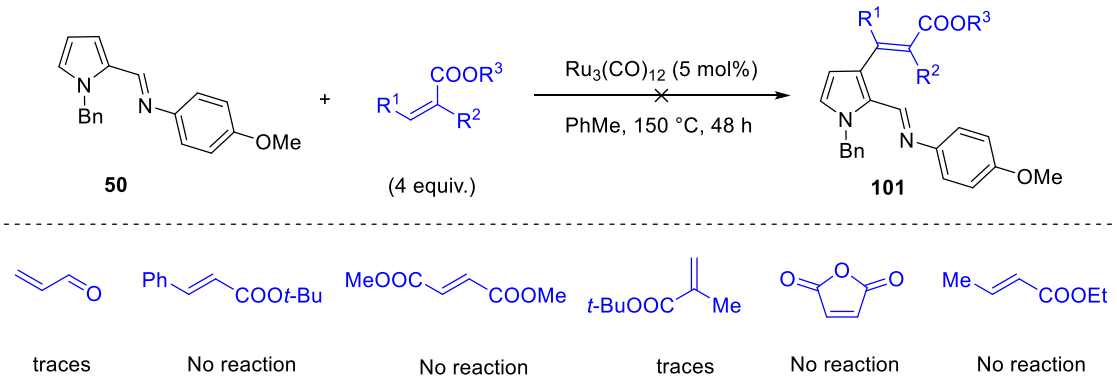
Scheme 115. *Ru(0)-catalyzed alkenylation of furan-based PMP-imines* ***10, 23*** *and* ***24****.*

We then passed to consider the remaining nitrogen- and sulfur-based 2-imino heterocyclopentadienes using the same acrylates **94a-d** as used with the furan-based imines and the same previously optimized reaction conditions. As shown in Scheme 116, the coupling yields for these heterocyclopentadiene imines are much more satisfactory, the desired products being isolated with good yields, over to 72% with compounds **98a-b, d** and **99a,d**. The general better behavior of these imines is likely due to the higher intrinsic nucleophilicity of their C3 position with respect to that of the furfural derivatives.



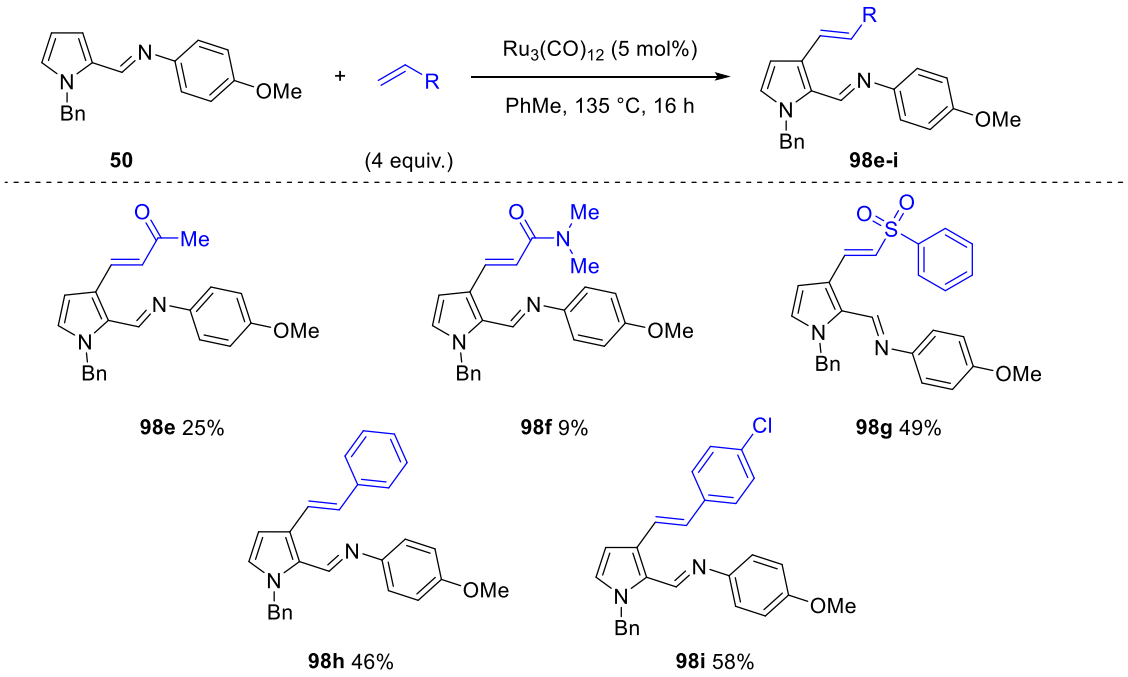
Scheme 116. *Ru(0)-catalyzed alkenylation of nitrogen-* ***50, 53*** *and sulfur* ***56*** *based PMP-imines.*

In view of the satisfactory results obtained with the nitrogen-based imines, we next considered their coupling with α- or β-substituted acrylates as well as acrolein (Scheme 117). Unfortunately, none of the new α,β-unsaturated electrophiles allowed to obtain any coupling product, despite increasing temperatures and reaction times.



Scheme 117. *Attempted Ru(0)-catalyzed alkenylation of PMP-imine* ***50*** *with substituted α,β-unsaturated systems.*

Finally, other monosubstituted electron-poor alkenes were considered as coupling partners for *N*-benzyl-2-formylpyrrole PMP-imine **50** (Scheme 118). Methyl vinyl ketone gave the expected adduct **98e** in 25% yield, while *N*,*N*-dimethyl acrylamide only in 9% yield of **98f**. Better results were obtained with phenyl vinyl sulfone **98g** (49%) and styrenes **98h** (46%) or **98i** (58%). In the case of styrenes, it is noteworthy how, playing with the presence/absence of CO, it is possible to switch from a carbonylative Murai coupling (vide supra) to an acceptorless alkenylation of the 2-arylimino heterocyclopentadienes.

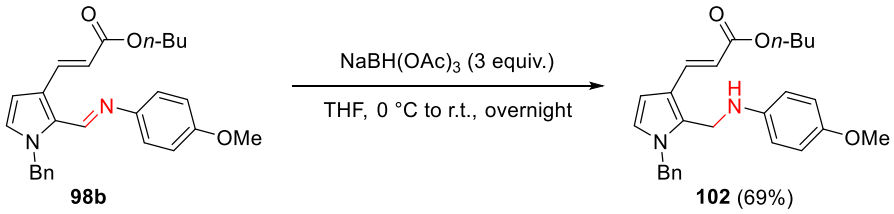


Scheme 118. *Ru(0)-catalyzed alkenylation of PMP-imine* ***50*** *with monosubstituted electron-poor alkenes.*

3.4. Synthetic applications and proposed mechanism

Once the substrate scope concluded, we focused our attention toward post-functional transformations of our products. Having already demonstrated that the quantitative imine hydrolysis to the parent aldehyde was possible with the products deriving from the Murai reaction, we decided to test the imine reduction.

Secondary aromatic amines derived from **98b** may be appealing targets, as original synthons as well as potentially biologically active molecules. Accordingly, we decided to perform a selective reduction of the imine function, without affecting the acrylate portion. Although $NaBH_4$ gave no reaction, treatment of **98b** with $NaBH(OAc)_3$ in THF allowed to isolate the expected secondary amine **102** in 69% yield (Scheme 119).



Scheme 119. *Reduction of the imine function of* ***98b****.*

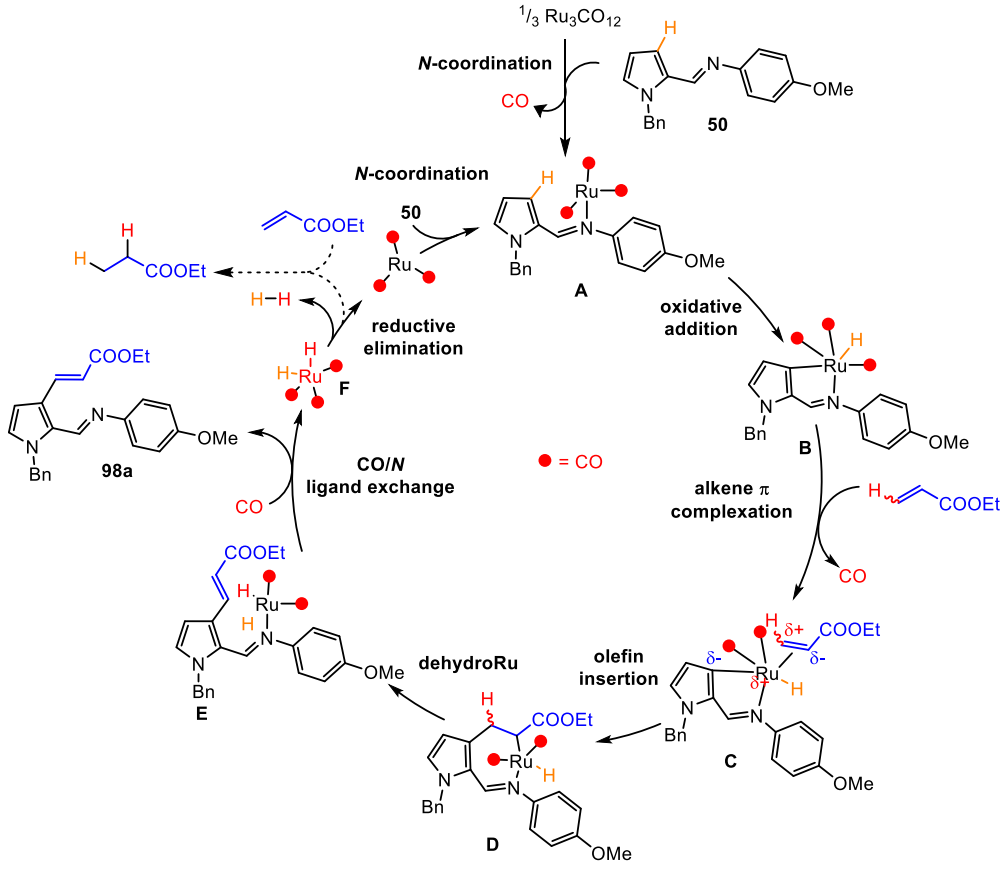
For reasons of time, it was not possible to optimize the yield of the reduction or to extend this procedure to other alkenylated products. The studies of this step as well as of the subsequent synthetic use of the resulting secondary amines are planned for future projects.

Finally, on the basis of the known reported literature on transition metal catalyzed arene alkenylations[166] and on our own results, we propose a mechanism for our newly discovered protocol (Scheme 120). In accord with the DFT calculation performed for the carbonylative Murai reaction (vide supra), we suppose the initial conversion of the trimeric $Ru_3(CO)_{12}$ into a mononuclear complex, which, after coordination by the imine nitrogen of the substrate **50** leads to intermediate **A**. Intramolecular oxidative addition of the C_3-H bond of the pyrrole ring to the coordinated ruthenium atom takes place, leading to the cyclic Ru(II) hydride complex **B**. Following alkene η^2-coordination at the metal center takes place by replacement of one ligated carbon monoxide leads to intermediate **C**. We notice here that the failure of the bidentate imine to catalyze the alkenylation process may be due to a forbidden π-coordination at this level, as the required coordination site is occupied by the nitrogen atom of the imine tail.

Alkene regioselective insertion into the Ru-C3 bond generates intermediate **D**. Following dehydroruthenation generates complex **E**, which upon CO/N ligand exchange releases the final product **98a** and the Ru(II) dihydride **F**. Reductive elimination from this latter generates H_2 and $Ru(CO)_3$, which is ready

[166] Tirler, C.; Ackermann, L. *Tetrahedron*, **2015**, *71*, 4543-4551.

to interact with a new molecule of substrate to start a new catalytic cycle.[167] Alternatively, speculate that excess acrylate is reduced to ethyl propionate by the Ru(II) dihydride.[168] This alternative would be in line with the beneficial effect of excess acrylate in the protocol.



Scheme 120. *Proposed reaction mechanism for the Ru(0)-catalyzed alkenylation of PMP-imine* ***50****.*

Study of the mechanism by DFT calculations, as well as by crystallographic analysis of intermediates and/or monitoring of the reaction via ReactIR are planned for the near future.

4. Conclusions and perspectives

The first introductory part of this chapter presents the aim of this new project and the reported methods for the alkenylation of aromatic and heteroaromatic rings, starting from the pioneering works of with Fujiwara and Moritani. Then, the focus was put on a selection of reported significant examples of arene alkenylations employing directing groups and transition metals other than palladium.

The work accomplished was then presented, which allowed to develop a novel method for the C3-selective ruthenium-catalyzed alkenylation of 2-imino heterocyclopentadienes, including oxygen-, nitrogen-

[167] Tang, S.; Zeng, L.; Lei, A. *J. Am. Chem. Soc*. **2018**, *140*, 13128-13135.

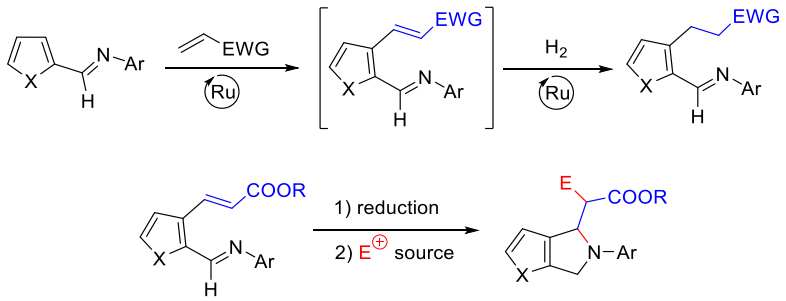
[168] Ru dihydrides are known. See for example: Abdur-Rashid, K.; Abbel, R.; Hadzovic A.; Lough, A. J.; Morris, R. H. *Inorg. Chem.* **2005**, *44*, 2483-2492.

and sulfur based heterocycles. In the case of the pyrrole nucleus, the coupling could be extended to a variety of electron-poor alkene partners with good results.

Worthy of note, in contrast to all the previously reported protocols, this method turns out to be oxidant-free (acceptorless). Indeed, the presence of an additional sacrificial external oxidant was not required. A plausible mechanism for this new transformation was also put forward.

This alkenylative C–H activation coupling is of special interest in the perspective of the green chemistry principles, and lays the foundation for a new mode of selective functionalization of heteroarenes.

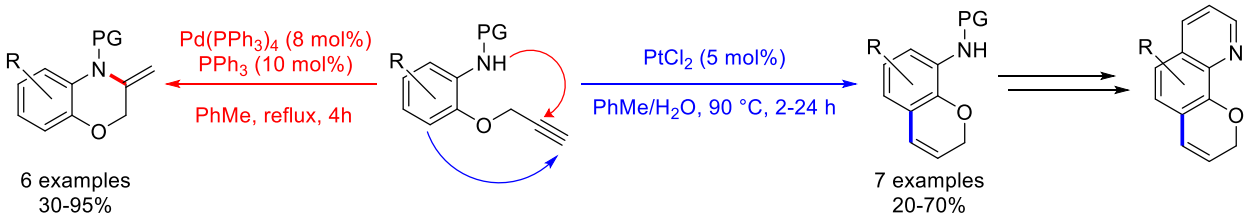
Future studies will be addressed to the study of the mechanism of this transformation via DFT computation, to the development of C3-selective Ru-catalyzed [alkenylation/hydrogenation] domino sequences, as well as to the development of new post-functional synthetic applications (Scheme 121).



Scheme 121. *Planned future studies.*

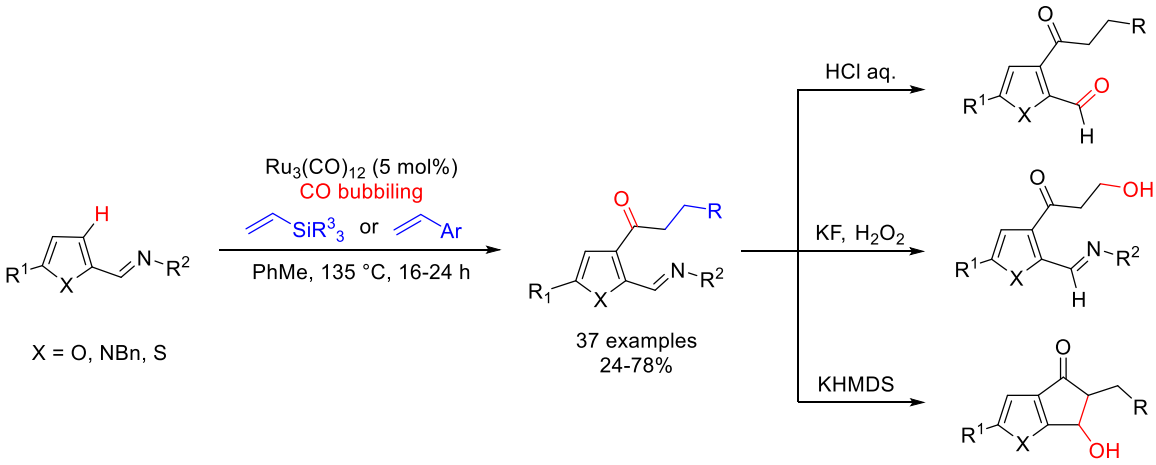
General Conclusion

This PhD work was addressed to the study of new methods for the synthesis and functionalization of heterocycles by activation of C-H bonds. The first part of the work focused on the development of a divergent method for the hydroamination and the hydroarylation of *o*-propargyl-2-aminophenols (Scheme 122).[169] Specifically, palladium and platinum catalysis allow the access to respectively benzoxazine and benzopyran derivatives, these latter being in turn precursors of pyrano[3,2-*h*]quinolones.



Scheme 122. *Pd(0)- and Pt(II)-catalyzed divergent syntheses of benzoxazine and benzopyran derivatives*

The second phase of the work concerned the study of the directed Ru(0) catalyzed carbonylative Murai reaction on 2-imino heterocylopentadienes. This study was successful and allowed to obtain selective acylation at position C3 of the heterocycles in the presence of a number of alkenes as reaction partners. DFT calculations allowed to shade light on the mechanism of this reaction. Some post-functionalization work enhanced the synthetic value of the method (Scheme 123).[170]

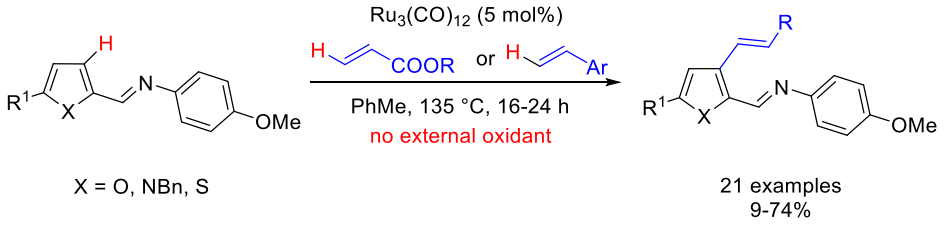


Scheme 123. *Ru(0) Carbonylative Murai reaction on 2-carboxyaldehyde heteroaromatic derivatives.*

The third and last part of the work was dedicated to the development of an acceptorless directed Ru(0)-catalyzed alkenylation of 2-imino heterocylopentadienes. In the course of studies directed along a logical continuation of the previous project, it was discovered that the Ru(0)-catalyzed coupling between 2-imino heterocylopentadienes and electron-poor alkenes afforded a C3 selective alkenylative coupling. This

[169] Christodoulou, M. S.; Giofrè, S.; Broggini, G.; Mazza, A.; Sala, R.; Beccalli, E.M. *Eur. J. Org. Chem.*, **2018**, 6176-6184.
[170] Sala, R.; Roudesly, F.; Veiros, L. F.; Broggini, G.; Oble, J.; Poli, G. *Adv. Synth. Catal.*, **2020**, *362*, 2486-2493.

new reaction could be successfully extended to oxygen-, nitrogen- and sulfur-based heterocycles, and in the case of the pyrrole ring, to a variety of electron-poor alkene partners. In contrast to all the previously reported protocols, this oxidative coupling turned out to be oxidant-free (acceptorless) (Scheme 124).



Scheme 124. *Acceptorless Ru(0)-catalyzed dehydrogenative coupling between 2-imino heterocylopentadienes and alkenes.*

Research oriented toward the activation/functionalization of C-H bonds has so far made significant progress. Nevertheless, further in-depth work will still be needed before this subject reaches a stage of maturity. This thesis work has contributed to enrich this field, and in particular to the development of the selective cyclization and C-H coupling of heterocyclic scaffolds, a key topic in the field of organic synthesis in general, and medicinal chemistry in particular.

Experimental Section

1. General Remarks

All reactions were carried out under an argon atmosphere by standard syringe and septa techniques. Glassware was flame-dried under vacuum or taken directly from the oven (100 °C) and let cool under vacuum prior to every use. Reagents and solvents were purchased from commercial sources and generally used as received. DCM, Et_2O, THF and DMF were dried on a Mbraun purification system MB SPS-800.

NMR spectra (^1H, ^{13}C,) were recorded on a Bruker AM 200 MHz, Bruker AM 300 MHz or on a Bruker AVANCE 400 MHz spectrophotometer. NMR experiments were carried out at room temperature in $CDCl_3$. Chemical shifts are given in parts per million (ppm) using the $CDCl_3$ residual non-deuterated signals as reference (δ ^1H = 7.26 ppm; δ ^{13}C = 77.16 ppm), the MeOD or the C_6D_6 residual non-deuterated signals as reference where indicated. The terms bs, m, s, d, t, q, sext and sept represent broad signal, multiplet, singlet, doublet, triplet and quartet, sextet and septuplet respectively. Coupling constants (*J*) are given in Hertz (Hz). For previously unknown compounds, a combination of ^{13}C, DEPT and 2D experiments (COSY, HSQC, HMBC) were used.

IR spectra were recorded with a Tensor 27 (ATR Diamond) Bruker spectrophotometer. IR spectra were reported as characteristic bands (cm^{-1}). High resolution mass spectra (HRMS) were obtained using a mass spectrometer MicroTOF from Bruker with an electron spray source (ESI) and a TOF detector at Institut Parisien de Chimie Moléculaire (FR 2769). Melting points were measured in capillary tubes on a Stuart Scientific SMP3 apparatus and are uncorrected. TLC analyses were performed on Merck 60 F254 silica gel and revealed with either an ultra-violet lamp (λ = 254 nm) or using “Pancaldi Reagent” and “Vanilline reagent” as a colour reagent. Purifications by flash column chromatography were performed using silica gel Merck Geduran® SI 60 (40-63 µm).

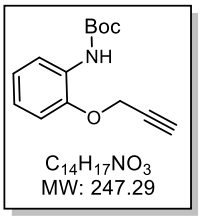
2. Divergent Pd/Pt-catalyzed hydroamination/hydroarylation cyclization

2.1. Preparation and characterization of starting material

General procedure (GP1) for the *N*-Boc-*O*-propargyl Ethers derivatives preparation

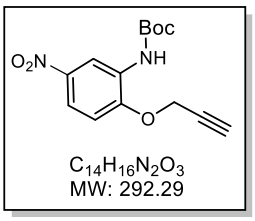
In a round-bottom flask equipped with magnetic stirrer, the appropriate aminophenol (1 equiv.) was introduced and dissolved in anhydrous THF (0.2 M). Then Boc_2O (1.05 equiv.) was added. The reaction mixture was let stir at room temperature overnight. The mixture was then filtered on silica pad with DCM and the solvent was evaporated at reduced pressure. The product was used in the next reaction without further purification. The *N*-Boc-carbamate (1 equiv.) was dissolved in THF/DMF (5:1, 0.2 M) under N_2 atmosphere, then K_2CO_3 (1.3 equiv..) was added and the solution cooled down at 0 °C. Propargyl bromide (80% in toluene, 1.3 equiv.) was subsequently added and the mixture was stirred for 24 h at r.t. The solvent was removed at reduced pressure and the crude was recovered with AcOEt and washed with Brine, dried with $MgSO_4$ and the solvent was evaporated at low pressure. The crude was purified by silica gel chromatography to give the final product.

Synthesis of *tert*-butyl (2-(prop-2-yn-1-yloxy)phenyl)carbamate (1a).



Prepared according to general procedure **GP1**, the reaction of aminophenol (327 mg, 3 mmol, 1 equiv.) with Boc_2O (687 mg, 3.15 mmol, 1.05 equiv.), K_2CO_3 (539 mg, 3.9 mmol, 1.3 equiv.) and propargyl bromide (310 μL, 3.9 mmol, 1.3 equiv.). The product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt (80/20) to afford 695 mg of **1a** (97% yield) as colorless oil. The data are in good agreement with that previously reported. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.11 (d, *J* = 5.3 Hz, 1H), 7.11 (s, 1H), 7.04–7.01 (m, 3H), 4.78 (d, *J* = 2.4 Hz, 2H), 2.60 (t, *J* = 2.4 Hz, 1H), 1.55 (s, 9H).[171]

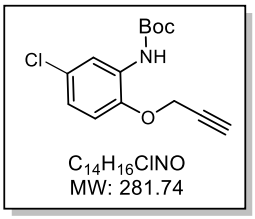
Synthesis of *tert*-butyl (5-nitro-2-(prop-2-yn-1-yloxy)phenyl)carbamate (1b).



Prepared according to general procedure **GP1**, the reaction of 2-amino-5-nitrophenol (462 mg, 3 mmol, 1 equiv.) with Boc_2O (687 mg, 3.15 mmol, 1.05 equiv.), K_2CO_3 (539 mg, 3.9 mmol, 1.3 equiv.) and propargyl bromide (310 μL, 3.9 mmol, 1.3 equiv.). The product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt (80/20) to afford 695 mg of **1b** (97% yield) as yellow solid. The data are in good agreement with that previously reported.[172] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.11 (d, *J* = 5.3 Hz, 1H), 7.11 (s, 1H), 7.04–7.01 (m, 3H), 4.78 (d, *J* = 2.4 Hz, 2H), 2.60 (t, *J* = 2.4 Hz, 1H), 1.55 (s, 9H).

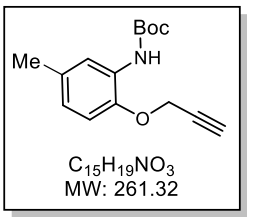
[171] Collot, M.; Wilms, C.; Mallet, J. -M. *RCS Adv.* **2015**, *5*, 6993-7000.

Synthesis of *tert*-butyl (5-chloro-2-(prop-2-yn-1-yloxy)phenyl)carbamate (1c).



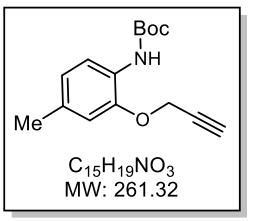
Prepared according to general procedure **GP1**, the reaction of 2-amino-5-chlorophenol (431 mg, 3 mmol, 1 equiv.) with Boc_2O (687 mg, 3.15 mmol, 1.05 equiv.), K_2CO_3 (539 mg, 3.9 mmol, 1.3 equiv.) and propargyl bromide (310 μL, 3.9 mmol, 1.3 equiv.). The product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt (90/10) to afford 768 mg of **1c** (94% yield) as white solid. The data are in good agreement with that previously reported.[171] **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 8.18 (s, 1H), 6.99-6.87 (m, 2H), 7.05 (bs, 1H), 4.75 (d, *J* = 2.6 Hz, 2H), 2.54 (t, *J* = 2.6 Hz, 1H), 1.54 (s, 9H).

Synthesis of *tert*-butyl (5-methyl-2-(prop-2-yn-1-yloxy)phenyl)carbamate (1d).



Prepared according to general procedure **GP1**, the reaction of 2-amino-5-methylphenol (365 mg, 3 mmol, 1 equiv.) with Boc_2O (687 mg, 3.15 mmol, 1.05 equiv.), K_2CO_3 (539 mg, 3.9 mmol, 1.3 equiv.) and propargyl bromide (310 μL, 3.9 mmol, 1.3 equiv.). The product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt (80/20) to afford 735 mg of **1d** (96% yield) as white solid. The data are in good agreement with that previously reported. [171] **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.97 (s, 1H), 7.03 (bs, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.75 (ddd, *J* = 8.3, 2.2, 0.8 Hz, 1H), 4.72 (d, *J* = 2.7 Hz, 2H), 2.53 (t, *J* = 2.5 Hz, 1H), 2.30 (s, 3H), 1.54 (s, 9H).

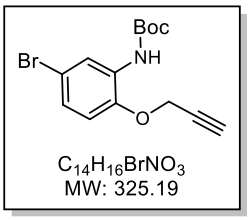
Synthesis of *tert*-butyl (4-methyl-2-(prop-2-yn-1-yloxy)phenyl)carbamate (1e).



Prepared according to general procedure **GP1**, the reaction of 2-amino-4-methylphenol (363 mg, 3 mmol, 1 equiv.) with Boc_2O (687 mg, 3.15 mmol, 1.05 equiv.), K_2CO_3 (539 mg, 3.9 mmol, 1.3 equiv.) and propargyl bromide (310 μL, 3.9 mmol, 1.3 equiv.). The product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt (80/20) to afford 634 mg of **1e** (81% yield) as yellow oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.93 (d, J = 7.2 Hz, 1 H), 6.95 (bs, 1H), 6.79-6.74 (m, 2H), 4.71 (d, *J* = 1.9 Hz, 2H) 2.54 (t, *J* = 2.1 Hz, 1H), 2.31 (s, 3H), 1.54 (s, 9H). **^{13}C-NMR (50 MHz, CDCl3):** δ = 152.7 (s), 145.6 (s), 132.0 (s), 126.0 (s), 122.4 (d), 118.5 (d), 112.7 (d), 80.1 (s), 78.3 (s), 75.8 (d), 56.5 (t), 28.3 (q), 21.1 (q). **IR (cm^{-1}):** ν 3220, 2930, 2120, 1720, 1550. **MS**: *m/z* calculated for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$: 284.1; found: 284.09.

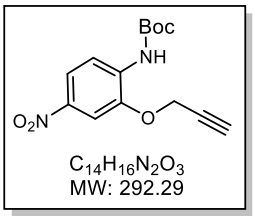
[172] Gazzola, S.; Beccalli, E. M.; Bernasconi, A.; Borelli, T.; Broggini, G.; Mazza, A. *Eur. J. Org. Chem.* **2016**, 4534-4544.

Synthesis of *tert*-butyl (4-methyl-2-(prop-2-yn-1-yloxy)phenyl)carbamate (1f).



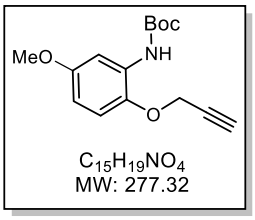
Prepared according to general procedure **GP1**, the reaction of 2-amino-4-methylphenol (564 mg, 3 mmol, 1 equiv.) with Boc_2O (687 mg, 3.15 mmol, 1.05 equiv.), K_2CO_3 (539 mg, 3.9 mmol, 1.3 equiv.) and propargyl bromide (310 μL, 3.9 mmol, 1.3 equiv.). The product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt (80/20) to afford 741 mg of **1f** (76% yield). **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 8.32 (s, 1H), 7.09 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.02 (bs, 1H), 6.83 (d, J = 8.6 Hz, 1H), 4.72 (d, J = 2.4 Hz, 2H), 2.55 (t, J = 2.4 Hz, 1H), 1.54 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ = 152.3 (s), 144.4 (s), 129.9 (s), 124.6 (s), 121.1 (d), 114.8 (d), 113.1 (d), 80.9 (s), 77.7 (d), 76.4 (s), 56.6 (t), 28.3 (q). **IR (cm^{-1}):** ν 3180, 2920, 2140, 1730, 1530. **MS**: *m*/*z* calculated for $C_4H_{17}BrNO_3$ $[M+H]^+$: 327.2; found: 327.19.

Synthesis of *tert*-butyl (4-nitro-2-(prop-2-yn-1-yloxy)phenyl)carbamate (1g).



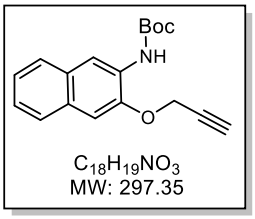
Prepared according to general procedure **GP1**, the reaction of 2-amino-4-nitrophenol (462 mg, 3 mmol, 1 equiv.) with Boc_2O (687 mg, 3.15 mmol, 1.05 equiv.), K_2CO_3 (539 mg, 3.9 mmol, 1.3 equiv.) and propargyl bromide (310 μL, 3.9 mmol, 1.3 equiv.). The product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt (80/20) to afford 701 mg of **1g** (80% yield) as yellow solid. **M.p.:** 110-112 °C. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 8.31 (d, *J* = 9.1 Hz, 1H), 7.95 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.87 (d, *J* = 2.2 Hz, 1H), 7.32 (bs, 1H), 4.87 (d, *J* = 2.2 Hz, 2H), 2.62 (t, *J* = 2.2 Hz, 1H), 1.54 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ = 151.9 (s), 144.5 (s), 141.9 (s), 135.1 (s), 118.6 (d), 116.8 (d), 107.0 (d), 83.8 (s), 81.8 (s), 77.4 (d), 56.9 (t), 28.2 (q). **IR (cm^{-1}):** ν 3427, 3274, 1729, 1506, 1475, 1339, 1230, 1149. **MS**: *m*/*z* calculated for $C_{14}H_{17}N_2O_3$ $[M+H]^+$: 293.3; found: 292.29.

Synthesis of *tert*-butyl (5-methoxy-2-(prop-2-yn-1-yloxy)phenyl)carbamate (1h).



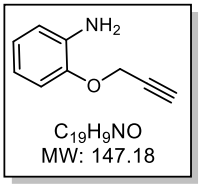
Prepared according to general procedure **GP1**, the reaction of 2-amino-5-nitrophenol (462 mg, 3 mmol, 1 equiv.) with Boc_2O (687 mg, 3.15 mmol, 1.05 equiv.), K_2CO_3 (539 mg, 3.9 mmol, 1.3 equiv.) and propargyl bromide (310 μL, 3.9 mmol, 1.3 equiv.). The product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt (60/10) to afford 823 mg of **1h** (99% yield) as white solid. The data are in good agreement with that previously reported. [171] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.79 (bs, 1H), 7.08 (bs, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 6.48 (dd, *J* = 8.9, 3.0 Hz, 1H), 4.67 (d, *J* = 2.4 Hz, 2H), 3.78 (s, 3H), 2.52 (t, *J* = 2.4 Hz, 1H), 1.52 (s, 9H).

Synthesis of *tert*-Butyl [3-(prop-2-yn-1-yloxy)naphthalene-2-yl]carbamate: (1i).



Prepared according to general procedure **GP1**, the reaction of 2-amino-4-methylphenol (564 mg, 3 mmol, 1 equiv.) with Boc_2O (687 mg, 3.15 mmol, 1.05 equiv.), K_2CO_3 (539 mg, 3.9 mmol, 1.3 equiv..) and propargyl bromide (310 μL, 3.9 mmol, 1.3 equiv..). The product was purified by flash column chromatography on silica gel eluting with hexane/AcOEt (80/20) to afford 856 mg of **1i** (96% yield) as yellow oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 8.54 (s, 1H), 7.72 (m, 1H), 7.67 (m, 1H), 7.35 (m, 3H), 7.23 (s, 1H), 4.89 (d, *J* = 2.4 Hz, 2H), 2.59 (t, *J* = 2.4 Hz, 1H), 1.57 (s, 9H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 152.6 (s), 145.4 (s), 129.7 (s), 129.3 (s), 128.3 (s), 127.3 (d), 126.3 (d), 124.7 (d), 124.6 (d), 114.7 (d), 106.7 (d), 80.6 (s), 76.8 (s), 76.3 (d), 56.3 (t), 28.4 (q). **IR (cm^{-1}):** ν 3430, 3240, 2124, 1710, 1536. **MS**: *m*/*z* calculated for $C_{18}H_{19}NNaO_3$ $[M+Na]^+$: 320.5; found: 320.49.

Synthesis of 2-(prop-2-yn-1-yloxy)phenyl)carbamate (1j).



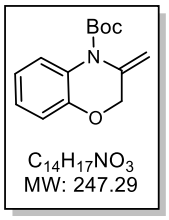
Prepared according a reported procedure,[173] the reaction of 2-nitrophenol (695 mg, 5 mmol, 1 equiv.) with K_2CO_3 (705 mg, 5.1 mmol, 1.01 equiv.) and propargyl bromide (714 mg, 6 mmol, 1.2 equiv.). The product was then converted into the corresponding amine to afford 559 mg of **1j** (76% yield) as white solid. The data are in good agreement with that previously reported.[172] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 6.97-6.93 (m, 1H), 6.86-6.80 (m, 1H), 6.74 (t, *J* = 8.3 Hz, 2H), 4.72 (d, *J* = 2.2 Hz, 2H), 2.52 (t, *J* = 2.1 Hz, 1H).

2.2. Preparation and characterization of cycled products

General Procedure (GP2) for the Pd-Catalyzed Hydroamination Reactions on Alkyne Derivatives

In a round bottom flask, $Pd(PPh_3)_4$ (0.04 mmol, 0.08 equiv.) and PPh_3 (0.04 mmol, 0.1 equiv.) were added to a solution of the suitable propargyloxy anilines derivative (0.4 mmol) in toluene/H_2O (10/1, 0.1 M) under nitrogen atmosphere. The reaction mixture was stirred at reflux for 4 h. The reaction mixture was filtered under reduced pressure on a Celite pad washing with AcOEt. The solvent was removed under reduced pressure and the crude purify by silica gel chromatography.

Synthesis of *tert*-butyl 3-methylene-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (2a).

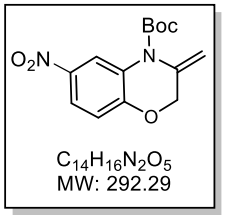


Prepared according to general procedure **GP2**, the reaction of **1a** (100 mg, 0.4 mmol, 1 equiv.) with $Pd(PPh_3)_4$ (35 mg, 0.03 mmol, 0.08 equiv.) and PPh_3 (10 mg, 0.04 mmol, 0.1 equiv.). The product was purified by flash column chromatography on silica gel to afford 94

[173] Zhou, Y.- G.; Yang, P.- Y.; H., X.- W. *J. Org. Chem.* **2005**, *70*, 5, 1679-1683.

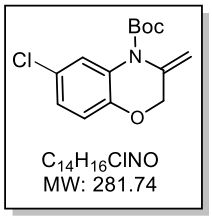
mg of **2a** (95% yield) as colourless oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.01-6.76 (m, 4H), 5.34 (s, 1H), 5.13 (s, 1H), 4.56 (s, 2H), 1.53 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 152.0 (s), 147.2 (s), 133.7 (s), 131.6 (s), 124.7 (d), 123.6 (d), 120.9 (d), 117.1 (d), 107.9 (t), 82.5 (s), 69.8 (t), 28.4 (q). **IR (cm^{-1}):** ν 3433, 3058, 2979, 2932, 2870, 1717, 1602. **MS**: *m*/*z* calculated for $C_{14}H_{17}NNaO_3$ $[M+Na]^+$: 270.2; found: 270.1.

Synthesis of *tert*-butyl 3-methylene-6-nitro-2H-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (2b).



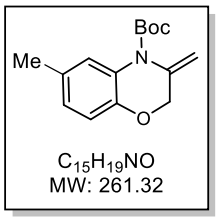
Prepared according to general procedure **GP2**, the reaction of **1b** (117 mg, 0.4 mmol, 1 equiv.) with $Pd(PPh_3)_4$ (35 mg, 0.03 mmol, 0.08 equiv.) and PPh_3 (10 mg, 0.04 mmol, 0.1 equiv.). The product was purified by flash column chromatography on silica gel to afford 96 mg of **2b** (82% yield) as orange solid. **M.p.**: 134-136°C. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 8.76 (d, *J* = 2.7 Hz, 1H), 7.89 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 5.43 (s, 1H), 5.35 (s, 1H), 4.66 (s, 2H), 1.57 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 156.1 (s), 151.6 (s), 143.0 (s), 134.0 (s), 129.6 (s), 120.3 (d), 119.6 (d), 117.3 (d), 111.5 (t), 81.8 (s), 69.7 (t), 28.5 (q). **IR (cm^{-1}):** ν 3436, 3128, 2923, 2851, 1721, 1588. **MS**: *m*/*z* calculated for $C_{14}H_{16}N_2NaO_5$ $[M+Na]^+$: 314.9; found: 315.0.

Synthesis of *tert*-butyl 6-chloro-3-methylene-2H-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (2c).



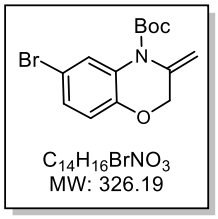
Prepared according to general procedure **GP2**, the reaction of **1c** (110 mg, 0.4 mmol, 1 equiv.) with $Pd(PPh_3)_4$ (35 mg, 0.03 mmol, 0.08 equiv.) and PPh_3 (10 mg, 0.04 mmol, 0.1 equiv.). The product was purified by flash column chromatography on silica gel to afford 98 mg of **2c** (87% yield) as colourless oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.79 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.35 (d, *J* = 0.5 Hz, 1H), 5.19 (d, *J* = 0.5 Hz, 1H), 4.54 (d, *J* = 0.5 Hz, 2H), 1.54 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 151.5 (s), 145.5 (s), 135.7 (s), 127.7 (s), 125.7 (s), 124.5 (d), 123.2 (d), 118.0 (d), 109.0 (t), 83.0 (s), 69.5 (t), 28.3 (q). **IR (cm^{-1}):** ν 3422, 3086, 2979, 2930, 1858, 1719. **MS**: *m*/*z* calculated for $C_{14}H_{17}ClNO$ $[M+H]^+$: 281.7; found: 281.0.

Synthesis of *tert*-butyl 6-methyl-3-methylene-2*H*-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (2d).



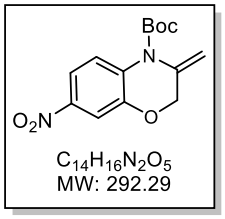
Prepared according to general procedure **GP2**, the reaction of **1d** (102 mg, 0.4 mmol, 1 equiv.) with $Pd(PPh_3)_4$ (35 mg, 0.03 mmol, 0.08 equiv.) and PPh_3 (10 mg, 0.04 mmol, 0.1 equiv.). The product was purified by flash column chromatography on silica gel to afford 92 mg of **2d** (88% yield) as colourless oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.53 (s, 1H), 6.95-6.67 (m, 2H), 5.34 (s, 1H), 5.15 (s, 1H), 4.54 (d, *J* = 0.6 Hz, 2H), 2.30 (s, 3H), 1.54 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 152.0 (s), 145.0 (s), 136.9 (s), 133.8 (s), 126.8 (s), 125.3 (d), 123.8 (d), 116.7 (d), 107.6 (t), 82.4 (s), 69.8 (t), 28.4 (q), 21.1 (q). **IR (cm^{-1}):** ν 3432, 3056, 2977, 2928, 1715. **MS**: *m*/*z* calculated for $C_{15}H_{22}NO_4$ $[M+H_2O]^+$: 278.9; found: 279.0.

Synthesis of *tert*-butyl 6-bromo-3-methylene-2*H*-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (2f).



Prepared according to general procedure **GP2**, the reaction of **1f** (130 mg, 0.4 mmol, 1 equiv.) with $Pd(PPh_3)_4$ (35 mg, 0.03 mmol, 0.08 equiv.) and PPh_3 (10 mg, 0.04 mmol, 0.1 equiv.). The product was purified by flash column chromatography on silica gel to afford 39 mg of **2f** (30% yield) as colourless oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.92 (d, *J* = 2.3 Hz, 1H), 7.07 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 5.35 (d, *J* = 0.6 Hz, 1H), 5.19 (d, *J* = 0.6 Hz, 1H), 4.54 (d, *J* = 0.7 Hz, 2H), 1.56 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 151.3 (s), 145.8 (s), 135.5 (s), 130.3 (s), 127.9 (s), 127.1 (d), 125.9 (d), 118.2 (d), 108.7 (t), 83.0 (s), 69.3 (t), 28.1 (q). **IR (cm^{-1}):** ν 3320, 2930, 2333, 1719. **MS**: *m/z* calculated for $C_{14}H16NNaO_3$ $[M+Na]^+$: 349.2; found: 349.2.

Synthesis of *tert*-butyl 3-methylene-7-nitro-2H-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (2g).

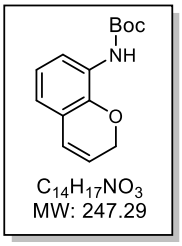


Prepared according to general procedure **GP2**, the reaction of **1g** (116 mg, 0.4 mmol, 1 equiv.) with $Pd(PPh_3)_4$ (35 mg, 0.03 mmol, 0.08 equiv.) and PPh_3 (10 mg, 0.04 mmol, 0.1 equiv.). The product was purified by flash column chromatography on silica gel to afford 113 mg of **2g** (97% yield) as yellow solid. **M.p.**: 96-98 °C. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.94 (d, *J* = 9.0 Hz, 1H), 7.77 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 5.38 (s, 1H), 5.27 (s, 1H), 4.61 (s, 2H), 1.55 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 151.1 (s), 146.1 (s), 143.6 (s), 134.4 (s), 132.6 (s), 122.5 (d), 116.0 (d), 112.7 (d), 110.2 (t), 83.7 (s), 69.1 (t), 28.1 (q). **IR (cm^{-1}):** ν 3432, 3127, 2922, 1926, 1719, 1515. **MS**: *m/z* calculated for $C_{14}H_{16}N_2NaO_5$ $[M+Na]^+$: 315.0; found: 315.0.

General Procedure (GP9) for the Pt-Catalyzed Hydroamination Reactions on Alkyne Derivatives

In a round bottom flask, to a solution of the suitable propargyl derivative (0.5 mmol) in toluene (0.2 M) was added $PtCl_2(MeCN)_2$ (0.025 mmol, 0.05 equiv..). The reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was concentrated under reduced pressure, brine was added and the mixture extracted with AcOEt. The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by silica gel chromatography.

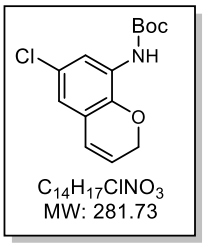
Synthesis of *tert*-butyl 2*H*-Chromen-8-ylcarbamate (3a).



Prepared according to general procedure **GP9**, the reaction of **1a** (124 mg, 0.5 mmol, 1 equiv.) with $PtCl_2(MeCN)_2$ (9 mg, 0.025 mmol, 0.05 equiv.). The product was purified by flash column chromatography on silica gel to afford 74 mg of **3a** (60% yield) as colourless oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.91 (d, J = 7.9 Hz, 1H), 6.93 (bs, 1H), 6.84 (t, *J* = 7.9 Hz, 1H), 6.64 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.41 (dt, *J* = 9.9, 1.8 Hz, 1H), 5.76 (dt, *J* = 9.9, 3.5 Hz, 1H),

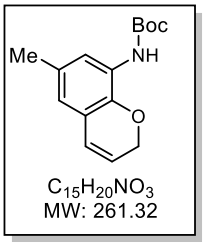
4.83 (dd, *J* = 3.5, 1.9 Hz, 2H), 1.54 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 152.9 (s), 141.8 (s), 127.1 (s), 124.9 (d), 123.3 (d), 121.6 (d), 121.4 (d), 120.3 (d), 118.7 (d), 80.5 (s), 66.0 (t), 28.6 (q). **IR (cm^{-1}):** ν 3425, 2970, 1920, 1720. **MS**: *m*/*z* calculated for $C_{14}H_{17}NNaO_3$ $[M+Na]^+$: 270.1; found: 270.0.

Synthesis of *tert*-butyl (6-chloro-2*H*-chromen-8-yl)carbamate (3c).



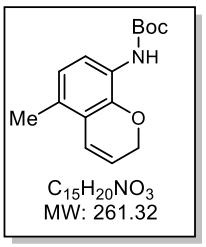
Prepared according to general procedure **GP9**, the reaction of **1c** (140 mg, 0.5 mmol, 1 equiv.) with $PtCl_2(MeCN)_2$ (9 mg, 0.025 mmol, 0.05 equiv.). The product was purified by flash column chromatography on silica gel to afford 49 mg of **3c** (35% yield) as colourless oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.99 (s, 1H), 6.94 (bs, 1H), 6.63 (d, *J* = 2.5 Hz, 1H), 6.34 (dt, *J* = 9.9, 1.9 Hz, 1H), 5.81 (dt, *J* = 9.9, 3.5 Hz, 1H), 4.84 (dd, *J* = 3.5, 1.9 Hz, 2H), 1.54 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 152.6 (s), 140.1 (s), 128.1 (s), 126.7 (s), 124.1 (d), 122.6 (s), 122.6 (d), 119.7 (d), 118.2 (d), 81.1 (s), 66.1 (t), 28.5 (q). **IR (cm^{-1}):** ν 3432, 2979, 2930, 1728. **MS**: *m*/*z* calculated for $C_{14}H_{16}ClNNaO_3$ $[M+Na]^+$: 304.0; found: 304.0.

Synthesis of *tert*-butyl (6-methyl-2*H*-chromen-8-yl)carbamate (3d).



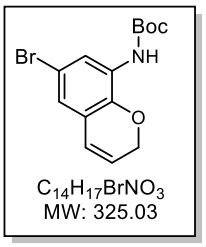
Prepared according to general procedure **GP9**, the reaction of **1d** (130 mg, 0.5 mmol, 1 equiv.) with $PtCl_2(MeCN)_2$ (9 mg, 0.025 mmol, 0.05 equiv.). The product was purified by flash column chromatography on silica gel to afford 91 mg of **3d** (70% yield) as colourless oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.72 (m, 1H), 6.88 (m, 1H), 6.46 (bs, 1H), 5.75 (dt, *J* = 9.8, 3.5 Hz, 1H), 4.79 (dd, *J* = 3.5, 1.8 Hz, 2H), 2.24 (s, 3H), 1.53 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 153.2 (s), 149.8 (s), 131.1 (s), 126.9 (s), 125.2 (d), 122.0 (d), 121.8 (s), 119.2 (d), 80.7 (s), 66.1 (t), 28.8 (q), 21.4 (q). **IR (cm^{-1}):** ν 3436, 2977, 2920, 1728. **MS**: *m*/*z* calculated for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$: 283.9; found: 284.0.

Synthesis of *tert*-butyl (5-methyl-2*H*-chromen-8-yl)carbamate (3e).



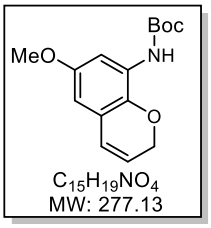
Prepared according to general procedure **GP9**, the reaction of **1e** (130 mg, 0.5 mmol, 1 equiv.) with $PtCl_2(MeCN)_2$ (9 mg, 0.025 mmol, 0.05 equiv.). The product was purified by flash column chromatography on silica gel to afford 85 mg of **3e** (65% yield) as colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.72 (m, 1H), 6.88 (m, 1H), 6.46 (bs, 1H), 5.75 (dt, *J* = 9.8, 3.5 Hz, 1H), 4.79 (dd, *J* = 3.5, 1.8 Hz, 2H), 2.24 (s, 3H), 1.53 (s, 9H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 152.8 (s), 141.9 (s), 127.6 (s), 124.8 (s), 122.5 (d), 122.1 (d), 121.1 (d), 120.3 (s), 118.0 (d), 80.6 (s), 65.0 (t), 28.3 (q), 17.8 (q). **IR (cm^{-1}):** ν 3437, 2984, 2923, 1730. **MS**: *m*/*z* calculated for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$: 284.1; found: 284.2.

Synthesis of *tert*-butyl (6-bromo-2*H*-chromen-8-yl)carbamate (3f).



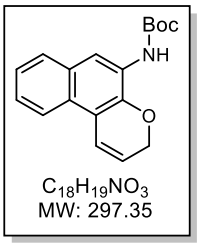
Prepared according to general procedure **GP9**, the reaction of **1f** (162 mg, 0.5 mmol, 1 equiv.) with $PtCl_2(MeCN)_2$ (9 mg, 0.025 mmol, 0.05 equiv.). The product was purified by flash column chromatography on silica gel to afford 33 mg of **3f** (20% yield) as colourless oil. **^{1}H-NMR (300 MHz, MeOD):** δ 7.91 (d, *J* = 2.1 Hz, 1H), 6.81 (d, J = 2.4 Hz, 1H), 6.37 (dt, *J* = 9.9, 2.1 Hz, 1H), 5.86 (dt, *J* = 9.9, 3.6 Hz, 1H) 4.84 (dd, *J* = 3.3, 2.1 Hz, 2H), 1.53 (s, 9H). **^{13}C-NMR (75 MHz, MeOD):** δ 153.1 (s), 141.6 (s), 127.9 (s), 123.6 (s), 123.3 (d), 122.9 (d), 122.6 (d), 121.5 (d), 112.6 (s), 80.3 (s), 65.5 (t), 27.3 (q). **IR (cm^{-1}):** ν 3437, 2984, 2923, 1730. **MS**: *m*/*z* calculated for $C_{14}H_{17}NNaO_3$ $[M+Na]^+$: 349.2; found: 349.2.

Synthesis of *tert*-butyl (6-methoxy-2*H*-chromen-8-yl)carbamate (3h).



Prepared according to general procedure **GP9**, the reaction of **1h** (162 mg, 0.5 mmol, 1 equiv.) with $PtCl_2(MeCN)_2$ (9 mg, 0.025 mmol, 0.05 equiv.). The product was purified by flash column chromatography on silica gel to afford 104 mg of **3h** (75% yield) as colourless oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.61 (d, *J* = 2.6 Hz, 1H), 6.94 (s, 1H), 6.37 (m, 1H), 5.81 (m, 1H) 4.75 (m, 2H), 3.76 (s, 3H), 1.52 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 154.1 (s), 152.6 (s), 135.5 (s), 127.4 (s), 124.8 (d), 122.6 (d), 122.2 (s), 105.8 (d), 103.8 (d), 80.4 (s), 65.6 (t), 55.8 (q), 28.4 (q). **IR (cm^{-1}):** ν 3435, 2911, 2924, 2844, 1727. **MS**: *m*/*z* calculated for $C_{15}H_{20}NNaO_4$ $[M+Na]^+$: 300.2; found: 300.1.

Synthesis of *tert*-butyl (3*H*-benzo[*f*]chromen-5-yl)carbamate (3i).

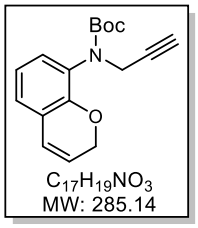


Prepared according to general procedure **GP9**, the reaction of **1i** (162 mg, 0.5 mmol, 1 equiv.) with $PtCl_2(MeCN)_2$ (9 mg, 0.025 mmol, 0.05 equiv.). The product was purified by flash column chromatography on silica gel to afford 65 mg of **3i** (44% yield) as colourless oil. **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 8.43 (s, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.35 (m, 2H), 7.22 (bs, 1H), 7.13 (dt, *J* = 10.0, 1.6 Hz, 1H), 5.93 (dt, *J* = 10.0, 3.9 Hz, 1H), 4.90 (dd, *J* = 3.9, 1.6 Hz, 2H), 1.60 (s, 9H). **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 152.7 (s), 141.9 (s), 129.5 (s), 128.2 (d), 127.1 (s), 125.6 (s), 124.9 (d), 124.3 (d), 121.1 (d), 120.9 (d), 119.9 (d), 115.0 (s), 114.9 (d), 80.6 (s), 65.6 (t), 28.3 (q). **IR (cm^{-1}):** ν 3300, 2950, 1940, 1720. **MS**: *m*/*z* calculated for $C_{15}H_{20}NNaO_4$ $[M+Na]^+$: 320.3; found: 320.4.

2.3. Further derivatization of cycled products

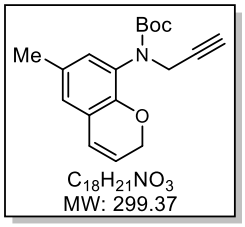
General Procedure (GP10) for the preparation of *tert*-Butyl 2*H*-Chromen-8-yl(prop-2-ynyl)carbamates. Under N_2 atmosphere, to a stirred solution of the compounds **3** (1 mmol) in THF/DMF (5 mL/1 mL) cooled to 0 °C, NaH (1.5 equiv.) was added and then a solution of propargyl bromide (80 % in PhMe, 1.5 equiv.) was added dropwise. The resulting mixture was stirred at r.t. for 3 h. The solvent was removed under reduced pressure was extracted with AcOEt. The solvent was removed under reduced pressure and the crude product purified by column chromatography (hexane/AcOEt, 5:1).

Synthesis of *tert*-Butyl (2*H*-Chromen-8-yl)(prop-2-ynyl)carbamate (4a).



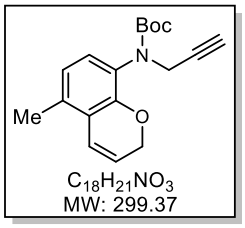
Prepared according procedure **GP10** from compound **3a**. The product was purified by flash column chromatography on silica gel to afford 205 mg of **4a** (72% yield) as colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.10 (s, 1H), 6.91 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.44 (d, *J* = 7.6 Hz, 1H), 5.79 (dt, *J* = 9.7, 3.4 Hz, 1H), 4.84 (dd, *J* = 3.3, 1.8 Hz, 2H), 4.30 (bs, 2H), 2.19 (t, *J* = 2.2 Hz, 1H), 1.35 (s, 9H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 149.4 (s), 129.4 (d), 128.8 (s), 126.4 (s), 125.5 (d), 124.5 (d), 123.2 (s), 122.0 (d), 120.5 (d), 80.4 (s), 72.0 (s), 71.5 (d), 65.5 (t), 38.3 (t), 28.2 (q). **IR (cm^{-1}):** ν 3291, 2978, 2932, 2121, 1697, 1604, 1583. **MS:** *m*/*z* calculated for $C_{17}H_{19}NNaO_3$ $[M + Na]^+$: 308.3; found 308.4.

Synthesis of *tert*-Butyl (6-Methyl-2*H*-chromen-8-yl)(prop-2-ynyl)carbamate (4d).



Prepared according procedure **GP10** from compound **3d**. The product was purified by flash column chromatography on silica gel to afford 210 mg of **4d** (70% yield) as colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 6.91 (m, 1H), 6.70 (d, *J* = 1.6 Hz, 1H), 6.38 (d, *J* = 9.8 Hz, 1H), 5.76 (dt, *J* = 9.8, 3.4 Hz, 1H), 4.77 (s, 2H), 4.27 (bs, 2H), 2.24 (s, 3H), 2.17 (t, *J* = 2.2 Hz, 1H), 1.38 (s, 9H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 155.0 (s), 147.3 (s), 130.2 (s), 129.7 (d), 128.8 (s), 126.3 (d), 124.9 (d), 123.2 (s), 122.3 (d), 80.6 (s), 71.6, (2C, s and d), 65.7 (t), 38.8 (t), 28.5 (q), 20.7 (q). **IR (cm^{-1}):** ν 3290, 2977, 2930, 2120, 1700, 1639, 1588. **MS:** *m*/*z* calculated for $C_{18}H_{21}NNaO_3$ $[M + Na]^+$: 322.1; found 322.1.

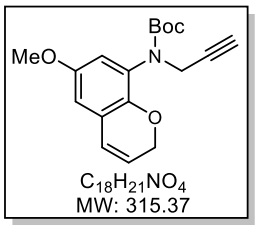
Synthesis of *tert*-Butyl (5-Methyl-2*H*-chromen-8-yl)(prop-2-ynyl)carbamate (4e).



Prepared according procedure **GP10** from compound **3e**. The product was purified by flash column chromatography on silica gel to afford 263 mg of **4e** (88% yield) as colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 6.97 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.60 (d, J = 10 Hz, 1H), 5.83 (dt, *J* = 10.0, 3.6 Hz, 1H), 4.73 (d, *J* = 1.7 Hz, 2H), 4.25 (bs, 2H), 2.27 (s, 3H), 2.15 (s, 1H), 1.37 (s, 9H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 152.8 (s), 141.9 (s), 127.6 (s), 124.8 (s), 122.5 (d), 122.1 (d), 121.1 (d), 120.3 (s), 118.0 (d), 80.6 (s), 65.0 (t), 28.3 (q),

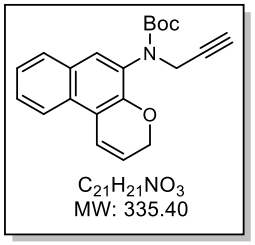
17.8 (q). **IR (cm^{-1}):** ν 3437, 2984, 2923, 1730. **MS**: *m*/*z* calculated for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$: 284.1; found: 284.2.

Synthesis of *tert*-Butyl (6-Methoxy-2*H*-chromen-8-yl)(prop-2-ynyl)carbamate (4h).



Prepared according procedure **GP10** from compound **3h**. The product was purified by flash column chromatography on silica gel to afford 227 mg of **4h** (72% yield) as colourless oil. **^{1}H-NMR (300 MHz, CDCl$_3$):** δ 6.67 (d, *J* = 2.8 Hz, 1H), 6.49 (d, *J* = 2.8 Hz, 1H), 6.39 (d, *J* = 9.6 Hz, 1H), 5.82 (dt, *J* = 9.6, 3.5 Hz, 1H), 4.73 (dd, *J* = 3.2, 1.7 Hz, 2H), 4.29 (bs, 2H), 3.74 (s, 3H), 2.18 (s, 1H), 1.39 (s, 9H). **^{13}C-NMR (75 MHz, CDCl$_3$):** δ 154.1 (s), 153.2 (s), 143.4 (s), 129.2 (s), 124.6 (d), 123.6 (s), 123.1 (d), 114.3 (d), 111.0 (d), 80.4 (s), 72.0 (s), 71.5 (d), 65.3 (t), 55.7 (q), 40.6 (t), 28.2 (q). **IR (cm^{-1}):** ν 3291, 2976, 2932, 2119, 1699, 1603, 1588. **MS:** *m*/*z* calculated for $C_{18}H_{21}NNaO_4$ $[M + Na]^+$: 338.8; found 338.8.

Synthesis of *tert*-Butyl (3*H*-Benzo[*f*]chromen-5-yl)(prop-2-yn-1-yl)carbamate (4i).

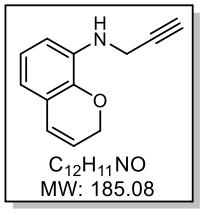


Prepared according procedure **GP10** from compound **3i**. The product was purified by flash column chromatography on silica gel to afford 174 mg of **4i** (52% yield) as colourless oil. **^{1}H-NMR (300 MHz, CDCl$_3$):** δ 7.92 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.71 (s, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 9.9 Hz, 1H), 5.94 (dt, *J* = 9.9, 3.8 Hz, 1H), 4.86 (dd, *J* = 3.8, 1.5 Hz, 2H), 4.41 (bs, 2H), 2.23 (s, 1H), 1.42 (s, 9H). **^{13}C-NMR (75 MHz, CDCl$_3$):** δ 154.7 (s), 148.6 (s), 130.1 (s), 129.1 (s), 128.8 (s), 128.6 (d), 128.2 (d), 126.8 (d), 124.1 (d), 121.3 (d), 121.2 (d), 120.6 (d), 116.7 (s), 80.7 (s), 79.9 (s), 71.9 (d), 65.2 (t), 38.9 (t), 28.3 (q). **IR (cm^{-1}):** ν 3200, 2910, 2110, 1700, 1590. **MS:** *m*/*z* calculated for for $C_{21}H_{21}NNaO_4$ $[M + Na]^+$: 358.4; found 358.4.

General Procedure (GP5) for the preparation of *N*-(Prop-2-ynyl)-2*H*-chromen-8-amines.

To a solution of compounds **4** (1 mmol) in DCM (5 mL) cooled to 0 °C, TFA (30 equiv.) was added whilst stirring. The resulting mixture was stirred at r.t. for 1 h, then diluted with a Na_2CO_3 solution (60 equiv.) and filtered. The filtered was extracted with DCM and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/AcOEt, 10:1).

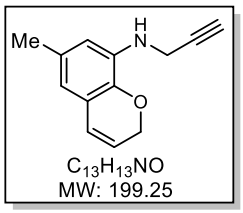
Synthesis of *N*-(Prop-2-ynyl)-2*H*-chromen-8-amine (5a):



Prepared according procedure **GP5** from compound **4a**. The product was purified by flash column chromatography on silica gel to afford 130 mg of **5a** (70% yield) as light yellow oil. **^{1}H-NMR (300 MHz, CDCl$_3$):** δ 6.85 (t, *J* = 7.8 Hz, 1H), 6.66 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.49 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.43 (dt, *J* = 9.8, 1.8 Hz, 1H), 5.78 (dt, *J* = 9.8, 3.6 Hz,

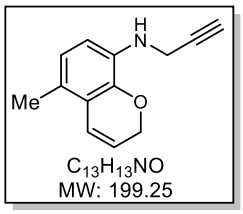
1H), 4.85 (dd, *J* = 3.6, 1.8 Hz, 2H), 4.11 (bs, 1H), 3.98 (d, *J* = 2.4 Hz, 2H), 2.25 (t, J = 2.4 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 141.1 (s), 135.5 (s), 125.0 (d), 121.5 (s), 121.4 (d), 121.3 (d), 116.2 (d), 111.7 (d), 81.2 (s), 71.1 (d), 65.5 (t), 33.4 (t). **IR (cm^{-1}):** ν 3288, 3044, 2840, 2113. **MS:** *m/z* calculated for $C_{12}H_{12}NO$ $[M + H]^+$: 186.2; found 186.2.

***N*-(Prop-2-ynyl)-6-methyl-2*H*-chromen-8-amine (5d):**



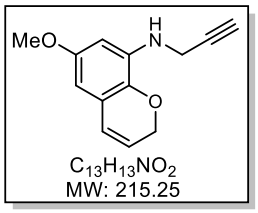
Prepared according procedure **GP5** from compound **4d**. The product was purified by flash column chromatography on silica gel to afford 139 mg of **5d** (70% yield) as light yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 6.45 (s, 1H), 6.38 (d, *J* = 9.8 Hz, 1H), 6.29 (s, 1H), 5.76 (dt, *J* = 9.8, 3.6 Hz, 1H), 4.78 (dd, *J* = 3.6, 1.8 Hz, 2H), 4.26 (s, 1H), 3.95 (d, *J* = 2.2 Hz, 2H), 2.26 (s, 3H), 2.23 (t, *J* = 2.2 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 139.0 (s), 135.2 (s), 130.6 (s), 125.0 (d), 121.4 (d), 121.3 (s), 116.5 (d), 112.4 (d), 81.2 (s), 71.1 (d), 65.4 (t), 33.4 (t), 21.1 (q). **IR (cm^{-1}):** ν 3288, 2917, 2848, 2175. **MS:** *m/z* calculated for $C_{13}H_{14}NO$ $[M + H]^+$: 199.2; found 199.3.

***N*-(Prop-2-ynyl)-5-methyl-2*H*-chromen-8-amine (5e).**



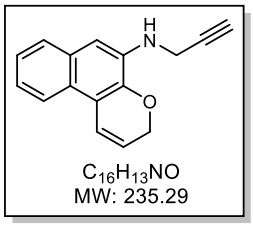
Prepared according procedure **GP5** from compound **4e**. The product was purified by flash column chromatography on silica gel to afford 185 mg of **5e** (93% yield) as brown oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 6.66 (d, *J* = 8.1 Hz, 1H), 6.60 (dt, *J* = 10.0, 1.8 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 5.82 (dt, *J* = 10.0, 3.6 Hz, 1H), 4.77 (dd, *J* = 3.6, 1.8 Hz, 2H), 4.04 (bs, 1H), 3.93 (d, *J* = 2.4 Hz, 2H), 2.25 (s, 3H); 2.22 (t, *J* = 2.4 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 141.6 (s), 133.7 (s), 123.6 (s), 122.5 (d), 122.4 (d), 121.1 (d), 120.4 (s), 111.6 (d), 81.3 (s), 71.1 (t), 64.8 (t), 33.7 (d), 17.8 (q). **IR (cm^{-1}):** ν 3290, 2914, 2851, 2178. **MS:** *m/z* calculated for $C_{13}H_{13}NNaO$ $[M + Na]^+$: 222.3; found 222.3.

***N*-(Prop-2-ynyl)-6-methoxy-2*H*-chromen-8-amine (5h).**



Prepared according procedure **GP5** from compound **4h**. The product was purified by flash column chromatography on silica gel to afford 161 mg of **5h** (75% yield) as light yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 6.39 (dt, *J* = 9.8, 1.8 Hz, 1H), 6.26 (d, *J* = 2.7 Hz, 1H), 6.03 (d, *J* = 2.7 Hz, 1H), 5.81 (dt, *J* = 9.8, 3.6 Hz, 1H), 4.76 (dd, *J* = 3.6, 1.8 Hz, 2H), 4.35 (bs, 1H), 3.95 (d, *J* = 2.4 Hz, 2H), 3.78 (s, 3H), 2.24 (t, *J* = 2.4 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 154.6 (s), 136.5 (s), 135.4 (s), 125.2 (d), 122.2 (d), 121.8 (s), 99.5 (d), 99.1 (d), 80.9 (s), 71.3 (d), 65.4 (t), 55.6 (q), 33.3 (t). **IR (cm^{-1}):** ν 3283, 3198, 2848, 2113. **MS:** *m/z* calculated for $C_{13}H_{13}NNaO_2$ $[M + Na]^+$: 238.3; found 238.2.

***N*-(Prop-2-yn-1-yl)-3*H*-benzo[*f*]chromen-5-amine (5i).**

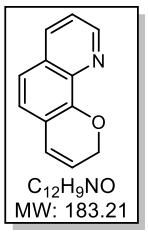


Prepared according procedure **GP5** from compound **4i**. The product was purified by flash column chromatography on silica gel to afford 165 mg of **5i** (70% yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.82 (d, *J* = 7.0 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.29 (m, 2H), 7.12 (dt, *J* = 10.0, 1.7 Hz, 1H), 6.87 (s, 1H), 5.91 (dt, *J* = 10.0, 3.8 Hz, 1H), 4.88 (dd, *J* = 3.8, 1.7 Hz, 2H), 4.63 (bs, 1H), 4.10 (d, *J* = 2.4 Hz, 2H), 2.25 (t, *J* = 2.4 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 142.6 (s), 135.9 (s), 130.2 (s), 126.5 (d), 124.1 (d), 123.9 (s), 123.0 (d), 121.3 (d), 121.0 (d), 119.7 (d), 114.8 (s), 105.8 (d), 80.6 (s), 71.3 (d), 65.4 (t), 33.1 (t). **IR (cm^{-1}):** ν 3310, 2910, 2100. **MS:** *m*/*z* calculated for $C_{16}H_{13}NNaO$ $[M + Na]^+$: 258.3; found 258.3.

General Procedure (GP6) for the preparation of pyrano[3,2-*h*]quinolones

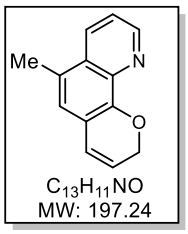
Compounds **5** (1 mmol) was added to a suspension of $Cu(OTf)_2$ (0.2 equiv.) in DCE (20 mL), under N_2. The mixture was heated at 80 °C whilst stirring for 5 h, then filtered and extracted with DCM. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/AcOEt, 7:1 to 1:2).

2*H*-Pyrano[3,2-*h*]quinoline (6a).



Prepared according procedure **GP6** from compound **5a**. The product was purified by flash column chromatography on silica gel to afford 110 mg of **6a** (60% yield) as colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.84 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.00 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.29 (m, 2H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.50 (dt, *J* = 9.8, 1.8 Hz, 1H), 5.85 (dt, *J* = 9.8, 3.6 Hz, 1H), 5.12 (dd, *J* = 3.6, 1.9 Hz, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 150.0 (d), 149.6 (s), 139.3 (s), 136.2 (d), 129.5 (s), 125.6 (d), 124.8 (d), 122.3 (d), 121.4 (d), 120.6 (s), 120.0 (d), 66.7 (t). **IR (cm^{-1}):** ν 2916, 2849, 2316. **MS:** *m*/*z* calculated for $C_{12}H_{10}NO$ $[M + H]^+$: 184.2; found 184.2.

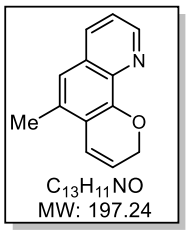
6-Methyl-2*H*-pyrano[3,2-*h*]quinoline (6d).



Prepared according procedure **GP6** from compound **5d**. The product was purified by flash column chromatography on silica gel to afford 93 mg of **6d** (47% yield) as brown oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.87 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.35 (dd, *J* = 8.2, 3.7 Hz, 1H), 7.00 (s, 1H), 6.48 (d, *J* = 9.6 Hz, 1H), 5.86 (d, *J* = 9.6 Hz, 1H), 5.10 (s, 2H), 2.54 (s, 3H).

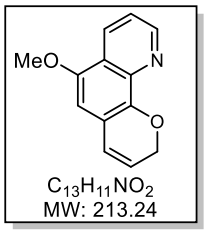
^{13}C-NMR (75 MHz, $CDCl_3$): δ 149.3 (d), 147.8 (s), 139.4 (s), 132.5 (d), 128.3 (s), 126.1 (s), 125.6 (d), 124.6 (d), 122.2 (d), 120.7 (d), 119.8 (s), 66.3 (t), 17.9 (q). **IR (cm^{-1}):** ν 2919, 2850. **MS:** *m*/*z* calculated for $C_{12}H_{12}NO$ $[M + H]^+$: 198.3; found 198.2.

5-Methyl-2*H*-pyrano[3,2-*h*]quinoline (6e).



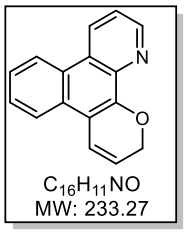
Prepared according procedure **GP6** from compound **5e**. The product was purified by flash column chromatography on silica gel to afford 108 mg of **6e** (55% yield) as yellow oil. **^{1}H-NMR (300 MHz, CD_3OD):** δ 8.63 (dd, *J* = 4.2, 1.2 Hz, 1H), 8.06 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.36 (dd, *J* = 8.1, 4.2 Hz, 1H), 7.16 (d, *J* = 0.6 Hz, 1H), 6.71 (dt, *J* = 9.9, 1.8 Hz, 1H), 5.99 (dt, *J* = 9.9, 3.6 Hz, 1H), 4.94 (dd, *J* = 3.6, 1.8 Hz, 2H), 2.40 (d, *J* = 0.9 Hz, 3H). **^{13}C-NMR (75 MHz, CD_3OD):** δ 148.6 (s), 148.0 (d), 137.3 (s), 135.8 (d), 133.4 (s), 129.0 (s), 122.2 (d), 121.4 (d), 121.2 (d), 120.6 (s), 119.4 (d), 64.9 (t), 17.8 (q). **IR (cm^{-1}):** ν 2923, 2847. **MS:** *m/z* calculated for $C_{12}H_{12}NO$ $[M + H]^+$: 198.2; found 198.2.

6-Methoxy-2*H*-pyrano[3,2-*h*]quinoline (6h).



Prepared according procedure **GP11** from compound **5h**. The product was purified by flash column chromatography on silica gel to afford 85 mg of **6h** (40% yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.87 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.45 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.31 (dd, *J* = 8.5, 4.2 Hz, 1H), 6.51 (s, 1H), 6.48 (dd, *J* = 9.7, 2.6 Hz, 1H), 5.90 (dt, *J* = 9.7, 3.6 Hz, 1H), 5.03 (dd, *J* = 3.6, 2.6 Hz, 2H), 3.93 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 150.0 (d), 148.8 (s); 143.0 (s), 139.1 (s), 131.1 (d), 124.9 (d), 122.8 (d), 121.3 (s), 120.3 (d), 120.1 (s), 103.2 (d), 66.0 (t), 55.8 (q). **IR (cm^{-1}):** ν 2917, 2849. **MS:** *m/z* calculated for $C_{12}H_{12}NO_2$ $[M + H]^+$: 214.4; found 214.3.

2*H*-Benzo[*f*]pyrano[3,2-*h*]quinoline (6i).

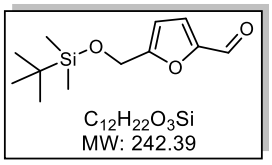


Prepared according procedure **GP6** from compound **5i**. The product was purified by flash column chromatography on silica gel to afford 105 mg of **6i** (45% yield) as yellow oil. **^{1}H-NMR (300 MHz, CD_3OD):** δ 9.17 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.86 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.71 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.14 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.68 (m, 3H), 7.29 (dt, *J* = 10.0, 1.8 Hz, 1H), 6.18 (dt, *J* = 10.0, 3.9 Hz, 1H), 5.04 (dd, *J* = 3.9, 1.8 Hz, 2H). **^{13}C-NMR (75 MHz, CD_3OD):** δ 148.5 (2C, s and d), 139.2 (s), 131.7 (d), 127.9 (s), 125.1 (d), 122.9 (d), 122.5 (d), 122.2 (s), 122.1 (s), 122.0 (d), 121.9 (d, 2C), 120.6 (s), 120.5 (d), 65.2 (t). **IR (cm^{-1}):** ν 2928, 2841. **MS:** *m/z* calculated for $C_{16}H_{11}NNaO_2$ $[M + Na]^+$: 256.3; found 256.3.

3. C3-carbonylative Murai reaction or heteroaromatic rings

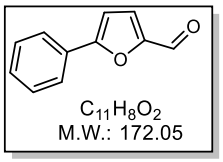
3.1. Preparation and characterization of starting material

Synthesis of 5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde (20).



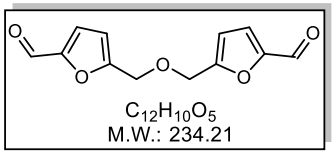
Following a reported procedure,[174] 5-(hydroxymethyl)furan-2-carbaldehyde (2.32 g, 20 mmol, 1 equiv.) was dissolved in DCM (44 mL, 0.2 M), imidazole (1.5 g, 22 mmol, 1.1 equiv.) was added and the mixture was stirred at room temperature for 15 min. Then *tert*-butyldimethylsilylchloride (3.22 g, 21.5 mmol, 1.07 equiv.) was added. The reaction mixture was let stir at room temperature for 24 h. The completion of the reaction was checked by TLC. After completion, water and DCM were added and the two phases separated. The aqueous phase was further extracted with DCM, and the organic phases were dried over $MgSO_4$ and filtrated. The solvent was finally evaporated under reduce pressure, affording 3.6 g of **20** (quantitative yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.59 (s, 1H), 7.20 (d, *J* = 3.6 Hz, 1H), 6.47 (d, *J* = 3.5 Hz, 1H), 4.74 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H). These data are in good agreement with those reported in literature.[174]

Synthesis of 5-phenylfuran-2-carbaldehyde (21).



Following a reported procedure,[175] furan-2-carbaldehyde (2.07 mL, 25 mmol, 5 equiv.), $PdCl_2$ (44.3 mg, 0.25 mmol, 0.05 equiv.), Bu_4NBr (1.6 g, 5 mmol, 1 equiv.) and KOAc (981 mg, 10 mmol, 2 equiv.) was dissolved in degassed DMF (50 mL, 0.2 M), and the mixture was stirred at 110 °C for 10 min. Then PhI (559 μL, 5 mmol, 1 equiv.) was added in a solution of DMF in 10 h. The reaction mixture was let stir at 110 °C for 16 h. The solution was warmed and put into water and the aqueous phase was extracted with three portions of AcOEt, the organic phases were dried over $MgSO_4$ and filtrated. The solvent was finally evaporated under reduce pressure. The crude product was purified by flash column chromatography eluting with Cyclohexane/AcOEt (90/10) affording 499 mg of **21** (58% yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.65 (s, 1H), 7.82 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.50-7.35 (m, 3H), 7.31 (d, *J* = 3.7 Hz, 1H), 6.84 (d, *J* = 3.7 Hz, 1H). These data are in good agreement with those reported in literature.[175]

Synthesis of 5,5'-(oxybis(methylene))bis(furan-2-carbaldehyde) (22).

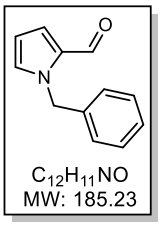


Following a reported procedure,[176] 5-(hydroxymethyl)furan-2-carbaldehyde (1.16 g, 10 mmol, 1 equiv.) was dissolved in benzene (30 mL, 0.3 M),

[174] Subbiah, S.; Simeonov, S. P.; Esperanca, J. M. S. S.; Rebelo, L. P. N., Afonso, C. A. M. *Green. Chem.,* **2013**, *15*, 2849-2853.
[175.] Mcclure, M. S.; Glover, B.; Mcsorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.*, **2001**, *3,* 1677-1680.
[176] Galkin, K. I.; Krivodaeva, E. A.; Romashov, L. V.; Zalesskiy, S. S.; Kachala, V. V.; Burykina, J. V.; Ananikov, V. P. *Angew. Chem. Int. Ed.,* **2016**, *55*, 8338-8342.

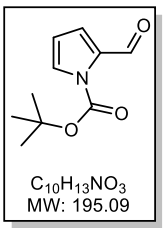
Amberlist 15 (410 mg, 20% w/w) was added and the mixture was let stir at reflux for 12 h using a Dean Stark system. The completion of the reaction was checked by TLC. After completion, the mixture was rapidly filtrated and the solvent evaporated under reduce pressure The crude solid was dissolved in the minimal amount of DCM and Et_2O was added drop by drop, the precipitate was washed with Et_2O and dried unde vacuo, to afford 807 mg of **22** (69% yield) as brown solid. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.63 (s, 1H), 7.21 (d, *J* = 3.2 Hz, 1H), 6.56 (d, *J* = 3.3 Hz, 1H), 4.63 (s, 2H). These data are in good agreement with those reported in literature.[176]

Synthesis of 1-benzyl-1*H*-pyrrole-2-carbaldehyde (33).



Following a modified version of a reported procedure,[177] 2-pyrrolecarboxaldehyde (1.902 g, 20 mmol, 1 equiv.) was dissolved in anhydrous THF (50 mL). The mixture was cooled at 0 °C and NaH (1.6 g, 40 mmol, 2 equiv.) was added slowly by portions. The mixture was stirred for 15 min at the same temperature, then benzyl bromide was added (4.76 mL, 40 mmol, 2 equiv.). The reaction was stirred overnight at room temperature. The mixture was then quenched with water, extracted with Et_2O, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure. The crude extract was then purified by silica gel flash chromatography eluting with Pentane/Et_2O (90/10) to afford 3.457 g of **33** (93% yield) as yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.57 (s, 1H), 7.38-7.20 (m, 3H), 7.18-7.12 (m, 2H), 6.97 (d, *J* = 3.5 Hz, 2H), 6.27 (t, *J* = 3.3 Hz, 1H), 5.57 (s, 2H). The spectral properties are in good agreement with those previously reported.[177]

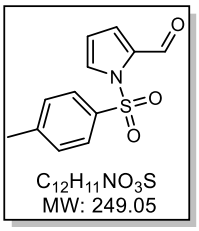
Synthesis of *tert*-butyl 2-formyl-1*H*-pyrrole-1-carboxylate (34).



Following a modified version of a reported procedure,[178] 2-pyrrolecarboxaldehyde (0.951 g, 10 mmol, 1 equiv.) was dissolved in anhydrous THF (20 mL), and the solution was added dropwise to a suspention of NaH (0.48 g, 12 mmol, 1.2 equiv.) in DMF (20 mL). The mixture was stirred for 1 h, then Boc_2O was added (2.4 g, 11 mmol, 1.1 equiv.). The reaction was stirred overnight at room temperature. The mixture was then quenched with water and extracted with Et_2O. The organic layers were collected, washed with water, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure. The crude extract was then purified by silica gel flash chromatography eluting with Pentane/Et_2O (90/10) to afford 1.943 g of **34** (quantitative yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.32 (s, 1H), 7.44 (dd, J = 3.0, 1.7 Hz, 1H), 7.19 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.28 (dd, *J* = 3.8, 3.0 Hz, 1H), 1.64 (s, 9H). The spectral properties are in good agreement with those previously reported.[177]

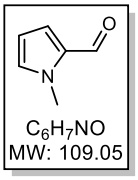
[177] Laha, J. K.; Bhimpuria, R. A.; Hunjan, M. K. *Chem. Eur. J.* **2017**, *23*, 2044-2050.
[178] Waser, J.; Gaspar, B.; Nambu, N.; Carreira, E. M. *J. Am. Chem. Soc,.* **2006**, *128*, 11693-11712.

Synthesis of 1-tosyl-1*H*-pyrrole-2-carbaldehyde (35).



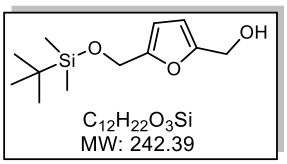
Following a modified version of a reported procedure,[177] 2-pyrrolecarboxaldehyde (0.476 g, 5 mmol, 1 equiv..) was dissolved in anhydrous DCM (10 mL, 0.5 M). After complete dissolution, *i*-Pr_2NEt (1.3 mL, 7.5 mmol, 1.5 equiv.), DMAP (0.031 g, 0.25 mmol, 0.05 equiv.) and tosyl chloride (1.049 g, 5.5 mmol, 1.1 equiv..) were added. The reaction was stirred overnight at room temperature. The mixture was then quenched with HCl 1 M and extracted with DCM. The organic layers were collected, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure. The crude extract was then purified by silica gel flash chromatography eluting with Cyclohexane/$PhCH_3$/EtOAc (50/40/10) to afford 0.933 g of **35** (75% yield) as white solid. **M.p.:** 150-152 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.97 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.61 (dd, *J* = 3.1, 1.7 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.15 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.40 (t, *J* = 3.4 Hz, 1H), 2.41 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 179.0 (d), 146.2 (s), 135.2 (s), 133.5 (s), 130.1 (d), 129.4 (d), 127.5 (d), 124.4 (d), 112.4 (d), 21.7 (d). **IR (cm^{-1}):** ν 3140, 1675, 1600, 1550, 1505, 1255, 1170, 725. **HRMS**: *m*/*z* calculated for $C_{12}H_{11}NNaO_3S$ $[M+Na]^+$: 272.0352; found 272.0355.

Synthesis of 1-methyl-1*H*-pyrrole-2-carbaldehyde (36).



Following a modified version of a reported procedure,[179] 2-pyrrolecarboxaldehyde (0.951 g, 10 mmol, 1 equiv.) was dissolved in anhydrous DMF (10 mL), and the solution was added dropwise to a suspension of NaH (0.48 g, 12 mmol, 1.2 equiv.) in DMF (20 mL). The mixture was stirred for 1 h, then methyliodide was added (0.985 mL, 11 mmol, 1.1 equiv.). The reaction was stirred overnight at room temperature. The mixture was then quenched with water, extracted with EtOAc, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure. The crude extract was then purified by silica gel flash chromatography eluting with Pentane/Et_2O (90/10) to afford 0.727 g of **36** (67% yield) as colorless oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.55 (d, *J* = 1.0 Hz, 1H), 6.91 (dd, *J* = 4.0, 1.7 Hz, 1H), 6.89-6.86 (m, 1H), 6.21 (dd, *J* = 4.1, 2.4 Hz, 1H), 3.96 (s, 3H). The spectral properties are in good agreement with those previously reported.[180]

Synthesis of (5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-yl)methanol (37)

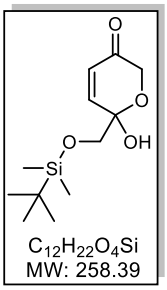


Following a reported procedure,[174] compound **21** (4.8 g, 20 mmol, 1 equiv.) was dissolved in MeOH (100 mL). The mixture was cooled at 0 °C and $NaBH_4$ (1.5 g, 40 mmol, 2 equiv.) was added by portions. The reaction mixture was let stir at room temperature for 1 h. After completion monitored by TLC, water and Et_2O were added and the two layers were separated. The aqueous phase was further extracted with Et_2O, and the

[179] Shang, H.; Tian, Y.; Luo, J.; Li, L.-Y.; Tang, Y.-F.; Zou, Z.-F. *RSC Advances*, **2016**, *6*, 30835-30839.
[180] Laurila, M. L.; Magnus, N. A.; Staszak, M. A. *Org. Process. Res. Dev.* **2009**, *13*, 1199-1201.

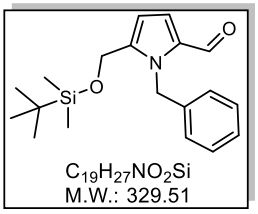
organic phases were dried over $MgSO_4$ and filtrated. The solvent was finally evaporated under reduce pressure affording 4.47 g of **37** (92% yield) as yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.22 (d, *J* = 3.1 Hz, 1H), 6.17 (d, *J* = 3.2 Hz, 1H), 4.63 (s, 2H), 4.58 (s, 2H), 1.71 (bs, 1H), 0.91 (s, 9H), 0.09 (s, 6H). These data are in good agreement with those reported in literature.[174]

Synthesis of 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-2*H*-pyran-3(6*H*)-one (38).



Following a reported procedure,[174] compound **37** (4.36 g, 18 mmol, 1 equiv.) was dissolved in DCM (100 mL). The mixture was cooled at 0 °C and *m*-CPBA (3.97 g, 23 mmol, 1.28 equiv.) was added. The reaction mixture was let stir at the same temperature for 30 min, then at room temperature for 4 h. After completion monitored by TLC, an aqueous solution of $Na_2S_2O_3$ was added followed by NaOH (1 M) to reach pH 7-8. The two phases were separated and the aqueous phase was further extracted with DCM. The organic phases were dried over $MgSO_4$ and filtrated. The solvent was finally evaporated under reduce pressure, affording 3.39 g of **38** (75% yield) as white solid. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 6.79 (d, *J* = 10.4 Hz, 1H), 6.16 (d, *J* = 10.4 Hz, 1H), 4.60 (d, *J* = 17.0 Hz, 1H), 4.14 (d, *J* = 16.9 Hz, 1H), 3.73 (dd, *J* = 28.5, 10.2 Hz, 2H), 0.93 (s, 9H), 0.12 (s, 6H). These data are in good agreement with those reported in literature.[174]

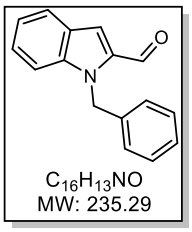
Synthesis of 1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-pyrrole-2-carbaldehyde (39).



Following a slightly modified version of a reported procedure,[181] compound **38** (3.61 g, 14 mmol, 1 equiv.) was dissolved in DCM (70 mL). Benzylamine (1.53 mL, 14 mmol, 1.5 equiv.) was added and the mixture was let stir at 50 °C for 6 h. The organic solvent was extracted with two portions of brine and dried over $MgSO_4$ The solvent was finally evaporated under reduce pressure. The crude was then purified by silica flash gel chromatography eluting with Penatne/Et_2O (92/8), affording 1.8 g of **39** (38% yield) as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.53 (s, 1H), 7.30.7.17 (m, 3H), 7.01-6.97 (m, 2H), 6.93 (d, *J* = 4.0 Hz, 1H), 6.24 (d, *J* = 4.0 Hz, 1H), 5.72 (s, 2H), 4.57 (s, 2H), 0.87 (s, 9H), 0.01 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 179.6 (d), 142.6 (s), 138.0 (s), 132.2 (s), 128.7 (d), 127.3 (d), 126.3 (d), 124.3 (d), 110.3 (d), 57.6 (t), 48.7 (t), 25.9 (q), 18.4 (s), 5.3 (q). **IR (cm^{-1}):** 2953, 2929, 2856, 1661, 1487, 1462, 1454, 1362, 1068. **HRMS:** *m*/*z* calculated for $C_{19}H_{27}NNaO_2Si$ $[M+Na]^+$: 352.1703; found 352.1714.

[181] Yuen, T. Y.; Eaton, S. E.; Woods, T. M.; Furket, D. P.; Choi, K. W.; Brimble, M. A., *Eur. J. Org. Chem*., **2014**, 1431-1437.

Synthesis of 1-benzyl-1*H*-indole-2-carbaldehyde (40).



Following a reported procedure,[182] indole (3.51 g, 30 mmol, 1 equiv.) was dissolved in anhydrous DMF (30 mL). The mixture was cooled at 0 °C and KOH (6.7 g, 120 mmol, 4 equiv.) was added. The mixture was stirred for 20 min at the same temperature, then benzyl bromide was added (4.28 mL, 36 mmol, 1.2 equiv.). The reaction mixture was stirred 1 h at room temperature and then poured onto ice. The organic layer was diluted with AcOEt and separated by aqueous one. The latter was extracted with AcOEt and then washed with brine. The combined organic layers were dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure. The crude was dissolved in anhydrous Et_2O (40 mL) under Ar atmosphere, then *n*-BuLi (2.5 M, 12 mL, 30 mmol, 1.1 equiv.) was added slowly at room temperature. The mixture was heated at reflux for 3 h, followed by the addition of DMF (5.3 mL, 40 mmol, 1.5 equiv.). The reaction was heated at reflux for other 3 h and monitored by TLC. The mixture was quenched with NH_4Cl at room temperature. The mixture was extracted with AcOEt, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure. The product was purified by silica gel flash chromatography eluting with Pentane/Et_2O (94/6) to afford 5.08 g of **40** (72% yield over two steps) as green solid. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.92 (s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.39-7.38 (m, 2H), 7.34 (s, 1H), 7.29-7.16 (m, 4H), 7.10 (dd, *J* = 8.1, 0.8 Hz, 2H), 5.86 (s, 2H). These data are in good agreement with those reported in literature.[183]

General procedure (GP7) for the imine derivatives preparation

Following a reported procedure for the preparation of imines,[92] in a round-bottom flask equipped with magnetic stirrer, the appropriate pyrrol/indol-aldehyde (1 equiv.) was introduced and dissolved in anhydrous DCM (0.5 M). The appropriate amine (1 equiv.) was then added, followed by $MgSO_4$ (2.5 equiv.) and PTSA (2 mg/mmol). The reaction mixture was let stir at room temperature overnight. The reaction course was followed by ^{1}H-NMR spectroscopy: if the reaction was not complete, one of the reagents and/or $MgSO_4$ was added, and the reaction mixture was let stir until completion. The mixture was then filtered, and the solvent evaporated at reduced pressure to give the crude product. The product was used in Ru-catalyzed reactions without further purification.

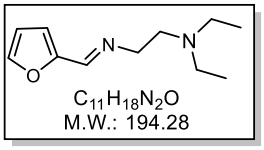
General procedure (GP8) for the imine derivatives preparation

Following a reported procedure for the preparation of imines,[95] in a round-bottom flask equipped with magnetic stirrer, the appropriate pyrrol/indol-aldehyde (1 equiv..) was introduced and dissolved in anhydrous Et_2O (0.1 M). The appropriate amine (1 equiv.) was added dropwise followed by molecular sieves (4 Å, 1.6 mm pellets, 4 g/mmol) and PTSA (2 mg/mmol). The reaction mixture was let stir at room

[182] Yang, Y. F.; Li, L. H.; He, Y. T.; Luo, J. Y.; Liang, Y. M. *Tetrahedron*, **2014**, *70*, 702-707.
[183] Bisway, S.; Singh, V.; Batra, S. J. *Tetrahedron,* **2010**, *66*, 7781-7786.

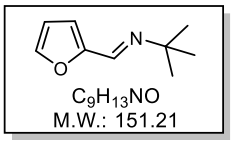
temperature overnight. The reaction course was followed by ^{1}H-NMR spectroscopy: if the reaction was not complete, one of the reagents was added, and the reaction mixture was let stir until completion. The molecular sieves were removed by filtration, and the solvent was removed by evaporation at reduced pressure to give the corresponding imine. The product was used in Ru-catalyzed reactions without further purification.

Synthesis of (E)-*N*,*N*-diethyl-2-((furan-2-ylmethylene)amino)ethan-1-amine (7).



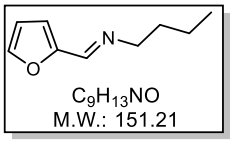
Prepared according to the general procedure **GP7**, the reaction of furan-2-carbaldehyde (0.25 mL, 5 mmol, 1 equiv.) *N*,*N*-diethylethylendiamine (704 μL, 5 mmol, 1 equiv.), in presence of $MgSO_4$ (2 equiv., 1.5 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous DCM (20 mL, 0.1 M) gave 940 mg of **7** (quantitative yield) as brown oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.07 (s, 1H), 7.49 (s, 1H), 6.70 (d, *J* = 3.4 Hz, 1H), 6.45 (dd, *J* = 3.2, 1.7 Hz, 1H), 3.57 (t, *J* = 6.9 Hz, 2H), 1.75-1.63 (m, 2H), 1.44-1.29 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). These data are in good agreement with those reported in literature.

Synthesis of (E)-*N*-*tert*-butyl-1-(furan-2-yl)methanimine (8).



Prepared according to the general procedure **GP7**, the reaction of furan-2-carbaldehyde (0.25 mL, 5 mmol, 1 equiv.) with *t*-butylamine (0.5 mL, 5 mmol, 1 equiv.), in presence of $MgSO_4$ (2 equiv., 1.5 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous DCM (20 mL, 0.1 M) gave 760 mg of **8** (quantitative yield) as brown oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.07 (s, 1H), 7.49 (s, 1H), 6.70 (d, *J* = 3.4 Hz, 1H), 6.45 (dd, *J* = 3.2, 1.7 Hz, 1H), 3.57 (t, *J* = 6.9 Hz, 2H), 1.75-1.63 (m, 2H), 1.44-1.29 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). These data are in good agreement with those reported in literature.

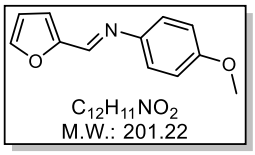
Synthesis of (*E*)-*N*-butyl-1-(furan-2-yl)methanimine (9).



Prepared according to the general procedure **GP7**, the reaction of furan-2-carbaldehyde (0.25 mL, 5 mmol, 1 equiv.) with butylamine (0.5 mL, 5 mmol, 1 equiv.), in presence of $MgSO_4$ (2 equiv., 1.5 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous DCM (20 mL, 0.1 M) gave 760 mg of **9** (quantitative yield) as brown oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.07 (s, 1H), 7.49 (s, 1H), 6.70 (d, *J* = 3.4 Hz, 1H), 6.45 (dd, *J* = 3.2, 1.7 Hz, 1H), 3.57 (t, *J* = 6.9 Hz, 2H), 1.75-1.63 (m, 2H), 1.44-1.29 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). These data are in good agreement with those reported in literature. [184]

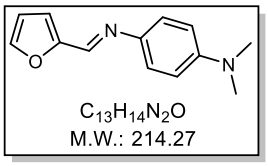
[184] Galletti, P.; Montecavalli, A.; Moretti, F.; Pasteris, A.; Samorai, C.; Tagliavi, E. *New. J. Chem.,* **2009**, *33*, 1859-1868.

Synthesis of (*E*)-1-(furan-2-yl)-*N*-(4-methoxyphenyl)methanimine (10).



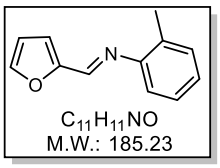
Prepared according to the general procedure **GP8**, the reaction of furan-2-carbaldehyde (0.4 mL, 5 mmol, 1 equiv.) with *p*-anisidine (0.6 g, 5 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv..) in anhydrous Et_2O (50 mL, 0.1 M) gave 0.98 g of **10** (quantitative yield) as brown solid. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.31 (s, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.27-7.24 (m, 2H), 6.97-6.89 (m, 3H), 6.54 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.83 (s, 3H). These data are in good agreement with those reported in literature.[179]

Synthesis of (*E*)-4-((furan-2-ylmethylene)amino)-*N*,*N*-dimethylaniline (11).



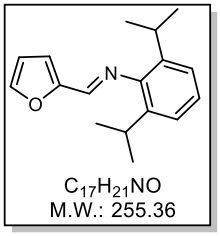
Prepared according to the general procedure **GP8**, the reaction of furan-2-carbaldehyde (0.83 mL, 10 mmol, 1 equiv.) with *N*,*N*-dimethylbenzene-1,4-diamine (1.4 g, 10 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 20 g) and PTSA (20 mg, 0.1 mmol, 0.01 equiv.) in anhydrous Et_2O (50 mL, 0.1 M) gave 1.8 g of **11** (82% yield) as brown solid. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.34 (s, 1H), 7.57 (d, *J* = 1.7 Hz, 1H), 7.31-7.26 (m, 2H), 6.85 (d, *J* = 3.4 Hz, 1H), 6.77-6.72 (m, 2H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H), 2.98 (s, 6H). These data are in good agreement with those reported in literature.[93]

Synthesis of (*E*)-1-(furan-2-yl)-*N*-(*o*-tolyl)methanimine (12).



Prepared according to the general procedure **GP7**, the reaction of furan-2-carbaldehyde (0.4 mL, 5 mmol, 1 equiv.) with *o*-toluidine (0,54 mL, 5 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 20 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (100 mL, 0.1 M) gave 925 mg of **12** (quantitative yield) as yellow solid. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.17 (s, 1H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.24-7.16 (m, 2H), 7.12 (td, *J* = 7.4, 1.3 Hz, 1H), 6.95 (d, *J* = 3.5 Hz, 1H), 6.92-6.86 (m, 1H), 6.56 (dd, *J* = 3.4, 1.8 Hz, 1H), 2.37 (s, 3H). These data are in good agreement with those reported in literature.[185]

Synthesis of (*E*)-*N*-(2,6-diisopropylphenyl)-1-(furan-2-yl)methanimine (13).

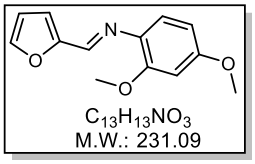


Prepared according to the general procedure **GP7**, the reaction of furan-2-carbaldehyde (0.4 mL, 5 mmol, 1 equiv.) with 2,6-diisopropylaniline (0.95 mL, 5 mmol, 1 equiv.), in presence of $MgSO_4$ (2 equiv., 1.5 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous DCM (8,5 mL, 0.2 M) gave 1.53 g of **13** (quantitative yield) as brown solid. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.98 (s, 1H), 7.64 (d, *J* = 1.2 Hz, 1H), 7.18-7.08

[185] Klimcizak, A. A.; Kuropatwa, A.; Lewkowski, J.; Szempai, J. *Med. Chem. Res.*, **2013**, *22*, 852-860.

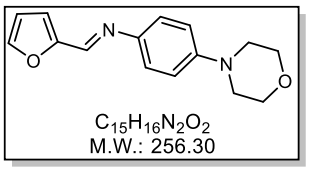
(m, 3H), 6.95 (d, *J* = 3.4 Hz, 1H), 6.58 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.00 (ep, *J* = 8.3 Hz, 2H), 1.17 (d, *J* = 6.9 Hz, 12H). These data are in good agreement with those reported in literature.[186]

Synthesis of (*E*)-*N*-(2,4-dimethoxyphenyl)-1-(furan-2-yl)methanimine (14).



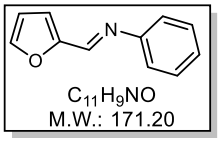
Prepared according to the general procedure **GP8**, the reaction of furan-2-carbaldehyde (0.4 mL, 5 mmol, 1 equiv.) with 2,4-dimethoxyaniline (0.8 g, 5 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (50 mL, 0.1 M) gave 1.0 g of **14** (87% yield) as brown oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.38 (s, 1H), 7.57 (d, *J* = 1.7 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.90 (d, *J* = 3.4 Hz, 1H), 6.56-6.45 (m, 3H), 3.87 (s, 3H), 3.82 (s, 3H). These data are in good agreement with those reported in literature.[187]

Synthesis of (*E*)-1-(furan-2-yl)-*N*-(4-morpholinophenyl)methanimine (15).



Prepared according to the general procedure **GP8**, the reaction of furan-2-carbaldehyde (0.25 mL, 3 mmol, 1 equiv.) with morpholine (534 mg, 3 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 6 g) and PTSA (6 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (20 mL, 0.1 M) gave 760 mg of **15** (quantitative yield) as yellow solid. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.32 (s, 1H), 7.59 (d, *J* = 1.7 Hz, 1H), 7.28-7.26 (m, 2H), 6.95-6.90 (m, 2H), 6.90 (d, *J* = 3.5 Hz, 1H), 6.54 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.87 (d, *J* = 4.0 Hz, 4H), 3.19 (t, *J* = 4.0 Hz, 4H). These data are in good agreement with those reported in literature.[188]

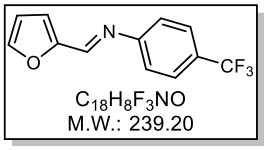
Synthesis of (*E*)-*N*-phenyl-1-(furan-2-yl)methanimine (16).



Prepared according to the general procedure **GP8**, the reaction of furan-2-carbaldehyde (0.83 mL, 10 mmol, 1 equiv.) with aniline (0.91 mL, 10 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (20 mL, 0.1 M) gave 1.7 g of **16** (quantitative yield) as brown oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.30 (s, 1H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.39 (dd, *J* = 8.6, 7.0 Hz, 2H), 7.26 (d, *J* = 1.9 Hz, 3H), 7.24 (s, 1H), 6.96 (d, *J* = 3.2 Hz, 1H), 6.56 (dd, *J* = 3.4, 1.8 Hz, 1H). These data are in good agreement with those reported in literature.[189]

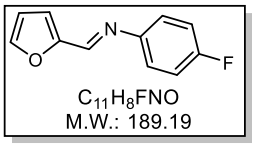
[186] Jiang, Y.; Guo, Y.; Zhu, X.; Song, D.; Wang, Y.; Song, X.; Verpourt, F.; Chang, X. *Inorg. Chem. Ada.*, **2011**, *376*, 144-151.
[187] Kouznetsov, V. V.; Mendez, L. Y. V.; Leal, S. M.; Cruz, U. M.; Coronado, C. A.; Gomez, C. M. M.; Bohorquez, A. R. R.; Rivero, P. E. *Lett. Drug. Des. Discov*. **2007**, *4*, 293-296.
[188] Panneerselvam, P.; Nair, P. P.; Vijayalakshmi, G.; Subramanian, E. H.; Sridhar, S. K. *Eur. J. Med. Chem.,* **2005**, *40*, 225-229.
[189] Moonen, K. Doctoral thesis: Synthesis of 4-phosphono β-lactams and related azaheterocyclic phosphonates, **2006**.

Synthesis of (*E*)-1-(furan-2-yl)-*N*-(4-(trifluoromethyl)phenyl)methanimine (17).



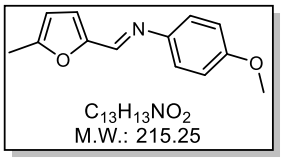
Prepared according to the general procedure **GP8**, the reaction of furan-2-carbaldehyde (0.4 mL, 5 mmol, 1 equiv.) with 4-(trifluoromethyl)aniline (0.6 mL, 5 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (20 mL, 0.1 M) gave 1.2 g of **17** (quantitative yield) as brown oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.26 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.34-7.23 (m, 3H), 7.03 (d, *J* = 3.6 Hz, 1H), 6.59 (dd, *J* = 3.5, 1.7 Hz, 1H). These data are in good agreement with those reported in literature.[93]

Synthesis of (*E*)-*N*-(4-fluorophenyl)-1-(furan-2-yl)methanimine (18).



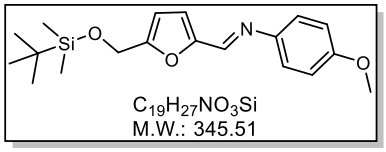
Prepared according to the general procedure **GP7**, the reaction of furan-2-carbaldehyde (0.95 mL, 10 mmol, 1 equiv.) with 4-fluoroaniline (0.83 mL, 5 mmol, 1 equiv.), $MgSO_4$ (2 equiv., 1.5 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous DCM (20 mL, 0.1 M) gave 1.89 g of **18** (quantitative yield) as brown oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.27 (s, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.23 (dd, *J* = 9.0, 5.0 Hz, 2H), 7.07 (t, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 3.5 Hz, 1H), 6.56 (dd, *J* = 3.4, 1.8 Hz, 1H). These data are in good agreement with those reported in literature.[190]

Synthesis of (*E*)-*N*-(4-methoxyphenyl)-1-(5-methylfuran-2-yl)methanimine (23).



Prepared according to the general procedure **GP8**, the reaction of 5-methylfuran-2-carbaldehyde (1 mL, 10 mmol, 1 equiv.) with *p*-anisidine (1.23 g, 10 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 30 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (100 mL, 0.1 M) gave 2.15 g of **23** (quantitative yield) as orange solid. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.19 (s, 1H), 7.25-7.21 (m, 2H), 6.93-6.89 (m, 2H), 6.79 (d, *J* = 3.3 Hz, 1H), 6.15 (dd, *J* = 3.3, 0.9 Hz, 1H), 3.82 (s, 3H), 2.42 (s, 3H). These data are in good agreement with those reported in literature. [191]

Synthesis of (*E*)-*N*-(4-methoxyphenyl)-1-(5-methylfuran-2-yl)methanimine (24).

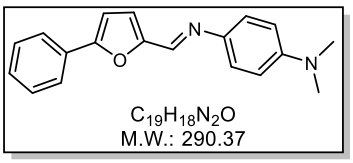


Prepared according to the general procedure **GP8**, the reaction of compound **20** (3.6 g, 15 mmol, 1 equiv.) with *p*-anisidine (1.85 g, 15 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 30 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (150 mL, 0.1 M) gave 5.19 g of **24** (quantitative yield) as orange oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** 8.25 (s, 1H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 3.5 Hz, 1H), 6.40 (d, *J* = 3.4 Hz, 1H), 4.77 (s, 2H), 3.82 (s, 3H), 0.93 (s, 9H), 0.11 (s, 6H). **^{13}C-NMR (75 MHz,**

[190] Iovel', I.; Golomba, L.; Popelis, Y.; Grinberga, S.; Lukevics, E. *Chem. Heterocycl. Compd*. **2000**, *36*, 779-786.
[191]. Simth, C. J.; Smith, C. D.; Nikbin, N.; Lev, S. V.; Baxandale, T. R. *Org. Biomol. Chem.,* **2011**, *9*, 1927-1937.

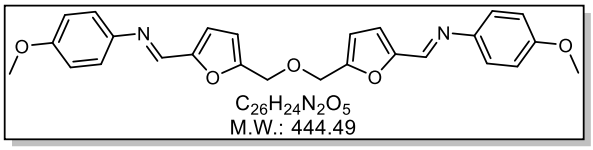
$CDCl_3$): δ 158.3 (s), 158.3 (s), 151.6 (s), 146.0 (d), 144.5 (s), 122.2 (d), 116.4 (d), 114.4 (d), 109.0 (d), 58.7 (t), 55.5 (q), 25.8 (q), 18.4 (s), -5.3 (q). **IR (cm^{-1}):** ν 2953, 2929, 1621, 1500, 1243, 1075, 830, 776. **HRMS**: *m/z* calculated for $C_{19}H_{28}NO_3Si$ $[M+H]^+$: 346.1838; found: 346.1838.

Synthesis of (*E*)-*N*,*N*-dimethyl-4-(((5-phenylfuran-2-yl)methylene)amino)aniline (25).



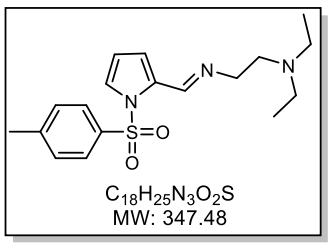
Prepared according to the general procedure **GP8**, the reaction of compound **21** (217 mg, 1.26 mmol, 1 equiv.) with *N*,*N*-dimethylbenzene-1,4-diamine (177 mg, 1.26 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 2.5 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (13 mL, 0.1 M) gave 264 mg of **25** (quantitative yield) as dark red solid. **M.p.:** 164-165 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** 8.37 (s, 1H), 7.87-7.77 (m, 2H), 7.45-7.39 (m, 2H), 7.35-7.28 (m, 3H), 7.03 (d, *J* = 2.9 Hz, 1H), 6.80 (d, *J* = 3.5 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 2H), 2.99 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 156.4 (s), 152.3 (s), 149.6 (d), 143.4 (d), 140.2 (s), 130.0 (d), 128.7 (d), 128.3 (d), 124.6 (d), 122.4 (d), 116.7 (s), 112.8 (d), 107.7 (d), 40.7 (q). **IR (cm^{-1}):** ν 2958, 2802, 1619, 1510, 1480, 1356, 1164, 819. **HRMS**: *m/z* calculated for $C_{19}H_{18}N_2O$ $[M+H]^+$: 291.1492; found: 291.1492.

Synthesis of ((1*E*,1'*E*)-1,1'-((oxybis(methylene))bis(furan-5,2-diyl))bis(*N*-(4-methoxyphenyl)methanimine) (26).



Prepared according to the general procedure **GP7**, the reaction of compound **22** (1.136 g, 4.47 mmol, 1 equiv.) with *p*-anisidine (1.1 g, 4.47 mmol, 2 equiv.), in presence of $MgSO_4$ (2.5 equiv., 2.7 g) and PTSA (15 mg, 0.05 mmol, 0.01 equiv.) in anhydrous DCM (45 mL, 0.1 M) gave 1.93 g of **26** (97% yield) as brown solid. **M.p.**: 139-141 °C **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.27 (s, 2H), 7.32-7.21 (m, 4H), 7.00-6.83 (m, 6H), 6.52 (d, *J* = 3.0 Hz, 2H), 4.64 (s, 4H), 3.82 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 158.4 (s), 154.5 (s), 152.5 (s), 145.9 (d), 144.4 (s), 122.3 (d), 116.1 (d), 114.4 (d), 111.7 (d), 64.4 (t), 55.5 (q). **IR (cm^{-1}):** ν 2908, 2936, 1623, 1498, 1242, 1027, 830, 795. **HRMS**: *m/z* calculated for $C_{26}H_{25}N_2O_5$ $[M+H]^+$: 445.1758; found: 445.1757.

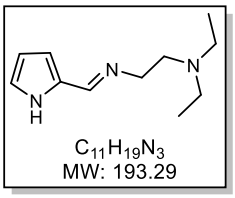
Synthesis of (*E*)-2-(((1-tosyl-pyrrol-2-yl)methylene)amino)-*N*,*N*-diethylethan-1-amine (41).



Prepared according to general procedure **GP7**, the reaction of **35** (499 mg, 2 mmol, 1 equiv.) with *N*,*N*-diethylethylendiamine (281 μL, 2 mmol, 1 equiv.), in presence of $MgSO_4$ (602 mg, 5 mmol, 2.5 equiv.) and PTSA (5 mg, 0.02 mmol, 0.01 equiv.) in anhydrous DCM (4 mL) gave 700 mg of **41** (quantitative yield) as orange oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.67 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.39 (dd, *J* = 3.2, 1.6 Hz, 1H), 7.32-7.27 (m, 2H), 6.91 (dd, *J* = 3.3, 1.5 Hz, 1H), 6.32 (t, *J* = 3.4 Hz, 1H),

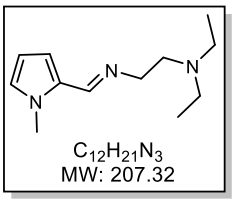
3.69 (t, *J* = 7.0 Hz, 2H), 2.73 (t, *J* = 7.1 Hz, 2H), 2.62 (q, *J* = 7.2 Hz, 4H), 2.41 (S, 3H), 1.06 (t, *J* = 7.1 Hz, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 152.1 (d), 145.5 (s), 136.1 (s), 132.5 (s), 130.2 (d), 126.9 (d), 125.4 (d), 116.3 (d), 112.9 (d), 59.9 (t), 53.5 (t), 47.6 (t), 21.7 (q), 12.0 (q). **IR (cm^{-1}):** ν 2971, 2805, 1629, 1595, 1455, 1400, 1245, 1183, 1052, 735, 672. **HRMS:** *m/z* calculated for $C_{18}H_{26}N_3O_2S$ $[M+H]^+$: 348.1740; found: 348.1745.

Synthesis of (*E*)-2-(((1*H*-pyrrol-2-yl)methylene)amino)-*N*,*N*-diethylethan-1-amine (42).



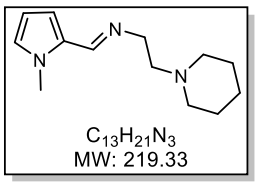
Prepared according to general procedure **GP7**, the reaction of 2-pyrrolecarboxaldehyde (190 mg, 2 mmol, 1 equiv.) with *N*,*N*-diethylethylendiamine (282 μL, 2 mmol, 1 equiv.), in presence of $MgSO_4$ (602 mg, 5 mmol, 2.5 equiv.) and PTSA (4 mg, 0.02 mmol, 0.01 equiv.) in anhydrous DCM (4 mL) gave 386 mg of **42** (quantitative yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.07 (d, *J* = 0.7 Hz, 1H), 6.88 (ddd, *J* = 2.7, 1.4, 0.8 Hz, 1H), 6.47 (ddt, *J* = 3.6, 1.5 Hz, 1H), 6.23 (dd, *J* = 3.6, 2.7 Hz, 1H), 3.66-3.59 (m, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.61 (q, *J* = 7.2 Hz, 4H), 1.05 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 152.4 (d), 130.1 (s), 122.1 (d), 114.5 (d), 109.8 (d), 58.7 (t), 53.9 (t), 47.6 (t), 11.9 (q). **IR (cm^{-1}):** ν 3152, 2970, 2843, 1636, 1554, 1455, 1418, 1203, 1028, 735. **HRMS:** *m/z* calculated for $C_{11}H_{20}N_3$ $[M+H]^+$: 194.1652; found: 194.1658.

Synthesis of (*E*)-2-(((1-methyl-pyrrol-2-yl)methylene)amino)-*N*,*N*-diethylethan-1-amine (43).



Prepared according to general procedure **GP7**, the reaction of **36** (218 mg, 2 mmol, 1 equiv.) with *N*,*N*-diethylethylendiamine (281 μL, 5 mmol, 1 equiv.), in presence of $MgSO_4$ (602 mg, 5 mmol, 2.5 equiv.) and PTSA (5 mg, 0.02 mmol, 0.01 equiv.) in anhydrous DCM (4 mL) gave 413 mg of **43** (quantitative yield) as orange oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.14 (s, 1H), 6.68 (t, *J* = 2.2 Hz, 1H), 6.47 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.12 (dd, *J* = 3.8, 2.5 Hz, 1H), 3.91 (s, 3H), 3.61 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.62 (q, *J* = 7.2 Hz, 4H), 1.06 (t, *J* = 7.1 Hz, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 153.1 (d), 130.0 (s), 127.7 (d), 115.9 (d), 108.1 (d), 60.5 (t), 54.1 (t), 47.7 (t), 36.5 (q), 12.1 (q). **IR (cm^{-1}):** ν 2969, 2835, 1640, 1529, 1479, 1470, 1207, 1059, 728. **HRMS:** *m/z* calculated for $C_{12}H_{22}N_3$ $[M+H]^+$: 208.1808; found: 208.1815.

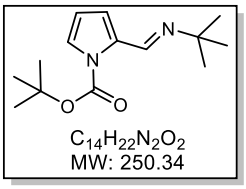
Synthesis of (*E*)-1-(1-methyl-1*H*-pyrrol-2-yl)-*N*-(2-(piperidin-1-yl)ethyl)methanimine (44).



Prepared according to general procedure **GP7**, the reaction of **36** (218 mg, 2 mmol, 1 equiv.) with 2-piperidinoethylamine (284 μL, 2 mmol, 1 equiv.), in presence of $MgSO_4$ (602 mg, 5 mmol, 2.5 equiv.) and PTSA (5 mg, 0.02 mmol, 0.01 equiv..) in anhydrous DCM (4 mL) gave 433 mg of **44** (quantitative yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.14 (s, 1H), 6.68 (t, *J* = 2.0 Hz, 1H), 6.47 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.12 (dd, *J* = 3.7, 2.6 Hz, 1H), 3.91 (s, 3H), 3.67 (t, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.50 (t, *J* = 5.2 Hz, 4H), 1.65-1.53 (m, 4H), 1.49-1.39 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 153.2 (d), 130.2 (s), 127.7 (d), 115.9 (d), 108.1 (d), 60.5 (t),

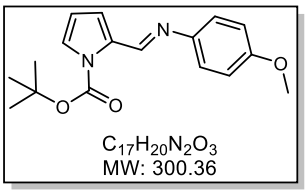
60.0 (t), 55.1 (t), 36.6 (q), 26.2 (t), 24.5 (t). **IR (cm^{-1}):** ν 2950, 2850, 1652, 1550, 1500, 1470, 1320, 1145, 750. **HRMS:** *m*/*z* calculated for $C_{13}H_{22}N_3$ $[M+H]^+$: 220.1808; found: 220.1814.

Synthesis of *tert*-butyl-(*E*)-2-((tert-butylimino)methyl)-1*H*-pyrrole-1-carboxylate (45).



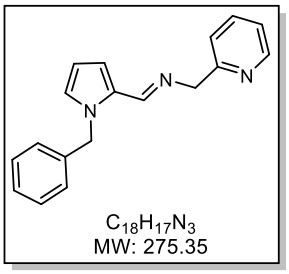
Prepared according to general procedure **GP7**, the reaction of **34** (390 mg, 2 mmol, 1 equiv.) with 2-piperidinoethylamine (231 μL, 2 mmol, 1 equiv.), in presence of $MgSO_4$ (602 mg, 5 mmol, 2.5 equiv.) and PTSA (5 mg, 0.02 mmol, 0.01 equiv.) in anhydrous DCM (4 mL) gave 473 mg of **45** (quantitative yield) as colorless oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.72 (s, 1H), 7.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.91-684 (m, 1H), 6.19 (td, *J* = 3.4, 0.6 Hz, 1H), 1.61 (s, 9H), 1.28 (s, 9H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 182.5 (s), 149.0 (d), 133.7 (s), 123.8 (d), 114.7 (d), 111.4 (d), 84.5 (s), 57.4 (s), 29.9 (q), 28.2 (q). **IR (cm^{-1}):** ν 2971, 1744, 1669, 1624, 1549, 1472, 1254, 1126, 738. **HRMS:** *m*/*z* calculated for $C_{14}H_{23}N_2O_2$ $[M+H]^+$: 251.1754; found: 251.1745.

Synthesis of *tert*-butyl-(*E*)-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrole-1-carboxylate (46).



Prepared according to general procedure **GP8**, the reaction of **34** (390 mg, 2 mmol, 1 equiv.) with *p*-anisidine (246 mg, 2 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 14 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (40 mL) gave 458 mg of **46** (76% yield) as orange oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.10 (s, 1H), 7.40 (dd, *J* = 3.2, 1.7 Hz, 1H), 7.25 (d, *J* = 9.1 Hz, 2H), 7.16 (ddd, *J* = 3.7, 1.7, 0.7 Hz, 1H), 6.93 (d, *J* = 9.1 Hz,23H), 6.30 (t, *J* = 3.4 Hz, 1H), 3.85 (s, 3H), 1.65 (s, 9H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 158.2 (s), 150.9 (d), 149.2 (s), 145.5 (s), 133.8 (s), 124.9 (d), 122.5 (d), 116.1 (d), 114.4 (d), 111.8 (d), 84.9 (s), 55.6 (q), 28.2 (q). **IR (cm^{-1}):** ν 2979, 2835, 1739, 1611, 1552, 1510, 1503, 1243, 1122, 1064, 732. **HRMS**: *m*/*z* calculated for $C_{17}H_{20}N_2NaO_3$ $[M+Na]^+$: 323.1366; found: 323.1372.

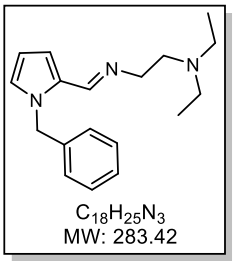
Synthesis of (*E*)-1-(1-benzyl-1*H*-pyrrol-2-yl)-*N*-(pyridin-2-ylmethyl)methanimine (47).



Prepared according to general procedure **GP7**, the reaction of **33** (370 mg, 2 mmol, 1 equiv.) with 2-picolylamine (206 μL, 2 mmol, 1 equiv.), in presence of $MgSO_4$ (602 mg, 12.5 mmol, 2.5 equiv.) and PTSA (4 mg, 0.02 mmol, 0.01 equiv.) in anhydrous DCM (4 mL) gave 550 mg of **47** (quantitative yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.50 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 8.28 (s, 1H), 7.46 (td, *J* = 7.7, 1.8 Hz 2H), 7.33-7.19 (m, 3H), 7.12-7.06 (m, 1H), 7.05-7.00 (m, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.83 (t, *J* = 2.2 Hz, 1H), 6.61 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.23 (dd, *J* = 3.8, 2.7 Hz, 1H), 5.73 (s, 2H), 4.78 (s, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 160.3 (s), 154.2 (d), 149.0 (d), 139.3 (s), 136.5 (d), 129.6 (s), 128.6 (d), 128.0 (d), 127.2 (d), 126.8 (d), 121.9 (d), 121.7 (d), 117.9 (d), 109.0 (D), 67.3 (t), 52.1 (t). **IR (cm^{-1}):**

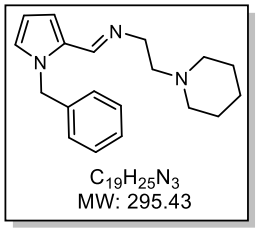
ν 3050, 1642, 1590, 1570, 1474, 1425, 1265, 728. **HRMS:** *m/z* calculated for $C_{18}H_{18}N_3$ $[M+H]^+$: 276.1495; found: 276.1503.

Synthesis of (*E*)-2-(((1-benzyl-1*H*-pyrrol-2-yl)methylene)amino)-*N*,*N*-diethylethan-1-amine (48).



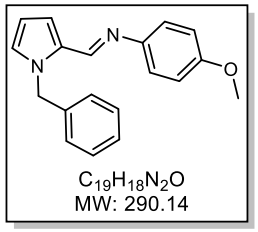
Prepared according to general procedure **GP7**, the reaction of **33** (926 mg, 5 mmol, 1 equiv.) with *N*,*N*-diethylethylendiamine (704 μL, 5 mmol, 1 equiv.), in presence of $MgSO_4$ (1.5 g, 12.5 mmol, 2.5 equiv.) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous DCM (10 mL) gave 1.42 g of **48** (quantitative yield) as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.12 (s, 1H), 7.32-7.17 (m, 3H), 7.10-7.04 (m, 2H), 6.76 (t, *J* = 2.2 Hz, 1H), 6.52 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.19 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.64 (s, 2H), 3.59-3.50 (m, 2H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.55 (q, *J* = 7.1 Hz, 4H), 1.00 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 152.9 (d), 139.1 (s), 129.8 (s), 128.6 (d), 127.3 (d), 127.2 (d), 127.1 (d), 116.6 (d), 108.8 (d), 60.2 (t), 53.9 (t), 51.7 (t), 47.6 (t), 12.0 (q). **IR (cm^{-1}):** ν 2970, 2928, 1640, 1490, 1465, 1419, 1370, 1306, 1074, 1027. **HRMS:** *m/z* calculated for $C_{18}H_{26}N_3$ $[M+H]^+$: 284.2127; found: 284.2110.

Synthesis of (*E*)-1-(1-benzyl-1*H*-pyrrol-2-yl)-*N*-(2-(piperidin-1-yl)ethyl)methanimine (49).



Prepared according to general procedure **GP7**, the reaction of **33** (926 mg, 5 mmol, 1 equiv.) with 2-piperidinoethylamine (710 μL, 5 mmol, 1 equiv.), in presence of $MgSO_4$ (1.5 g, 12.5 mmol, 2.5 equiv.) and PTSA (10 mg, 0.05 mmol, 0.01 equiv..) in anhydrous DCM (10 mL,) gave 1.47 g of **49** (quantitative yield) as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.14 (s, 1H), 7.34-7.17 (m, 3H), 7.12-7.02 (m, 2H), 6.79 (t, *J* = 2.2 Hz, 1H), 6.54 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.21 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.67 (s, 2H), 3.62 (td, *J* = 7.2, 1.3 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.43 (t, *J* = 5.3 Hz, 4H), 1.63-1.53 (m, 4H), 1.48-1.36 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 152.9 (d), 139.2 (s), 129.8 (s), 128.6 (d), 127.3 (d), 127.2 (d), 127.1 (d), 116.6 (d), 108.8 (d), 60.2 (t), 59.8 (t), 55.0 (t), 51.7 (t), 26.1 (t), 24.4 (t). **IR (cm^{-1}):** ν 2931, 2840, 1650, 1639, 1487, 1474, 1448, 1422, 1307, 1077, 721. **HRMS:** *m/z* calculated for $C_{19}H_{26}N_3$ $[M+H]^+$: 296.2121; found: 296.2128.

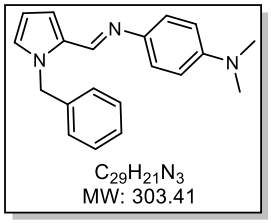
Synthesis of (*E*)-1-(1-benzyl-1*H*-pyrrol-2-yl)-*N*-(4-methoxyphenyl)methanimine (50).



Prepared according to general procedure **GP8**, the reaction of **33** (926 mg, 5 mmol, 1 equiv.) with *p*-anisidine (615 mg, 5 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (50 mL) gave 1.49 g of **50** (quantitative yield) as yellow solid. **M.p.**: 93-94 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.32 (s, 1H), 7.37-7.23 (m, 3H), 7.23-7.17 (m, 2H), 7.08 (d, *J* = 9.1 Hz, 2H), 6.93-6.86 (m, 3H), 6.73 (dd, *J* = 3.9, 1.7 Hz, 1H), 6.29 (dd, *J* = 3.9, 2.7 Hz, 1H), 5.80 (s, 2H), 3.83 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 157.7 (s), 149.2 (d), 145.8 (s), 138.9 (s), 130.3 (s), 128.7 (d), 128.4 (d),

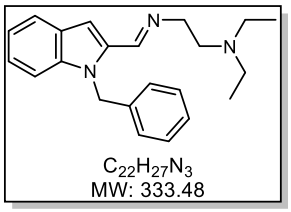
127.4 (d), 127.3 (d), 121.8 (d), 118.7 (d), 114.4 (d), 109.4 (d), 55.6 (q), 52.1 (t). **IR (cm^{-1}):** ν 2942, 2834, 1619, 1501, 1463, 1417, 1300, 1238. **HRMS**: *m/z* calculated for $C_{19}H_{19}N_2O$ $[M+H]^+$: 291.1497; found: 291.1483.

Synthesis of (*E*)-4-(((1-benzyl-1*H*-pyrrol-2-yl)methylene)amino)-*N*,*N*-dimethylaniline (51).



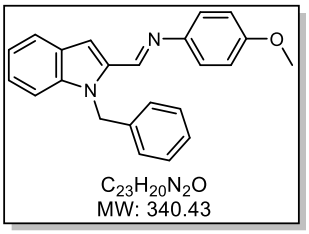
Prepared according to general procedure **GP8**, the reaction of **33** (926 mg, 5 mmol, 1 equiv.) with dimethyl-4-phenylendiamine (702 mg, 5 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (50 mL) gave 1.49 g of **51** (98% yield) as brown solid**. M.p.**: 97-98 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.33 (s, 1H), 7.31-7.22 (m, 3H), 7.19-7.17 (m, 2H), 7.08 (d, *J* = 9.0 Hz, 2H), 6.85 (t, *J* = 2.1 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.67 (dd, *J* = 3.9, 1.8 Hz, 1H), 6.24 (dd, *J* = 3.9, 2.6 Hz, 1H), 5.78 (s, 2H), 2.94 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 149.0 (s), 147.3 (d), 142.0 (s), 139.0 (s), 130.6 (s), 128.6 (d), 127.8 (d), 127.3 (d), 127.3 (d), 127.2 (d), 121.8 (d), 117.8 (d), 113.3 (d), 109.2 (d), 52.0 (t), 41.0 (q). **IR (cm^{-1}):** ν 3026, 2853, 1660, 1615, 11512, 1471, 1312, 1220, 723. **HRMS**: *m/z* calculated for $C_{20}H_{22}N_3$ $[M+H]^+$: 304.1814; found: 304.1811.

Synthesis of (*E*)-2-(((1-benzyl-1*H*-indol-2-yl)methylene)amino)-*N*,*N*-diethylethan-1-amine (52).



Prepared according to general procedure **GP7**, the reaction of **40** (1.18 g, 5 mmol, 1 equiv.) with *N*,*N*-diethylethylendiamine (704 µL, 5 mmol, 1 equiv.), in presence of $MgSO_4$ (1.5 g, 12.5 mmol, 2.5 equiv.) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous DCM (10 mL) gave 1.67 g of **52** (quantitative yield) as yellow solid. **M.p.:** 60-62 °C. **^{1}H-NMR (300 MHz, C_6D_6):** δ 8.13 (s, 1H), 7.69-7.66 (m, 1H), 7.13-7.11 (m, 3H), 7.00-6.94 (m, 5H), 6.75 (s, 1H), 5.93 (s, 2H), 3.48 (t, *J* = 6.6 Hz, 2H), 2.59 (t, *J* = 6.6 Hz, 2H), 2.38 (q, *J* = 7.1 Hz, 4H), 0.91 (t, *J* = 7.1 Hz, 6H). **^{13}C-NMR (75 MHz, C_6D_6):** δ 153.8 (d), 140.0 (s), 139.0 (s), 135.2 (s, 2C), 128.2 (d), 126.6 (d), 126.4 (d), 124.1 (d), 121.7 (d), 120.3 (d), 110.5 (d), 110.4 (d), 61.0 (t), 53.9 (t), 47.8 (t), 47.4 (t), 12.2 (q) **IR (cm^{-1}):** ν 2967, 2810, 1643, 1456, 1351. **HRMS**: *m/z* calculated for $C_{22}H_{28}N_3$ $[M+H]^+$: 334.2278; found: 334.2278.

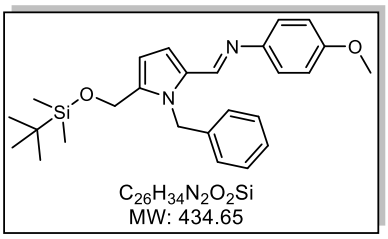
Synthesis of (*E*)-1-(1-benzyl-1*H*-indol-2-yl)-*N*-(4-methoxyphenyl)methanimine (53).



Prepared according to general procedure **GP8**, the reaction of **40** (1.18 g, 5 mmol, 1 equiv.) with *p*-anisidine (615 mg, 5 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (50 mL) gave 1.7 g of **53** (quantitative yield) as yellow solid. **M.p.:** 114-116 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.58 (s, 1H), 7.72 (d, *J* = 10.3 Hz, 1H), 7.39 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.34-7.12 (m, 9H), 7.07 (d, *J* = 0.5 Hz, 1H), 6.95-6.91 (m, 2H), 6.12 (s, 2H), 3.85 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 198.2 (s), 149.7 (d), 144.8 (s), 140.1 (s), 138.8 (s), 135.5 (s), 128.4

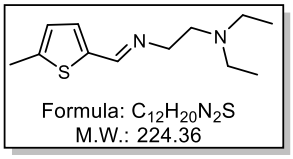
(d), 127.4 (s), 126.9 (s), 126.7 (d), 124.6 (d), 122.0 (d), 121.8 (d), 120.4 (d), 114.4 (d), 111.8 (d), 110.5 (d), 55.5 (t), 48.1 (q) **IR (cm^{-1}):** ν 3030, 2931, 2833, 1620, 1497, 1452, 1242, 1028, 828. **HRMS**: *m*/*z* calculated for $C_{23}H_{21}N_2O$ $[M+H]^+$: 341.1648; found: 341.1648.

Synthesis of (*E*)-1-(1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-pyrrol-2-yl)-*N*-(4-methoxyphenyl)methanimine (54).



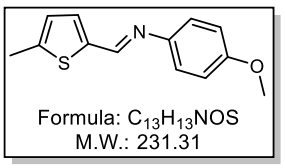
Prepared according to general procedure **GP8**, the reaction of compound **39** (1.65 g, 5 mmol, 1 equiv.) with *p*-anisidine (615 mg, 5 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (50 mL) gave 2.17 g of **54** (quantitative yield) as yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.26 (s, 1H), 7.28-7.25 (m, 2H), 7.23-7.19 (m, 1H), 7.06-7.03 (m, 2H), 7.02-6.98 (m, 2H), 6.87-6.83 (m, 2H), 6.68 (d, *J* = 3.9 Hz, 1H), 6.21 (d, *J* = 3.7 Hz, 1H), 5.93 (s, 2H), 4.60 (s, 2H), 3.79 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 157.5 (s), 149.1 (d), 145.7 (s), 139.1 (s), 138.7 (s), 131.4 (d), 128.4 (d), 126.8 (d), 126.3 (d), 121.7 (d), 117.3 (d), 114.3 (d), 109.6 (d), 57.7 (t), 55.5 (q), 48.5 (t), 25.9 (q), 18.3 (s), -5.3 (q). **IR (cm^{-1}):** ν 2951, 2855, 1620, 1505, 1453, 1241, 1031, 830. **HRMS**: *m*/*z* calculated for $C_{26}H_{35}N_2O_2Si$ $[M+H]^+$: 435.2463; found: 435.2460.

Synthesis of (*E*)-*N*,*N*-diethyl-2-(((5-methylthiophen-2-yl)methylene)amino)ethan-1-amine (55).



Prepared according to the general procedure **GP7**, the reaction of 5-methylthiophene-2-carbaldehyde (0.525 mL, 5 mmol, 1 equiv.) *N*,*N*-diethylethylendiamine (704 μL, 5 mmol, 1 equiv.), in presence of $MgSO_4$ (1.5 g, 12.5 mmol, 2.5 equiv.) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous DCM (10 mL) gave 1.09 g of **55** (97% yield) as brown oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.26 (s, 1H), 7.06 (d, J = 3.5 Hz, 1H), 6.70 (dd, J = 3.5, 1.0 Hz, 1H), 3.64 (t, J = 6.8 Hz, 2H), 2.74 (t, J = 9.4 Hz, 2H), 2.59 (q, J = 7.1 Hz, 4H), 2.47 (s, 3H), 1.03 (t, J = 7.2 Hz, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 155.0 (d), 143.9 (s), 140.4 (s) 130.6 (d), 125.6 (d), 59.5 (t), 53.5 (t), 47.6 (t), 15.8 (q), 12.0 (q). **IR (cm^{-1}):** ν 2967, 2928, 1631, 1477, 1382, 1203, 1066, 795. **HRMS**: *m*/*z* calculated for $C_{12}H_{21}N_2S$ $[M+H]^+$: 225.1420; found: 225.1421.

Synthesis of (*E*)-*N*-(4-methoxyphenyl)-1-(5-methylthiophen-2-yl)methanimine (56).



Prepared according to the general procedure **GP8**, the reaction of 5-methylthiophene-2-carbaldehyde (0.525 mL, 5 mmol, 1 equiv.) with *p*-anisidine (0.6 g, 5 mmol, 1 equiv.), in presence of molecular sieves (4 Å, 10 g) and PTSA (10 mg, 0.05 mmol, 0.01 equiv.) in anhydrous Et_2O (50 mL, 0.1 M) gave 1.15 g of **56** (quantitative yield) as yellow solid. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.47 (s, 1H), 7.24 (d, *J* = 3.5 Hz, 1H), 7.20

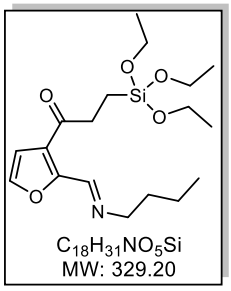
(dd, *J* = 8.9, 2.1 Hz, 2H), 6.90 (dd, *J* = 8.9, 2.1 Hz, 2H), 6.78 (d, *J* = 2.6 Hz, 1H), 3.82 (s, 3H), 2.54 (s, 3H). These data are in good agreement with those reported in literature.[192]

3.2. Preparation and characterization of acylated compounds

General procedure (GP9) for the Ruthenium catalyzed acylation of 2-aldimine-*N*/*O*-containing heterocycles derivatives

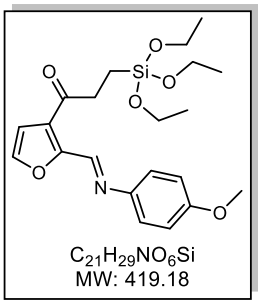
To ace pressure tube, dried under vacuum, was added the $Ru_3(CO)_{12}$ (16 mg, 0.025 mmol, 0.05 equiv.). The aldimine-pyrrole (or indole) (0.5 mmol, 1 equiv.) dissolved in PhMe (0.5 M), was then added followed by the vinyl partner (2-4 mmol, 4-8 equiv.). The solution was bubbled with CO gas for 5 min and heated at 135 °C for 16 h. The mixture was filtered over celite and washed with DCM. The volatiles were removed under reduced pressure and the crude was then purified by deactivated silica column chromatography affording the corresponding product.

Synthesis of (*E*)-1-(2-((butylimino)methyl)furan-3-yl)-3-(triethoxysilyl)propan-1-one (9a).



Prepared according to the general procedure **GP9** from the reaction of compound **9** (76 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane (421 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (70/30) to afford 49 mg of **9a** (21% yield) as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.71 (dd, *J* = 2.0, 1.2 Hz, 1H), 7.49-7.42 (m, 1H), 6.75 (dd, *J* = 10.2, 2.0 Hz, 1H), 3.84 (q, *J* = 7.0 Hz, 6H), 3.67 (t, *J* = 7.0 Hz, 2H), 2.91-2.80 (m, 2H), 1.75-1.67 (m, 2H), 1.37 (d, *J* = 7.4 Hz, 2H), 1.23 (t, *J* = 7.0 Hz, 9H), 1.02-0.95 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** 196.6 (s), 152.6 (s), 150.8 (d), 143.9 (d), 125.6 (s), 110.9 (d), 61.9 (t), 58.5 (t), 25.2 (t), 32.8 (t), 20.4 (t), 18.3 (q), 13.8 (q), 3.9 (t).**IR (cm^{-1}):** ν 2972, 2928, 1681, 1557, 1457, 1262, 1072, 934. **HRMS**: *m*/*z* calculated for $C_{18}H_{32}NO_5Si$ $[M+H]^+$: 370.2050; found: 370.2044.

Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)-3-(triethoxysilyl)propan-1-one (28a).

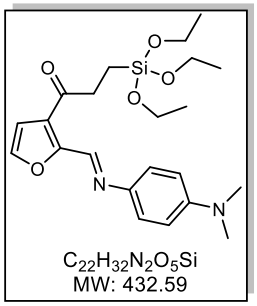


Prepared according to the general procedure **GP9** from the reaction of compound **10** (100 mg, 0.5 mmol, 1 equi..) with triethoxyvinylsilane **27a** (421 μL, 0.5 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (50/50) to afford 138 mg of **28a** (66% yield) as brown solid. **M.p.:** 62-63 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.01 (s, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 2.0 Hz, 1H), 3.85 (q, *J* = 6.8 Hz, 9H), 2.97-2.89 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 9H), 1.04-0.98 (m, 2H). **^{13}C-NMR**

[192] Qu, J.; Cao, C. -T.; Cao, C. *J. Phys. Org. Chem.* **2018**; *31*, e3799.

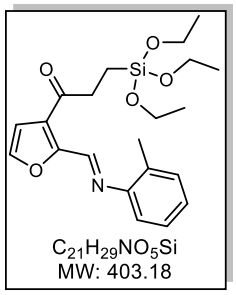
(101 MHz, $CDCl_3$): δ 196.5 (s), 159.3 (s), 153.2 (s), 146.3 (d), 144.4 (d), 143.6 (s), 126.8 (s), 123.0 (d), 114.4 (d), 111.4 (d), 58.5 (t), 55.5 (q), 35.3 (t), 18.3 (q), 3.9 (t). **IR (cm^{-1}):** ν 2973, 2893, 1679, 1550, 1505, 1490, 1245, 1070, 769. **HRMS**: *m/z* calculated for $C_{21}H_{30}NO_6Si$ $[M+H]^+$: 420.1842; found: 420.1834.

Synthesis of (*E*)-1-(2-(((4-(dimethylamino)phenyl)imino)methyl)furan-3-yl)-3-(triethoxysilyl)propan-1-one (11a).



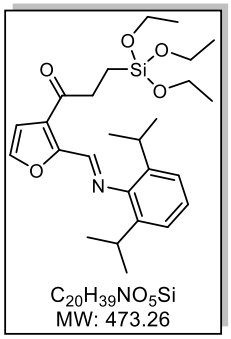
Prepared according to the general procedure **GP9** from the reaction of compound **11** (107 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/AcOEt (70/30) to afford 82 mg of **11a** (38% yield) as red solid. **M.p.:** 70-71 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.04 (s, 1H), 7.52-7.50 (m, 1H), 7.42-7.38 (m, 2H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.73-6.69 (m, 2H), 3.84 (q, *J* = 7.0 Hz, 6H), 2.99 (s, 6H), 2.93-2.89 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 9H), 1.04-0.97 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.5 (s), 153.9 (s), 150.3 (s), 143.9 (d), 143.2 (d), 139.3 (s), 125.8 (s), 123.3 (d), 112.4 (d), 111.3 (d), 58.5 (t), 40.5 (q), 35.2 (q), 18.3 (t), 3.9 (t). **IR (cm^{-1}):** ν 2974, 2889, 1677, 1572, 1577, 1306, 1103, 1076, 936. **HRMS**: *m/z* calculated for $C_{22}H_{33}N_2O_5Si$ $[M+H]^+$: 433.2159; found: 433.2148.

Synthesis of (*E*)-1-(2-((*o*-tolylimino)methyl)furan-3-yl)-3-(triethoxysilyl)propan-1-one (12a).



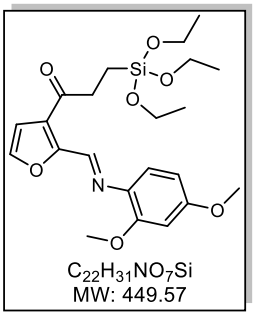
Prepared according to the general procedure **GP9** from the reaction of compound **12** (93 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/AcOEt (90/10) to afford 54 mg of **12a** (27% yield) as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.83 (s, 2H), 7.58 (d, *J* = 2.0 Hz, 2H), 7.23-7.12 (m, 7H), 6.98 (dd, *J* = 7.5, 1.2 Hz, 2H), 6.83 (d, *J* = 2.0 Hz, 2H), 3.84 (q, *J* = 7.0 Hz, 12H), 2.99-2.90 (m, 4H), 2.38 (s, 6H), 1.23 (t, *J* = 7.0 Hz, 18H), 1.04-0.97 (m, 4H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.4 (s), 152.9 (s), 150.6 (s), 148.6 (d), 144.6 (d), 132.3 (s), 130.4 (d), 127.4 (s), 126.7 (d), 126.5 (d), 117.8 (d), 111.4 (d), 58.5 (t), 35.3 (t), 18.3 (q), 17.9 (q), 3.9 (t). **IR (cm^{-1}):** ν 2973, 2925, 1683, 1554, 1390, 1262, 1101, 1075, 936. **HRMS**: *m/z* calculated for $C_{21}H_{30}NO_5Si$ $[M+H]^+$: 404.1893; found: 404.1898.

Synthesis of (*E*)-1-(2-(((2,6-diisopropylphenyl)imino)methyl)furan-3-yl)-3-(triethoxysilyl)propan-1-one (13a).



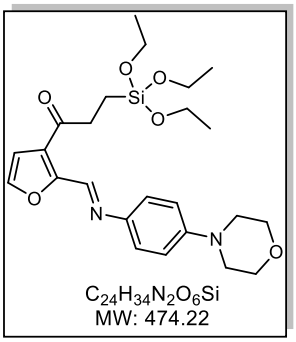
Prepared according to the general procedure **GP9** from the reaction of compound **13** (128 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/AcOEt (80/20) to afford 37 mg of **13a** (16% yield) as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.63 (s, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.17-7.09 (m, 3H), 6.86 (d, *J* = 2.0 Hz, 1H), 3.82 (q, *J* = 7.0 Hz, 6H), 3.01-2.90 (m, 4H), 1.21 (t, *J* = 7.0 Hz, 9H), 1.17 (d, *J* = 6.9 Hz, 12H), 1.01-0.95 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.1 (s), 151.1 (d), 152.1 (s), 148.8 (s), 144.8 (d), 137.5 (s), 127.6 (s), 124.6 (d), 123.0 (d), 111.3 (d), 58.5 (t), 35.3 (t), 27.9 (d), 23.7 (q), 18.3 (q), 3.8 (t). **IR (cm^{-1}):** ν 2963, 2927, 1665, 1629, 1567, 1261, 1101, 1070, 937. **HRMS**: *m/z* calculated for $C_{20}H_{40}NO_5Si$ $[M+H]^+$: 474.2676; found: 474.2669.

Synthesis of (*E*)-1-(2-(((2,4-dimethoxyphenyl)imino)methyl)furan-3-yl)-3-(triethoxysilyl)propan-1-one (14a).



Prepared according to the general procedure **GP9** from the reaction of compound **14** (107 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/AcOEt (70/30) to afford 52 mg of **14a** (23% yield) as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.08 (s, 1H), 7.55-7.51 (m, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.53 (d, *J* = 2.5 Hz, 1H), 6.49 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.89 (s, 3H), 3.88-3.81 (m, 9H), 2.96-2.87 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 9H), 1.04-0.97 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.4 (s), 160.2 (s), 154.8 (s), 153.6 (s), 146.6 (d), 144.2 (d), 133.3 (s), 126.5 (s), 121.1 (d), 111.3 (d), 104.5 (d), 99.2 (d), 58.5 (t), 55.8 (q), 55.5 (q), 35.2 (t), 18.3 (q), 3.9 (t) **IR (cm^{-1}):** ν 2973, 2927, 1679, 1572, 1489, 1262, 1208, 1103, 1076, 936. **HRMS**: *m/z* calculated for $C_{22}H_{32}NO_7Si$ $[M+H]^+$: 450.1948; found: 450.1942.

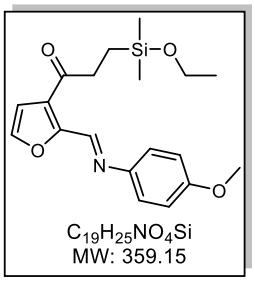
Synthesis of (*E*)-1-(2-(((4-morpholinophenyl)imino)methyl)furan-3-yl)-3-(triethoxysilyl)propan-1-one (15a).



Prepared according to the general procedure **GP9** from the reaction of compound **15** (127 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/AcOEt/ (60/40) to afford 88 mg of **15a** (37% yield) as yellow solid. **M.p.:** 77-78 °C. **^{1}H-NMR (400**

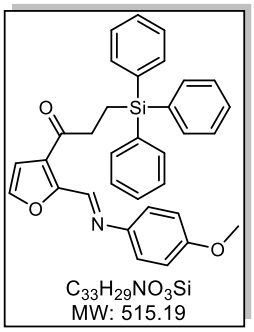
MHz, $CDCl_3$): δ 9.06 (d, *J* = 2.2 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.45-7.39 (m, 2H), 6.97-6.93 (m, 2H), 6.85 (d, *J* = 2.0 Hz, 1H), 3.91-3.84 (m, 10H), 3.24 (t, *J* = 4.8 Hz, 4H), 2.99-2.92 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 9H), 1.07-1.00 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 190.5 (s), 153.5 (s), 150.8 (s), 145.3 (d), 144.2 (d), 142.4 (s), 126.5 (s), 123.0 (d), 115.6 (d), 111.4 (d), 66.8 (t), 58.5 (t), 48.9 (t), 32.2 (t), 19.3 (q), 3.9 (t). **IR (cm^{-1}):** ν.2972, 2982, 1680, 1618, 1510, 1450, 1262, 1238, 1103, 1077, 932. **HRMS**: *m/z* calculated for $C_{24}H_{35}N_2O_6Si$ $[M+H]^+$: 475.2264; found: 475.2258.

Synthesis of (*E*)-3-(ethoxydimethylsilyl)-1-(2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)propan-1-one (28b).



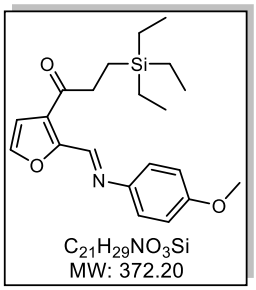
Prepared according to the general procedure **GP9** from the reaction of compound **10** (100 mg, 0.5 mmol, 1 equiv.) with dimethylethoxyvinylsilane **27b** (325 μL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (50/50) (53% yield) to afford 95 mg of the imine **28b** as yellow solid. **M.p.:** 50-52 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.99 (s, 1H), 7.54 (d, *J* = 1.7 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 1.8 Hz, 1H), 3.81 (s, 3H), 3.67 (q, *J* = 7.0 Hz, 2H), 2.95-2.76 (m, 2H), 1.18 (t, *J* = 7.0 Hz, 3H), 1.03-0.89 (m, 2H), 0.15 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** 197.0 (s), 159.3 (s), 153.3 (s), 146.3 (d), 144.4 (d), 143.6 (s), 126.8 (s), 123.0 (d), 114.4 (d), 111.3 (d), 58.3 (t), 55.5 (q), 35.6 (t), 18.5 (q), 9.9 (t), -2.1 (q). **IR (cm^{-1}):** ν 2957, 2897, 1678, 1549, 1506, 1491, 1247, 1076, 832. **HRMS**: m/z calculated for $C_{19}H_{26}NO_4Si$ $[M+H]^+$: 360.1631; found: 360.1637.

Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)-3-(triphenylsilyl)propan-1-one (28c).



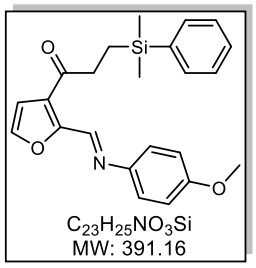
Prepared according to the general procedure **GP9** from the reaction of compound **10** (100 mg, 0.5 mmol, 1 equiv.) with triphenylvinylsilane **27c** (573 mg, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (50/50) (63% yield) to afford 162 mg of the imine **28c** as yellow solid. **M.p**.: 65-67 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.93 (s, 1H), 7.62-7.54 (m, 6H), 7.48 (d, *J* = 1.9 Hz, 1H), 7.46-7.33 (m, 11H), 6.95-6.92 (m, 2H), 6.57 (d, *J* = 2.0 Hz, 1H), 3.84 (s, 3H), 3.00-2.87 (m, 2H), 1.86-1.76 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.6 (s), 159.3 (s), 153.3 (s), 146.2 (d), 144.3 (d), 143.6 (s), 135.6 (d), 134.2 (s), 129.8 (d), 128.1 (d), 126.7 (s), 123.0 (d), 114.4 (d), 111.3 (d), 55.5 (q), 36.3 (t), 6.7 (t). **IR (cm^{-1}):** ν 3068, 2928, 1678, 1620, 1503, 1428, 1247, 1110, 702. **HRMS**: *m/z* calculated for $C_{34}H_{30}NO_3Si$ $[M+H]^+$: 516.1989; found: 516.1988.

Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)-3-(triethylsilyl)propan-1-one (28d).



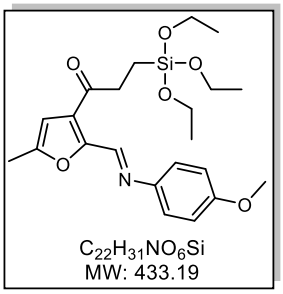
Prepared according to the general procedure **GP9** from the reaction compound **10** (100 mg, 0.5 mmol, 1 equiv.) with triethylvinylsilane **27d** (369 µL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (65/35) (65% yield) to afford 121 mg of the imine **28d** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.00 (s, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.42-7.32 (m, 2H), 6.96-6.86 (m, 2H), 6.76 (d, *J* = 1.9 Hz, 1H), 3.81 (s, 3H), 2.83-2.69 (m, 2H), 1.00-0.86 (m, 11H), 0.62-0.50 (m, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.4 (s), 159.3 (s), 153.4 (s), 146.3 (d), 144.4 (d), 143.6 (s), 126.7 (s), 123.0 (d), 114.4 (d), 111.3 (d), 55.4 (q), 36.3 (t), 7.4 (q), 5.3 (t), 3.2 (t). **IR (cm^{-1}):** ν 2952, 28752, 1678, 1549, 1506, 1247, 1034, 933. **HRMS**: m/z calculated for $C_{21}H_{30}NO_3Si$ $[M+H]^+$: 372.1989; found: 372.1990.

Synthesis of (*E*)-3-(dimethyl(phenyl)silyl)-1-(2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)propan-1-one (28e).



Prepared according to the general procedure **GP9** from the reaction of compound **10** (100 mg, 0.5 mmol, 1 equiv.) with dimethylphenylvinylsilane **27e** (368 µL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (60/40) (53% yield) to afford 95 mg of the imine **28e** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** 8.96 (s, 1H), 7.52 (s, 3H), 7.40-7.33 (m, 5H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.66 (s, 1H), 3.84 (s, 3H), 2.82-2.73 (m, 2H), 1.19-1.11 (m, 2H), 0.34 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.1 (s), 159.3 (s), 153.3 (s), 146.3 (d), 144.3 (d), 143.6 (s), 138.1 (s), 133.5 (d), 129.2 (d), 127.9 (d), 126.7 (s), 123.0 (d), 114.4 (d), 111.3 (d), 55.5 (q), 36.3 (t), 9.5 (t), -3.1 (q). **IR (cm^{-1}):** ν 2953, 1676, 1504, 1489, 1243, 1031, 829. **HRMS**: *m/z* calculated for $C_{23}H_{26}NO_3Si$ $[M+H]^+$: 392.1676; found: 392.1677.

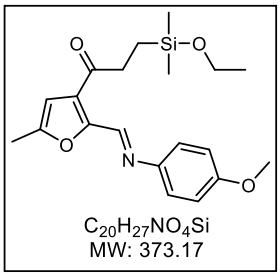
Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylfuran-3-yl)-3-(triethoxysilyl)propan-1-one (29a).



Prepared according to the general procedure **GP9** from the reaction compound **23** (107 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 µL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (60/40) (54% yield) to afford 117 mg of the imine **29a** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.93 (d, *J* = 1.7 Hz, 1H), 7.36-7.32 (m, 2H), 6.92-6.88 (m, 2H), 6.43 (d, J = 1.0 Hz, 1H), 3.86-3.81 (m, 9H), 2.92-2.84 (m, 2H), 2.43 (d, *J* = 0.9 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 9H), 1.02-0.95 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 196.7 (s), 159.0 (s), 155.4 (s), 151.9 (s), 146.6 (d), 144.1 (s), 128.2 (s), 122.9 (d), 114.3 (d), 107.9 (d), 58.5 (t),

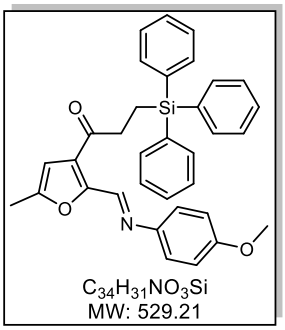
55.4 (q), 35.3 (t), 18.3 (q), 13.9 (q), 3.9 (t). **IR (cm^{-1}):** ν 2973, 2891, 1678, 1531, 1501, 1394, 1244, 1071, 936. **HRMS**: m/z calculated for $C_{22}H_{32}NO_6Si$ $[M+H]^+$: 434.1993; found: 434.1990.

Synthesis of (*E*)-3-(ethoxydimethylsilyl)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylfuran-3-yl)propan-1-one (29b).



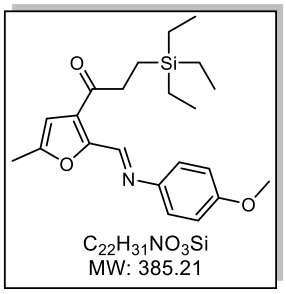
Prepared according to the general procedure **GP9** from the reaction of compound **23** (107 mg, 0.5 mmol, 1 equiv.) with dimethylethoxyvinylsilane **27b** (325 µL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (60/40) (46% yield) to afford 85 mg of the imine **29b** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.92 (s, 1H), 7.33 (d, *J* = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 6.40 (s, 1H), 3.81 (s, 3H), 3.66 (q, *J* = 7.0 Hz, 2H), 2.85-2.76 (m, 2H), 2.42 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 3H), 1.00-0.90 (m, 2H), 0.14 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.2 (s), 159.0 (s), 155.4 (s), 152.0 (s), 146.6 (d), 144.0 (s), 128.2 (s), 122.9 (s), 114.3 (d), 107.8 (d), 58.3 (t), 55.4 (q), 35.6 (t), 18.5 (q), 13.9 (q), 9.9 (t), -2.1 (q). **IR (cm^{-1}):** ν 2969, 2698, 1676, 1593, 1501, 1396, 1246, 1077, 832. **HRMS**: *m/z* calculated for $C_{20}H_{28}NO_4Si$ $[M+H]^+$: 371.1782; found: 372.1783.

Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylfuran-3-yl)-3-(triphenylsilyl)propan-1-one (29c).



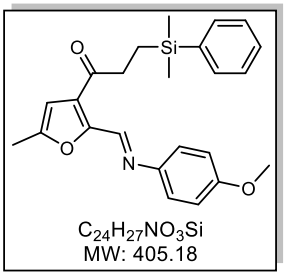
Prepared according to the general procedure **G93** from the reaction of compound **23** (107 mg, 0.5 mmol, 1 equiv.) with triphenylvinylsilane **27c** (573 mg, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (60/40) (69% yield) to afford 178 mg of the imine **29c** as yellow solid. **M.p.:** 59-61 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.85 (s, 1H), 7.58-7.55 (m, 6H), 7.42-7.37 (m, 8H), 7.37-7.35 (m, 1H), 7.34-7.31 (m, 2H), 6.94-6.90 (m, 2H), 6.17 (d, *J* = 1.0 Hz, 1H), 3.84 (s, 3H), 2.91-2.85 (m, 2H), 2.38 (d, *J* = 0.9 Hz, 3H), 1.80-1.73 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.8 (s), 159.0 (s), 155.3 (s), 152.0 (s), 146.5 (d), 144.0 (s), 135.6 (d), 134.2 (s), 129.7 (d), 128.1 (d), 122.9 (d), 114.4 (d), 107.7 (d), 55.5 (q), 36.2 (t), 13.8 (q), 6.7 (t). **IR (cm^{-1}):** ν 3068, 1677, 1532, 1501, 1427, 1396, 1246, 1110, 941. **HRMS**: *m/z* calculated for $C_{34}H_{32}NO_3Si$ $[M+H]^+$: 530.2146; found: 530.2145.

Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylfuran-3-yl)-3-(triethylsilyl)propan-1-one (29d).



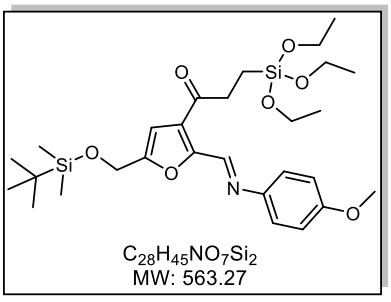
Prepared according to the general procedure **GP9** from the reaction of compound **23** (107 mg, 0.5 mmol, 1 equiv.) with triethylvinylsilane **27d** (369 μL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) (73% yield) to afford 141 mg of the imine **29d** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.83 (s, 1H), 7.29-7.19 (m, 2H), 6.86-6.74 (m, 2H), 6.28 (s, 1H), 3.71 (s, 3H), 2.72-2.54 (m, 2H), 2.33 (s, 3H), 0.91-0.74 (m, 11H), 0.46 (q, *J* = 7.9 Hz, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.7 (s), 159.0 (s), 155.4 (s), 152.1 (s), 146.7 (d), 144.1 (s), 128.2 (s), 122.9 (d), 114.4 (d), 107.8 (d), 55.4 (q), 36.3 (t), 13.9 (q), 7.4 (q), 5.3 (t), 3.7 (t). **IR (cm^{-1}):** ν 2951, 2874, 1678, 1531, 1501, 1395, 1245, 1163, 831, 794. **HRMS**: *m/z* calculated for $C_{22}H_{32}NO_3Si$ $[M+H]^+$: 386.2146; found: 386.2145.

Synthesis of (*E*)-3-(dimethyl(phenyl)silyl)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylfuran-3-yl)propan-1-one (29e).



Prepared according to the general procedure **GP9** from the reaction of compound **23** (107 mg, 0.5 mmol, 1 equiv.) with dimethylphenylvinylsilane **27e** (368 μL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (70/30) (67% yield) to afford 137 mg of the imine **29e** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** 8.89 (s, 1H), 7.58-7.45 (m, 2H), 7.40-7.30 (m, 5H), 6.95-6.90 (m, 2H), 6.27 (s, 1H), 3.83 (s, 3H), 2.77-2.68 (m, 2H), 2.42 (s, 3H), 1.17-1.09 (m, 2H), 0.33 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.3 (s), 159.0 (s), 155.4 (s), 152.0 (s), 146.6 (d), 144.1 (s), 138.2 (s), 133.6 (d), 129.2 (d), 128.1 (s), 127.9 (d), 122.9 (d), 114.4 (d), 107.8 (d), 55.5 (q), 36.3 (t), 13.9 (q), 9.5 (t), -3.1 (q). **IR (cm^{-1}):** ν 2974, 2894, 1667, 1502, 1382, 1249, 1067, 879. **HRMS**: *m/z* calculated for $C_{24}H_{28}NO_3Si$ $[M+H]^+$: 406.1833; found: 406.1832.

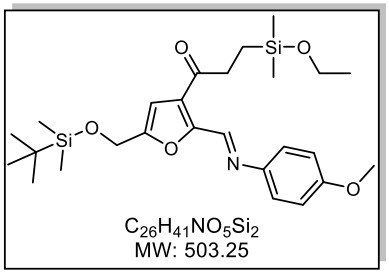
Synthesis of (*E*)-1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)-3-(triethoxysilyl)propan-1-one (30a).



Prepared according to the general procedure **GP9** from the reaction of compound **24** (173 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (90/10) to afford 151 mg of **30a** (54% yield) as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.96 (d, *J* = 0.6 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 0.7 Hz, 1H), 4.78 (s, 2H), 3.88-3.80 (m, 9H), 2.96-2.86 (m, 2H), 1.23

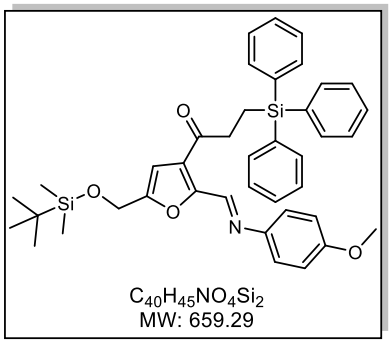
(td, *J* = 7.0, 0.8 Hz, 9H), 1.03-0.98 (m, 2H), 0.94 (d, *J* = 0.8 Hz, 9H), 0.13 (d, *J* = 0.7 Hz, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.7 (s), 159.1 (s), 157.7 (s), 152.3 (s), 146.6 (d), 143.9 (s), 127.8 (s), 122.9 (d), 114.4 (d), 107.8 (d), 58.7 (t), 58.5 (t), 55.5 (q), 35.3 (t), 25.8 (q), 18.4 (s), 18.3 (q), 3.9 (t), -5.3 (q). **IR (cm^{-1}):** ν 2972, 2929, 1681, 1532, 1502, 1247, 1102, 1078, 835. **HRMS**: *m*/*z* calculated for $C_{28}H_{46}NO_7Si_2$ $[M+H]^+$: 564.2807; found: 564.2811.

Synthesis of (*E*)-1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)-3-(ethoxydimethylsilyl)propan-1-one (30b).



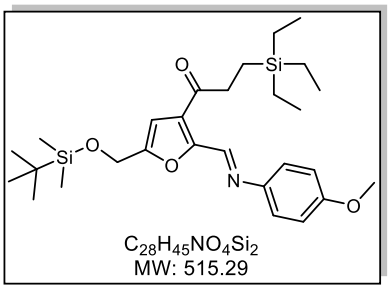
Prepared according to the general procedure **GP9** from the reaction of compound **24** (172 mg, 0.5 mmol, 1 equiv.) with dimethylethoxyvinylsilane **27b** (325 μL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (90/10) (39% yield) to afford 99 mg of the imine **30b** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.95 (s, 1H), 7.34 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.64 (s, 1H), 4.79 (s, 2H), 3.83 (s, 3H), 3.68 (q, *J* = 7.0 Hz, 2H), 2.92-2.78 (m, 2H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.02-0.92 (m, 11H), 0.16 (s, 6H), 0.13 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.3 (s), 159.1 (s), 157.7 (s), 152.4 (s), 146.6 (d), 143.9 (s), 127.7 (s), 122.9 (d), 114.4 (d), 107.7 (d), 58.7 (t), 58.4 (t), 55.5 (q), 35.6 (t), 25.8 (q), 18.5 (q), 18.4 (s), 10.0 (t), -2.1 (q), -5.3 (q). **IR (cm^{-1}):** ν 2954, 2929, 2857, 1680, 1502, 1248, 1105, 1080, 835. **HRMS**: *m*/*z* calculated for $C_{26}H_{41}NO_5Si_2$ $[M+H]^+$: 504.2596; found: 504.2594.

Synthesis of (*E*)-1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)-3-(triphenylsilyl)propan-1-one (30c).



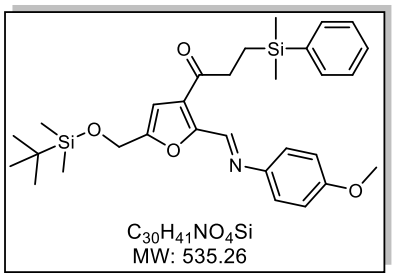
Prepared according to the general procedure **GP9** from the reaction of compound **24** (173 mg, 0.5 mmol, 1 equiv.) with triphenylvinylsilane **27c** (573 mg, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (90/10) (64% yield) to afford 129 mg of the imine **30c** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.89 (s, 1H), 7.60-7.56 (m, 6H), 7.43-7.40 (m, 5H), 7.40-7.36 (m, 4H), 7.36-7.32 (m, 2H), 6.96-6.90 (m, 2H), 6.45 (d, *J* = 0.8 Hz, 1H), 4.75 (d, *J* = 0.9 Hz, 2H), 3.84 (s, 3H), 2.97-2.88 (m, 2H), 1.83-1.76 (m, 2H), 0.94 (s, 9H), 0.13 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.8 (s), 159.1 (s), 157.6 (s), 152.4 (s), 146.5 (d), 143.9 (s), 135.6 (d), 134.2 (s), 129.7 (d), 128.0 (d), 127.7 (s), 123.0 (d), 114.4 (d), 107.7 (d), 58.6 (t), 55.5 (q), 36.6 (t), 25.9 (q), 18.4 (d), 6.7 (t), -5.3 (q). **IR (cm^{-1}):** ν 2953, 2929, 1679, 1531, 1501, 1428, 1247, 1110, 835, 701. **HRMS**: *m*/*z* calculated for $C_{40}H_{46}NO_4Si_2$ $[M+H]^+$: 660.2957; found: 660.2961.

Synthesis of (*E*)-1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)-3-(triethylsilyl)propan-1-one (30d).



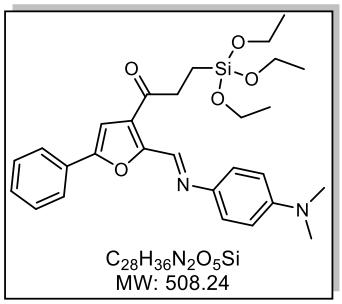
Prepared according to the general procedure **GP9** from the reaction of compound **24** (172 mg, 0.5 mmol, 1 equiv.) with triethylvinylsilane **27d** (369 μL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) (55% yield) to afford 113 mg of the imine **30d** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.96 (s, 1H), 7.38-7.32 (m, 2H), 6.95-6.88 (m, 2H), 6.62 (s, 1H), 4.79 (s, 2H), 3.83 (s, 3H), 2.83-2.70 (m, 2H), 1.00-0.89 (m, 21H), 0.57 (q, *J* = 7.9 Hz, 6H), 0.16-0.10 (m, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.8 (s), 159.1 (s), 157.7 (s), 152.5 (s), 146.6 (d), 143.9 (s), 127.7 (s), 122.9 (d), 114.4 (d), 107.7 (d), 58.7 (t), 55.5 (q), 36.3 (t), 25.8 (q), 18.4 (s), 7.4 (q), 5.6 (t), 3.2 (t), -5.3 (q). **IR (cm^{-1}):** ν 2952, 2835, 1679, 1502, 1464, 1247, 1007, 836. **HRMS**: *m/z* calculated for $C_{28}H_{46}NO_4Si_2$ $[M+H]^+$: 516.2960; found: 516.2960.

Syntesis of (*E*)-1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)-3-(dimethyl(phenyl)silyl)propan-1-one (30e).



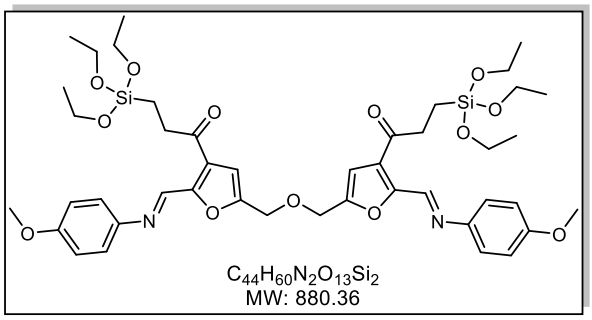
Prepared according to the general procedure **GP9** from the reaction of compound **24** (172 mg, 0.5 mmol, 1 equiv.) with dimethylphenylvinylsilane **27e** (368 μL, 2 mmol, 4 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (85/15) (63% yield) to afford 169 mg of the imine **30e** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.91 (s, 1H), 7.57-7.48 (m, 2H), 7.41-7.31 (m, 5H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.52 (s, 1H), 4.77 (s, 2H), 3.84 (s, 3H), 2.85-2.68 (m, 2H), 1.19-1.09 (m, 2H), 0.94 (s, 9H), 0.33 (s, 6H), 0.13 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.3 (s), 159.1 (s), 157.6 (s), 152.4 (s), 146.6 (d), 143.9 (s), 138.1 (s), 133.5 (d), 129.2 (d), 127.9 (d), 127.7 (s), 122.9 (d), 114.4 (d), 107.7 (d), 58.6 (t), 55.5 (q), 36.3 (t), 25.8 (q), 18.4 (s), 9.6 (t), -3.1 (q), -5.3 (q). **IR (cm^{-1}):** ν 2929, 2857, 1679, 1531, 1501, 1247, 1130, 834, 779. **HRMS**: m/z calculated for $C_{30}H_{41}NO_4Si$ $[M+H]^+$: 536.2647; found: 536.2653.

Synthesis of (*E*)-1-(2-(((4-(dimethylamino)phenyl)imino)methyl)-5-phenylfuran-3-yl)-3-(triethoxysilyl)propan-1-one (31a).



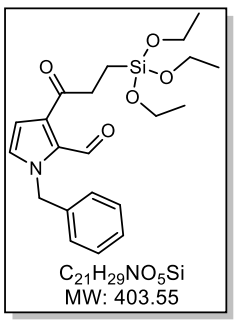
Prepared according to the general procedure **GP9** from the reaction of compound **25** (145 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (70/30) to afford 132 mg of **31a** (52% yield) as red oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.98 (s, 1H), 7.78 (d, J = 7.2 Hz, 2H), 7.39-7.28 (m, 5H), 6.96 (s, 1H), 6.66 (d, *J* = 9.0 Hz, 2H), 3.79 (q, *J* = 7.0 Hz, 6H), 2.94-2.88 (m, 8H), 1.18 (t, *J* = 7.0 Hz, 9H), 1.03-0.92 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 196.6 (s), 155.2 (s), 153.1 (s), 150.2 (s), 143.3 (d), 139.8 (s), 129.2 (s), 128.8 (d), 128.7 (d), 127.8 (s), 124.9 (d), 123.3 (d), 112.4 (d), 106.2 (d), 58.5 (t), 40.5 (q), 35.3 (t), 18.3 (q), 3.9 (t). **IR (cm^{-1}):** ν 2973, 2924, 1678, 1616, 1573, 1512, 1358, 1166, 1101, 1078, 950. **HRMS**: *m/z* calculated for $C_{28}H_{37}N_2O_5Si$ $[M+H]^+$: 509.2466; found: 509.2473.

Synthesis of 1,1'-((oxybis(methylene))bis(2-((*E*)-((4-methoxyphenyl)imino)methyl)furan-5,3-diyl))bis(3-(triethoxysilyl)propan-1-one) (32a).



Prepared according to the general procedure **GP9** from the reaction of compound **26** (222 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (842 μL, 2 mmol, 8 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/AcOEt (60/40) to afford 101 mg of **32a** (24% yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.97 (s, 2H), 7.35 (d, *J* = 8.9 Hz, 4H), 6.92 (d, *J* = 8.9 Hz, 4H), 6.82 (s, 2H), 4.69 (s, 2H), 3.87-3.80 (m, 18H), 3.02-2.79 (m, 4H), 1.22 (t, *J* = 7.0 Hz, 18H), 1.05-0.94 (m, 4H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.4 (s), 159.2 (s), 153.6 (s), 153.2 (s), 146.4 (d), 143.8 (s), 127.6 (s), 123.0 (d), 114.4 (d), 110.7 (d), 64.5 (t), 58.5 (t), 55.5 (q), 35.3 (t), 18.3 (q), 3.8 (t). **IR (cm^{-1}):** ν 2974, 2926, 1680, 1502, 1247, 1101, 1077, 809. **HRMS**: *m/z* calculated for $C_{44}H_{61}N_2O_{13}Si_2$ $[M+H]^+$: 881.3707; found: 881.3709.

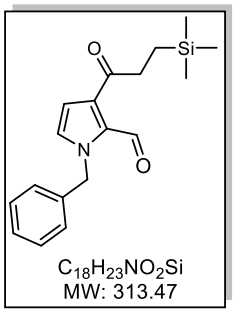
Synthesis of 1-benzyl-3-(3-(triethoxysilyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (60a).



Prepared according to general procedure **GP9** from the reaction of **48** (142 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (422 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on silica gel eluting with Pentane/Et_2O (70/30) to afford 112 mg of **60a** (56% yield) as yellow oil. **^{1}H-NMR (300**

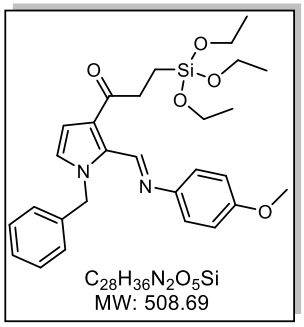
MHz, $CDCl_3$): δ 10.35 (s, 1H), 7.32-7.25 (m, 3H), 7.14 (dd, *J* = 7.5, 1.9 Hz, 2H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.64 (d, *J* = 2.8 Hz, 1H), 5.59 (s, 2H), 3.84 (q, *J* = 7.0 Hz, 6H), 2.98-2.93 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 9H), 1.04-0.98 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.7 (s), 184.3 (d), 136.8 (s), 132.0 (s), 130.9 (s), 128.9 (d), 128.8 (d), 128.1 (d), 127.6 (d), 111.5 (d), 58.7 (t), 53.2 (t), 34.5 (t), 18.5 (q), 4.4 (t). **IR (cm^{-1}):** ν 2974, 2883, 1665, 1540, 1487, 1460, 1263, 1070, 779. **HRMS:** *m/z* calculated for $C_{21}H_{29}NNaO_5Si$ $[M+Na]^+$: 426.1707; found: 426.1693.

Synthesis of 1-benzyl-3-(3-(trimethylsilyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (60f).



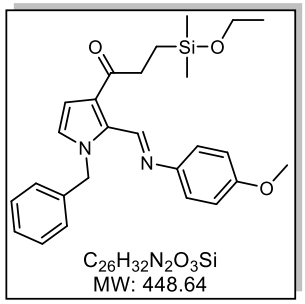
Prepared according to general procedure **GP9** from the reaction of **48** (142 mg, 0.5 mmol, 1 equiv.) with trimethylvinylsilane **27f** (300 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on silica gel eluting with Pentane/Et_2O (95/5) to afford 55.3 mg (35% yield) of **60f** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.34 (s, 1H), 7.35-7.27 (m, 3H), 7.17-7.13 (m, 2H), 6.86 (dd, *J* = 2.9, 0.9 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 5.60 (s, 2H), 2.85-2.79 (m, 2H), 0.93-0.87 (m, 2H), 0.04 (s, 9H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 198.7 (s), 184.3 (d), 136.8 (s), 132.0 (s), 131.0 (s), 129.0 (d), 128.9 (d), 128.1 (d), 127.6 (d), 111.4 (d), 53.2 (t), 35.7 (t), 11.2 (t), 1.6 (q). **IR (cm^{-1}):** ν 2952, 2925, 1658, 1522, 1487, 1454, 1423, 1368. **HRMS**: *m/z* calculated for $C_{18}H_{23}NO_2SiNa$ $[M+Na]^+$: 336.1390; found: 336.1393.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(triethoxysilyl)propan-1-one (62a).



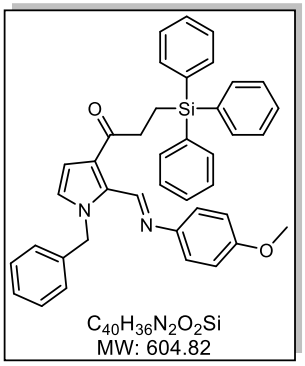
Prepared according to general procedure **GP9** from the reaction of **50** (145 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/Et_3N (75/25/1) to afford 168 mg of **62a** (66% yield) as green oil, with the presence of traces of the corresponding aldehyde. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.32 (s, 1H), 7.35-7.24 (m, 3H), 7.23-7.17 (m, 4H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 3.0 Hz, 1H), 6.68 (d, *J* = 3.0 Hz, 1H), 5.90 (s, 2H), 3.88 (q, *J* = 7.0 Hz, 6H), 3.82 (s, 3H), 3.02-2.96 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 9H), 1.09-1.03 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.9 (s), 158.4 (s), 151.1 (d), 144.9 (s), 138.1 (s), 131.5 (s), 128.7 (d), 127.5 (d), 127.4 (d), 127.2 (q), 126.7 (d), 122.4 (d), 114.4 (d), 110.9 (d), 58.6 (t), 55.6 (q), 53.1 (t), 34.1 (t), 18.4 (q), 4.5 (t). **IR (cm^{-1}):** ν 2976, 2896, 1660, 1617, 1504, 1483, 1435, 1245, 1074, 725. **HRMS:** *m/z* calculated for $C_{28}H_{36}N_2NaO_5Si$ $[M+Na]^+$: 531.2286; found: 531.2276.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(ethoxydimethylsilyl)propan-1-one (62b).



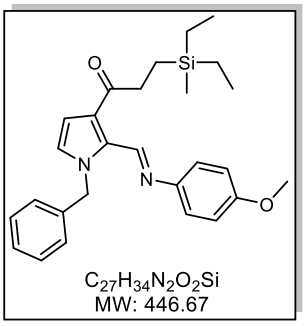
Prepared according to general procedure **GP9** from the reaction of **50** (145 mg, 0.5 mmol, 1 equiv.) with ethoxydimethylvinylsilane **27b** (325 μL, 2 mmol, 4 equiv.). The crude mixtue was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/NEt_3 (75/25/1) to afford 113 mg (51% yield) of **62b** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.28 (s, 1H), 7.33-7.25 (m, 3H), 7.19-7.14 (m, 4H), 6.87 (dd, *J* = 2.8, 0.9 Hz, 2H), 6.77 (d, *J* = 2.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 5.88 (s, 2H), 3.81 (s, 3H), 3.69 (q, *J* = 7.0 Hz, 2H), 2.91-2.85 (m, 2H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.02-0.96 (m, 2H), 0.16 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 198.4 (s), 158.3 (s), 151.0 (d), 144.8 (s), 137.9 (s), 131.5 (s), 128.6 (d), 127.5 (d), 127.3 (d), 127.1 (s), 126.6 (d), 122.3 (d), 114.3 (d), 110.8 (d), 58.3 (t), 55.5 (q), 53.1 (t), 34.4 (t), 18.6 (q), 10.5 (t), -2.1 (q). **IR (cm^{-1}):** ν 2958, 1661, 1618, 1504, 1483, 1245, 1077, 851, 721. **HRMS**: *m*/*z* calculated for $C_{26}H_{33}N_2O_3Si$ $[M+H]^+$: 449.2255; found: 449.2251.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(triphenylsilyl)propan-1-one (62c).



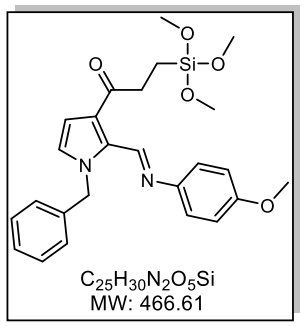
Prepared according to general procedure **GP9** from the reaction of **50** (145 mg, 0.5 mmol, 1 equiv.) with triphenylvinylsilane **27c** (573 mg, 2 mmol, 4 equiv.). The crude mixtue was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/Et_3N (75/25/1) (73% yield) to afford 234 mg of **62c** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.27 (s, 1H), 7.62-7.59 (m, 6H), 7.44-7.37 (m, 9H), 7.32-7.28 (m, 3H), 7.21-7.17 (m, 3H), 6.78 (dd, *J* = 2.8, 0.6 Hz, 2H), 6.72 (d, *J* = 2.8 Hz, 1H), 6,44 (d, *J* = 2.8 Hz, 1H), 5.89 (s, 2H), 3.84 (s, 3H), 3.02-2.96 (m, 2H), 1.85-1.79 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 198.0 (s), 158.4 (d), 151.0 (s), 144.8 (s), 138.0 (d), 135.6 (s), 134.6 (s), 131.6 (s), 129.6 (d), 128.6 (d), 128.0 (d), 127.5 (d), 127.3 (d), 127.0 (s), 126.6 (d), 122.4 (d), 114.3 (d), 110.8 (d), 55.5 (q), 53.1 (t), 35.1 (t), -7.4 (t). **IR (cm^{-1}):** ν 3067, 2834, 1659, 1616, 1482, 1454, 1396, 1244, 1109, 700. **HRMS**: *m*/*z* calculated for $C_{40}H_{37}N_2O_2Si$ $[M+H]^+$: 605.2619; found: 605.2618.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(diethyl(methyl)silyl)propan-1-one (62g).



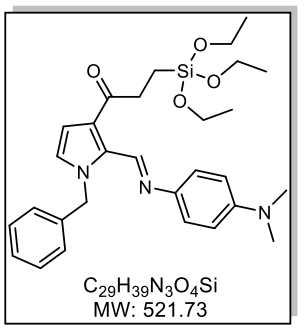
Prepared according to general procedure **GP9** from the reaction of **50** (145 mg, 0.5 mmol, 1 equiv.) with diethylmethylvinylsilane **27g** (342 μL, 2 mmol, 4 equiv.). The crude mixtue was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/Et_3N (90/10/1) to afford 154 mg (69% yield) of **62g** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.32 (s, 1H), 7.34-7.22 (m, 3H), 7.20-7.15 (m, 4H), 6.88 (dd, *J* = 2.8, 0.9 Hz, 2H), 6.78 (d, *J* = 2.9 Hz, 1H), 6.61 (d, *J* = 3.0 Hz, 1H), 5.89 (s, 2H), 3.81 (s, 3H), 2.83-2.77 (m, 2H), 0.99-0.89 (m, 8H), 0.56 (q, *J* = 7.6 Hz. 4H), 0.01 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 198.9 (s), 158.3 (s), 151.0 (d), 144.8 (d), 138.0 (s), 131.5 (s), 128.6 (d), 127.5 (d), 127.3 (d), 127.1 (s), 126.6 (d), 122.3 (d), 114.3 (d), 110.8 (d), 55.5 (q), 53.1 (t), 35.2 (t), 7.6 (t), 7.4 (q), 5.0 (t), -6.2 (q). **IR (cm^{-1}):** ν 2953, 1659, 1617, 1503, 1482, 1244, 731. **HRMS**: *m*/*z* calculated for $C_{27}H_{35}N_2O_2Si$ $[M+H]^+$: 447.2462; found: 447.2458.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(trimethoxysilyl)propan-1-one (62h).



Prepared according to general procedure **GP9** from the reaction of **50** (145 mg, 0.5 mmol, 1 equiv.) with trimethoxylvinylsilane **27h** (305 μL, 2 mmol, 4 equiv.). The crude mixtue was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (50/50) to afford 99 mg (55% yield) of **62h** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.32 (s, 1H), 7.35-7.28 (m, 4H), 7.21-7.18 (m, 3H), 6.90 (d, *J* = 9.1 Hz, 2H), 6.80 (d, *J* = 3.0 Hz, 1H), 6.68 (d, *J* = 3.0 Hz, 1H), 5.89 (s, 2H), 3.82 (s, 3H), 3.63 (s, 9H), 3.02-2.96 (m, 2H), 1.10-1.04 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 190.45 (s), 158.3 (s), 150.9 (d), 144.7 (s), 137.9 (s), 131.4 (s), 128.6 (d), 127.5 (d), 127.31 (d), 127.0 (s), 122.3 (d), 114.8 (d), 114.3 (d), 110.8 (d), 55.5 (q), 53.1 (t), 50.6 (q), 33.7 (t), 2.9 (t). **IR (cm^{-1}):** ν 3103, 2941, 2839, 1661, 1609, 1501, 1240, 1184, 1074, 805. **HRMS**: *m*/*z* calculated for $C_{25}H_{31}N_2O_5Si$ $[M+H]^+$: 467.1997; found: 467.1996.

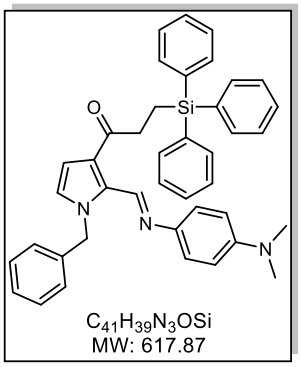
Synthesis of (*E*)-1-(1-benzyl-2-(((4-(dimethylamino)phenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(triethoxysilyl)propan-1-one (63a).



Prepared according to general procedure **GP9** from the reaction of **51** (152 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.) in toluene/DCM (9/1) mixture. The crude product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/Et_3N

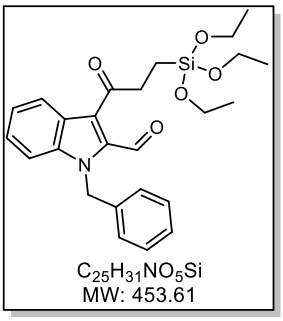
(75/25/1) to afford 160 mg of **63a** (62% yield) as green solid. **M.p.:** 78-80 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.33 (s, 1H), 7.32-7.24 (m, 3H), 7.24-7.18 (m, 4H), 6.73 (d, *J* = 3.0 Hz, 1H), 6.70 (d, *J* = 9.1 Hz, 2H), 6.63 (d, *J* = 3.0 Hz, 1H), 5.90 (s, 2H), 3.85 (q, *J* = 7.0 Hz, 6H), 2.97-2.90 (m, 8H), 1.24 (t, *J* = 7.0 Hz, 9H), 1.07-0.98 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.9 (s), 149.7 (s), 148.7 (d), 141.0 (s), 138.3 (s), 132.2 (s), 128.7 (d), 127.6 (d), 127.5 (d), 126.6 (s), 126.3 (d), 122.5 (d), 113.0 (d), 110.9 (d), 58.6 (t), 53.1 (t), 40.9 (q), 34.1 (t), 18.5 (q), 4.5 (t). **IR (cm^{-1}):** ν 2973, 2883, 1665, 1540, 1487, 1460, 1263, 1070, 779. **HRMS:** *m*/*z* calculated for $C_{29}H_{39}N_3NaO_4Si$ $[M+H]^+$: 522.2783; found: 522.2771.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-(dimethylamino)phenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(triphenylsilyl)propan-1-one (63c).



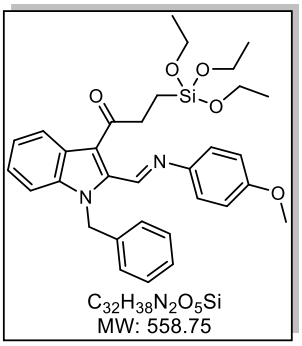
Prepared according to general procedure **GP9** from the reaction of **51** (151 mg, 0.5 mmol, 1 equiv.) with triphenylvinylsilane **27c** (575 mg, 2 mmol, 4 equiv.). The crude mixtue was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/Et_3N (75/25/1) to afford 191 mg (62% yield) of **63c** as orange solid. **M.p.:** 87-89 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.29 (s, 1H), 7.57 (dd, *J* = 7.5, 1.8 Hz, 7H), 7.43-7.33 (m, 11H), 7.28-7.16 (m, 4H), 6.72-6.66 (m, 3H), 6.38 (d, *J* = 3.0 Hz, 1H), 5.88 (s, 2H), 2.96-2.91 (m, 8H), 1.81-1.76 (m, 2H). **^{13}C-NMR** (**75 MHz, $CDCl_3$):** δ 197.9 (s), 149.6 (s), 148.5 (d), 140.7 (s), 138.1 (s), 136.6 (d), 134.6 (s), 132.2 (s), 130.0 (d), 128.5 (d), 128.1 (d), 128.0 (d), 127.4 (d), 126.3 (s), 126.1 (d), 122.4 (d), 122.8 (d), 110.6 (d), 53.0 (t), 40.8 (q), 35.1 (t), 7.4 (t). **IR (cm^{-1}):** ν 2896, 1658, 1617, 1514, 1482, 1428, 1110, 699. **HRMS**: *m*/*z* calculated for $C_{41}H_{40}N_3OSi$ $[M+H]^+$: 618.2941; found: 618.2935.

Synthesis of 1-benzyl-3-(3-(triethoxysilyl)propanoyl)-1*H*-indole-2-carbaldehyde (52a).



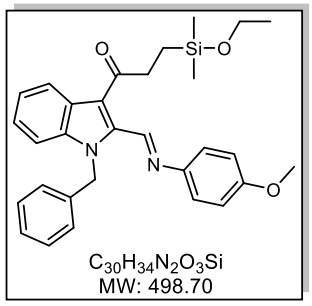
Prepared according to general procedure **GP9** from the reaction of **52** (171 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on silica gel eluting with Pentane/Et_2O (80/20) to afford 37 mg of (16% yield) **52a** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.52 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.51-7.27 (m, 4H), 7.24-7.20 (m, 2H), 7.09-7.09 (m, 2H), 5.88 (s, 2H), 3.87 (q, *J* = 7.0 Hz, 6H), 3.28-3.22 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 9H), 1.18-1.11 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 198.4 (s), 186.7 (d), 138.6 (s), 136.7 (s), 135.7 (s), 128.7 (d), 127.6 (d), 126.8 (d), 126.5 (d), 124.8 (s), 124.3 (s), 123.4 (d), 122.8 (d), 111.8 (d), 58.5 (t), 48.4 (t), 37.6 (t), 18.3 (q), 4.6 (t). **IR (cm^{-1}):** ν 2975, 2892, 1671, 1499, 1486, 1072, 744. **HRMS**: *m*/*z* calculated for $C_{25}H_{31}NNaO_5Si$ $[M+Na]^+$: 476.1864; found: 476.1863.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-indole-3-yl)-3-(triethoxysilyl)propan-1-one (64a).



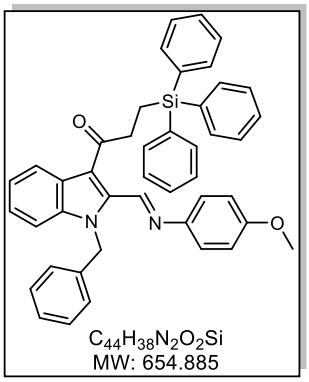
Prepared according to general procedure **GP9** from the reaction of **53** (170 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (75/25) to afford 137 mg (49% yield) of **64a** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.45 (s, 1H), 8.10-8.07 (m, 1H), 7.46-7.42 (m, 1H), 7.36-7.33 (m, 2H), 7.29-7.26 (m, 3H), 7.26-7.23 (m, 2H), 7.17-7.14 (m, 2H), 6.94-6.91 (m, 2H), 6.20 (s, 2H), 3.91 (q, *J* = 7.0 Hz, 6H), 3.85 (s, 3H), 3.31-3.25 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 9H), 1.21-1.16 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 198.3 (s), 158.9 (s), 151.7 (d), 144.1 (s), 138.7 (s), 138.4 (s), 137.7 (s), 128.5 (d), 127.1 (d), 126.6 (d), 125.2 (s), 124.7 (d), 122.7 (d), 122.6 (d), 121.8 (d), 119.7 (s), 114.3 (d), 111.4 (d), 58.5 (t), 58.4 (q), 48.7 (t), 37.3 (t), 18.3 (q), 4.6 (t). **IR (cm^{-1}):** ν 2972, 1649, 1615, 1489, 1246, 1070, 726. **HRMS**: *m/z* calculated for $C_{32}H_{39}N_2O_5Si$ $[M+H]^+$: 559.2623; found: 559.2623.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-indol-3-yl)-3-(ethoxydimethylsilyl)propan-1-one (64b).



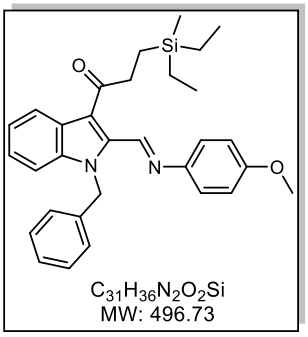
Prepared according to general procedure **GP9** from the reaction of **53** (171 mg, 0.5 mmol, 1 equiv.) with ethoxydimethylvinylsilane **27b** (325 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/NEt_3 (80/20/1) to afford 112 mg (45% yield) of **64b** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.42 (s, 1H), 8.01 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.46-7.40 (m, 1H), 7.35-7.31 (m, 2H), 7.29-7.20 (m, 5H), 7.14 (d, *J* = 6.8 Hz, 2H), 6.93-6.87 (m, 2H), 6.18 (s, 2H), 3.83 (s, 3H), 3.73 (q, *J* = 7.0 Hz, 2H), 3.24-3.16 (m, 2H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.17-1.09 (m, 2H), 0.29-0.15 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** 198.9 (s), 159.0 (s), 151.6 (d), 144.1 (s), 138.7 (s), 138.5 (s), 137.7 (s), 128.5 (d), 127.2 (d), 126.6 (d), 125.2 (s), 124.7 (d), 122.7 (d), 122.6 (d), 121.7 (d), 119.8 (s), 114.4 (d), 111.4 (d), 58.4 (t), 55.5 (q), 48.8 (t), 37.7 (t), 18.6 (q), 10.5 (t), -1.9 (q). **IR (cm^{-1}):** ν 2958, 1650, 1617, 1508, 1490, 1427, 1074, 1031, 832. **HRMS**: *m/z* calculated for $C_{30}H_{35}N_2O_3Si$ $[M+H]^+$: 499.2417; found: 499.2405.

(*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-indol-3-yl)-3-(triphenylsilyl)propan-1-one (64c).



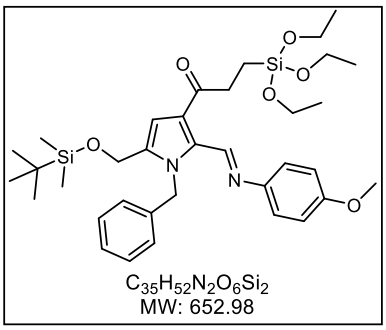
Prepared according to general procedure **GP9** from the reaction of **53** (170 mg, 0.5 mmol, 1 equiv.) with triphenylvinylsilane **27c** (573 mg, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/NEt_3 (75/25/1) to afford 275 mg (84% yield) of **64c** as yellow solid. **M.p.:** 133-135 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.31 (s, 1H), 7.62 (dd, *J* = 7.8, 1.7 Hz, 6H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.41-7.35 (m, 10H), 7.26-7.19 (m, 6H), 7.14-7.09 (m, 3H), 6.91-6.87 (m, 2H), 6.14 (s, 2H), 3.83 (s, 3H), 3.24-3.20 (m, 2H), 1.93-1.89 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 198.3 (s), 158.9 (s), 151.6 (d), 144.0 (s), 138.6 (s), 138.5 (s), 137.6 (s), 135.6 (d), 134.5 (s), 129.6 (d), 128.5 (d), 128.0 (d), 127.1 (d), 126.6 (d), 125.0 (s), 124.5 (d), 122.7 (d), 122.5 (d), 121.6 (d), 119.5 (s), 114.3 (d), 111.3 (d), 55.5 (q), 48.7 (t), 38.5 (t), 7.2 (t). **IR (cm^{-1}):** ν 3069, 1650, 1618, 1509, 1490, 1428, 1249, 1077, 702. **HRMS**: *m*/*z* calculated for $C_{44}H_{39}N_2O_2Si$ $[M+H]^+$: 655.2775; found: 655.2777.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-indol-3-yl)-3-(diethyl(methyl)silyl)propan-1-one (64g).



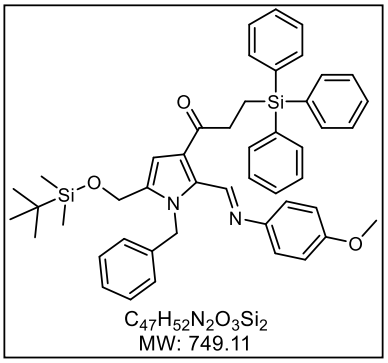
Prepared according to general procedure **GP9** from the reaction of **53** (171 mg, 0.5 mmol, 1 equiv.) with diethylmethylvinylsilane **27g** (342 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/NEt_3 (90/10/1) to afford 174 mg (70% yield) of **64g** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.41 (s, 1H), 7.96-7.93 (m, 1H), 7.44-7.42 (m, 1H), 7.33-7.31 (m, 2H), 7.27-7.20 (m, 4H), 7.15-7.12 (m, 3H), 6.92-6.88 (m, 2H), 6.18 (s, 2H), 3.82 (s, 3H), 3.12-3.09 (m, 2H), 1.06-1.02 (m, 2H), 0.98 (t, *J* = 7.9 Hz, 6H), 0.60 (q, *J* = 7.9 Hz, 4H), 0.04 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 199.3 (s), 159.0 (s), 151.7 (d), 144.1 (s), 138.7 (s), 138.5 (s), 137.7 (s), 128.5 (d), 127.2 (d), 126.6 (d), 125.2 (s), 124.6 (d), 122.7 (d), 122.6 (d), 121.6 (d) 119.8 (s), 114.4 (d), 111.5 (d), 55.5 (q), 48.8 (t), 38.4 (t), 7.4 (q), 7.3 (t), 5.0 (t), -6.1 (q). **IR (cm^{-1}):** ν 2950, 2862, 1648, 1615, 1487, 1461, 1245, 1029, 790. **HRMS**: *m*/*z* calculated for $C_{31}H_{37}N_2NaO_2Si$ $[M+H]^+$: 497.2619; found: 497.2615.

Synthesis of (*E*)-1-(1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(triethoxysilyl)propan-1-one (65a).



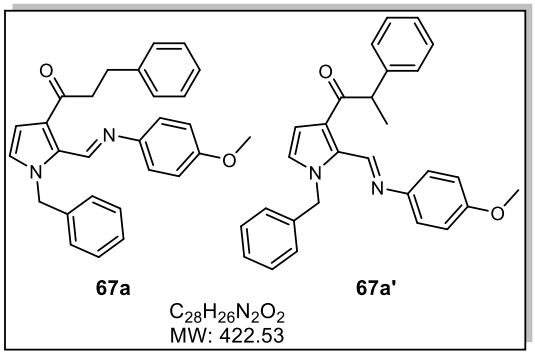
Prepared according to general procedure **GP9** from the reaction of **54** (208 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **27a** (421 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/Et_3N (90/10/1) to afford 238 mg (73% yield) of **65a** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.27 (s, 1H), 7.29-7.24 (m, 2H), 7.22-7.16 (m, 1H), 7.11 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.06-7.00 (m, 2H), 6.87-6.80 (m, 2H), 6.60 (s, 1H), 6.08 (s, 2H), 4.56 (s, 2H), 3.86 (q, *J* = 7.0 Hz, 6H), 3.79 (s, 3H), 2.99-2.93 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 9H), 1.06-1.01 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.8 (s), 158.2 (s), 151.0 (d), 144.8 (s), 138.2 (s), 137.0 (s), 132.5 (s), 128.4 (d), 126.9 (d), 126.3 (d), 125.9 (s), 122.3 (d), 114.2 (d), 110.9 (d), 58.5 (t), 57.5 (t), 55.5 (q), 49.5 (t), 34.1 (t), 25.8 (q), 18.3 (q), 18.3 (t), 4.3 (s), -5.3 (q). **IR (cm^{-1}):** ν 2926, 2885, 1663, 1617, 1506, 1481, 1389, 1245, 1071, 775. **HRMS**: *m*/*z* calculated for $C_{35}H_{53}N_2O_6Si_2$ $[M+H]^+$: 653.3442; found: 653.3434.

Synthesis of (*E*)-1-(1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(triphenylsilyl)propan-1-one (65c).



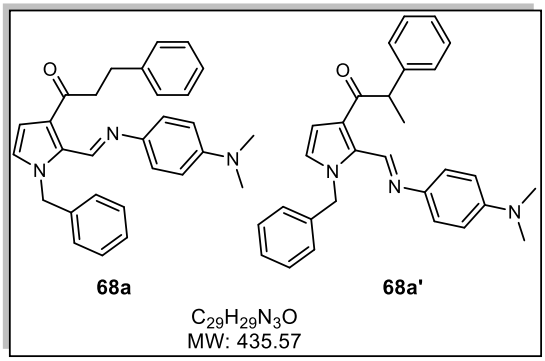
Prepared according to general procedure **GP9** from the reaction of **54** (208 mg, 0.5 mmol, 1 equiv.) with triphenylvinylsilane **27c** (573 mg, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/Et_3N (90/10/1) to afford 258 mg (69% yield) of **65c** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.23 (s, 1H), 7.60 (dd, *J* = 7.4, 1.7 Hz, 6H), 7.43-7.35 (m, 10H), 7.30-7.18 (m, 2H), 7.11 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 7.0 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.34 (s, 1H), 6.06 (s, 2H), 4.50 (s, 2H), 3.80 (s, 3H), 3.03- 2.92 (m, 2H), 1.89-1.74 (m, 2H), 0.88 (s, 9H), 0.02 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.9 (s), 158.3 (s), 151.0 (d), 144.8 (s), 138.2 (s), 137.0 (s), 135.6 (d), 134.6 (s), 132.7 (s), 129.7 (d), 129.6 (d), 128.4 (d), 128.0 (d), 128.0 (d), 126.9 (d), 126.2 (d), 125.8 (s), 122.3 (d), 114.2 (d), 110.8 (d), 57.5 (t), 55.5 (q), 49.5 (t), 35.2 (t), 25.8 (q), 18.3 (t), 7.4 (s), -5.3 (q). **IR (cm^{-1}):** ν 2953, 2928, 1662, 1617, 1506, 1482, 1246, 1111, 835, 700. **HRMS**: *m*/*z* calculated for $C_{47}H_{53}N_2O_3Si_2$ $[M+H]^+$: 749.3595; found: 749.3590.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-2-phenylpropan-1-one (67a) and **(*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-phenylpropan-1-one (67a').**



Prepared according to general procedure **GP9** from the reaction of **50** (145 mg, 0.5 mmol, 1 equiv.) with styrene **66a** (230 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) to afford 165 mg (78% yield, **67a**/**67a'**: 73/27) of **67a** and **67a'** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.34 (s, 1H, **67a'**), 9.33 (s, 1H, **67a**), 9.36-9.26 (m, 18H, 9H **67a** + 9H **67a'**), 7.23-7.17 (m, 6H, 3H **67a** + 3H **67a'**), 6.94-6.87 (m, 4H, 2H **67a** + 2H **67a'**), 6.79 (d, *J* = 2.8 Hz, 1H, **67a**), 6.71 (d, *J* = 2.8 Hz, 1H, **67a'**), 6.63 (d, *J* = 2.8 Hz, 1H, **67a**), 6.61 (d, *J* = 2.8 Hz, 1H, **67a'**), 5.97-5.79 (m, 3H, 2H **67a** + 1H **67a'**), 5.78 (d, *J* = 14.9 Hz, 1H, **67a'**), 4.53 (q, *J* = 6.9 Hz, 1H, **67a'**), 3.85 (s, 3H, **67a**), 3.84 (s, 3H, **67a'**), 3.25-3.18 (m, 2H, **67a**), 3.12-3.06 (m, 2H, **67a**), 1.54 (d, *J* = 6.9 Hz, 3H, **67a'**). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.8 (s, **67a'**), 196.6 (s, **67a**), 158.3 (s, **67a** + **67a'**), 151.1 (d, **67a'**), 151.0 (d, **67a**), 144.7 (s, **67a** + **67a'**), 142.0 (s, **67a'**), 141.5 (s, **67a**), 137.9 (s, **67a**), 137.8 (s, **67a'**), 132.3 (s, **67a'**), 132.0 (s, **67a**), 128.8 (d, **67a'**), 128.6 (d, **67a**), 128.6 (d, **67a'**), 128.5 (d, **67a** + **67a'**), 128.4 (d, **67a**), 127.8 (d, **67a'**), 127.5 (d, **67a**), 127.4 (d, **67a'**), 127.4 (d, **67a'**), 127.3 (d, **67a**), 127.2 (s, **67a** + **67a'**), 126.7 (d, **67a'**), 126.6 (d, **67a**), 126.0 (d, **67a**), 122.3 (d, **67a** + **67a'**), 114.3 (d, **67a** + **67a'**), 111.3 (d, **67a'**), 110.9 (d, **67a**), 55.5 (q, **J** + **J'**), 53.1 (t, **67a**), 53.0 (t, **67a'**), 49.8 (d, **67a'**), 42.5 (t, **67a**), 30.3 (t, **67a**), 19.1 (q, **67a'**). **IR (cm^{-1}):** ν 2930, 1657, 1615, 1502, 1481, 1243, 732, 697. **HRMS**: *m*/*z* calculated for $C_{28}H_{27}N_2O_2$ $[M+H]^+$: 423.2067; found: 423.2063.

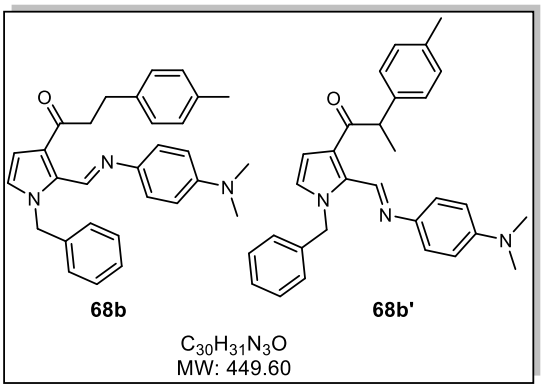
Synthesis of (*E*)-1-(1-benzyl-2-(((4-(dimethylamino)phenyl)imino)methyl)-1*H*-pyrrol-3-yl)-2-phenylpropan-1-one (68a) and **(*E*)-1-(1-benzyl-2-(((4-(dimethylamino)phenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-phenylpropan-1-one (68a').**



Prepared according to general procedure **GP9** from the reaction of **51** (151 mg, 0.5 mmol, 1 equiv.) with styrene **66a** (230 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) to afford 163 mg (75% yield, **68a**/**68a'**: 72/28) of a mixture of **68a** and **68a'** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.40 (s, 1H, **68a**), 9.39 (s, 1H, **68a'**), 7.39 7.20 (m, 24H, 12H **68a** + 12H **68a'**), 6.76-6.72 (m, 6H, 3H **68a** + 3H **68a'**), 6.68 (d, *J* = 2.8 Hz, 1H, **68a'**), 6.61 (d, *J* = 2.8 Hz, 1H, **68a'**), 6.00-5.81 (m, 3H, 2H **68a** + 1H **68a'**), 5.79 (d, *J* = 14.9 Hz, 1H,

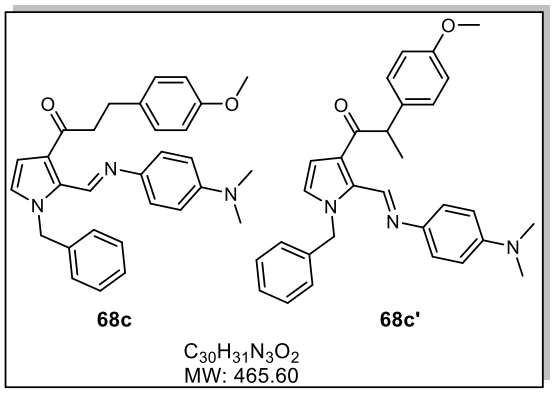
68a'), 4.53 (q, *J* = 6.9 Hz, 1H, **68a'**), 3.25-3.18 (m, 2H, **68a'**), 3.12-3.06 (m, 2H, **68a'**), 3.00 (s, 6H, **68a**), 2.99 (s, 6H, **68a'**), 1.55 (d, *J* = 6.9 Hz, 3H, **68a'**). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.7 (s, **68a'**), 197.5 (s, **68a**), 149.6 (s, **68a** + **68a'**), 148.9 (d, **68a'**), 148.4 (d, **68a**), 142.2 (s, **68a'**), 142.6 (s, **68a**), 140.7 (s, **68a'**), 140.6 (s, **68a**), 138.1 (s, **68a**), 138.0 (s, **68a'**), 132.9 (s, **68a'**), 132.2 (s, **68a**), 128.8 (d, **68a'**), 128.7 (d, **68a**), 128.6 (d, **68a**), 128.5 (d, **68a'**), 128.5 (d, **68a**), 128.4 (d, **68a**), 127.8 (d, **68a'**), 127.5 (d, **68a'**), 127.4 (d, **68a**), 126.7 (d, **68a'**), 126.5 (s, **68a** + **68a'**), 126.2 (d, **68a** + **68a'**), 126.1 (d, **68a'**), 126.0 (d, **68a**), , 122.4 (d, **68a** + **68a'**), 112.8 (d, **68a** + **68a'**), 111.2 (d, **68a'**), 110.7 (d, **68a**), 53.0 (t, **68a**), 52.9 (t, **68a'**), 49.7 (d, **68a'**), 42.5 (t, **68a**), 40.8 (q, **68a** + **68a'**), 30.4 (t, **68a**), 19.2 (q, **68a'**). **IR (cm^{-1}):** ν 2929, 1656, 1616, 1481, 1354, 907, 723. **HRMS**: *m/z* calculated for $C_{29}H_{30}N_3O$ $[M+H]^+$: 436.2383; found: 436.2378.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-(dimethylamino)phenyl)imino)methyl)-1*H*-pyrrol-3-yl)-2-(*p*-tolyl)propan-1-one (68b) and **(*E*)-1-(1-benzyl-2-(((4-(dimethylamino)phenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(*p*-tolyl)propan-1-one (68b').**



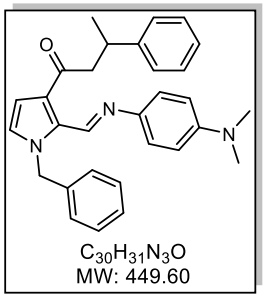
Prepared according to general procedure **GP9** from the reaction of compound **51** (152 mg, 0.5 mmol, 1 equiv.) with 4-methylstyrene **66b** (528 μL, 4 mmol, 8 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (75/25) to afford 161 mg (71% yield, **68b**/**68b'**: 69/31) of **68b** and **68b'** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.39 (s, 1H, **68b'**), 9.38 (s, 1H, **68b**), 7-35-7.13 (m, 22H, 11H **68b** + 11H **68b'**), 6.76-6.72 (m, 5H, 2H **68b** + 3H **68b'**), 6.67 (d, *J* = 3.0 Hz, 1H, **68b'**), 6.61 (d, *J* = 2.9 Hz, 2H, **68b**), 6.00-5.93 (m, 3H, 2H **68b** + 1H **68b'**), 5.78 (d, *J* = 14.9 Hz, 1H, **68b'**), 4.49 (q, *J* = 6.6 Hz, 1H, **68b'**), 3.21-3.16 (m, 2H, **68b**), 3.06-3.03 (m, 2H, **68b**), 3.00 (s, 6H, **68b**), 2.99 (s, 6H, **68b'**), 2.36 (s, 3H, **68b**), 2.33 (s, 3H, **68b'**), 1.52 (d, *J* = 6.9 Hz, 3H, **68b'**). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.9 (s, **68b'**), 196.6 (s, **68b**), 149.6 (s, **68b**), 149.6 (s, **68b'**), 148.7 (d, **68b'**), 148.5 (d, **68b**), 140.7 (s, **68b'**), 140.7 (s, **68b**), 139.1 (s, **68b'**), 138.5 (s, **68b**), 138.1 (s, **68b**), 138.0 (s, **68b'**), 136.2 (s, **68b'**), 135.5 (s, **68b**), 132.9 (s, **68b'**), 132.2 (s, **68b**), 129.5 (d, **68b'**), 129.2 (d, **68b**), 128.6 (d, **68b**), 128.5 (d, **68b'**), 128.3 (d, **68b** + **68b'**), 127.6 (d, **68b** + **68b'**), 127.5 (d, **68b** + **68b'**), 127.4 (d, **68b** + **68b'**), 126.5 (s, **68b** + **68b'**), 122.4 (d, **68b** + **68b'**), 112.8 (d, **68b** + **68b'**), 111.2 (d, **68b'**), 110.7 (d, **68b**), 53.0 (t, **68b**), 52.9 (t, **68b'**), 49.2 (d, **68b'**), 42.7 (t, **68b**), 40.7 (q, **68b** + **68b'**), 29.9 (t, **68b**), 21.1 (q, **68b**), 21.0 (q, **68b'**), 19.2 (q, **68b'**). **IR (cm^{-1}):** ν 3053, 2983, 1656, 1617, 1513, 1481, 1264, 730, 701. **HRMS**: *m/z* calculated for $C_{30}H_{32}N_3O$ $[M+H]^+$: 450.2540; found: 450.2538.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-(dimethylamino)phenyl)imino)methyl)-1*H*-pyrrol-3-yl)-2-(4-methoxyphenyl)propan-1-one (68c) and **(*E*)-1-(1-benzyl-2-(((4-(dimethylamino)phenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(4-methoxyphenyl)propan-1-one (68c')**.



Prepared according to general procedure **GP9** from the reaction of compound **51** (152 mg, 0.5 mmol, 1 equiv.) with 4-methoxystyrene **66c** (536 μL, 4 mmol, 8 equiv.). The imine was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (70/30) to afford 153 mg (66% yield, **68c**/**68c'**: 51/49) of **68c** and **68c'** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.42 (s, 1H, **68c'**), 9.40 (s, 1H, **68c**), 7-36-7.21 (m, 18H, 9H **68c** + 9H **68c'**), 6.91-6.88 (m, 4H, 2H **68c** + 2H **68c'**), 6.78-6.73 (m, 5H, 2H **68c** + 3H **68c'**), 6.69 (d, *J* = 3.0 Hz, 1H, **68c'**), 6.63 (t, *J* = 2.8 Hz, 2H **68c**), 6.00-5.94 (m, 3H, 2H **68c** + 1H **68c'**), 5.80 (d, *J* = 14.9 Hz, 1H, **68c'**), 4.50 (q, *J* = 6.6 Hz, 1H, **68c'**), 3.82 (s, 3H, **68c**), 3.80 (s, 3H, **68c'**), 3.22-3.17 (m, 2H, **68c**), 3.07-3.00 (m, 14H, 8H **68c** + 6H **68c'**), 1.54 (d, *J* = 6.9 Hz, 3H, **68c'**). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 198.0 (s, **68c'**), 196.7 (s, **68c**), 158.4 (s, **68c**), 157.9 (s, **68c'**), 149.6 (s, **68c** + **68c'**), 148.6 (d, **68c'**), 148.5 (d, **68c**), 140.7 (s, **68c** + **68c'**), 138.1 (s, **68c**), 138.0 (s, **68c'**), 134.3 (s, **68c**), 133.7 (s, **68c'**), 133.0 (s, **68c**), 132.2 (s, **68c'**), 129.4 (d, **68c**), 128.8 (d, **68c'**), 128.6 (d, **68c**), 128.5 (d, **68c'**), 127.5 (d, **68c'**), 127.4 (d, 2C **68c** + **68c'**), 126.6 (s, **68c**), 126.2 (d, **68c**), 126.2 (s, **68c'**), 126.1 (d, **68c'**), 122.5 (d, **68c** + **68c'**), 114.2 (d, **68c'**), 113.9 (d, **68c**), 112.8 (d, **68c** + **68c'**), 111.2 (d, **68c**), 110.8 (d, **68c'**), 55.3 (q, **68c**), 55.2 (q, **68c'**), 53.0 (q, **68c** + **68c'**), 48.8 (d, **68c'**), 42.8 (t, **68c**), 40.7 (q, **68c** + **68c'**), 29.6 (t, **68c**), 19.2 (q, **68c'**). **IR (cm^{-1}):** ν 2931, 1655, 1615, 1511, 1480, 1246, 906, 820. **HRMS**: *m/z* calculated for $C_{30}H_{32}N_3O_2$ $[M+H]^+$: 466.2489; found: 466.2488.

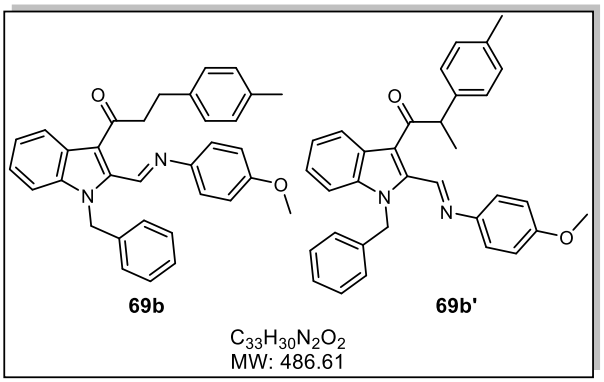
Synthesis of (*E*)-1-(1-benzyl-2-(((4-(dimethylamino)phenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-phenylbutan-1-one (68d).



Prepared according to general procedure **GP9** from the reaction of **51** (151 mg, 0.5 mmol, 1 equiv.) with prop-1-en-2-ylbenzene (520 μL, 2 mmol, 8 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (90/10) to afford 68 mg of **68d** and of the corresponding aldehyde (ratio 4/1) (31 % yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.41 (s, 1H), 7.47-7.26 (m, 12H), 6.85-6.81 (m, 2H), 6.69 (d, *J* = 3.0 Hz, 1H), 6.01-5.69 (m, 2H), 3.68-3.53 (m, 1H), 3.27 (dd, *J* = 14.7, 6.7 Hz, 1H), 3.18 (dd, *J* = 14.6, 6.7 Hz, 1H), 3.08 (s, 5H), 1.46 (d, *J* = 6.9 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 196.4 (s), 149.6 (s), 148.5 (d), 146.9 (s), 140.7 (s), 138.1 (s), 132.2 (s), 128.8 (d), 128.5 (d), 128.4 (d), 127.4 (d), 127.4 (d), 127.0 (d), 126.9 (d), 126.1 (s), 122.4 (d), 111.8 (d),

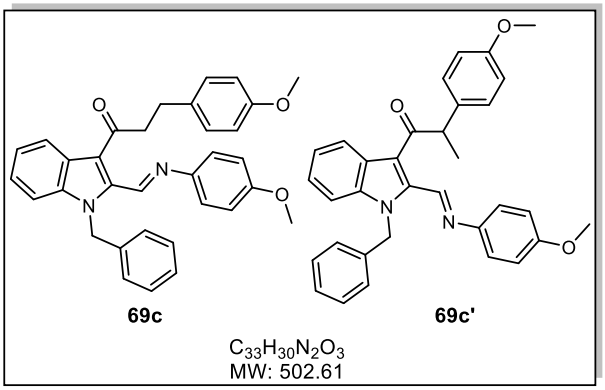
110.8 (d), 53.0 (t), 49.2 (t), 40.7 (q), 25.8 (d), 21.8 (q). **IR (cm^{-1}):** ν 2925, 1670, 1517, 1398, 1343, 1076, 817, 700. **HRMS**: *m/z* calculated for $C_{30}H_{31}N_3O$ [M+H]$^+$: 450.2540; found: 450.2540.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-indol-3-yl)-2-(*p*-tolyl)propan-1-one (69b) and **(*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-indol-3-yl)-3-(*p*-tolyl)propan-1-one (69b').**



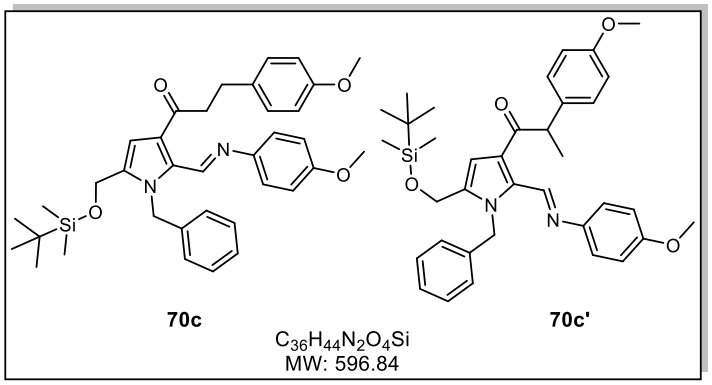
Prepared according to general procedure **GP9** from the reaction of **53** (171 mg, 0.5 mmol, 1 equiv.) with 4-methylstyrene **66b** (528 μL, 4 mmol, 8 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/NEt_3 (80/20/1) to afford 153 mg (63% yield, **69b**/**69b'**: 87/13) of **69b** and **69b'** as yellow solid. **M.p.:** 126-128 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.37 (d, *J* = 1.8 Hz, 1H, **69b**), 9.17 (d, *J* = 2.0 Hz, 1H, **69b'**), 8.04-8.01 (m, 1H, **69b'**), 7.96 (d, *J* = 8.0 Hz, 1H, **69b**), 7.42 (d, *J* = 7.8 Hz, 1H, **69b**), 7.38-7.19 (m, 19H, 9H **69b** + 10H **69b'**), 7.14-7.07 (m, 8H, 4H **69b** + 4H **69b'**), 6.92-6.88 (m, 4H, 2H **69b** + 2H **69b'**), 6.18 (s, 2H, **69b**), 6.11 (d, *J* = 15.4 Hz, 2H, **69b'**), 4.82 (q, *J* = 13.7 Hz, 1H, **69b'**), 3.83 (s, 3H, **69b**), 3.83 (s, 3H, **69b'**), 3.49-3.45 (m, 2H, **69b**), 3.15- 3.11 (m, 2H, **69b**), 2.33 (s, 3H, **69b**), 2.29 (s, 3H, **69b'**), 1.64 (d, *J* = 6.9 Hz, 3H, **69b'**). **^{13}C-NMR (101 MHz, $CDCl_3$):** 197.2 (s, **69b**), 197.1 (s, **69b'**), 159.0 (s, **69b**), 158.9 (s, **69b'**), 151.5 (d, **69b**), 151.1 (d, **69b'**), 144.1 (s, **69b** + **69b'**), 138.7 (s, **69b**), 138.7 (s, **69b'**), 138.6 (s, **69b'**), 138.6 (s, **69b**), 138.3 (s, **69b**), 138.1 (s, **69b'**), 137.7 (s, **69b'**), 137.6 (s, **69b**), 135.6 (s, **69b**), 135.5 (s, **69b'**), 129.4 (d, **69b'**), 129.2 (d, **69b**), 128.5 (d, **69b**), 128.5 (d, **69b'**), 128.4 (d, **68b**), 127.8 (d, **69b'**), 127.2 (d, **69b**), 127.1 (d, **69b'**), 126.6 (d, **69b**), 126.6 (s, **69b'**), 125.2 (s, **69b** + **69b'**), 124.7 (d, **69b** + **69b'**), 121.7 (d, **69b** + **69b'**), 121.7 (d, **69b'**), 121.7 (d, **69b**), 121.6 (d, **69b**), 121.5 (d, **69b'**) 119.9 (s, **69b** + **69b'**) 114.4 (d, **69b**), 114.3 (d, **69b'**), 111.4 (d, **69b**), 111.3 (d, **69b'**) 55.5 (q, **69b** + **69b'**), 51.0 (d, **69b'**), 48.8 (t, **69b**), 48.7 (t, **69b'**), 45.8 (t, **69b**), 29.9 (t, **69b**), 21.0 (q, **69b** + **69b'**), 19.5 (q, **69b'**). **IR (cm^{-1}):** ν 2936, 1647, 1615, 1507, 1489, 1247, 1031, 832. **HRMS**: *m/z* calculated for $C_{33}H_{30}N_2NaO_2$ [M+Na]$^+$: 509.2199; found: 509.2197.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-indol-3-yl)-2-(4-methoxyphenyl)propan-1-one (69c) and **(*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-indol-3-yl)-3-(4-methoxyphenyl)propan-1-one (69c').**



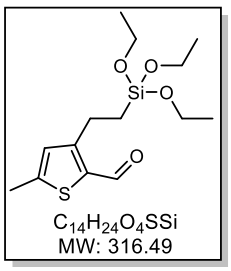
Prepared according to general procedure **GP9** from the reaction of **53** (171 mg, 0.5 mmol, 1 equiv.) with 4-methoxystyrene **66c** (536 μL, 4 mmol, 8 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O/NEt_3 (75/25/1) to afford 152 mg (60% yield, **69c** /**69c'**: 88/12) of **69c** and **69c'** as yellow solid. **M.p.:** 111-112 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.41 (s, 1H, **69c**), 9.20 (s, 1H, **69c'**), 8.07-8.05 (m, 1H, **69c'**), 8.00 (dd, *J* = 7.0, 1.5 Hz, 1H, **69c**), 7.46-7.44 (m, 1H, **69c**), 7.41-7.22 (m, 17H, 8H **69c** + 9H **69c'**), 7.18-7.16 (m, 2H, **69c**), 7.13-7.10 (m, 2H, **69c'**), 6.98-6.85 (m, 10H, 5H **69c** + 5H **69c'**), 6.80 (dd, *J* = 6.6, 2.1 Hz, 1H, **69c'**), 6.20 (s, 2H, **69c**), 6.14 (d, *J* = 11.7 Hz, 2H, **69c'**), 4.84 (q, *J* = 7.0 Hz, 1H, **69c'**), 3.86 (s, 3H, **69c**), 3.85 (s, 3H, **69c'**), 3.82 (s, 3H, **69c**), 3.78 (s, 3H, **69c'**), 3.51-3.47 (m, 2H, **69c**), 3.17-3.14 (m, 2H, **69c**), 1.68 (d, *J* = 6.9 Hz, 3H, **69c'**). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 199.5 (s, **69c'**), 197.2 (s, **69c**), 159.0 (s, **69c**), 158.9 (s, **69c'**), 158.4 (s, **69c'**), 158.0 (s, **69c**), 151.5 (d, **69c**), 151.0 (d, **69c'**), 144.1 (s, **69c** + **69c'**), 138.7 (s, **69c**), 138.7 (s, **69c'**), 138.6 (s, **69c'**), 138.5 (s, **69c**), 137.6 (s, **69c** + **69c'**), 133.4 (s, **69c**), 133.2 (s, **69c'**), 129.4 (d, **69c**), 129.0 (d, **69c'**), 128.6 (d, **69c**), 128.5 (d, **69c'**), 127.2 (d, **69c**), 127.2 (d, **69c'**), 126.6 (d, **69c**), 126.6 (d, **69c'**), 125.2 (s, **69c**), 125.0 (s, **69c'**), 124.7 (d, **69c** + **69c'**), 122.7 (d, **69c** + **69c'**), 122.7 (d, **69c**), 122.6 (d, **69c'**), 121.6 (d, **69c**), 121.5 (d, **69c'**), 120.5 (s, **69c'**), 119.9 (s, **69c**), 114.4 (d, **69c**), 114.4 (d, **69c'**), 114.1 (d, **69c'**), 114.0 (d, **69c**), 111.5 (d, **69c**), 111.3 (d, **69c'**), 55.5 (q, **69c** + **69c'**), 55.2 (q, **69c**), 55.2 (q, **69c'**), 50.6 (d, **69c'**), 48.8 (t, **69c**), 48.7 (t, **69c'**), 45.9 (t, **69c**), 29.5 (t, **69c**), 19.5 (q, **69c'**). **IR (cm^{-1}):** ν 2931, 2834, 1647, 1612, 1510, 1462, 1246, 1033, 831. **HRMS**: *m/z* calculated for $C_{33}H_{31}N_2O_3$ $[M+H]^+$: 503.2329; found: 503.2329.

Synthesis of (*E*)-1-(1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-2-(4-methoxyphenyl)propan-1-one (70c) and **(*E*)-1-(1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-(4-methoxyphenyl)propan-1-one (70c').**



Prepared according to general procedure **GP9** from the reaction of **54** (208 mg, 0.5 mmol, 1 equiv.) with 4-methoxystyrene **66c** (536 μL, 4 mmol, 8 equiv.). The crude mixture was purified by flash column chromatography on silica gel eluting with Pentane/Et_2O/NEt_3 (85/15/1) to afford 167 mg (56% yield, **70c**/**70c'**: 64/36) of **70c** and **70c'** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.28 (s, 1H, **70c'**), 9.26 (s, 1H, **70c**), 7.29-7.21 (m, 6H, 3H **70c** + 3H **70c'**), 7.20-7.14 (m, 4H, 2H **70c** + 2H **70c'**), 7.13-7.07 (m, 4H, 2H **70c** + 2H **70c'**), 7.03-6.98 (m, 4H, 2H **70c** + 2H **70c'**), 6.87-6.81 (m, 8H, 4H **70c** + 4H **70c'**), 6.54 (s, 1H, **70c**), 6.53 (s, 1H, **70c'**), 6.10-6.06 (m, 3H, 2H **70c** + 1H **70c'**), 5.94 (d, *J* = 14.2 Hz, 1H, **70c'**), 4.53 (s, 2H, **70c**), 4.49 (s, 2H, **70c'**), 4.44 (q, *J* = 6.9 Hz, 1H, **70c'**), 3.80 (s, 3H, **70c**), 3.79 (s, 3H, **70c**), 3.78 (s, 3H, **70c'**), 3.77 (s, 3H, **70c'**), 3.18-3.12 (m, 2H, **70c**), 3.02-2.95 (m, 2H, **70c**), 1.49 (d, *J* = 6.9 Hz, 3H, **70c'**), 0.88 (s, 9H, **70c**), 0.86 (s, 9H, **70c**), 0.02 (s, 6H, **70c**), -0.01 (s, 3H, **70c'**), -0.04 (s, 3H, **70c'**). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 198.1 (s, **70c'**), 196.7 (s, **70c**), 158.4 (s, **70c'**), 158.3 (s, **70c**), 158.2 (s, **70c'**), 157.9 (s, **70c**), 151.0 (d, **70c'**), 150.9 (s, **70c**), 144.8 (s, **70c** + **70c'**), 138.1 (s, **70c**), 138.1 (s, **70c'**), 137.1 (s, **70c**), 137.0 (s, **70c'**), 134.2 (s, **70c'**), 133.6 (s, **70c'**), 133.4 (s, **70c'**), 132.7 (s, **70c**), 129.3 (d, **70c**), 128.8 (d, **70c'**), 128.4 (d, **70c**), 128.4 (d, **70c'**), 126.9 (d, **70c**), 126.8 (d, **70c'**), 126.3 (d, **70c'**), 126.3 (d, **70c**), 126.1 (s, **70c**), 125.7 (s, **70c'**), 122.3 (d, **70c'**), 122.3 (d, **70c**), 114.2 (d, **70c'**), 114.2 (d, **70c'**), 113.9 (d, **70c**), 113.7 (d, **70c'**), 111.3 (d, **70c'**), 110.9 (d, **70c**), 57.5. (t, **70c'**), 57.5 (t, **70c**), 55.5 (q, **70c** + **70c'**), 55.3 (q, **70c**), 55.2 (q, **70c'**), 49.6 (t, **70c**), 49.5 (t, **70c'**), 49.0 (d, **70c'**), 42.9 (t, **70c**), 29.5 (t, **70c**), 25.8 (q, **70c**), 25.8 (q, **70c'**), 19.2 (q, **U'**), 18.3 (s, **70c**), 18.2 (s, **70c'**), -5.33 (q, **70c**), -5.33 (q, **70c'**). **IR (cm^{-1}):** ν 2952, 2930, 1659, 1613, 1507, 1453, 1242, 1162, 1003, 831. **HRMS**: *m*/*z* calculated for $C_{36}H_{45}N_2O_4Si$ $[M+H]^+$: 597.3149; found: 597.3141.

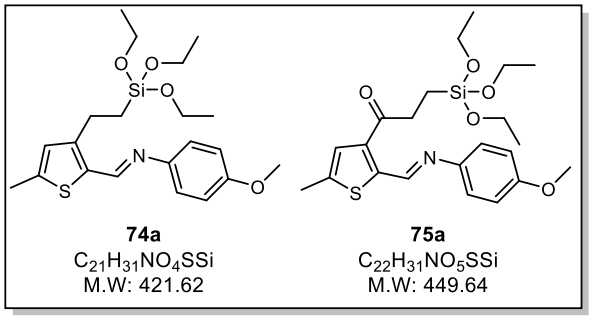
Synthesis of 5-methyl-3-(2-(triethoxysilyl)ethyl)thiophene-2-carbaldehyde (73).



Prepared according to general procedure **GP3** from the reaction of **71** (115 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **28a** (422 μL, 2 mmol, 4 equiv.), without emplying CO atmosphere. The crude product was purified by flash column chromatography on silica gel eluting with Pentane/Et_2O (90/10) to afford 51 mg of **73** (32% yield) as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.94 (s, 1H), 6.73 (s, 1H), 3.81 (q, *J* = 7.0 Hz, 6H), 3.06-2.88 (m, 2H), 2.50 (d, *J* = 0.6 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 9H), 1.02-

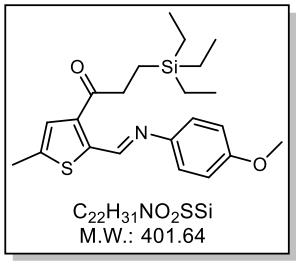
0.95 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 181.6 (d), 155.4 (s), 150.6 (s), 135.2 (s), 129.3 (d) , 58.5 (t), 21.8 (t), 18.3 (q), 16.2 (q), 12.9 (t). **IR (cm^{-1}):** ν 2974, 2926, 1655, 1444, 1101, 1076, 959. **HRMS:** *m/z* calculated for $C_{14}H_{24}NaO_4SSi$ $[M+Na]^+$: 339.1057; found: 339.1062.

Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylthiophen-3-yl)-3-(triethoxysilyl)propan-1-one (74a) and **(*E*)-*N*-(4-methoxyphenyl)-1-(5-methyl-3-(2-(triethoxysilyl)ethyl)thiophen-2-yl)methanimine (75a).**



Prepared according to general procedure **GP3** from the reaction of **72** (115 mg, 0.5 mmol, 1 equiv.) with triethoxyvinylsilane **28a** (422 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on silica gel eluting with Pentane/Et_2O (90/10) to afford 42 mg of **74a** (2% yield) as yellow oil and 141 mg of **75a** (63% yield) as yellow oil. **(74) ^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.57 (s, 1H), 7.22-7.15 (m, 2H), 6.92-6.87 (m, 2H), 6.66 (d, *J* = 0.8 Hz, 1H), 3.85-3.77 (m, 9H), 2.91-2.81 (m, 2H), 2.47 (d, *J* = 0.8 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 9H), 1.03-0.92 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 157.9 (s), 150.1 (d), 149.4 (s), 145.3 (s), 144.4 (s), 133.9 (s), 128.2 (d), 122.2 (d), 114.3 (d), 58.5 (t), 55.5 (q), 21.7 (t), 18.3 (q), 15.9 (q), 12.7 (t). **IR** (cm^{-1}): ν 2971, 2981, 1611, 1505, 1245, 1076, 958, 799. **HRMS:** *m/z* calculated for $C_{21}H_{32}NO_5SSi$ $[M+H]^+$: 421.1748; found: 421.1749. **(75) ^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.29 (s, 1H), 7.27 (dd, *J* = 8.9, 2.0 Hz, 2H), 7.13 (s, 1H), 6.89 (dd, *J* = 8.9, 2.0 Hz, 2H), 3.87-3.81 (m, 9H), 2.99-2.90 (m, 2H), 2.51 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 9H), 1.04-0.98 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.9 (s), 158.7 (s), 151.8 (d), 146.2 (s), 144.0 (s), 143.3 (s), 139.6 (s), 127.0 (d), 122.8 (d), 114.3 (d), 58.5 (t), 55.5 (q), 35.6 (t), 18.3 (q), 15.7 (q), -4.2 (t). **IR (cm^{-1}):** ν 2975, 2893, 1679, 1507, 1469, 1247, 1103, 960. **HRMS:** *m/z* calculated for $C_{22}H_{31}NNaO_5SSi$ $[M+H]^+$: 472.1584; found: 472.1586.

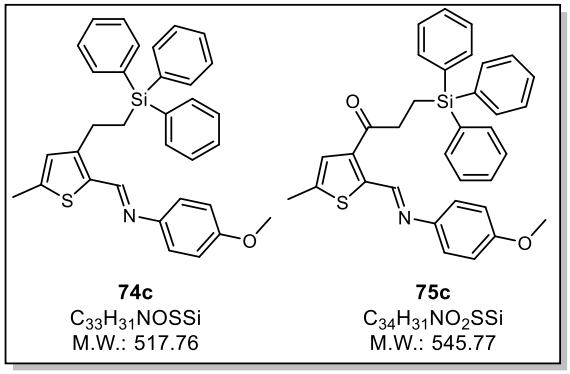
Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylthiophen-3-yl)-3-(triethylsilyl)propan-1-one (75d).



Prepared according to general procedure **GP3** from the reaction of **72** (115 mg, 0.5 mmol, 1 equiv.) with triethylvinylsilane **28d** (369 μL, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on silica gel eluting with Pentane/Et_2O (94/6) to afford 121 mg of **75d** (60% yield) as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.21 (s, 1H), 7.20 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 0.7 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 3.72 (s, 3H), 2.79-2.65 (m, 2H), 2.42 (s, 3H), 0.94-0.78 (m, 11H), 0.49 (q, *J* = 7.9 Hz, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.8 (s), 158.7 (s), 151.8 (d), 146.3 (s), 144.0 (s), 143.3 (s), 139.6 (s), 126.9 (d), 122.8 (d), 114.3 (d), 55.5 (q), 36.6 (t), 15.7 (q), 7.4 (q), 5.5 (t), 3.2 (t). **IR (cm^{-1}):** ν 2952, 2975,

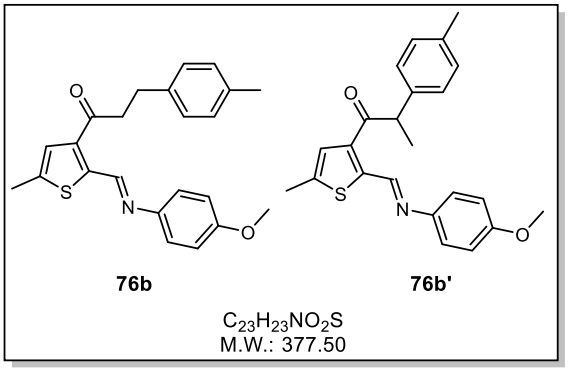
2016, 1951, 1677, 1610, 1503, 1466, 1244, 1034, 734. **HRMS:** *m*/*z* calculated for $C_{22}H_{32}NO_2SSi$ $[M+H]^+$: 425.1771; found: 425.1778.

Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylthiophen-3-yl)-3-(triphenylsilyl)propan-1-one (74c) and **(*E*)-*N*-(4-methoxyphenyl)-1-(5-methyl-3-(2-(triphenylsilyl)ethyl)thiophen-2-yl)methanimine (75c).**



Prepared according to general procedure **GP3** from the reaction of **72** (115 mg, 0.5 mmol, 1 equiv.) with triphenylvinylsilane **28c** (573 mg, 2 mmol, 4 equiv.). The crude product was purified by flash column chromatography on silica gel eluting with Pentane/Et_2O (90/10) to afford 78 mg of **74c** (30% yield) as yellow oil and 96 mg of **75c** (35% yield) as yellow oil **(74c) M.p.:** 121-124 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.35 (s, 1H), 7.63-7.53 (m, 6H), 7.46-7.35 (m, 9H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.64 (s, 1H), 3.85 (s, 3H), 3.01-2.86 (m, 2H), 2.47 (s, 3H), 1.79-1.70 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 158.0 (s), 149.6 (s), 149.6 (d), 145.0 (s), 144.6 (s), 135.6 (d), 134.5 (s), 133.8 (s), 129.7 (d), 128.2 (d), 128.1 (d), 122.3 (d), 114.3 (d), 55.6 (q), 22.9 (t), 16.1 (t), 15.9 (q). **IR (cm^{-1}):** ν 2928, 1659, 1610, 1506, 1245, 1110, 701. **HRMS:** *m*/*z* calculated for $C_{33}H_{31}NNaOSSi$ $[M+Na]^+$: 540.1788; found: 540.1793. **(75c) M.p.:** 123-125 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.11 (s, 1H), 7.48 (dd, *J* = 7.4, 1.7 Hz, 6H), 7.33-7.24 (m, 9H), 7.18 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 0.8 Hz, 1H), 3.72 (s, 3H), 2.95-2.77 (m, 2H), 2.34 (s, 3H), 1.75-1.65 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.0 (s), 158.8 (s), 151.8 (d), 146.4 (s), 144.0 (s), 143.3 (s), 139.5 (s), 135.6 (d), 134.3 (s), 129.7 (d), 128.1 (d), 126.9 (d), 122.9 (d), 114.3 (d), 55.5 (q), 36.6 (t), 15.7 (q), 7.1 (t). **IR (cm^{-1}):** ν 3070, 1676, 1610, 1506, 1467, 1247, 1111, 702. **HRMS:** *m*/*z* calculated for $C_{34}H_{31}NO_5SSi$ $[M+Na]^+$: 568.1737; found: 568.1745.

Synthesis of (*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylthiophen-3-yl)-2-(*p*-tolyl)propan-1-one (76b) and **(*E*)-1-(2-(((4-methoxyphenyl)imino)methyl)-5-methylthiophen-3-yl)-3-(*p*-tolyl)propan-1-one (76b').**



Prepared according to general procedure **GP3** from the reaction of **72** (115 mg, 0.5 mmol, 1 equiv.) with 4-methylstyrene **66b** (528 µL, 2 mmol, 8 equiv.). The crude product was purified by flash column chromatography on silica gel eluting with Pentane/Et_2O (80/20) to afford 59 mg (**76b**/**76b'**: 71/29) of **76b** and **76b'** (31% yield) as

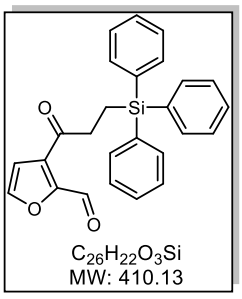
yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.32 (s, 1H, **76b'**), 9.30 (s, 1H, **76b**), 7.30 (d, *J* = 8.9 Hz, 2H **76b** + 2H **76b'**), 7.20-7.07 (m, 5H **76b** + 5H **76b'**), 6.96-6.89 (m, 2H **76b** + 2H **76b'**), 4.37 (q, *J* = 6.8 Hz, 1H, **76b'**), 3.84 (s, 3H **76b** + 3H **76b'**), 3.17 (t, *J* = 7.6 Hz, 2H, **76b**), 3.02 (t, *J* = 7.6 Hz, 2H, **76b**), 2.50 (s, 3H, **76b**), 2.44 (s, 3H, **76b'**), 2.34 (s, 3H, **76b**), 2.32 (s, 3H, **76b'**), 1.51 (d, *J* = 6.9 Hz, 3H, **76b'**). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.0 (s, **76b'**), 195.8 (s, **76b**), 158.8 (s, **76b**), 158.7 (s, **76b'**), 151.9 (d, **76b'**), 151.7 (d, **76b**), 147.3 (s, **76b'**), 146.5 (s, **76b**), 144.0 (s, **76b'**), 143.9 (s, **76b**), 143.4 (s, **76b**), 143.0 (s, **76b'**), 139.6 (s, **76b** + **76b'**), 137.9 (s, **76b**), 137.8 (s, **76b'**), 136.8 (s, **76b'**), 135.7 (s, **76b**), 129.8 (d, **76b'**), 129.2 (d, **76b**), 128.3 (d, **76b**), 127.6 (d, **76b'**), 127.3 (d, **76b'**), 127.0 (d, **76b**), 122.9 (d, **76b** + **76b'**), 114.3 (d, **76b**), 114.3 (d, **76b'**), 55.5 (q, **76b** + **76b'**), 50.7 (d, **76b'**), 44.0 (t, **76b**), 29.6 (t, **76b**), 21.1 (q, **76b'**), 21.0 (q, **76b**), 19.2 (q, **76b'**), 15.8 (q, **76b'**), 15.7 (q, **76b**). **IR (cm^{-1}):** ν 2922, 1673, 1606, 11504, 1465, 1246, 1108, 1033, 832. **HRMS:** *m*/*z* calculated for $C_{23}H_{24}NO_2S$ $[M+H]^+$: 378.1522; found: 378.1523.

3.3. Hydrolyzed products and post functional transformations

General procedure (GP10) for the synthesis of 2-aldehydepyrrole and 2-aldehydeindole derivatives

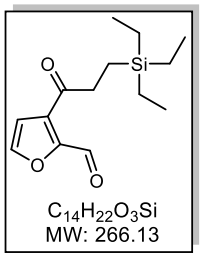
In a round-bottom flask equipped with magnetic stirrer, the 2-aldiminepyrrole or 2-aldimineindole derivatives (1 equiv.) was introduced and dissolved in anhydrous Et_2O (0.25 M). Then an aqueous solution of HCl (2 equiv., 1 M) was added dropwise. The reaction mixture was let stir at room temperature until completion followed by TLC. The organic phases were extracted with a satured solution of NaCl, dried on $MgSO_4$ and the solvent removed by evaporation at reduced pressure.

Synthesis of 3-(3-(triphenylsilyl)propanoyl)furan-2-carbaldehyde (77c).



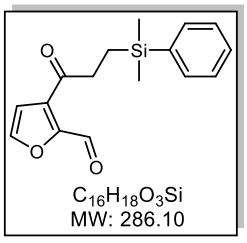
Following the procedure **GP10,** in a round-bottom flask equipped with magnetic stirrer, the compound **28c** (88 mg) was introduced and dissolved in Et_2O (3 mL). Then it was added dropwise HCl (1 mL, 1 M in water). The reaction mixture was let stir at room temperature for 3 h. The mixture was extracted with two portions of Brine, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure to afford 70 mg (quantitative yield) of the aldehyde **77c** as brown solid. **M.p.:** 81-82 C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.03 (d, *J* = 0.8 Hz, 1H), 7.59-7.53 (m, 7H), 7.46-7.41 (m, 3H), 7.41-7.38 (m, 5H), 7.36 (t, *J* = 1.7 Hz, 1H), 6.59 (d, *J* = 1.8 Hz, 1H), 3.01-2.92 (m, 2H), 1.82-1.76 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.0 (s), 179.8 (d), 151.5 (s), 146.6 (d), 135.5 (d), 134.0 (s), 131.7 (s), 129.8 (d), 128.1 (d), 111.6 (d), 36.6 (t), 6.6 (t). **IR (cm^{-1}):** ν 3068, 2919, 1689, 1404, 1428, 1404, 1255, 1110, 701. **HRMS**: *m*/*z* calculated for $C_{26}H_{21}NaO_3Si$ $[M+Na]^+$: 433.1236; found: 433.1230.

Synthesis of 3-(3-(triethylsilyl)propanoyl)furan-2-carbaldehyde (77d).



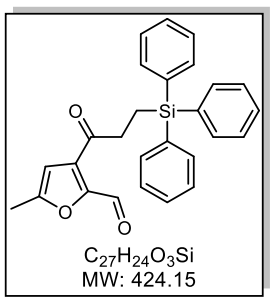
Following the procedure **GP10,** in a round-bottom flask equipped with magnetic stirrer, the compound **28d** (121 mg) was introduced and dissolved in Et_2O (3 mL). Then it was added dropwise HCl (1 mL, 1 M in water). The reaction mixture was let stir at room temperature for 3 h. The mixture was extracted with two portions of Brine, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure to afford 86 mg (quantitative yield) of the aldehyde **77d** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.13 (s, 1H), 7.65 (s, 1H), 6.80 (s, 1H), 2.89-2.79 (m, 2H), 0.98-0.88 (m, 11H), 0.56 (q, *J* = 7.9 Hz, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.9 (s), 179.9 (d), 151.6 (s), 146.7 (d), 131.9 (s), 111.8 (d), 36.6 (t), 7.3 (q), 5.2 (t), 3.2 (t). **IR (cm^{-1}):** ν 2953, 2875, 1686, 1565, 1483, 1405, 1255, 1015, 934. **HRMS**: *m/z* calculated for $C_{14}H_{23}O_3Si$ $[M+H]^+$: 267.1411; found: 267.1411.

Synthesis of 3-(3-(dimethyl(phenyl)silyl)propanoyl)furan-2-carbaldehyde (77e).



Following the procedure **GP10,** in a round-bottom flask equipped with magnetic stirrer, the compound **28e** (95 mg) was introduced and dissolved in Et_2O (3 mL). Then it was added dropwise HCl (1 mL, 1 M in water). The reaction mixture was let stir at room temperature for 3 h. The mixture was extracted with two portions of Brine, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure to afford 69 mg (quantitative yield) of the aldehyde **77e** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.07 (s, 1H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.52 (dd, *J* = 6.4, 3.0 Hz, 2H), 7.40-7.34 (m, 3H), 6.69 (d, *J* = 1.7 Hz, 1H), 2.87-2.75 (m, 2H), 1.20-1.09 (m, 2H), 0.34 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 196.5 (s), 179.8 (d), 151.6 (s), 146.7 (d), 137.9 (s), 133.6 (d), 131.8 (s), 129.3 (d), 128.0 (d), 111.7 (d) 36.6 (t), 9.5 (t), -3.2 (q). **IR (cm^{-1}):** ν 2954, 2894, 1681, 1403, 1252, 1113, 936, 837. **HRMS**: *m/z* calculated for $C_{16}H_{19}O_3Si$ $[M+H]^+$: 287.1098; found: 287.1098.

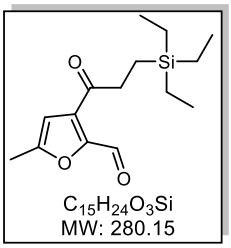
Synthesis of 5-methyl-3-(3-(triphenylsilyl)propanoyl)furan-2-carbaldehyde (78c).



Following the procedure **GP10,** in a round-bottom flask equipped with magnetic stirrer, the compound **29c** (178 mg) was introduced and dissolved in Et_2O (3 mL). Then it was added dropwise HCl (1 mL, 1 M in water). The reaction mixture was let stir at room temperature for 3 h. The mixture was extracted with two portions of Brine, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure to afford 142 mg (quantitative yield) of the aldehyde **78c** as yellow solid. **M.p.:** 113-114 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.93 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 6H), 7.45-7.37 (m, 7.1 Hz, 9H), 6.20 (s, 1H), 2.97-2.88 (m, 2H), 2.37 (s, 3H), 1.82-1.73 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.3 (s), 179.3 (d), 158.2 (s), 150.5 (s), 135.6 (d), 134.1 (s), 133.3 (s), 129.8 (d), 128.1 (d), 108.3 (d), 36.5 (t), 13.9 (q),

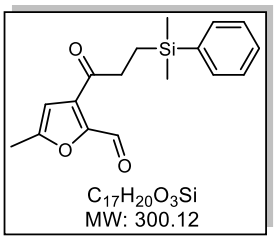
6.6 (t). **IR (cm^{-1}):** ν 3068, 1675, 1528, 1427, 1392, 1110, 943. **HRMS**: m/z calculated for $C_{27}H_{24}NaO_3Si$ $[M+Na]^+$: 447.1387; found: 447.1387.

Synthesis of 5-methyl-3-(3-(triethylsilyl)propanoyl)furan-2-carbaldehyde (78d).



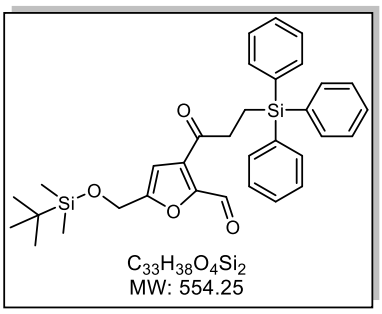
Following the procedure **GP10,** in a round-bottom flask equipped with magnetic stirrer, the compound **28d** (152 mg) was introduced and dissolved in Et_2O (3 mL). Then it was added dropwise HCl (1 mL, 1 M in water). The reaction mixture was let stir at room temperature for 3 h. The mixture was extracted with two portions of Brine, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure to afford 110 mg (quantitative yield) of the aldehyde **78d** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.02 (s, 1H), 6.42 (s, 1H), 2.84-2.72 (m, 2H), 2.42 (s, 3H), 0.98-0.86 (m, 11H), 0.56 (q, *J* = 7.9 Hz, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.2 (s), 179.4 (d), 158.3 (s), 150.6 (s), 133.4 (s), 108.4 (d), 36.6 (t), 13.9 (q), 7.35 (q), 5.2 (t), 3.2 (t). **IR (cm^{-1}):** ν 2952, 2875, 1678, 1528, 1392, 1233, 1004, 940, 783. **HRMS**: *m/z* calculated for $C_{14}H_{23}O_3Si$ $[M+H]^+$: 281.1567; found: 281.1568.

Synthesis of 3-(3-(dimethyl(phenyl)silyl)propanoyl)-5-methylfuran-2-carbaldehyde (78e).



Following the procedure **GP10,** in a round-bottom flask equipped with magnetic stirrer, the compound **29e** (137 mg) was introduced and dissolved in Et_2O (3 mL). Then it was added dropwise HCl (1 mL, 1 M in water). The reaction mixture was let stir at room temperature for 3 h. The mixture was extracted with two portions of Brine, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure to afford 101 mg (quantitative yield) of the aldehyde **78e** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 9.83 (s, 1H), 7.38 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.26-7.21 (m, 3H), 6.17 (s, 1H), 2.71-2.57 (m, 2H), 2.26 (s, 3H), 1.04-0.95 (m, 2H), 0.20 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 196.8 (s), 179.3 (d), 158.3 (s), 150.1 (s), 138.0 (s), 133.6 (d), 133.4 (s), 129.2 (d), 127.9 (d), 108.4 (d), 36.6 (t), 13.9 (q), 9.5 (t), -3.2 (q). **IR (cm^{-1}):** ν 2954, 2896, 1676, 1527, 1392, 1247, 1113, 943. 814. **HRMS**: *m/z* calculated for $C_{17}H_{20}O_3Si$ $[M+H]^+$: 323.1074; found: 323.1073.

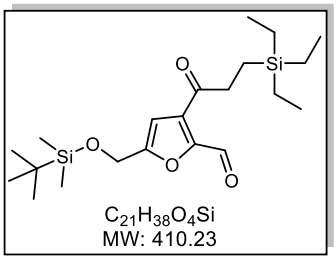
Synthesis of 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(3-(triphenylsilyl)propanoyl)furan-2-carbaldehyde (79c).



Following the procedure **GP10,** in a round-bottom flask equipped with magnetic stirrer, the compound **30c** (117 mg) was introduced and dissolved in Et_2O (3 mL). Then it was added dropwise HCl (1 mL, 1 M in water). The reaction mixture was let stir at room temperature for 3 h. The mixture was extracted with two portions of Brine, dried on $MgSO_4$,

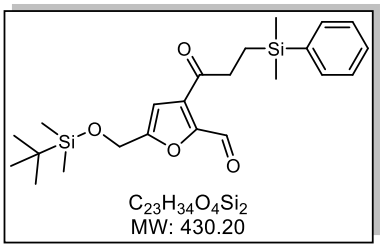
filtrated and the volatiles were evaporated under reduce pressure to afford 96 mg (quantitative yield) of the aldehyde **79c** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.99 (s, 1H), 7.60-7.56 (m, 6H), 7.47-7.37 (m, 9H), 6.47 (s, 1H), 4.69 (d, *J* = 0.8 Hz, 2H), 3.00-2.93 (m, 2H), 1.84-1.75 (m, 2H), 0.93 (s, 9H), 0.12 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.3 (s), 179.6 (d), 160.1 (s), 150.6 (s), 135.6 (d), 134.1 (s), 132.8 (s), 129.8 (d), 128.1 (d), 108.1 (d), 58.4 (t), 36.6 (t), 25.8 (q), 18.3 (s), 6.6 (t), -5.4 (q). **IR (cm^{-1}):** ν 3069, 2929, 1682, 1529, 1428, 1110, 827, 701. **HRMS**: *m*/*z* calculated for $C_{33}H_{39}O_4Si_2$ $[M+H]^+$: 555.2380; found: 555.2381.

Synthesis of 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(3-(triethylsilyl)propanoyl)furan-2-carbaldehyde (79d).



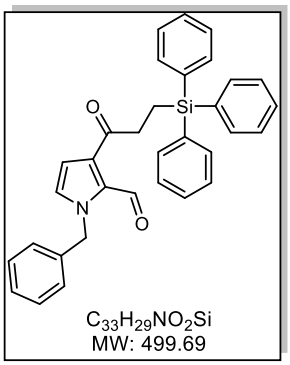
Following the procedure **GP10,** in a round-bottom flask equipped with magnetic stirrer, the compound **30d** (113 mg) was introduced and dissolved in Et_2O (3 mL). Then it was added dropwise HCl (1 mL, 1 M in water). The reaction mixture was let stir at room temperature for 3 h. The mixture was extracted with two portions of Brine, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure to afford 90 mg (quantitative yield) of the aldehyde **79d** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.08 (s, 1H), 6.64 (s, 1H), 4.74 (s, 2H), 2.86-2.76 (m, 2H), 0.99-0.88 (m, 20H), 0.57 (q, *J* = 7.9 Hz, 6H), 0.13 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.2 (s), 179.7 (d), 160.3 (s), 150.88 (s), 132.8 (s), 108.2 (d), 58.4 (t), 36.6 (t), 25.7 (q), 18.3 (s), 7.3 (q), 5.5 (t), 3.2 (t), -5.4 (q). **IR (cm^{-1}):** ν 2925, 2854, 1686, 1463, 1253, 1092, 838, 781. **HRMS**: *m*/*z* calculated for $C_{21}H_{39}O_4Si$ $[M+H]^+$: 411.2381; found: 411.2381.

Synthesis of 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(3-(dimethyl(phenyl)silyl)propanoyl)furan-2-carbaldehyde (79e).



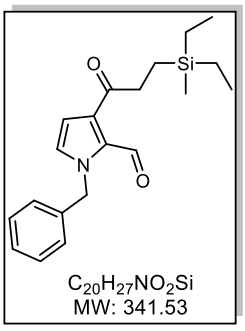
Following the procedure **GP10,** in a round-bottom flask equipped with magnetic stirrer, the compound **30e** (169 mg) was introduced and dissolved in Et_2O (3 mL). Then it was added dropwise HCl (1 mL, 1 M in water). The reaction mixture was let stir at room temperature for 3 h. The mixture was extracted with two portions of Brine, dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure to afford 136 mg (quantitative yield) of the aldehyde **79e** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.02 (s, 1H), 7.57-7.46 (m, 2H), 7.44-7.32 (m, 2H), 6.54 (s, 1H), 4.71 (s, 2H), 2.88-2.69 (m, 2H), 1.21-1.10 (m, 2H), 0.93 (s, 9H), 0.34 (s, 6H), 0.12 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.7 (s), 179.6 (d), 160.2 (s), 150.7 (s), 137.9 (s), 133.5 (d), 132.8 (s), 129.2 (d), 127.9 (d), 108.2 (d), 58.4 (t), 36.6 (t), 25.8 (q), 18.3 (s), 9.5 (t), -3.1 (q), -3.4 (q). **IR (cm^{-1}):** ν 2929, 2857, 1679, 1529, 1250, 1111, 941, 832, 777. **HRMS**: *m*/*z* calculated for $C_{23}H_{35}O_4Si_2$ $[M+H]^+$: 431.2068; found: 431.2069.

Synthesis of 1-benzyl-3-(3-(triphenylsilyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (60c).



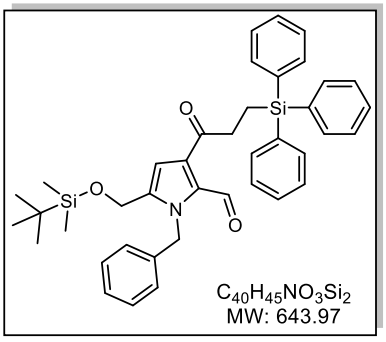
Prepared according to general procedure **GP9** from the reaction of (*E*)-*N*1-((1-benzyl-1*H*-pyrrol-2-yl)methylene)-*N*2,*N*2-diethylethane-1,2-diamine **48** (142 mg, 0.5 mmol, 1 equi.v) and triphenylvinylsilane **28c** (573 mg, 2 mmol, 4 equi.v). The crude product was purified by flash chromatography on silica gel eluting with Pentane/Et_2O (80/20) to afford 126 mg (50% yield) of **60c** as yellow oil. The same product could be obtained according to general procedure **GP10** from the reaction of compound **62c** (234 mg, 0.47 mmol, 1 equiv.) and HCl (1 mL, 1 mmol, 2 equiv.) in Et_2O (2 mL) to afford 178 mg (quantitative yield) of **60c** as yellow solid. **M.p.**: 95-96 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.30 (d, *J* = 0.8, 1H), 7.60-7.57 (m, 6H), 7.46-7.36 (m, 9H), 7.32-7.26 (m, 3H), 7.15-7.13 (m, 2H), 6.79 (dd, *J* = 2.8, 0.6 Hz, 1H), 6.39 (d, *J* = 2.8 Hz, 1H), 5.57 (s, 2H), 3.01-2.95 (m, 2H), 1.83-1.78 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.8 (s), 184.2 (d), 136.7 (s), 135.7 (d), 134.5 (s), 131.8 (s), 130.9 (s), 129.8 (d), 128.9 (d), 128.8 (d), 128.2 (d), 128.1 (d), 127.5 (d), 111.4 (d), 53.1 (t), 35.3 (t), 7.3 (t). **IR (cm^{-1}):** ν 3069, 2924, 1659, 1524, 1488, 1456, 1428, 1370. **HRMS**: *m*/*z* calculated for $C_{33}H_{29}NNaO_2Si$ $[M+Na]^+$: 522.1860; found: 522.1858.

Synthesis of 1-benzyl-3-(3-(diethyl(methyl)silyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (80g).



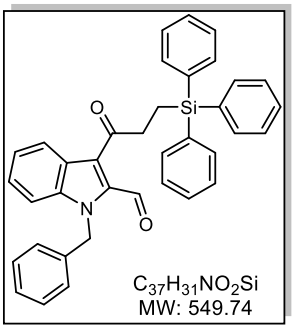
Prepared according to general procedure **GP9** from the reaction of (*E*)-*N*1-((1-benzyl-1*H*-pyrrol-2-yl)methylene)-*N*2,*N*2-diethylethane-1,2-diamine **48** (142 mg, 0.5 mmol, 1 equiv.) and diethylmethylvinylsilane **28g** (0.342 mL, 2 mmol, 4 equiv.). The crude product was purified by flash chromatography on silica gel eluting with Pentane/Et_2O (95/5 to 90/10) to afford 95 mg (56% yield) of **80g** as yellow oil. The same product could be obtained according to general procedure **GP10** from the reaction of compound **62g** (154 mg, 0.45 mmol, 1 equiv.) and HCl (1 mL, 1 mmol, 2.22 equiv.) in Et_2O (2 mL) over 30 min to afford 116 mg (quantitative yield) of **80g** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.37 (s, 1H), 7.37-7.28 (m, 3H), 7.19-7.16 (m, 2H), 6.89 (dd, *J* = 2.8, 0.9 Hz, 1H), 6.61 (d, *J* = 2.8 Hz, 1H), 5.62 (s, 2H), 2.86-2.80 (m, 2H), 1.00-0.90 (m, 8H), 0.57 (q, *J* = 7.6 Hz. 4H), -0.01 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 198.8 (s), 184.3 (d), 136.8 (s), 132.0 (s), 131.0 (s), 128.9 (d), 128.8 (d), 128.1 (d), 127.6 (d), 111.4 (d), 53.2 (t), 35.6 (t), 7.7 (t), 7.6 (t), 5.1 (q), -6.2 (q). **IR (cm^{-1}):** ν 2953, 2876, 1660, 1524, 1489, 1457, 1424, 1370. **HRMS**: *m*/*z* calculated for $C_{20}H_{27}NNaO_2Si$ $[M+Na]^+$: 364.1703; found: 364.1704.

Synthesis of 1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(3-(triphenylsilyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (81c).



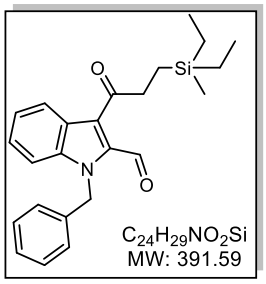
Prepared according to general procedure **GP10** from the reaction of compound **65c** (258 mg, 0.4 mmol, 1 equiv.) and HCl (1 mL, 1 mmol, 2.5 equiv.) in Et_2O (3 mL) over 2 h to afford 222 mg (quantitative yield) of **81c** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.26 (s, 1H), 7.58 (dd, *J* = 7.6, 1.8 Hz, 6H), 7.49-7.33 (m, 10H), 7.27-7.23 (m, 2H), 6.93 (d, *J* = 6.4 Hz, 2H), 6.33 (s, 1H), 5.73 (s, 2H), 4.49 (s, 2H), 3.03-2.92 (m, 2H), 1.85-1.74 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.7 (s), 184.0 (d), 139.5 (s), 136.9 (s), 135.6 (d), 134.4 (s), 131.7 (s), 130.7 (s), 129.6 (d), 128.6 (d), 128.0 (d), 127.3 (d), 126.1 (d), 111.1 (d), 57.2 (t), 49.3 (t), 35.4 (t), 25.8 (q), 18.2 (t), 7.2 (s), -5.4 (q). **IR (cm^{-1}):** ν 2953, 2930, 1671, 1512, 1247, 1036, 836. **HRMS**: *m/z* calculated for $C_{40}H_{45}NNaO_3Si_2$ $[M+Na]^+$: 666.2830; found: 666.2831.

Synthesis of 1-benzyl-3-(3-(triphenylsilyl)propanoyl)-1*H*-indole-2-carbaldehyde (82c).



Prepared according to general procedure **GP10** from the reaction of compound **64c** (275 mg, 0.5 equiv.) and HCl (3 mL, 3 mmol, 6 equiv.) in Et_2O (5 mL) over 1 h to afford 231 mg (quantitative yield) of **82c** as yellow solid. **M.p.:** 96-97 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.35 (s, 1H), 7.62-7.56 (m, 7H), 7.43-7.36 (m, 11H), 7.25-7.21 (m, 3H), 7.17 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.7 Hz, 2H), 5.84 (s, 2H), 3.25-3.21 (m, 2H), 1.93-1.89 (m, 2H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 198.3 (s), 186.7 (d), 138.5 (s), 136.7 (s), 135.7 (s), 135.6 (d), 134.3 (s), 129.7 (d), 128.7 (d), 128.0 (d), 127.6 (d), 126.6 (d), 126.5 (d), 124.4 (s), 124.0 (s), 123.3 (d), 122.5 (d), 111.8 (d), 48.3 (t), 38.7 (t), 7.2 (t). **IR (cm^{-1}):** ν 3067, 2908, 1671, 1498, 1465, 1427, 1110, 700. **HRMS**: m/z calculated for $C_{37}H_{31}NNaO_2Si$ $[M+Na]^+$: 572.2016; found: 572.2017.

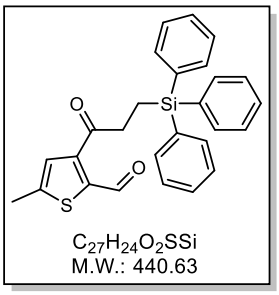
Synthesis of 1-benzyl-3-(3-(diethyl(methyl)silyl)propanoyl)-1*H*-indole-2-carbaldehyde (83g).



Prepared according to general procedure **GP10** from the reaction of compound **64d** (174 mg, 0.44 mmol, 1 equiv.) and HCl (3 mL, 3 mmol, 6.8 equiv.) in Et_2O (5 mL) over 1 h to afford 137 mg (quantitative yield) of **82g** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.53 (s, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.50-7.43 (m, 2H), 7.41-7.37 (m, 1H), 7.29-7.25 (m, 3H), 7.12-7.09 (m, 2H), 5.90 (s, 2H), 3.18-3.11 (m, 2H), 1.09-1.04 (m, 2H), 1.01 (t, *J* = 7.9 Hz, 6H), 0.62 (q, *J* = 8.0 Hz, 4H), 0.06 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 199.2 (s), 186.6 (d), 138.7 (s), 136.7 (s), 135.7 (s), 128.7 (d), 127.6 (d), 126.8 (d), 126.5 (d), 124.8 (s), 124.2 (s), 123.4 (d), 122.6 (d), 111.9 (d), 48.4 (t), 38.7 (t), 7.4 (t), 7.4 (q), 5.0 (t), -6.1 (q). **IR**

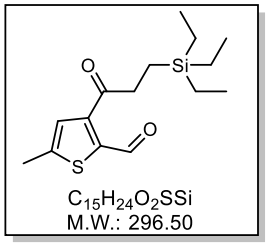
(cm^{-1}): ν 2950, 2874, 1670, 1497, 1464, 1410, 1023, 742. **HRMS**: m/z calculated for $C_{24}H_{30}NO_2Si$ $[M+H]^+$: 392.2040; found: 392.2049.

Synthesis of 5-methyl-3-(3-(triphenylsilyl)propanoyl)thiophene-2-carbaldehyde (83c).



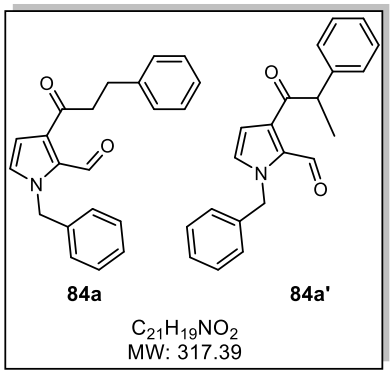
Prepared according to general procedure **GP10** from the reaction of compound **75c** (96 mg, 0.17 mmol, 1 equiv.) and HCl (1.5 mL, 1.5 mmol, 5 equiv.) in Et_2O (3 mL) over 3 h to afford 75 mg (quantitative yield) of **83c** as yellow solid. **M.p.:** 91-93 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.15 (s, 1H), 7.52-7.43 (m, 6H), 7.35-7.25 (m, 9H), 6.80 (s, 1H), 2.98-2.78 (m, 2H), 2.39 (d, *J* = 0.7 Hz, 3H), 1.80-1.60 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 196.6 (s), 184.8 (d), 149.1 (s), 144.8 (s), 144.1 (s), 135.6 (d), 134.1 (s), 129.8 (d), 128.1 (d), 127.7 (d), 36.7 (t), 16.0 (q), 7.3 (t). **IR (cm^{-1}):** ν 3068, 2924, 1657, 1463, 1427, 1246, 1110, 700. **HRMS:** *m/z* calculated for $C_{27}H_{25}O_2SSi$ $[M+H]^+$: 441.1339; found: 441.1339.

Synthesis of 5-methyl-3-(3-(triethylsilyl)propanoyl)thiophene-2-carbaldehyde (83d)



Prepared according to general procedure **GP10** from the reaction of compound **75d** (121 mg, 0.3 mmol, 1 equiv.) and HCl (1.5 mL, 1.5 mmol, 5 equiv.) in Et_2O (3 mL) over 3 h to afford 87 mg (quantitative yield) of **83d** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.34 (s, 1H), 7.13 (s, 1H), 2.85-2.76 (m, 2H), 2.55 (s, 3H), 0.99-0.87 (m, 11H), 0.56 (q, *J* = 7.9 Hz, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.5 (s), 184.8 (d), 149.2 (s), 144.8 (s), 144.4 (d), 127.7 (d), 36.7 (t), 16.0 (q), 7.4 (q), 5.5 (t), 3.2 (t). **IR (cm^{-1}):** ν 2951, 2874, 2015, 1656, 1451, 1216, 1015, 732. **HRMS:** *m/z* calculated for $C_{15}H_{25}NO_2SSi$ $[M+H]^+$: 297.1339; found: 297.1339.

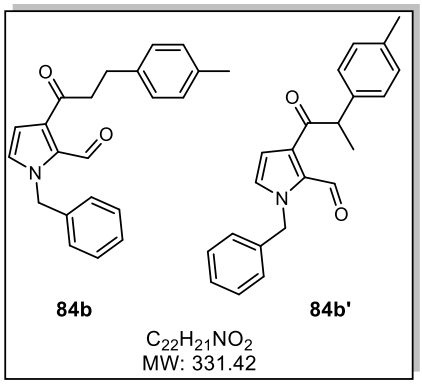
Synthesis of 1-benzyl-3-(2-phenylpropanoyl)-1*H*-pyrrole-2-carbaldehyde (84a) and **1-benzyl-3-(3-phenylpropanoyl)-1*H*-pyrrole-2-carbaldehyde (84a').**



Prepared according to general procedure **GP9** from the reaction of (*E*)-*N*1-((1-benzyl-1*H*-pyrrol-2-yl)methylene)-*N*2,*N*2-diethylethane-1,2-diamine **28** (142 mg, 0.5 mmol, 1 equiv.) and styrene **66a** (0.23 mL, 2 mmol, 4 equiv.). The crude product was purified by flash chromatography on silica gel eluting with Pentane/Et_2O (90/10 to 80/20) to afford 66 mg (42% yield, **84a**/**84a'**: 67/33)of **84a** and **84a'** as yellow oil. The same product could be obtained according to general procedure **GP10** from the reaction of the mixture of compounds **68a** and **68a'** (106 mg, 0.5 mmol, 1 equiv.) and HCl (1 mL, 1 mmol, 2 equiv.) in Et_2O (2 mL) over 30 min to afford 92 mg (quantitative yield, **84a** /**84a'**:72/28) of **84a** and **84a'** as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.40 (d, *J* =

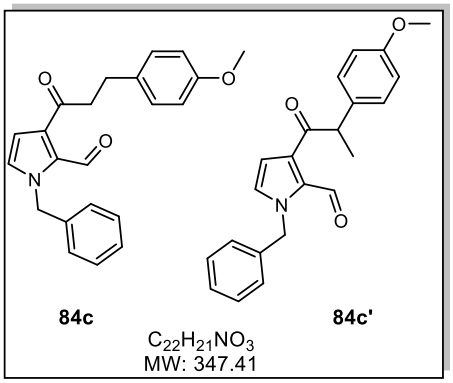
0.8 Hz, 1H, **84a**), 10.39 (d, *J* = 0.8 Hz, 1H, **84a'**), 7.38-7.20 (m, 16H, 8H **84a** + 8H **84a'**), 7.19-7.13 (m, 4H, 2H **84a** + 2H **84a'**), 6.88 (d, *J* = 2.8 Hz, 1H, **84a**), 6.78 (d, *J* = 2.8 Hz, 1H, **84a'**), 6.61 (d, *J* = 2.8 Hz, 1H, **84a**), 6.58 (d, *J* = 2.8 Hz, 1H, **84a'**), 5.65-5.60 (m, 3H, 2H **84a** + 1H **84a'**), 5.48 (d, *J* = 14.9 Hz, 1H, **84a'**), 4.49 (q, *J* = 6.9 Hz, 1H, **84a'**), 3.26-3.21 (m, 2H, **84a**), 3.10-3.05 (m, 2H, **84a**), 1.55 (d, *J* = 6.9 Hz, 3H, **84a'**). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 197.4 (s, **84a'**), 196.4 (s, **84a**), 184.2 (d, **84a'**), 184.1 (d, **84a**), 141.4 (s, **84a'**), 141.1 (s, **84a**), 136.6 (s, **84a**), 136.5 (s, **84a'**), 131.9 (s, **84a**), 131.7 (s, **84a'**), 131.4 (s, **84a'**), 130.8 (s, **84a**), 129.0 (d, **84a**), 128.9 (d, **84a'**), 128.8 (d, **84a**) 128.7 (d, **84a'**), 128.6 (d, **84a'**), 128.5 (d, **84a**), 128.4 (d, **84a**), 128.0 (d, **84a**), 127.9 (d, **84a'**), 127.8 (d, **84a'**), 127.5 (d, **84a'**), 127.4 (d, **84a**), 127.0 (d, **84a'**), 126.1 (d, **84a**), 111.8 (d, **84a'**), 111.4 (d, **84a**), 53.1 (t, **84a**), 53.0 (t, **84a'**), 50.3 (d, **84a'**), 42.6 (t, **84a**), 30.1 (t, **84a**), 19.0 (q, **84a'**). **IR (cm^{-1}):** ν 2925, 1654, 1486, 1452, 1395, 717, 695. **HRMS**: *m*/z calculated for $C_{21}H_{19}NNaO_2$ $[M+Na]^+$: 340.1308; found: 340.1310.

Synthesis of 1-benzyl-3-(2-(*p*-tolyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (84b) and **1-benzyl-3-(3-(*p*-tolyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (84b').**



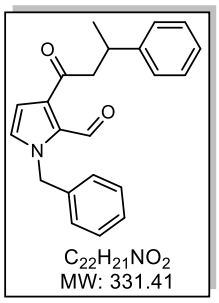
Prepared according to general procedure **GP9** from the reaction of (*E*)-*N*1-((1-benzyl-1*H*-pyrrol-2-yl)methylene)-*N*2,*N*2-diethylethane-1,2-diamine **28** (142 mg, 0.5 mmol, 1 equiv.) and *p*-methylstyrene **66b** (0.265 mL, 2 mmol, 4 equiv.). The crude product was purified by flash chromatography on silica gel eluting with Pentane/Et_2O (90/10 to 80/20) to afford 77.8 mg (47% yield, **84b /84b'**:75/25) of **84b** and **84b'** as yellow solid. The same product could be obtained according to general procedure **GP10** from the reaction of the mixture of compounds **68b** and **68b'** (161 mg, 0.5 mmol, 1 equiv.) and HCl (1 mL, 1 mmol, 2 equiv.) in Et_2O (2 mL) over 30 min to afford 119 mg (quantitative yield, **84b /84b'**: 60/40) of **84b** and **84b'** as yellow solid. **M.p.:** 72-73 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.39 (d, *J* = 0.7 Hz, 1H, **84b**), 10.38 (d, *J* = 0.7 Hz, 1H, **84b'**), 7.37-7.28 (m, 6H, 3H **84b** + 3H **84b'**), 7.23-7.13 (m, 12H, 6H **84b** + 6H **84b'**), 6.88 (d, *J* = 2.8 Hz, 1H, **84b**), 6.78 (d, *J* = 2.8 Hz, 1H, **84b'**), 6.61 (d, *J* = 2.8 Hz, 1H, **84b**), 6.57 (d, *J* = 2.8 Hz, 1H, **84b'**), 5.64-5.60 (m, 3H, 2H **84b** + 1H **84b'**), 5.49 (d, *J* = 14.9 Hz, 1H, **84b'**), 4.45 (q, *J* = 6.9 Hz, 1H, **84b'**), 3.22-3.18 (m, 2H **84b**), 3.05-3.02 (m, 2H, **84b**), 2.35 (s, 3H, **84b**), 2.34 (s, 3H, **84b'**), 1.52 (d, *J* = 6.9 Hz, 3H, **84b'**). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.7 (s, **84b'**), 196.5 (s, **84b**), 184.2 (d, **84b'**), 184.1 (d, **84b**), 138.4 (s, **84b'**), 138.0 (s, **84b**), 136.6 (s, **84b'**), 136.6 (s, **84b**), 136.5 (s, **84b'**), 135.6 (s, **84b**), 131.9 (s, **84b**), 131.7 (s, **84b'**), 131.4 (s, **84b'**), 130.8 (s, **84b**), 129.6 (d, **84b'**), 129.2 (d, **84b**), 128.8 (d, **84b**), 128.8 (d, **84b**), 128.6 (d, **84b'**), 128.3 (d, **84b** + **84b'**), 128.0 (d, **84b**), 128.0 (d, **84b'**), 127.6 (d, **84b'**), 127.5 (d, **84b'**), 127.4 (d, **84b**), 111.8 (d, **84b'**), 111.4 (d, **84b**), 53.1 (t, **84b**), 53.0 (t, **84b '**), 49.9 (d, **84b'**), 42.8 (t, **84b**), 29.8 (t, **84b**), 21.0 (q, **84b**), 21.0 (q, **84b'**), 19.0 (q, **84b'**). **IR (cm^{-1}):** ν 2924, 1656, 1514, 1486, 1395, 1263, 906. **HRMS**: *m*/*z* calculated for $C_{22}H_{21}NNaO_2$ $[M+Na]^+$: 354.1465; found: 354.1464.

Synthesis of 1-benzyl-3-(2-(4-methoxyphenyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (84c) and **1-benzyl-3-(3-(4-methoxyphenyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (84c').**



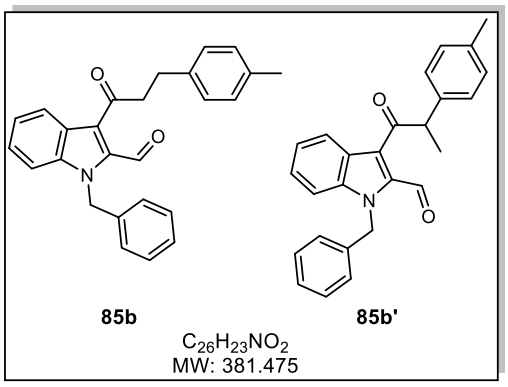
Prepared according to general procedure **GP9** from the reaction of (*E*)-*N*1-((1-benzyl-1*H*-pyrrol-2-yl)methylene)-*N*2,*N*2-diethylethane-1,2-diamine **28** (142 mg, 0.5 mmol, 1 equiv.) and *p*-methoxystyrene (0.276 mL, 2 mmol, 4 equiv.). The crude product was purified by flash chromatography on silica gel eluting with Pentane/Et_2O (90/10 to 80/20) to afford 56 mg of **84c** and **84c'** (32% yield, **84c**/**84c'**:60/40) as yellow solid. The same product could be obtained according to general procedure **GP10** from the reaction of the mixture of compounds **68c** and **68c'** (153 mg, 0.44 mmol, 1 equiv.) and HCl (1 mL, 1 mmol, 2.27 equiv.) in Et_2O (3 mL) over 30 min to afford 114 mg (quantitative yield, **84c**/**84c'**: 51/49) of **84c** and **84c'** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.39 (d, *J* = 0.7 Hz, 1H, **84c**), 10.38 (d, *J* = 0.7 Hz, 1H, **84c'**), 7.35-7.27 (m, 6H, 3H **84c** + 3H **84c'**), 7.23-7.11 (m, 8H, 4H **84c** + 4H **84c'**), 6.87-6.82 (m, 5H, 3H **84c** + 2H **84c'**), 6.75 (d, *J* = 2.8 Hz, 1H, **84c'**), 6.57 (d, *J* = 2.8 Hz, 1H, **84c**), 6.53 (d, *J* = 2.8 Hz, 1H, **84c'**), 5.61-5.58 (m, 3H, 2H **84c** + 1H **84c'**), 5.47 (d, *J* = 14.9 Hz, 1H, **84c'**), 4.40 (q, *J* = 6.9 Hz, 1H, **84c'**), 3.79 (s, 3H, **84c**), 3.77 (s, 3H, **84c'**), 3.18-3.14 (m, 2H **84c**), 3.00-2.97 (m, 2H, **84c**), 1.48 (d, *J* = 6.9 Hz, 3H, **84c'**). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.8 (s, **84c**), 197.6 (s, **84c'**), 184.2 (d, **84c**), 184.1 (d, **84c'**), 158.6 (s, **84c**), 158.0 (s, **84c'**), 136.6 (s, **84c**), 136.5 (s, **84c'**), 133.4 (s, **84c'**), 133.2 (s, **84c**), 131.9 (s, **84c'**), 131.7 (s, **84c**), 131.4 (s, **84c**), 130.8 (s, **84c'**), 129.3 (d, **84c**), 129.8 (d, **84c'**) 128.7 (d, 2C **84c**), 128.6 (d, **84c'**), 128.0 (d, **84c**), 127.9 (d, **84c'**), 127.5 (d, **84c'**), 127.4 (d, **84c'**), 114.3 (d, **84c** + **84c'**), 113.9 (d, **84c** + **84c'**), 111.7 (d, **84c'**), 111.4 (d, **84c**), 55.3 (q, **84c**), 55.2 (q, **84c'**), 53.1 (t, **84c**), 53.0 (t, **84c'**), 49.4 (d, **84c'**), 42.9 (t, **84c**), 29.3 (t, **84c**), 19.0 (q, **84c'**). **IR (cm^{-1}):** ν 2928, 1656, 1511, 1486, 1244, 1031, 905. **HRMS**: *m*/*z* calculated for $C_{22}H_{21}NNaO_3$ $[M+Na]^+$: 370.1414; found: 370.1413.

Synthesis of 1-benzyl-3-(3-phenylbutanoyl)-1H-pyrrole-2-carbaldehyde (84d).



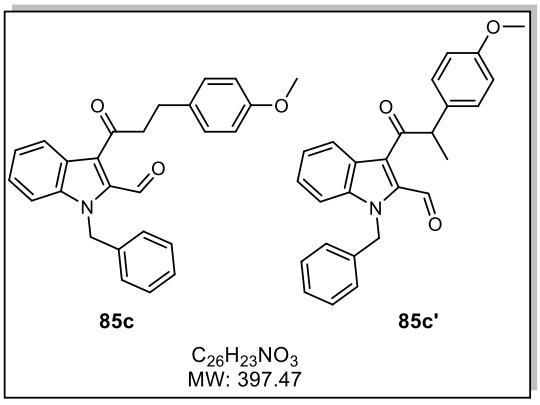
Prepared according to general procedure **GP10** from the reaction of compound **67d** (68 mg, 0.15 mmol, 1 equiv.) and HCl (1 mL, 1 mmol, 2.27 equiv.) in Et_2O (3 mL) over 2 h to afford 50 mg (quantitative yield) of **84d** and as yellow oil. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 10.40 (d, *J* = 0.6 Hz, 1H), 7.48-7.22 (m, 11H), 6.95 (d, *J* = 2.6 Hz, 1H), 6.68 (d, *J* = 2.8 Hz, 1H), 5.42 (d, *J* = 161.9 Hz, 2H), 3.66-3.52 (m, 1H), 3.30 (dd, *J* = 16.1, 6.0 Hz, 1H), 3.18 (dd, *J* = 16.1, 8.1 Hz, 1H), 1.45 (dd, *J* = 9.4, 7.0 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 196.3 (s), 184.1 (d), 146.4 (s), 136.5 (s), 132.4 (d), 130.8 (d), 128.8 (d), 128.5 (s), 128.0 (d), 127.4 (d), 126.8 (d), 126.3 (s), 111.4 (d), 53.0 (t), 49.5 (t), 35.8 (d), 21.9 (q). **IR (cm^{-1}):** ν 2961, 2926, 1657, 1487, 1396, 1271, 1121, 760, 699. **HRMS**: *m*/*z* calculated for $C_{22}H_{22}NO_2$ $[M+H]^+$: 332.1645; found: 332.1645.

Synthesis of 1-benzyl-3-(2-(*p*-tolyl)propanoyl)-1*H*-indole-2-carbaldehyde (85b) and **1-benzyl-3-(3-(*p*-tolyl)propanoyl)-1*H*-indole-2-carbaldehyde (85b').**



Prepared according to general procedure **GP10** from the reaction of the mixture of compounds **69b** and **69b'** (153 mg, 0.4 mmol, 1 equiv.) and HCl (3 mL, 3 mmol, 7.5 equiv.) in Et_2O (5 mL) over 30 min to afford 120 mg (quantitative yield, **85b**/**85b'**: 87/13) of **85b** and **85b'** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.51 (s, 1H, **85b**), 10.23 (s, 1H, **85b'**), 8.05-8.01 (m, 1H **85b** + 1H **85b'**), 7.50-7.41 (m, 2H **85b** + 2H **85b'**), 7.37-7.33 (m, 1H **85b** + 1H **85b'**), 7.29-7.24 (m, 3H **85b** + 3H **85b'**), 7.22-7.14 (m, 3H **85b** + 3H **85b'**), 7.11-7.09 (m, 2H **85b** + 2H **85b'**), 7.02-6.99 (m, 1H **85b** + 1H **85b'**), 5.90 (s, 2H, **85b**), 5.83 (d, *J* = 9.5 Hz, 2H, **85b'**), 4.77 (q, *J* =6.9 Hz, 1H, **85b'**) 3.53- 3.49 (m, 2H, **85b**), 3.19-3.15 (m, 2H, **85b**), 2.36 (s, 3H, **85b**), 2.31 (s, 3H, **85b'**), 1.69 (d, *J* = 6.9 Hz, 3H, **85b**). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 199.4 (s, **85b'**), 197.1 (s, **85b**), 186.6 (d, **85b**), 185.5 (d, **85b'**), 138.6 (s, **85b**), 138.6 (s, **85b'**), 137.9 (s, **85b**), 137.4 (s, **85b'**), 136.7 (s, **85b'**), 136.7 (s, **85b**), 135.8 (s, **85b**), 135.7 (s, **85b**), 135.4 (s, **85b'**), 135.4 (s, **85b'**), 129.6 (d, **85b'**), 129.2 (d, **85b**), 128.7 (d, **85b**), 128.7 (d, **85b'**), 128.4 (d, **85b** + **85b'**), 127.7 (d, **85b'**), 127.6 (d, **85b**), 126.9 (d, **85b'**), 126.8 (d, **85b**), 126.5 (d, **85b**), 126.4 (d, **85b'**), 124.7 (s, **85b** + **85b'**), 124.2 (s, **85b**), 124.0 (s, **85b'**), 123.5 (d, **85b**), 123.2 (d, **85b'**), 122.6 (d, **85b**), 122.4 (d, **85b'**), 111.9 (d, **85b**), 111.7 (d, **85b'**), 52.0 (d, **85b'**), 48.4 (t, **85b**), 48.3 (t, **85b'**), 45.8 (t, **85b**), 29.8 (t, **85b**), 21.0 (q, **85b** + **85b'**), 19.0 (q, **85b'**). **IR (cm^{-1}):** ν 2922, 1670, 1497, 1464, 1410, 1083, 744. **HRMS**: *m/z* calculated for $C_{26}H_{24}NO_2$ $[M+H]^+$: 382.1802; found: 382.1801

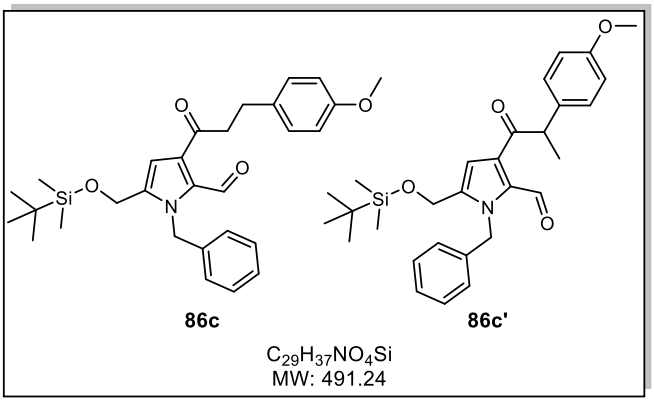
Synthesis of 1-benzyl-3-(2-(4-methoxyphenyl)propanoyl)-1*H*-indole-2-carbaldehyde (85c) and **1-benzyl-3-(3-(4-methoxyphenyl)propanoyl)-1*H*-indole-2-carbaldehyde (85c').**



Prepared according to general procedure **GP10** from the reaction of the mixture of compounds **69c** and **69c'** (152 mg, 0.38 mmol, 1 equiv.) and HCl (3 mL, 3 mmol, 7.9 equiv.) in Et_2O (5 mL) over 1 h to afford 120 mg (quantitative yield, **85c**/**85c'**: 88/12) of **85c** and **85c'** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.50 (s, 1H, **85c**), 10.22 (s, 1H, **85c'**), 8.03 (m, 2H, 1H **85c** + 1H **85c'**), 7.50-7.41 (m, 4H, 2H **85c** + 2H **85c'**), 7.38-7.34 (m, 2H, 1H **85c** + 1H **85c'**), 7.31-7.22 (m, 12H, 6H **85c** + 6H **85c'**), 7.11-7.09 (m, 2H, 1H **85c** + 1H **85c'**), 6.90-6.87 (m, 4H, 2H **85c** + 2H **85c'**), 5.89 (s, 2H, **85c**), 5.83 (d, *J* = 6.3 Hz, 2H, **85c'**), 4.76 (q, *J* = 6.9 Hz, 1H, **85c'**), 3.82 (s, 3H, **85c**), 3.77 (s, 3H, **85c'**), 3.49 (t, *J* = 7.5 Hz, 2H, **85c**), 3.15 (t, *J* = 7.6 Hz, 2H, **85c**), 1.68 (d, *J* = 6.8 Hz, 3H, **85c'**). **^{13}C-NMR (101 MHz, $CDCl_3$):**

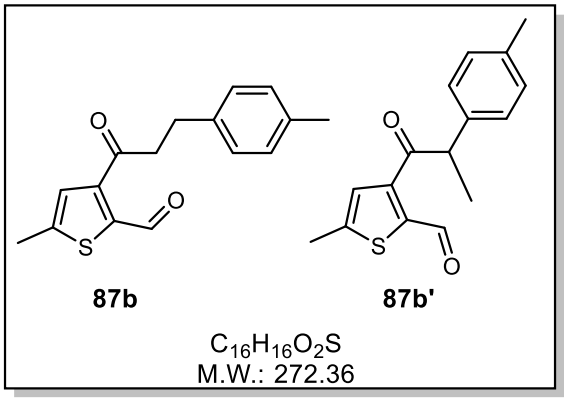
δ 199.55 (s, **85c'**), 197.21 (s, **85c**), 186.6 (d, **85c**), 185.4 (d, **85c'**), 158.6 (s, **85c'**), 158.1 (s, **85c**), 138.6 (s, **85c**), 138.6 (s, **85c**), 136.7 (s, **85c'**), 136.7 (s, **85c**), 135.7 (s, **85c**), 135.4 (s, **85c'**), 133.0 (s, **85c**), 132.4 (s, **85c'**), 129.4 (d, **85c**), 128.9 (d, **85c'**), 128.7 (d, **85c**), 128.7 (d, **85c'**), 127.6 (d, **85c**), 127.5 (d, **85c'**), 126.9 (d, **85c'**), 126.9 (d, **85c**), 126.5 (d, **85c**), 126.4 (d, **85c'**), 124.8 (s, **85c** + **85c'**), 124.2 (s, **85c**), 124.0 (s, **85c'**), 123.5 (d, **85c**), 123.2 (d, **85c'**), 122.6 (d, **85c**), 122.4 (d, **85c'**), 114.2 (d, **85c'**), 114.0 (d, **85c**), 111.9 (d, **85c**), 111.8 (d, **85c'**), 55.3 (q, **85c**), 55.2 (q, **85c'**), 51.6 (d, **85c'**), 48.4 (t, **85c**), 48.3 (t, **85c'**), 46.0 (t, **85c**), 29.4 (t, **85c**), 19.0 (q, **85c'**). **IR (cm^{-1}):** ν 2927, 1688, 1510, 1497, 1464, 1245, 1076, 1031, 727. **HRMS**: *m*/*z* calculated for $C_{26}H_{23}NNaO_3$ $[M+H]^+$: 420.1570; found: 420.1570.

Synthesis of 1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-(4-methoxyphenyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (86c) and **1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(3-(4-methoxyphenyl)propanoyl)-1*H*-pyrrole-2-carbaldehyde (86c').**



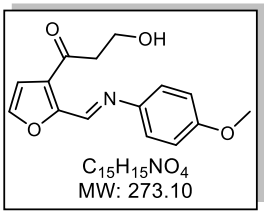
Prepared according to general procedure **GP10** from the reaction of the mixture of compounds **70c** and **70c'** (167 mg, 0.34 mmol, 1 equiv.) and HCl (1 mL, 1 mmol, 2.94 equiv.) in Et_2O (3 mL) over 2 h to afford 137 mg (quantitative yield, **86c**/**86c'**: 64/36) of **86c** and **86c'** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.34 (s, 1H, **86c**), 10.31 (s, 1H, **86c'**), 7.31-7.15 (m, 10H, 5H **86c** + 5H **86c'**), 6.96 (dd, *J* = 8.1, 1.4 Hz, 2H, 1H **86c** + 1H **86c'**), 6.94-6.90 (m, 2H, 1H **86c** + 1H **86c'**), 6.88-6.82 (m, 4H, 2H **86c** + 2H **86c'**), 6.55 (s, 1H, **86c**), 6.49 (s, 1H, **86c'**), 5.77-5.73 (m, 3H, 2H **86c** + 1H **86c'**), 5.65.5.61 (d, *J* = 15.8 Hz, 1H, **86c'**), 4.55 (s, 2H, **86c**), 4.49 (s, 2H, **86c'**), 4.41 (q, *J* = 6.9 Hz, 1H, **86c'**), 3.79 (s, 3H, **86c**), 3.78 (s, 3H, **86c'**), 3.17 (t, *J* = 7.6 Hz, 2H, **86c**), 3.01 (t, *J* = 6.9 Hz, 2H, **86c**), 1.50 (d, *J* = 6.9 Hz, 3H, **86c'**), 0.87 (s, 9H, **86c**), 0.85 (s, 9H, **86c'**), 0.03 (s, 6H, **86c**), -0.02 (s, 3H, **86c'**), -0.04 (s, 3H, **86c'**). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.8 (s, **86c'**), 197.6 (s, **86c**), 184.0 (d, **86c**), 184.0 (d, **86c'**), 158.6 (s, **86c'**), 158.0 (s, **86c**),139.7 (s, **86c**), 139.6 (s, **86c'**), 136.9 (s, **86c**), 136.8 (s, **86c'**), 133.5 (s, **86c'**), 133.2 (s, **86c**), 132.3 (s, **86c'**), 131.7 (s, **86c**), 131.0 (s, **86c**), 130.9 (s, **86c'**), 129.3 (s, **86c**), 128.8 (d, **86c'**), 128.6 (d, **86c**), 128.6 (d, **86c'**), 127.4 (d, **86c**), 127.3 (d, **86c'**), 126.1 (d, **86c** + **86c'**), 114.4 (d, **86c'**), 114.0 (d, **86c**), 111.6 (d, **86c'**), 111.3 (d, **86c**), 57.2 (t, **86c** + **86c'**), 55.3 (q, **86c**), 55.2 (q, **86c'**), 49.6 (d, **86c'**), 49.4 (t, **86c**), 49.3 (t, **86c'**), 43.0 (t, **86c**), 29.3 (t, **86c**), 27.8 (q, **86c**), 27.8 (q, **86c'**), 19.0 (q, **86c'**), 18.2 (s, **86c**), 18.2 (s, **86c'**), -5.4 (q, **86c**), -5.4 (q, **86c'**). **IR (cm^{-1}):** ν 2927, 2955, 1661, 1428, 1110, 1066, 836. **HRMS**: *m*/*z* calculated for $C_{29}H_{37}NNaO_4Si$ $[M+Na]^+$: 514.2383; found: 514.2383.

Synthesis of 5-methyl-3-(2-(*p*-tolyl)propanoyl)thiophene-2-carbaldehyde (87b) and **5-methyl-3-(3-(*p*-tolyl)propanoyl)thiophene-2-carbaldehyde (87b').**



Prepared according to general procedure **GP10** from the reaction of compound **76b** and **76b'** (59 mg, 0.21 mmol, 1 equiv.) and HCl (1.5 mL, 1.5 mmol, 5 equiv.) in Et_2O (3 mL) over 3 h to afford 56 (quantitative yield, **87b**/**87b'**: 79/21) of **87b** and **87b'** as yellow solid. **M.p.:** 68-70 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.36 (s, 1H, **87b**), 10.31 (s, 1H, **87b'**), 7.13 (m, 5H **87b** + 5H **87b'**), 4.34 (q, *J* = 6.8 Hz, 1H, **87b'**), 3.19 (t, *J* = 7.5 Hz, 2H, **87b**), 3.02 (t, *J* = 7.5 Hz, 2H, **87b**), 2.54 (s, 3H, **87b**), 2.47 (s, 3H, **87b'**), 2.32 (m, 3H **87b** + 3H **87b'**), 1.51 (d, *J* = 6.8 Hz, 3H, **87b'**). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.8 (s, **87b'**), 195.5 (s, **87b**), 184.8 (d, **87b**), 184.8 (d, **87b'**), 149.3 (s, **87b**), 148.9 (s, **87b'**), 145.4 (s, **87b'**), 144.9 (s, **87b**), 144.6 (s, **87b'**), 144.3 (s, **87b**), 137.5 (s, **87b**), 137.1 (s, **87b'**), 137.1 (s, **87b'**), 135.9 (s, **87b**), 129.9 (d, **87b'**), 129.3 (d, **87b**), 128.2 (d, **87b**), 127.9 (d, **87b'**), 127.8 (d, **87b**), 127.6 (d, **87b'**), 51.1 (d, **87b'**), 44.0 (t, **87b**), 29.4 (t, **87b**), 21.0 (q, **87b'**), 21.0 (q, **87b**), 19.0 (q, **87b'**), 16.1 (q, **87b'**), 16.0 (q, **87b**). **IR (cm^{-1}):** ν 2922, 1679, 1655, 1450, 1370, 1212, 812. **HRMS:** *m/z* calculated for $C_{16}H_{17}O_2S$ $[M+H]^+$: 273.0944; found: 273.0944.

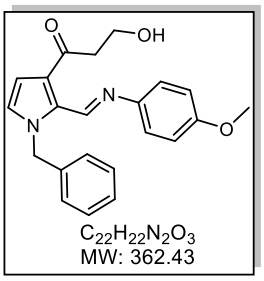
Synthesis of (E)-3-hydroxy-1-(2-(((4-methoxyphenyl)imino)methyl)furan-3-yl)propan-1-one (88).



Following a modified version of a reported procedure,[193] the compound **28a** (32 mg, 0.076 mmol, 1 equiv.) was dissolved in a co-solvent system THF/MeOH 1:1 (0.2 mL, 0.1 M). Then KF (9 mg, 0.16 mmol, 2 equiv.), $KHCO_3$ (15 mg, 0.16 mmol, 2 equiv.) and H_2O_2 (67 μL, 0.8 mmol 10 equiv.) was added. The mixture was stirred for 10 min at 0 °C and then for 4 h at room temperature. The mixture was then quenched with aqueous NaOH, extracted with two portions of AcOEt dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure. The crude extract was then purified by deactivated silica gel flash chromatography eluting with Pentane/AcOEt (20/80) to afford 11 mg of **88** (52% yield) as brown solid. **M.p.:** 97-98 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.99 (s, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.39 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 1.9 Hz, 1H), 4.02 (q, J = 5.6 Hz, 2H), 3.84 (s, 3H), 3.11 (t, J = 5.3 Hz, 2H), 2.47 (s, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 196.4 (s), 159.5 (s), 153.6 (s), 145.9 (d), 144.5 (d), 143.4 (s), 126.7 (s), 123.0 (d), 114.5 (d), 111.3 (d), 57.8 (t), 55.5 (q), 43.4 (t). **IR (cm^{-1}):** ν 3340, 2927, 1668, 1578, 1489, 1248, 1031, 762. **HRMS**: m/z calculated for $C_{15}H_{16}NO_4$ $[M+H]^+$: 274.1074; found: 274.1074.

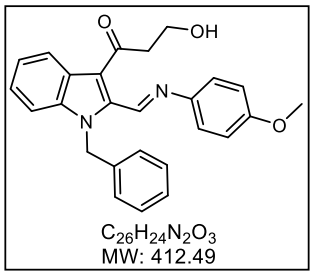
[193] Sunderhaus, J.D.; Lam, H.; Dudley G. B. *Org. Lett.,* **2003**, *5*, 4571-4573.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-3-hydroxypropan-1-one (90).



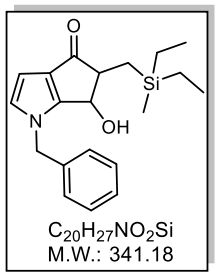
Following a modified version of a reported procedure,[193] compound **62a** (18 mg, 0.04 mmol, 1 equiv.) was dissolved in a co-solvent system THF/MeOH 1:1 (1 mL, 0.1 M). KF (12 mg, 0.16 mmol, 4 equiv.), $KHCO_3$ (16 mg, 0.16 mmol, 4 equiv.) and H_2O_2 (105 μL, 1.2 mmol, 30 equiv.) were added and the mixture was stirred for 6 h min at 60 °C. Then, the reaction mixture was quenched with aqueous NaOH, extracted with two portions of AcOEt dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure. The crude extract was then purified by deactivated silica gel flash chromatography eluting with Pentane/AcOEt (40/60) to afford 8.1 mg (56% yield) of **90** as yellow solid. **M.p.:** 84-85 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.26 (s, 1H), 7.31-7.26 (m, 3H), 7.19-7.16 (m, 4H), 6.90-6.88 (m, 2H), 6.78 (d, *J* = 3.0 Hz, 1H), 6.63 (d, *J* = 3.0 Hz, 1H), 5.88 (s, 2H), 3.99 (t, *J* = 5.2 Hz, 2H), 3.81 (s, 3H), 3.12 (t, *J* = 5.3 Hz, 2H), 2.89 (bs, 1H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.7 (s), 158.45 (s), 150.6 (d), 144.6 (s), 137.7 (s), 131.8 (s), 128.6 (d), 127.6 (d), 127.3 (d), 126.9 (d), 126.8 (s), 122.3 (d), 114.4 (d), 111.1 (d), 58.4 (t), 55.5 (q), 53.1 (t), 42.2 (t). **IR (cm^{-1}):** ν 3383, 2931, 1652, 1615, 1502, 1482, 1243, 1029, 726. **HRMS**: *m*/*z* calculated for $C_{22}H_{23}N_2O_3$ $[M+H]^+$: 363.1703; found: 363.1703.

Synthesis of (*E*)-1-(1-benzyl-2-(((4-methoxyphenyl)imino)methyl)-1*H*-indol-3-yl)-3-hydroxypropan-1-one (91).



Following a modified version of a reported procedure,[22] compound **64b** (42 mg, 0.08 mmol, 1 equiv.) was dissolved in a co-solvent system THF/MeOH 1:1 (1 mL, 0.1 M). KF (31 mg, 0.32 mmol, 4 equiv.), $KHCO_3$ (35 mg, 0.32 mmol, 4 equiv.) and H_2O_2 (215 μL, 2.4 mmol, 30 equiv.) were added and the mixture was stirred for 6 h at 60 °C. Then, the reaction mixture was quenched with aqueous NaOH, extracted with two portions of AcOEt dried on $MgSO_4$, filtrated and the volatiles were evaporated under reduce pressure. The crude extract was then purified by deactivated silica gel flash chromatography eluting with Pentane/AcOEt (60/40) to afford 23 mg (69% yield) of **91** as yellow solid. **M.p.:** 133-134 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 9.43 (s, 1H), 8.02 (dd, *J* = 6.3, 2.7 Hz, 1H), 7.44 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.36-7.32 (m, 2H), 7.29-7.20 (m, 5H), 7.15-7.10 (m, 2H), 6.95-6.89 (m, 2H), 6.18 (d, *J* = 7.5 Hz, 2H), 4.12 (t, *J* = 5.2 Hz, 2H), 3.83 (s, 3H), 3.41 (t, J = 5.2 Hz, 2H), 2.80 (bs, 1H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 197.9 (s), 159.1 (s), 151.3 (d), 143.9 (s), 139.0 (s), 138.7 (s), 137.4 (s), 128.6 (d), 127.3 (d), 126.6 (d), 125.3 (s), 124.9 (d), 123.0 (d), 122.7 (d), 121.5 (d), 119.2 (s), 114.4 (d), 111.6 (d), 58.5 (t), 55.5 (q), 48.8 (t), 45.4 (t). **IR** (cm^{-1}): ν 3410, 2954, 1642, 1507, 1248, 1031, 832. **HRMS**: *m*/*z* calculated for $C_{22}H_{22}N_2NaO_3$ $[M+H]^+$: 435.1685; found: 435.1618.

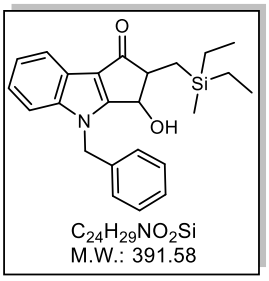
Synthesis of 1-benzyl-5-((diethyl(methyl)silyl)methyl)-6-hydroxy-5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one (92).



$C_{20}H_{27}NO_2Si$
M.W.: 341.18

In a round bottom flask equipped with magnetic stirrer, compound **62g** (83 mg, 0.24 mmol, 1 equiv.) was dissolved in THF (1.2 mL, 0.2 M). Then KHMDS (63 µL, 0.29 mmol, 1.2 equiv., 1 M in THF) was added. The mixture was stirred at room temperature for 6 h at 60 °C, filtered over celite and washed with DCM and the volatiles were evaporated under reduce pressure. The crude extract was then purified by silica gel flash chromatography eluting with Pentane/Et_2O (70/30) to afford 31 mg (38% yield) of **92** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.39-7.33 (m, *J* = 3.2 Hz, 3H), 7.22 (dd, *J* = 7.2, 0.8 Hz, 2H), 6.84 (d, *J* = 3.0 Hz, 1H), 6.29 (d, *J* = 3.0 Hz, 1H), 5.17 (d, *J* = 3.6 Hz, 2H), 4.60 (d, *J* = 1.9 Hz, 1H), 2.71 (ddd, *J* = 11.3, 4.0, 2.0 Hz, 1H), 1.28 (dd, *J* = 15.0, 4.0 Hz, 2H), 0.93 (td, *J* = 7.8, 2.2 Hz, 6H), 0.70-0.52 (m, 5H), 0.02 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.7 (S), 155.1 (s), 136.2 (s), 130.2 (d), 129.0 (d), 128.3 (d), 127.4 (d), 126.7 (s), 102.9 (d), 71.6 (d), 60.6 (d), 51.5 (t), 13.9 (t), 7.3 (q), 5.6 (t), 5.4 (t), -5.5 (q). **IR (cm^{-1}):** ν 3345, 2952, 2874, 1678, 1513, 1455, 1251, 980. **HRMS**: *m/z* calculated for $C_{20}H_{28}NO_2Si$ $[M+H]^+$: 342.1889; found: 342.1885.

Synthesis of 4-benzyl-2-((diethyl(methyl)silyl)methyl)-3-hydroxy-3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one (93).



$C_{24}H_{29}NO_2Si$
M.W.: 391.58

In a round bottom flask equipped with magnetic stirrer, compound **64g** (83 mg, 0.21 mmol, 1 equiv.) was dissolved in THF (1.1 mL, 0.2 M). Then, KHMDS (55 µL, 0.25 mmol, 1.2 equiv., 1 M in THF) was added. The mixture was stirred for 6 h at 60 °C, filtered over celite and washed with DCM and the volatiles were evaporated under reduce pressure. The crude extract was then purified by silica gel flash chromatography eluting with Pentane/AcOEt (60/40) to afford 39 mg (47% yield) of **93** as yellow solid. **M.p.:** 122-124 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.93-7.85 (m, 1H), 7.43-7.12 (m, 8H), 5.44 (d, *J* = 16.0 Hz, 1H), 5.35 (d, *J* = 16.0 Hz, 1H), 4.77 (s, 1H), 2.77 (ddd, *J* = 11.2, 4.1, 2.0 Hz, 1H), 1.29 (dd, *J* = 15.0, 4.2 Hz, 2H), 0.93 (td, *J* = 7.9, 2.0 Hz, 6H), 0.67 (dd, *J* = 15.0, 11.2 Hz, 1H), 0.63-0.52 (m, 4H), 0.03 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 196.2 (s), 166.3 (s), 143.0 (s), 135.9 (s), 129.0 (d), 128.0 (d), 126.9 (d), 124.2 (d), 122.6 (d), 121.7 (d), 121.0 (s), 118.8 (s), 111.0 (d), 72.1 (d), 59.9 (d), 48.3 (t), 14.2 (t), 7.3 (q), 5.5 (t), 5.4 (t), -5.9 (q). **IR (cm^{-1}):** ν 2951, 2873, 1661, 1476, 1446, 1264, 732. **HRMS**: *m/z* calculated for $C_{24}H_{29}NNaO_2Si$ $[M+H]^+$: 414.1865; found: 414.1857.

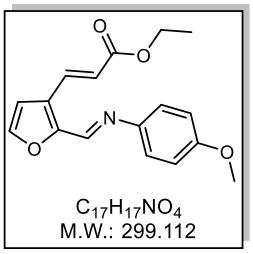
4. Acceptorless Fujiwara Moritani reaction

4.1. Preparation and characterization of alkenylated compounds

General procedure (GP11) for the Ruthenium vinylation Fujiwara-Moritani type reaction of 2-aldimineheteroaromatic derivatives

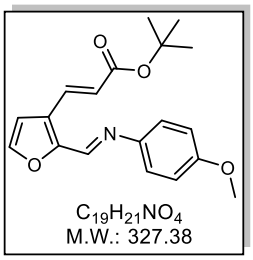
To ace pressure tube, dried under vacuum, was added the $Ru_3(CO)_{12}$ (16 mg, 0.025 mmol, 0.05 equiv.). The aldimine (0.5 mmol, 1 equiv.) dissolved in PhMe (0.5 M), was then added followed by the acrylate partner (2 mmol, 4 equiv.). The solution was heated at 135 °C for 16-24 h. The mixture was filtered over celite and washed with DCM. The volatiles were removed under reduced pressure and the crude was then purified by deactivated silica column chromatography affording the corresponding product.

Synthesis of Ethyl (*E*)-3-(2-((*E*)-((4-methoxyphenyl)imino)methyl)furan-3-yl)acrylate (95a).



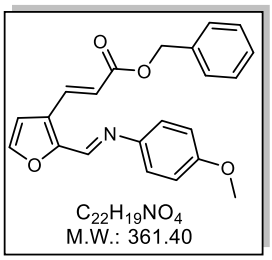
Prepared according to general procedure **GP11** from the reaction of **10** (100 mg, 0.5 mmol, 1 equiv.) with ethyl acrylate **94a** (225 μL, 2 mmol, 4 equiv.) under nitrogen atmosphere. The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (75/25) to afford 68 mg (46% yield) of **95a** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.46 (s, 1H), 7.96 (d, *J* = 15.8 Hz, 1H), 7.45 (d, *J* = 1.3 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.63 (d, *J* = 1.6 Hz, 1H), 6.23 (d, *J* = 15.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 166.6 (s), 159.0 (s), 150.7 (s), 145.4 (d), 143.9 (s), 143.4 (d), 133.1 (d), 125.7 (s), 122.6 (d), 120.8 (d), 114.5 (d), 109.5 (d), 60.6 (t), 55.5 (q), 14.3 (q). **IR (cm^{-1}):** ν 2928, 1685, 1508, 1247, 1179, 1031, 762. **HRMS:** *m*/*z* calculated for $C_{17}H_{18}NO_4$ $[M+H]^+$: 300.1230; found: 300.1231.

Synthesis of *tert*-butyl (*E*)-3-(2-((*E*)-((4-methoxyphenyl)imino)methyl)furan-3-yl)acrylate (95c).



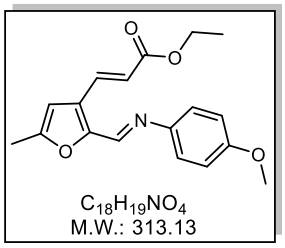
Prepared according to general procedure **GP11** from the reaction of **10** (100 mg, 0.5 mmol, 1 equiv.) with *t*-butyl acrylate **94c** (290 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) to afford 63 mg (38% yield) of **95c** as yellow solid. **M.p.:** 103-105 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.53 (s, 1H), 7.95 (d, *J* = 15.8 Hz, 1H), 7.55 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.95 (dd, *J* = 8.5, 6.6 Hz, 2H), 6.71 (s, 1H), 6.26 (d, *J* = 15.7 Hz, 1H), 3.84 (s, 3H), 1.54 (s, 9H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 166.0 (s), 159.0 (s), 150.4 (s), 145.7 (d), 143.9 (s), 132.0 (d), 126.0 (s), 122.6 (d), 122.3 (d), 114.5 (d), 112.2 (d), 109.5 (d), 80.8 (s), 55.5 (q), 28.2 (q). **IR (cm^{-1}):** ν 2928, 1695, 1631, 1506, 1244, 1145, 854. **HRMS:** *m*/*z* calculated for $C_{19}H_{21}NO_4$ $[M+H]^+$: 328.1549; found: 328.1549.

Synthesis of Benzyl (*E*)-3-(2-((*E*)-((4-methoxyphenyl)imino)methyl)furan-3-yl)acrylate (95d).



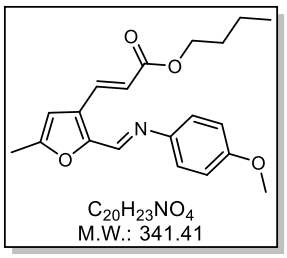
Prepared according to general procedure **GP11** from the reaction of **10** (100 mg, 0.5 mmol, 1 equiv.) with benzyl acrylate **94d** (300 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Hexane/Et_2O (85/15) to afford 115 mg (46% yield) of **95d** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.44 (s, 1H), 8.05 (d, *J* = 15.8 Hz, 1H), 7.44 (s, 1H), 7.34-7.20 (m, 7H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.61 (s, 1H), 6.27 (d, *J* = 15.8 Hz, 1H), 5.17 (s, 2H), 3.74 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 166.4 (s), 159.1 (s), 150.8 (s), 145.4 (d), 143.8 (s), 143.5 (d), 136.0 (s), 133.9 (d), 128.6 (d), 128.3 (d), 128.3 (d), 125.5 (s), 122.6 (d), 120.3 (d), 114.5 (d), 109.5 (d), 66.5 (t), 55.5 (q). **IR (cm^{-1}):** ν 2918, 1708, 1614, 1493, 1247, 1142. **HRMS:** *m/z* calculated for $C_{22}H_{19}NNaO_4$ $[M+Na]^+$: 384.1212; found: 384.1213.

Synthesis of Ethyl (*E*)-3-(2-((*E*)-((4-methoxyphenyl)imino)methyl)-5-methylfuran-3-yl)acrylate (96a).



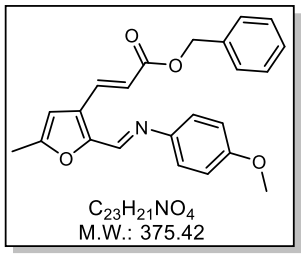
Prepared according to general procedure **GP11** from the reaction of **23** (107 mg, 0.5 mmol, 1 equiv.) with ethyl acrylate **94a** (225 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) to afford 51 mg (37% yield) of **96a** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.45 (s, 1H), 7.91 (d, *J* = 15.7 Hz, 1H), 7.28 (t, *J* = 6.1 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.32 (s, 1H), 6.23 (d, *J* = 15.7 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.40 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 166.7 (s), 158.7 (d), 156.6 (s), 149.6 (s), 144.3 (s), 143.2 (s), 133.0 (d), 127.5 (s), 122.5 (d), 120.3 (d), 114.4 (d), 105.8 (d), 60.6 (t), 55.5 (q), 14.3 (q), 13.9 (q). **IR (cm^{-1}):** ν 2980, 1704, 1614, 1500, 1295, 1242, 1174, 1031, 831. **HRMS:** *m/z* calculated for $C_{18}H_{19}NNaO_4$ $[M+Na]^+$: 336.1206; found: 336.1207.

Synthesis of Butyl (*E*)-3-(2-((*E*)-((4-methoxyphenyl)imino)methyl)-5-methylfuran-3-yl)acrylate (96b).



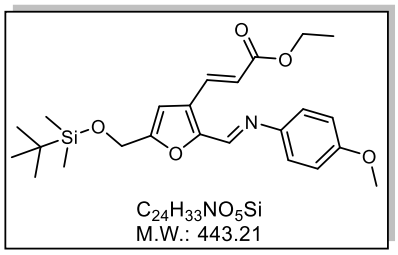
Prepared according to general procedure **GP11** from the reaction of **23** (107 mg, 0.5 mmol, 1 equiv.) with butyl acrylate **94b** (287 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with hexane/AcOEt (70/30) to afford 64 mg (38% yield) of **96b** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.47 (s, 1H), 7.92 (d, *J* = 15.7 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.34 (s, 1H), 6.25 (d, *J* = 15.7 Hz, 1H), 4.21 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 2.42 (s, 3H), 1.72-1.66 (m, 2H), 1.47-1.41 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 166.8 (s), 158.8 (s), 156.5 (s), 149.7 (s), 144.3 (s), 143.2 (d), 133.1 (d), 127.5 (s), 122.5 (d), 120.4 (d), 114.4 (d), 105.9 (d), 64.5 (t), 55.5 (q), 30.8 (t), 19.2 (t), 13.9 (q), 13.7 (q). **IR (cm^{-1}):** ν 2958, 1706, 1629, 1501, 1244, 1175, 1033. **HRMS:** *m/z* calculated for $C_{20}H_{24}NO_4$ $[M+H]^+$: 342.1705; found: 342.1706.

Synthesis of Benzyl (*E*)-3-(2-((*E*)-((4-methoxyphenyl)imino)methyl)-5-methylfuran-3-yl)acrylate (96d).



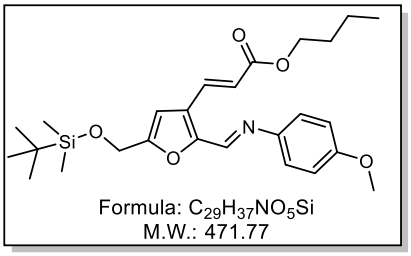
Prepared according to general procedure **GP11** from the reaction of **23** (107 mg, 0.5 mmol, 1 equiv.) with benzyl acrylate **94d** (300 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica 96d as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.37 (s, 1H), 7.92 (d, *J* = 15.7 Hz, 1H), 7.33-7.24 (m, 5H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.30-6.16 (m, 2H), 5.17 (s, 2H), 3.74 (s, 3H), 2.31 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 166.5 (s), 158.8 (s), 156.6 (s), 149.8 (s), 144.3 (s), 143.2 (d), 136.0 (s), 133.8 (d), 128.6 (d), 128.3 (d, 2C), 127.3 (s), 122.5 (d), 119.9 (d), 114.5 (d), 105.8 (d), 66.5 (t), 55.5 (q), 13.9 (q). **IR (cm^{-1}):** ν 2937, 1704, 1608, 1257, 1169, 1055. **HRMS:** *m*/*z* calculated for $C_{23}H_{22}NO_4$ $[M+H]^+$: 376.1549; found: 376.1552.

Synthesis of Ethyl (*E*)-3-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-((*E*)-((4-methoxyphenyl)imino)methyl)furan-3-yl)acrylate (97a).



Prepared according to general procedure **GP11** from the reaction of **24** (174 mg, 0.5 mmol, 1 equiv.) with ethyl acrylate **94a** (225 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (90/10) to afford 86 mg (39% yield) of **97a** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.49 (s, 1H), 8.02 (d, *J* = 15.8 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.57 (s, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 4.74 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 166.7 (s), 158.9 (d), 158.5 (s), 150.0 (s), 144.1 (s), 143.7 (s), 133.3 (d), 126.7 (s), 122.5 (d), 120.6 (d), 114.4 (d), 106.0 (d), 60.6 (t), 58.6 (t), 55.5 (q), 25.8 (q), 18.4 (s), 14.3 (q), -5.3 (q). **IR (cm^{-1}):** ν 2954, 2930, 1708, 1616, 1501, 1246, 1176, 1033, 834. **HRMS:** *m*/*z* calculated for $C_{24}H_{34}NO_5Si$ $[M+H]^+$: 444.2199; found: 444.2201.

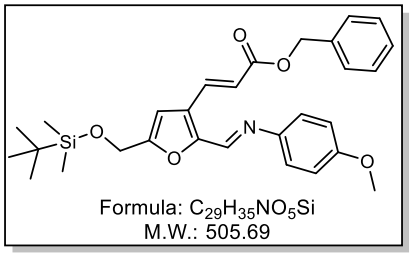
Synthesis of Butyl (*E*)-3-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-((*E*)-((4-methoxyphenyl)imino)methyl)furan-3-yl)acrylate (97b).



Prepared according to general procedure **GP11** from the reaction of **24** (174 mg, 0.5 mmol, 1 equiv.) with butyl acrylate **94b** (287 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (90/10) to afford 114 mg (48% yield) of **97b** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.49 (s, 1H), 8.04 (d, *J* = 15.8 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.58 (s, 1H), 6.31 (d, *J* = 15.8 Hz, 1H), 4.75 (s, 2H), 4.22 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 1.69 (d, *J* = 7.0 Hz, 2H), 1.44 (sext, *J* = 7.4 Hz, 2H), 0.99-0.93 (m, 12H), 0.12 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 166.8 (s), 158.9 (s),

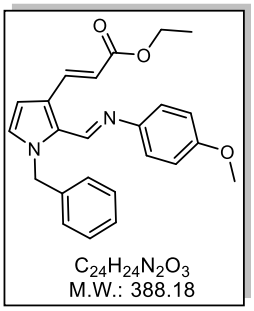
158.6 (s), 149.9 (s), 144.1 (s), 143.7 (d), 133.3(d), 126.8 (s), 122.5 (d), 120.7 (d), 114.5 (d), 106.0 (d), 64.6 (t), 58.6 (t), 55.5 (q), 30.8 (t), 25.8 (q), 19.2 (t), 18.4 (s), 13.7 (q), -5.3 (q). **IR (cm^{-1}):** ν 2928, 1695, 1631, 1506, 1244, 1145, 1034, 854. **HRMS:** *m/z* calculated for $C_{26}H_{38}NO_5Si$ $[M+H]^+$: 472.2519; found: 472.2520.

Synthesis of benzyl (*E*)-3-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-((*E*)-((4-methoxyphenyl)imino)methyl)furan-3-yl)acrylate (97d).



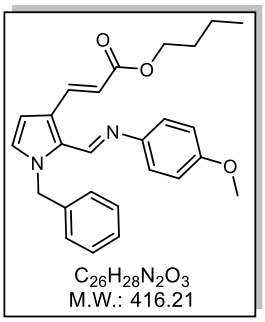
Prepared according to general procedure **GP11** from the reaction of **24** (174 mg, 0.5 mmol, 1 equiv.) with benzyl acrylate **94d** (300 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with hexane/Et_2O (85/15) to afford 115 mg (46% yield) of **97d** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.50 (s, 1H), 8.14 (d, *J* = 15.8 Hz, 1H), 7.44-7.34 (m, 6H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.58 (s, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 5.26 (s, 2H), 4.75 (s, 2H), 3.84 (s, 3H), 0.94 (s, 9H), 0.13 (s, 6H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 166.5 (s), 158.9 (s), 158.5 (s), 150.2 (s), 144.1 (s), 143.8 (d), 136.0 (s), 134.1 (d), 128.6 (d), 128.3 (d), 126.5 (s), 122.6 (d), 122.3 (d), 120.2 (d), 114.5 (d) 106.0 (d), 66.5 (t), 58.6 (t), 55.5 (q), 25.9 (q), 18.4 (s), -5.3 (q). **IR (cm^{-1}):** ν 2954, 2929, 1712, 1632, 1617, 1502, 1248, 1164, 836. **HRMS:** *m/z* calculated for $C_{29}H_{36}NO_5Si$ $[M+H]^+$: 506.2363; found: 506.2365.

Synthesis of Ethyl (*E*)-3-(1-benzyl-2-((*E*)-((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)acrylate (98a).



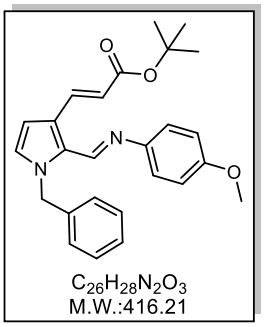
Prepared according to general procedure **GP11** from the reaction of **50** (141 mg, 0.5 mmol, 1 equiv.) with ethyl acrylate **94a** (225 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (70/30) to afford 139 mg (74% yield) of **98a** as yellow solid. **M.p.:** 84-85 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.53 (s, 1H), 7.92 (d, *J* = 15.6 Hz, 1H), 7.25-7.15 (m, 3H), 7.08 (d, *J* = 6.9 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.76 (d, *J* = 2.9 Hz, 1H), 6.43 (d, *J* = 2.9 Hz, 1H), 6.17 (d, *J* = 15.6 Hz, 1H), 5.69 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 167.5 (s), 158.1 (s), 146.1 (d), 145.1 (s), 138.1 (s), 135.7 (d), 129.2 (s), 128.8 (d), 128.6 (d), 127.4 (d), 127.1 (d), 126.6 (s), 121.9 (d), 116.2 (d), 114.4 (d), 106.8 (d), 60.2 (t), 55.5 (q), 52.6 (t), 14.4 (q). **IR (cm^{-1}):** ν 2979, 1696, 1613, 1502, 1438, 1242, 1151, 1035, 831. **HRMS:** *m/z* calculated for $C_{24}H_{25}N_2O_3$ $[M+H]^+$: 411.1679; found: 411.1679.

Synthesis of Butyl (*E*)-3-(1-benzyl-2-((*E*)-((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)acrylate (98b).



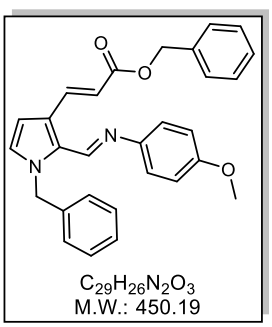
Prepared according to general procedure **GP11** from the reaction of **50** (141 mg, 0.5 mmol, 1 equiv.) with butyl acrylate **94b** (306 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) to afford 154 mg (74% yield) of **98b** as yellow solid. **M.p.:** 88-89 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.63 (s, 1H), 8.04 (d, *J* = 15.6 Hz, 1H), 7.36-7.29 (m, 2H), 7.29-7.25 (m, 1H), 7.18 (d, *J* = 7.1 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.53 (d, *J* = 2.8 Hz, 1H), 6.27 (d, *J* = 15.6 Hz, 1H), 5.78 (s, 2H), 4.22 (t, *J* = 6.7 Hz, 2H), 3.83 (s, 3H), 1.70 (quint, *J* = 7.2 Hz, 2H), 1.46 (sext, *J* = 1.5 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 167.6 (s), 158.2 (s), 146.1 (d), 145.1 (s), 138.14 (s), 135.7 (d), 129.2 (s), 128.8 (d), 128.6 (d), 127.5 (d), 127.1 (d), 126.6 (s), 121.9 (d), 116.2 (d), 114.4 (d), 106.9 (d), 64.2 (t), 55.5 (q), 52.6 (t), 30.9 (t), 19.2 (t), 13.8 (q). **IR (cm^{-1}):** ν 2957, 1701, 1615, 1503, 1439, 1245, 1173, 1153, 831. **HRMS:** *m*/*z* calculated for $C_{26}H_{28}N_2NaO_3$ $[M+Na]^+$: 433.1992; found: 433.1995.

Synthesis of *tert*-Butyl (*E*)-3-(1-benzyl-2-((*E*)-((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)acrylate (98c).



Prepared according to general procedure **GP11** from the reaction of **50** (141 mg, 0.5 mmol, 1 equiv.) with *tert*-butyl acrylate **94c** (290 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (90/10) to afford 109 mg (52% yield) of **98c** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.64 (s, 1H), 7.98 (d, *J* = 15.6 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.27 (dd, *J* = 9.9, 4.5 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 2.9 Hz, 1H), 6.53 (d, *J* = 2.9 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.78 (s, 2H), 3.84 (s, 3H), 1.57 (s, 9H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 167.0 (s), 158.1 (s), 146.1 (d), 145.1 (s), 138.2 (s), 134.8 (d), 129.0 (s), 128.7 (d), 128.6 (d), 127.4 (d), 127.1 (d), 126.8 (s), 121.9 (d), 118.1 (d), 114.4 (d), 106.8 (d), 80.1 (s), 55.5 (q), 52.6 (t), 28.3 (q). **IR (cm^{-1}):** ν 2976, 2931, 1697, 1615, 1503, 1244, 1140, 1033, 831. **HRMS:** *m*/*z* calculated for $C_{26}H_{28}N_2NaO_3$ $[M+Na]^+$: 439.1992; found: 439.1993.

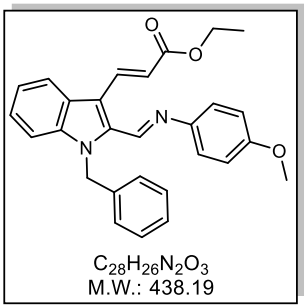
Synthesis of Benzyl (*E*)-3-(1-benzyl-2-((*E*)-((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)acrylate (98d).



Prepared according to general procedure **GP11** from the reaction of **50** (141 mg, 0.5 mmol, 1 equiv.) with benzyl acryalte **94d** (306 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) to afford 172 mg (72% yield) of **98d** as yellow solid. **M.p.:** 117-119°C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.49 (s, 1H), 7.98 (t, *J* = 12.7

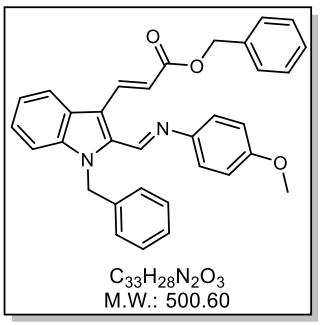
Hz, 1H), 7.32-7.13 (m, 8H), 7.05 (d, *J* = 7.1 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 2.7 Hz, 1H), 6.40 (d, *J* = 2.7 Hz, 1H), 6.20 (d, *J* = 15.6 Hz, 1H), 5.61 (d, *J* = 18.4 Hz, 2H), 5.14 (s, 2H), 3.70 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 167.4 (s), 158.2 (s), 146.0 (d), 145.0 (s), 138.1 (s), 136.5 (d), 136.4 (s), 129.4 (s), 128.8 (d), 128.7 (d), 128.6 (d), 128.2 (d), 128.1 (d), 127.5 (d), 127.1 (d), 126.5 (s), 122.0 (d), 115.7 (d), 114.4 (d), 106.9 (d), 66.1 (t), 55.5 (q), 52.6 (t). **IR (cm^{-1}):** ν 2955, 1702, 1614, 1502, 1439, 1244, 1149, 1029, 730. **HRMS:** *m*/*z* calculated for $C_{29}H_{26}N_2NaO_3$ $[M+Na]^+$: 473.1836; found: 473.1842.

Synthesis of Ethyl (*E*)-3-(1-benzyl-2-((*E*)-((4-methoxyphenyl)imino)methyl)-1*H*-indole-3-yl)acrylate (99a).



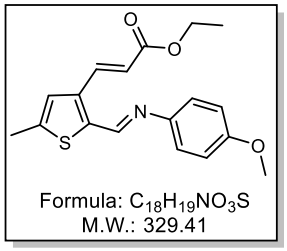
Prepared according to general procedure **GP11** from the reaction of **53** (171 mg, 0.5 mmol, 1 equiv.) with ethyl acrylate **94a** (225 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) to afford 164 mg (75% yield) of **99a** as yellow solid. **M.p.:** 139-141 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.93 (s, 1H), 8.32 (d, *J* = 15.9 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.41-7.32 (m, 2H), 7.29-7.21 (m, 4H), 7.21-7.17 (m, 2H), 7.12 (d, *J* = 6.9 Hz, 2H), 6.97-6.87 (m, 2H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.11 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 167.8 (s), 158.9 (s), 146.6 (d), 144.3 (s), 139.7 (s), 137.9 (s), 135.7 (d), 135.0 (s), 128.5 (d), 127.1 (d), 126.6 (d), 125.5 (d), 125.3 (s), 122.3 (d), 122.1 (d), 121.6 (d), 117.8 (s), 116.9 (d), 114.5 (d), 111.0 (d), 60.4 (t), 55.5 (q), 48.4 (t), 14.4 (q). **IR (cm^{-1}):** ν 2980, 2904, 1702, 1614, 1492, 1465, 1247, 1175, 1030, 831. **HRMS:** *m*/*z* calculated for $C_{28}H_{26}N_2NaO_3$ $[M+Na]^+$: 461.1836; found: 461.1836.

Synthesis of Benzyl (*E*)-3-(1-benzyl-2-((*E*)-((4-methoxyphenyl)imino)methyl)-1*H*-indole-3-yl)acrylate (99d).



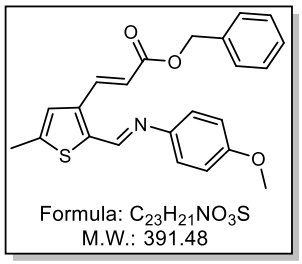
Prepared according to general procedure **GP11** from the reaction of **53** (171 mg, 0.5 mmol, 1 equiv.) with benzyl acrylate **94d** (306 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (90/10) to afford 172 mg (69% yield) of **99d** as yellow solid. **M.p.:** 142-143 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.92 (s, 1H), 8.39 (d, *J* = 15.9 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.39-7.33 (m, 7H), 7.18 (d, *J* = 8.9 Hz, 2H), 7.12 (d, *J* = 6.7 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 1H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.58 (d, *J* = 8.9 Hz, 1H), 6.10 (s, 2H), 5.30 (s, 2H), 3.84 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 167.7 (s), 158.9 (s), 146.5 (d), 144.3 (s), 139.7 (s), 137.9 (s, 2C), 136.4 (d), 135.2 (s), 128.6 (d), 128.3 (d), 127.2 (d), 126.6 (d), 125.6 (d), 125.3 (s), 122.4 (d), 122.2 (d), 121.6 (d), 117.6 (s), 116.3 (d), 115.0 (d), 114.7 (d), 114.5 (d), 111.0 (d), 66.2 (t), 55.6 (q), 48.4 (t). **IR (cm^{-1}):** ν 3034, 2953, 1708, 1618, 1497, 1249, 1167, 1031. **HRMS:** *m*/*z* calculated for $C_{33}H_{28}N_2NaO_3$ $[M+Na]^+$: 523.1992; found: 523.1995.

Synthesis of Ethyl (*E*)-3-(2-((*E*)-((4-methoxyphenyl)imino)methyl)-5-methylthiophen-3-yl)acrylate (100a).



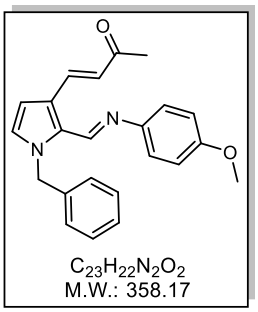
Prepared according to general procedure **GP11** from the reaction of **56** (115 mg, 0.5 mmol, 1 equiv.) with ethyl acrylate **94a** (225 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) to afford 79 mg (48% yield) of **100a** as yellow solid. **M.p.:** 89-90 °C. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.67 (s, 1H), 7.87 (d, *J* = 15.7 Hz, 1H), 7.19-7.12 (m, 2H), 6.88 (s, 1H), 6.87-6.80 (m, 2H), 6.20 (d, *J* = 15.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 2.41 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 167.0 (s), 158.6 (s), 148.1 (d), 144.8 (s), 144.2 (s), 141.5 (s), 138.7 (s), 134.8 (d), 124.3 (d), 122.5 (d), 119.8 (d), 114.4 (d), 60.7 (t), 55.5 (q), 15.9 (q), 14.3 (q). **IR (cm^{-1}):** ν 2978, 2934, 1705, 1609, 1471, 1291, 1245, 1173, 1034, 831. **HRMS**: *m*/*z* calculated for $C_{18}H_{19}NNaO_3S$ $[M+Na]^+$: 352.0978; found: 352.0978.

Synthesis of Benzyl (*E*)-3-(2-((*E*)-((4-methoxyphenyl)imino)methyl)-5-methylthiophen-3-yl)acrylate (100d).



Prepared according to general procedure **GP11** from the reaction of **56** (115 mg, 0.5 mmol, 1 equiv.) with benzyl acrylate **94d** (306 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (80/20) to afford 134 mg (68% yield) of **100d** as yellow solid. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.65 (s, 1H), 7.92 (d, *J* = 15.7 Hz, 1H), 7.27 (m, 5H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.85 (s, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.24 (d, *J* = 15.7 Hz, 1H), 5.15 (s, 2H), 3.72 (s, 3H), 2.37 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 165.8 (s), 157.6 (s), 146.9 (d), 143.8 (s), 143.1 (s), 140.7 (s), 137.5 (s), 135.0 (s), 134.4 (d), 127.6 (d), 127.2 (d), 127.2 (d), 123.2 (d), 121.5 (d), 118.3 (d), 113.4 (d), 65.4 (t), 54.4 (q), 14.8 (q). **IR (cm^{-1}):** ν 2924, 1710, 1609, 1506, 1472, 1214, 1163, 1033. **HRMS**: *m*/*z* calculated for $C_{18}H_{19}NNaO_3S$ $[M+Na]^+$: 414.1140; found: 414.1146.

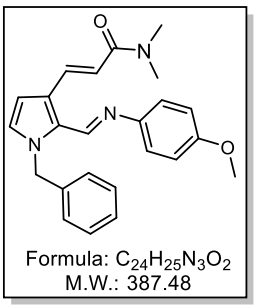
Synthesis of (*E*)-4-(1-benzyl-2-((*E*)-((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)but-3-en-2-one (98e).



Prepared according to general procedure **GP11** from the reaction of **50** (141 mg, 0.5 mmol, 1 equiv.) with but-3-en-2-one (162 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated **98e** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.61 (s, 1H), 8.01 (d, *J* = 15.9 Hz, 1H), 7.35-7.28 (m, 3H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 2.8 Hz, 1H), 6.59 (d, *J* = 15.1 Hz, 2H), 5.73 (s, 2H), 3.84 (s, 3H), 2.37 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 198.4 (s), 158.3 (s), 146.0 (d), 145.0 (s), 137.9 (s), 135.1 (d), 129.8 (s), 128.7 (d), 128.7 (d), 127.6 (d), 127.0 (d), 126.3 (s), 125.5 (d), 121.9 (d), 114.4 (d), 107.0 (d), 55.5 (q), 52.5 (t), 27.6 (q). **IR (cm^{-1}):** ν

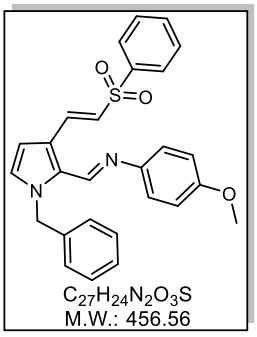
2933, 1611, 1502, 1438, 1244, 1032, 832. **HRMS:** *m*/*z* calculated for $C_{23}H_{22}N_2NaO_2$ $[M+Na]^+$: 381.1573 ; found: 381.1573.

Synthesis of (*E*)-3-(1-benzyl-2-((*E*)-((4-methoxyphenyl)imino)methyl)-1*H*-pyrrol-3-yl)-*N*,*N*-dimethylacrylamide (98f)



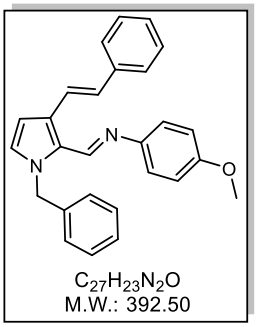
Prepared according to general procedure **GP11** from the reaction of **50** (141 mg, 0.5 mmol, 1 equiv.) *N*,*N*-dimethylacrylamide (206 μL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (20/80) to afford 17 mg (9% yield) of **98f** as yellow oil. **M.p.:** 105-107 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.67 (s, 1H), 7.98 (d, *J* = 15.0 Hz, 1H), 7.33-7.24 (m, 4H), 7.17 (d, *J* = 7.1 Hz, 2H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.90-6.86 (m, 2H), 6.84 (d, *J* = 2.9 Hz, 1H), 6.71 (d, *J* = 15.0 Hz, 1H), 6.50 (d, *J* = 2.8 Hz, 1H), 5.80 (s, 2H), 3.82 (s, 3H), 3.16 (s, 3H), 3.07 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 167.1 (s), 158.0 (s), 146.4 (d), 145.1 (s), 138.4 (s), 133.4 (d), 128.9 (s), 128.6 (d), 128.5 (d), 127.6 (s), 127.4 (d), 127.2 (d), 122.0 (d), 115.5 (d), 114.3 (d), 106.4 (d), 55.5 (q), 52.6 (t), 37.3 (q), 35.9 (q). **IR (cm^{-1}):** ν 2928, 2012, 1940, 1643, 1614, 1502, 1439, 1391, 1244, 1139, 1032. **HRMS**: *m*/*z* calculated for $C_{24}H_{26}N_3O_2$ $[M+H]^+$: 388.2020; found: 388.2028.

Synthesis of (*E*)-1-(1-benzyl-3-((*E*)-2-(phenylsulfonyl)vinyl)-1H-pyrrol-2-yl)-N-(4-methoxyphenyl)methanimine (98g).



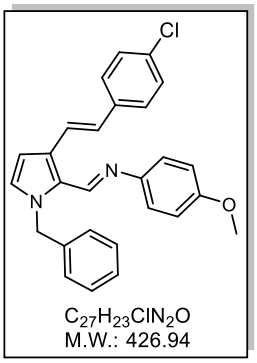
Prepared according to general procedure **GP11** from the reaction of **50** (141 mg, 0.5 mmol, 1 equiv.) with phenylvinylsulphone (336 mg, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (70/30) to afford 112 mg (49% yield) of **98g** as yellow solid. **M.p.:** 113-115 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.48 (s, 1H), 7.41-7.32 (m, 3H), 7.25-7.19 (m, 4H), 7.16-7.13 (m, 2H), 7.08 (d, *J* = 7.1 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 16.0 Hz, 1H), 6.82-6.77 (m, 3H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.66 (s, 2H), 3.72 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 158.5 (s), 145.4 (d), 144.6 (s), 141.4 (s), 137.7 (s), 134.3 (d), 133.0 (d), 130.1 (s), 129.2 (d), 128.8 (d), 128.7 (d), 127.6 (d), 127.5 (d), 127.1 (d), 124.4 (d), 123.8 (s), 122.1 (d), 114.5 (d), 107.3 (d), 55.6 (q), 52.6 (t). **IR (cm^{-1}):** ν 1608, 1502, 1443, 1314, 1243, 1143, 1031, 761, 726. **HRMS:** *m*/*z* calculated for $C_{27}H_{24}N_2NaO_3S$ $[M+Na]^+$: 479.1405; found: 479.1408.

Synthesis of (*E*)-1-(1-benzyl-3-((*E*)-styryl)-1*H*-pyrrol-2-yl)-*N*-(4-methoxyphenyl)methanimine (98h).



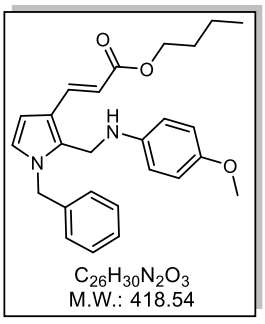
Prepared according to general procedure **GP10** from the reaction of **50** (141 mg, 0.5 mmol, 1 equiv.) with styrene (230 µL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with hexane/Et_2O (90/10) to afford 90 mg (46% yield) of **98h** as brown solid. **M.p.:** 90-91 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.49 (s, 1H), 7.42-7.33 (m, 3H), 7.28-7.19 (m, 4H), 7.19-7.12 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.91-6.77 (m, 4H), 6.46 (d, *J* = 2.5 Hz, 1H), 5.67 (s, 2H), 3.73 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 158.8 (s), 146.9 (d), 145.7 (s), 138.6 (s), 137.9 (s), 137.1 (s), 128.8 (d), 128.6 (d), 128.6 (d), 128.3 (d), 127.3 (d), 127.2 (d), 127.1 (d), 126.8 (s), 126.2 (d), 121.8 (d), 119.8 (d), 114.4 (d), 115.9 (d), 55.5 (q), 52.5 (t). **IR (cm^{-1}):** ν 2927, 1613, 1502, 1438, 1243, 1033, 734. **HRMS:** *m*/*z* calculated for $C_{27}H_{23}N_2NaO$ $[M+Na]^+$: 415.1787; found: 415.1791.

Synthesis of (*E*)-1-(1-benzyl-3-((*E*)-4-chlorostyryl)-1*H*-pyrrol-2-yl)-N-(4-methoxyphenyl)methanimine (98i).



Prepared according to general procedure **GP11** from the reaction of **50** (141 mg, 0.5 mmol, 1 equiv.) with chlorostyrene (254 µL, 2 mmol, 4 equiv.). The crude mixture was purified by flash column chromatography on deactivated silica gel eluting with hexane/Et_2O (90/10) to afford 123 mg (58% yield) of **98i** as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.50 (s, 1H), 7.36 (m, 3H), 7.21 (dd, *J* = 15.9, 6.4 Hz, 5H), 7.10 (d, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.85-6.78 (m, 4H), 6.47 (d, *J* = 2.6 Hz, 1H), 5.66 (s, 2H), 3.75 (s, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 157.8 (s), 146.8 (d), 145.9 (s), 138.56 (s, 2C), 136.4 (s), 132.6 (s), 129.7 (s), 128.8 (d), 128.6 (d), 128.6 (d), 127.4 (d), 127.3 (d), 127.1 (d), 126.7 (d), 121.8 (d), 120.6 (d), 114.4 (d), 55.6 (q), 52.4 (t). **IR (cm^{-1}):** ν 2918, 1696, 1615, 1506, 1245, 1176. **HRMS:** *m*/*z* calculated for $C_{27}H_{23}ClN_2NaO$ $[M+Na]^+$: 449.1397; found: 449.1396.

Synthesis of Butyl (*E*)-3-(1-benzyl-2-(((4-methoxyphenyl)amino)methyl)-1*H*-pyrrol-3-yl)acrylate (102).



Following a modified version of a reported procedure,[194] the compound **98b** (72 mg, 0.17 mmol, 1 equiv.) was dissolved in THF (1.72 mL, 0.1 M). The miixture was cool down at 0 °C and then $NaBH(OAc)_3$ (73 mg, 0.52 mmol, 3 equiv.). The reaction was stirred at room temperature for one night. The product was purified by flash column chromatography on deactivated silica gel eluting with Pentane/Et_2O (75/25) to afford 49 mg (69% yield) of **102** as brown oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.70 (d, *J* = 15.6 Hz, 1H), 7.37-7.28 (m, 3H), 7.02 (d, *J* = 7.0 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 6.72 (d, *J* = 2.3 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 2H), 6.46 (d, *J* = 2.2 Hz, 1H), 6.15 (d, *J* = 15.5 Hz, 1H), 5.16

[194] Khaliel, S.; Nadakumar, M. V.; Krautscheid, H.; Scheneider C. *Synlett*, **2008**, *7*, 2705-2707.

(s, 2H), 4.24-4.12 (m, 3H), 3.76 (s, 3H), 1.71-1.61 (m, 2H), 1.44-1.39 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C-NMR (101 MHz, $CDCl_3$):** δ 168.0 (s), 152.7 (s), 141.7 (s) 137.5 (s), 136.8 (d), 131.8 (s), 128.9 (d), 127.8 (d), 126.5 (d), 124.1 (d), 129.6 (s), 114.9 (d), 114.6 (d), 113.8 (d), 106.8 (d), 64.0 (t), 55.8 (q), 50.9 (t), 38.6 (t), 30.9 (t), 19.2 (t), 13.8 (q). **IR (cm^{-1}):** ν 3054, 2970, 1711, 1421, 1265, 1453. **HRMS:** *m*/*z* calculated for $C_{26}H_{31}N_2O_3$ $[M+H]^+$: 419.2335; found: 419.2338.

List of Published Papers

- **"Divergent Palladium- and Platinum-Catalyzed Intramolecular Hydroamination/Hydroarylation of *O*-Propargyl-2-aminophenols"**. M. S. Christodoulou, S. Giofrè, G. Broggini, A. Mazza, R. Sala, E. M. Beccalli. *Eur. J. Org. Chem.*, **2018**, 6176-6184.
- **"Palladium-catalyzed carbopalladiation/cyclization of allenes"**. R. Sala, G. Broggini. *Target in Heterocyclic Systems*, **2018**, *22*, 138-164.
- **"Iodoamination of Alkenyl Sulfonamides by Potassium Iodide and Hydrogen Peroxide in Aqueous Medium"**. S. Giofrè, R. Sala, E. M. Beccalli, L. Lo Presti, G. Broggini. *Helv. Chim. Acta*, **2019**, *102*, *7*, e1900088.
- **"Intramolecular Aminoazidation of Unactivated Terminal Alkenes by Palladium-Catalyzed Reactions with Hydrogen Peroxide as the Oxidant"**. F. Foschi, C. Loro, R. Sala, J. Oble, L. Lo Presti, E. M. Beccalli, G. Poli, G. Broggini. *Org. Lett*., **2020**, *22*, 1402-1406.
- **"Ru-Catalyzed Carbonylative Murai Reaction: Directed C3-Acylation of Biomass-Derived 2-Formyl Heteroaromatics"**. R. Sala, F. Roudesly, L. F. Veiros, G. Broggini, J. Oble, G. Poli. *Adv. Synth. Catal.*, **2020**, *362*, 2486-2493.
- **Transition Metal Catalyzed Azidation Reactions** R. Sala, C. Loro, F. Foschi, and G. Broggini *Catalysts* 2020, *10*, 1173-1239.

Acknowledgements

What is a Doctor in Chemistry if not a master degree student who believes too much in the future or a PhD student who has realized too much late his destiny? But what's done is done, so let's start the acknowledgements. I apologize in advance "to my four readers" (cit.) if they do not understand some citations: to each his own.

In primis, I want to dedicate this work to my grandparents, my grandfather Giovanni and my grandmother Mariuccia: I believe you are seeing this moment and I hope it's better of what you were expecting. Thank you for the patience, we finished a long trip, I'm proud and I hope you so.

Immediately after, could I not thank those who made all this possible? Professor Gianluigi Broggini is of course the first of the list, not only because he gave me this possibility, but also because he made a bet choosing me as student and that I hope I made him win. Maybe there was some skirmish, but surely there were many more goals and satisfactions. And in the end he is "our Gianni", just like that in his own way, so you can't ask for anything better. And then there is the Parisian front. Two names and I have already explained everything: Prof. Giovanni Poli and Dr., wait now Prof. Julie Oble. There are too many ways to describe my relationship with Giovanni: "Les Italiens", "Ciccio and Giova", many others, and my favourite ever "Ronaldo and The Coach". He always spurred me on and I owe him so much as a friend and mentor. Then the real boss arrives. Julie is the one I define as organization, help, comparison and support. Her "Bobbyyyyyyyy" screamed in the corridor to know where you were gave you that feeling of home that the ROCS group lives on: the PERFECTION.

Ok, ROCS team. A group of fellow soldiers in war: Alejandro, Alex, Miriam, Fabrice and Frank to control us poor desperate people with the guns. Greta and her faithful instagram, Karen and the Cuban dance, the half-man Joao and his beers, Milene and our songs, Fares and the carbon monoxide, the faithful classmate Islem and Filipa and Dylan, maybe my best friend in Paris, who help me from the first day with my nasty French with patience and irony. A special mention for Yang: the emblem of Chinese culture transplanted to Europe who guaranteed only exciting days for better or for worse.

The Como group is instead a kaleidoscope of personality: Pippo and his sugars, Silvia and the denksports and the trio Sara/Clem/Lizeth with the "magic bullet". In "Dottorandi on the road" I found two amazing men, Mirco and Scap. The first one is so professional and "PURE" exhilarating, while the second one is the companion of adventures, conferences, horrible courses and whoever has more has more: IRREPLACEABLE. Giano, Gio and Gioele are "my evil party" where fantasy meets epic, what else to add? Bonnie and Giulio, for you the sentence is simple: a few days after I met you, I thought for both of

them "They must be my friends". From "Mansion of Madness" to Lucca I realized that I'm lucky to know you, thank for all.

In my PhD, I'm not able to count the number of people I have known. Ghittu, Fede, Lety, Shara, Zambra, Jasmin, Trovats, Fabio, Drylands, Giulietta, Dilo, Nadia, Marta, Cerio and also all the students of high school and educational workshops that I followed: you are great. Thank you also to Francy, for the everyday support and for the happy moments. Two special mentions: the first one is for Camilla, one unexpected colleague with whom I laughed a lot in the third year. There were a lot of jokes and sidelong glances for everyday events in the "cube". The other mention is for Alessandro/Andrea/Alessio/Marco Ceriani, probably my best student, who transformed each single day in lab into a hilarious adventure. From Ettore to the "Nanoputians", from "Piazzetta" to "Rotavapor" there are too memories to resume Ale in one event: all of them are characteristic of his personality.

Let's open another macro world, the "APPUNTI OF STARCAZZEN": my best friends from Pavia University and someone even before. The trip to Paris to give me "SOME NEWS" is not enough. "The faithful companion of Charles Ravencourt" is not enough. The barbecues, the New Year Day and the evenings at the Valhalla are not enough. Manga and Anime, Board games and "Tetsuo Mori" are not enough. Erry, Dabbo, Sonia, Bric, Aly, Anto, #9, Barby, Sara are not enough. For what? They are not enough to say how much I am lucky to have a great group of friends with my same interests, ready for each stupid idea even before to say it, a group on which you can rely in any situation and which never lose on the way even in the most difficult situations. THANK YOU GUYS.

Some short lines to say a great great great thank you to my parents, Cinzia and Massimo. They give me the possibility to study (only this is a huge gift) surely making sacrifice. They support and endure me in too many occasions, always believing in me, even when I didn't believe in myself. Thank you again, now it's time to repay.

Last, but not least, as usual, I want speak about Federica, who is my shoulder from 8 years now. My girlfriend is a fixed point in my life: confidant, friend, partner, help, resource and much more. Without being honeyed, I just want to say that I'm glad you are here and that I couldn't do without it anymore. Thanks for everything, Love.

(Please, at this point image the music of "Avengers: Endgame")

Now it's time to close the acknowledgements, to wait a minute and to realize that I have finished also this chapter: ***a new life is starting****.*

Transition metal catalyzed cyclizations and C-H couplings of heterocyclic scaffolds

This thesis work is consecrated to the study of transition metal-catalyzed C-H activation processes for the synthesis or the functionalization of heterocycles. First, a new example of divergent catalysis was developed, which involves the employment of palladium tetrakis complex for the hydroamination or Pt(II) salts for the C-H hydroarylation reaction of *O*-propargyloxy anilines. The resulting benzopyranes are lately employed through a three steps efficient synthesis for the preparation of pyrano[3,2-*h*]quinolins.

A new efficient version of Ru(0)-catalyzed carbonylative Murai reaction for the C3-H acylation was investigated using bidentate or aromatic imines as directing group. The coupling with vinylsilanes or styrenes was extended to a series of pentatomic heterocycles with moderate or excellent yields and the reaxtion mechanism was clarified by DFT calculation.

Lastly, a totally new oxidant-free version of Ru(0)-catalyzed Fujiwara-Moritani reaction was studied. The trimeric complex of $Ru_3(CO)_{12}$ was employed for the C3-alkenylation with acrylates or electronpoor olefins with moderate or excellent yields. The reaction mechanism seems to proceed, after the activation step and the olefin insertion, through a β-elimination step followed by a reductive elimination of the metal species formed.

Keywords: Ruthenium; Transition Metals; Catalysis; Heterocycles; Hydroamination; Hydroarylation; Murai; Fujiwara-Moritani.

Cyclisations catalysées par un métal de transition et couplages C-H d'échafaudages hétérocycliques

Ce travail de thèse est consacré à l'étude des processus d'activation C-H catalysés par les métaux de transition pour la synthèse ou la fonctionnalisation d'hétérocycles. Tout d'abord, un nouvel exemple de catalyse divergente a été développé, qui implique l'utilisation du complexe tétrakis de palladium pour l'hydroamination ou des sels de Pt(II) pour la réaction d'hydroarylation C-H des *O*-propargyloxy anilines. Les benzopyranes résultants sont récemment employés à travers une synthèse efficace en trois étapes pour la préparation de pyrano [3,2-*h*] quinolines.

Une nouvelle version efficace de la réaction carbonylative de Murai catalysée par Ru(0) pour l'acylation C3-H a été étudiée en utilisant des imines bidentées ou aromatiques comme groupe directeur. Le couplage avec des vinylsilanes ou des styrènes a été étendu à une série d'hétérocycles pentatomiques avec des rendements modérés ou excellents et le mécanisme de réextion a été clarifié par calcul DFT.

Enfin, une toute nouvelle version sans oxydant de la réaction Fujiwara-Moritani catalysée par Ru(0) a été étudiée. Le complexe trimérique de $Ru_3(CO)_{12}$ a été utilisé pour l'alcénylation en C3 avec des acrylates ou des oléfines pauvres en électrons avec des rendements modérés ou excellents. Le mécanisme de réaction semble se dérouler, après l'étape d'activation et l'insertion d'oléfine, par une étape de β-élimination suivie d'une élimination réductrice de l'espèce métallique formée.

Mots clés: Ruthénium; Métaux de transition; Catalyse; Hétérocycles; Hydroamination; Hydroarylation; Murai; Fujiwara-Moritani.