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Electrophilic activation of allenenes and allenynes: Analogies and differences between Brønsted and Lewis acidic activation

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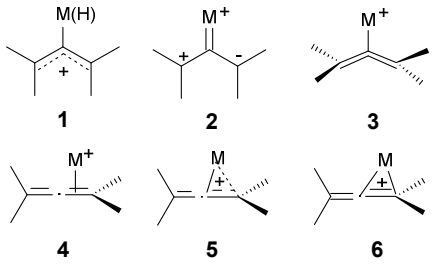
This Tutorial Review summarizes recent examples of electrophilic activation of allenes with particular focus on analogies and differences between Lewis and Brønsted acid activation of these versatile substrates. The aim of this article is to present a general overview of the possibilities offered to chemists using complementary modes of catalysis and to emphasize advantages and limitations of each approach, thereby providing the means to expand the scope of this powerful synthetic methodology.

Introduction

The unique features of allenes have always fascinated chemists and their role in organic synthesis surged considerably over the past decades. The electron-deficient nature of allene central carbon atoms may be exacerbated in the presence of electrophilic activators such as Lewis or Brønsted acid catalysts and thus exploited to trigger chemical transformations.[1] The former has been the subject of intensive research, significantly increasing the scope of allene chemistry in synthetic methodology. Scheme 1 depicts the structure of proposed reactive intermediates that may be formed upon activation of allenes in the presence of electrophilic species. While complex **1** has been proposed for both Brønsted and Lewis acid-mediated processes, intermediates **2-6** appear to be restricted to Lewis acids only.

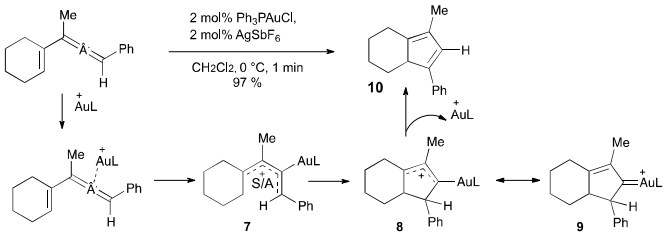


Scheme 1. Proposed intermediates upon activation of allenes by an electrophile.

All of these formal intermediates share a common point. By reducing the electron density of the central carbon atom upon electrophilic activation, using either a proton or a transition metal, these activated species can smoothly react with a neighbouring insaturation and thus form the corresponding carbocycle. Throughout this Tutorial Review we will present the reactivity of allenes towards alkenes and alkynes, and describe the influence of the tether length between reacting partners on the product distribution of intramolecular reactions. To gain insights on the reactivity of activated allenes towards heteroatoms as nucleophiles we suggest excellent and exhaustive recent reviews.[2,3] For each type of cyclization, Lewis acid-catalyzed processes are first exemplified followed by the corresponding Brønsted acid-mediated transformations. Since a complete description of this research area exceeds the scope of this review, a limited selection of examples will be presented.[1] Our choice was prompted by the need to present analogies and differences between different types of allene activations in a scholarly manner, rather than providing a complete enumeration of the vast literature covering this field.

Cyclizations of Allenenes

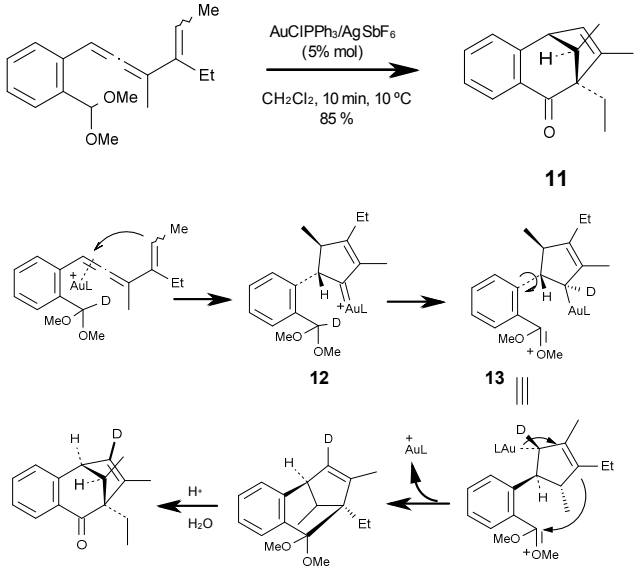
Among Lewis acids, transition metals with a pronounced π-acidic character surged over the past few years, many catalytic systems being based on gold and platinum for instance. Gold(I)-catalyzed cycloisomerization of vinyl allenes constitutes a powerful method to access substituted cyclopentadienes (Scheme 2).[4] Pentadienyl cation **7**, generated by coordination of a cationic gold catalyst on the allene function can undergo an electrocyclic ring closure to form the corresponding allyl-gold intermediate **8** or its carbene resonance form **9**. Subsequent intramolecular 1,2-hydrogen shift then led to the formation of the desired cyclopentadiene **10** with concomitant regeneration of the catalyst. Remarkably, this process can occur smoothly in a few minutes at low temperatures.



Scheme 2. Synthesis of cyclopentadienes via gold catalysis.

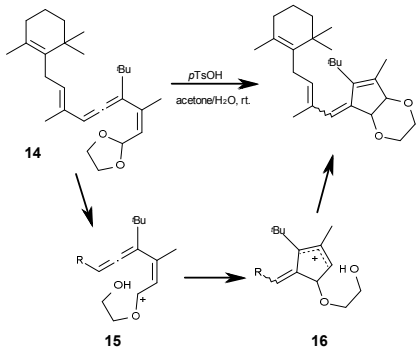
Bhunia and Liu reported the synthesis of bicyclo[3.2.1]oct-6-en-2-ones **11** (Scheme 3) and the sequence involves an atypical

activation of sp^3 C-H bond by gold catalyst.[5] On the basis of results observed using deuterium-labeled substrates, they proposed a mechanism whereby intermediate gold carbenoid complex **12** can undergo a 1,5-deuterium shift to give allyl gold species, which can then cyclize by reacting with oxonium cation **13** in a process reminiscent of a S_N2'.



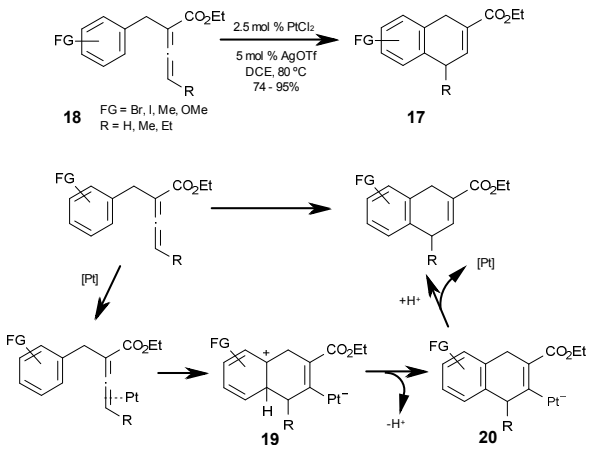
Scheme 3. Tandem cyclization/C-H activation by cationic gold catalyst.

A somewhat similar Brønsted acid-catalysed reaction has been reported by de Lera.[6] The cyclization of vinylallene **14** (Scheme 4) was serendipitously discovered while attempting to deprotect its acetal group. The authors proposed that protonation of the latter could form **15**, which then underwent a Nazarov-type cyclization to provide intermediate **16**, which was eventually trapped by the free hydroxyl group.



Scheme 4. Reaction of vinylallenes in the presence of Brønsted acids.

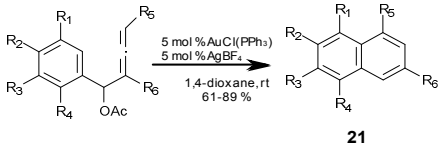
Similarly, formal allylallenes have been widely studied in the context of electrophilic activations. For example, upon cyclization, these substrates can selectively deliver substituted cyclohexadienes. Lee and Mo described a catalytic method to obtain 1,4-dihydronaphthalenes **17** from ethyl 2-benzyl-2,3-alkadienoates (**18**, Scheme 5).[7]



Scheme 5. Platinum catalyzed synthesis of dihydronaphthalenes.

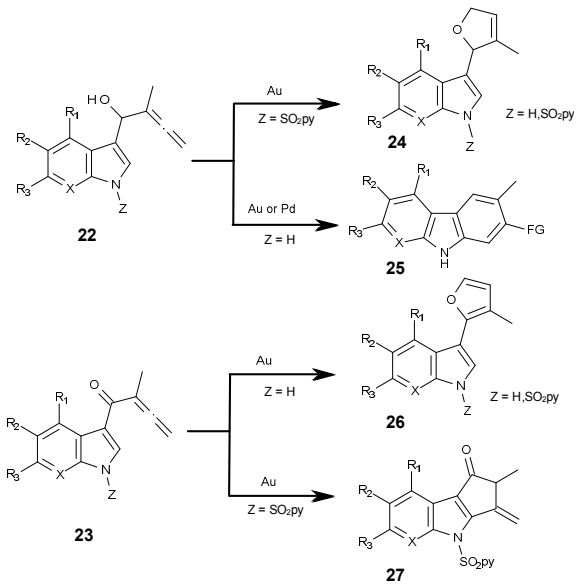
The reaction could be initiated by activation of the allenyl group in the presence of a platinum catalyst, followed by 6-*endo-trig* cyclization to afford zwitterionic vinylplatinum intermediate **19**. Rearomatization to **20** and subsequent protonolysis provided the 1,4-dihydronaphthalene derivative liberating the metal catalyst. This example demonstrates that a suitably tethered aryl group can formally behave as an alkene moiety in that context.

In the presence of leaving group strategically introduced at the allylic position, polysubstituted naphthalenes such as **21** could be efficiently prepared using gold catalysis (Scheme 6) following a similar strategy.[8] The cationic gold species were generated in situ in the presence of silver salts.



Scheme 6. Access to functionalized naphthalenes.

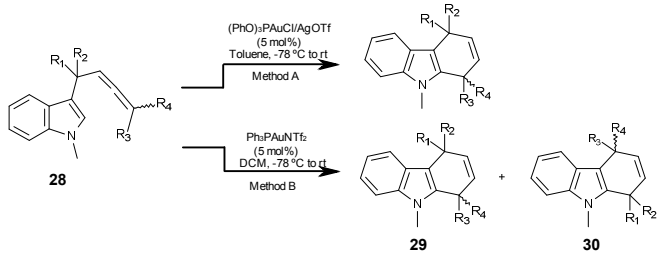
By using indoles instead of the aromatic fragment, Alcaide and Almendros reported a Lewis acid-catalyzed benzannulation of allenes to afford substituted carbazoles or furylindoles.[9] The process can be mediated by both gold and palladium catalysts and remarkably, a distinct reactivity (namely, oxycyclization versus carbocyclization) was observed for allenols **22** and allenones **23**, respectively (Scheme 7).



Scheme 7. Divergent reactivity of allenols and allenones.

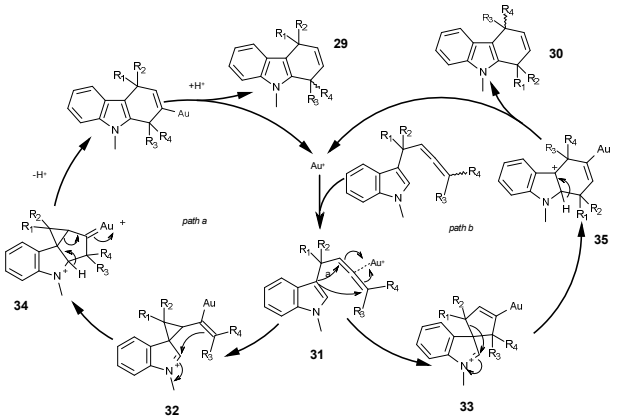
N-protected derivatives **22** afforded dihydrofuranyl-indoles **24**, while unprotected ones allowed the selective formation of the benzannulated products **25**. Furan derivatives **26** could be obtained from unprotected allenones **23** *via* gold(I) catalyst, while fused tricyclic compounds **27** were observed in reactions involving protected substrates. In all cases, the reaction was thought to take place following coordination of the Lewis acid with the least hindered double bond of the allene moiety.

By using disubstituted substrates at the α position (such as **28**, Scheme 8) gold can mediate the synthesis of dihydrocarbazoles.[10] The process gives access to synthetically challenging structures, although selectivity seems to be influenced by both the substrate substitutions and reaction conditions (catalyst and solvent).



Scheme 8. Access to functionalized dihydrocarbazoles.

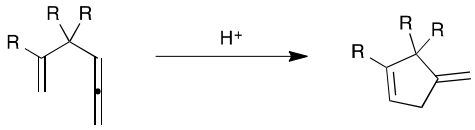
The mechanisms proposed for these reactions (Scheme 9) emphasizes how subtle factors can govern the outcome of these sequences in Lewis acid-catalyzed allene activated reactions. To rationalize the formation of regioisomers **29** and **30**, it has been proposed that the substrate substitution pattern can impact on the favored allene activation/cyclization pathway. In other words, intermediate **31** (Scheme 9) could be seen as the analogue of either complexes **5** or **6** (Scheme 1), which can potentially lead to intermediates **32** or **33**. Interestingly, intermediates **32** could afford the gold carbenoid **34** upon 5-*exo-trig* cyclization, whose rearomatization triggers cyclopropane ring-opening, eventually leading to **29** *via* proto-demetalation. On the contrary, vinyl gold complex **33** could evolve via C-migration to intermediate **35** producing **30** upon protonolysis.



Scheme 9. Rational formation of dihydrocarbazoles regioisomers.

Beside gold-catalysis, synthetic methods to access the biologically relevant carbazole core were reported exploiting the p-acidity of platinum[11] and palladium[12] based catalyst using indole-tethered allenes as substrates.

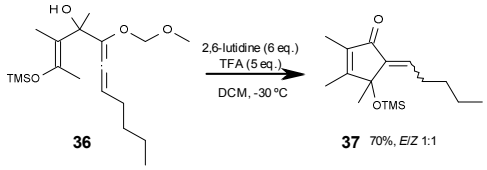
Upon exposure to Brønsted acids, β-allenyl alkenes undergo cyclopentannelation *via* a Nazarov cyclization (Scheme 10).[9] Allylallenes, either isolated or formed *in situ* are particularly good substrates in this methodology given that they cyclize under very mild reaction conditions as a result of a low activation energy barrier.



Scheme 10. Nazarov cyclization of allenylallenes.

For instance, widely used allenyl vinyl ketones are in many cases too reactive to be directly isolated, undergoing cyclization during workup.[13] It has been proposed that the ease of cyclization arise mainly from three factors; 1. polarization of the enol ether substituted allene motif, 2. a favourable conformation of the allene tethered to the alkene and 3. the removal of the allenic bond strain during the cyclization. For comparison purposes, divinyl ketones often require stoichiometric amounts of strong Brønsted (or Lewis) acids, usually in combination with high temperatures.

One of the first reports on acid catalyzed Nazarov cyclizations of allenenes dates back to 1989.[14] Tertiary alcohols **36** can be cyclized to yield cyclopentenones **37** in good yields (Scheme 11). While the mild conditions adopted allowed to preserve labile functions such as a TMS group, the geometry of the exocyclic double bond could not be controlled and a 1:1 *E*/*Z* ratio was observed.



Scheme 11. Access to cyclopentenones from allylallenols.

Owing to the ubiquitous presence of the cyclopentenone core in biologically relevant molecules, this strategy has found broad application in total synthesis.[15-19] Figure 1 demonstrates the versatility of this approach, further illustrating how electrophilic activation of allylallenes by means of a Brønsted acid can represent an effective tool for synthetic chemistry. A recent review excellently summarizes both progress accomplished in this field in the last twenty five years and their relevance in total synthesis.[20]

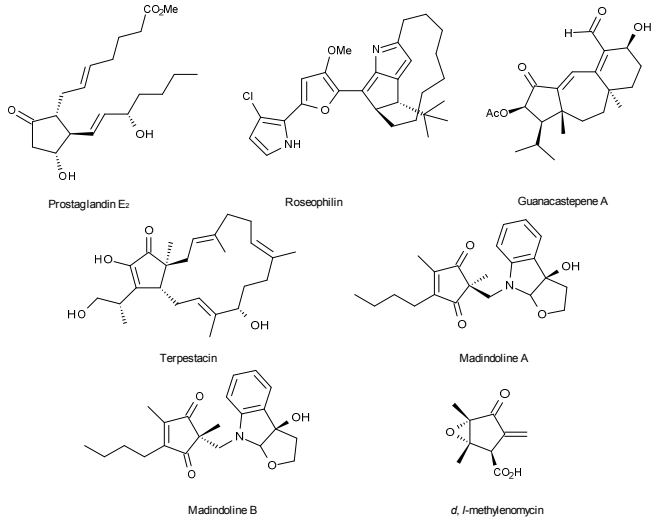
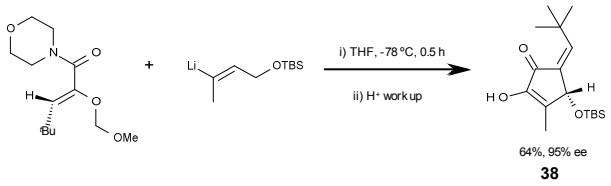


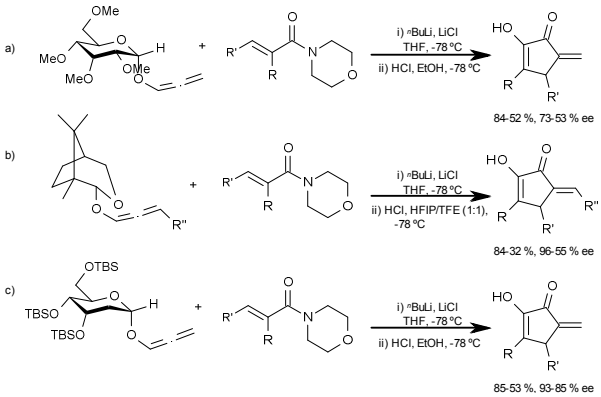
Figure 1. Synthetic applications of Brønsted acid activation of allylallenols.

Activation of allenes with a Brønsted acid can enable the transfer of axial chirality from an enantioenriched substrate to access chiral cyclopentenones. Scheme 12 depicts an example in which the substrate was generated *in situ* by reacting vinyl lithium with an acrylamide. Upon acidic work-up, the cyclized product **38** could be recovered with a good retention of chiral information.[21]



Scheme 12. Transfer of axial to central chirality from enantioenriched allenes.

As a complementary approach, the desired allenyl vinyl ketone used as substrate for this cyclization can be prepared from a lithium allene in combination with an acrylamide. As in the above mentioned case, through a simple acidic work-up cyclopentenones can be easily recovered in good yields at the end of these sequences.[22-24] This strategic change was used in combination with allenes bearing a chiral auxiliary to access cyclopentenones in an enantioselective manner. An interesting possibility is to take advantage of chiral allenyl ethers that can be easily prepared from readily available enantiopure substrates. The group that ensure the enantioselectivity of the reaction can be hydrolyzed at the end of the sequence (Scheme 13). The first generation of chiral auxiliary, shown in scheme 13a, was based on D-glucose and resulted in moderate yields and enantioselectivities.[22] A camphor based second generation auxiliary performed better with moderate to good yields and enantioselectivies as well as higher tolerance of substitution on both the allene and the amide partners (Scheme 13b).[23] Remarkably, complete control of the exocyclic double bond was observed, the *E* isomer only being recovered. This might be favoured by the strong acid medium used (39 mol equiv. of HCl in 1:1 HFIP/TFE mixture at -78 °C) that could induce isomerization of the double bond to provide the thermodynamically most favoured isomer. Scheme 13c shows the third iteration of this strategy. It involved a sugar-based auxiliary derived from a α-2-deoxy-D-glucose backbone-containing bulky TBS protecting groups, thereby providing the desired products in good to excellent enantioselectivies.[24] It is worth noting that careful control of the reaction conditions adopted while quenching the reaction mixture played a decisive role underlying the enantioselectivity of the process.



Scheme 13. Enantioselective cyclization from chiral allenyl ethers.

The mechanism of chiral transfer using a chiral auxiliary has been studied in detail. With regards to glycoside-based substrates, it has been proposed that during the cyclization step, the oxygen atom of the pyran ring helps stabilizating the cationic intermediate through its oxygen lone pairs. This effect locks the most favourable conformation and thus allows efficient transfer of chiral information. This interaction between lone pair and carbocation occured with concomitant switch of the favoured pyran conformation,[25] bringing the substituent at the 4-position of the glycoside in an axial position and thus efficiently blocking one face for the cyclization in transition state **39** (Figure 2). This rationale is consistent with the improvement observed upon removal of substituent on the 2-position of the sugar. This facilitated the conformational switch in the transition states, thereby increasing the steric demand of the protecting groups from methyl ethers to bulkier TBS groups.

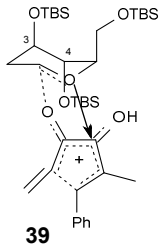
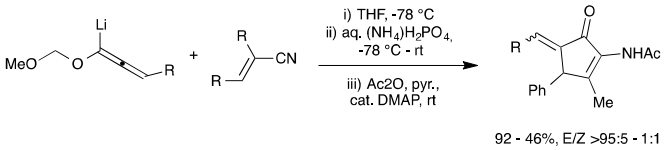


Figure 2. Proposed transition state responsible for efficient transfer of chiral information.

Tius and co-workers reported an example where the geometry of the exocyclic double bond could be controlled by treating the allenene *in situ* with an organolitium followed by the addition of a stoichiometric amount of electrophile.[26] While overall

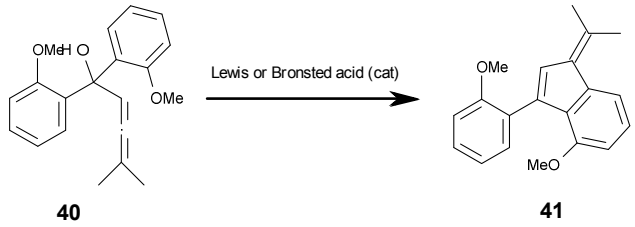
yields were moderate, it was possible to selectively recover *E* isomers employing alkyl halides as electrophiles, *Z* isomers being obtained upon addition of trimethylsilyl chloride instead. Remarkably, authors reported that the use of Lewis acids in these sequences did not enable a control of the exocyclic double bond geometry, always resulting in equal mixtures of the two isomers.

Replacing acrylamides with acrylonitriles leads to the synthesis of α-aminocyclopentenones.[27] In most cases, for sake of simplicity, an acylation step using acetic anhydride was performed prior to purification, thus delivering products in their amide form (Scheme 14). Yields of the aminocyclopentenones were moderate to good and control of *E/Z* selectivity proved to be highly substrate dependant in these cases.



Scheme 14. Access to α-amidocyclopentenones.

An electron rich aryl group can display the same reactivity of the olefin partner under acidic activation. A Nazarov-type cyclization can indeed occur from allenols **40** to smoothly deliver benzofulvene **41** (Scheme 15). Interestingly, the cyclization can be performed in a catalytic amount of Brønsted and Lewis acids.[28]

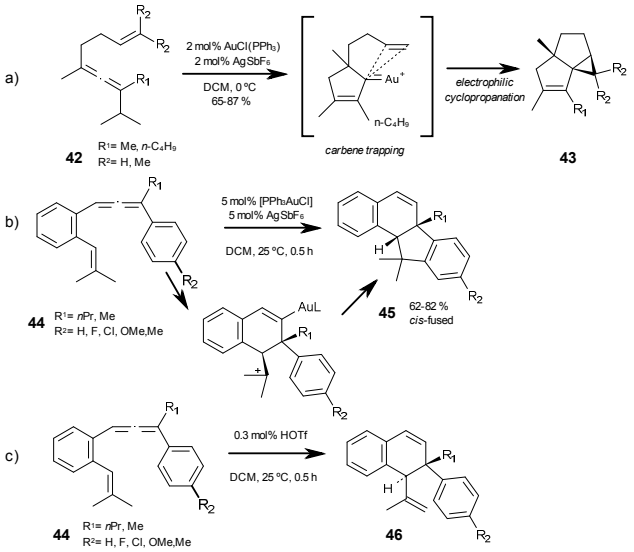


Scheme 15. Synthesis of benzofulvenes from biarylallenols.

Allenes can be efficiently generated *in situ* by isomerization of the corresponding alkynes. By using this synthetic strategy, cyclopentenones could be accessed in the presence of a Brønsted acid.[29] Cyclopentenones were obtained from enynes by generating the reactive allene *in situ*. Addition of trifluoroacetic acid was used to promote the cyclization.

It should be mentioned that it is possible to employ cumulenes as substrates. Activation of cumulene-enes by means of a relatively weak Brønsted acid such as potassium dihydrogen phosphate could selectively afford cyclopentenones bearing an exocyclic allene.[30]

Upon π-acidic activation using a cationic gold catalyst, homoallylallenes such as **42** (Scheme 16, top) could form a gold carbenoid intermediate that smoothly underwent cyclopropanation eventually delivering tricyclic product **43**. The proposed Nazarov-like mechanism was confirmed by theoretical studies and the method delivered three carbocycles in a diastereoselective fashion.[31]

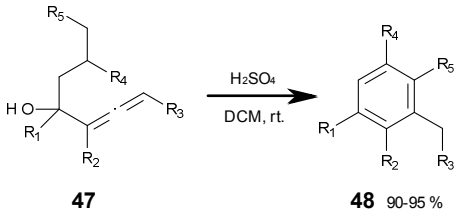


Scheme 16. Access to tricyclic frameworks via Au(I) catalysis.

Liu and co-workers reported a different reactivity when the tether was a rigid arene.[32] Using a Lewis acid, the intramolecular annulation of 1-aryl-1-allen-6-enes **44** in CH_2Cl_2 delivered selectively *cis*-fused [4.3.0]carbocycles **45** through a six-membered ring vinylgold complex intermediate (Scheme 16, way b).

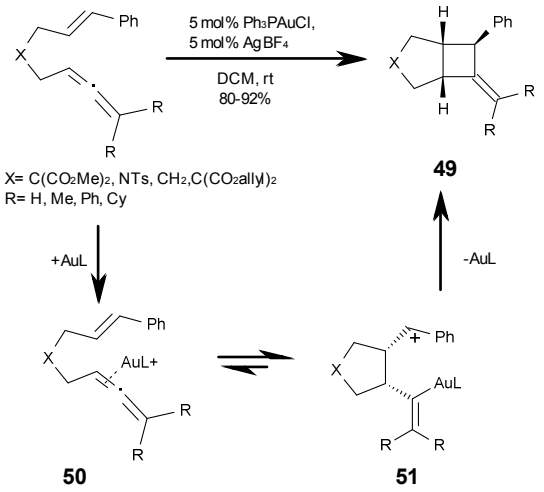
Remarkably, a divergent pathway was observed using a Brønsted acid catalyst (Scheme 16, way c). In this case the final cyclization did not occur and the relative configuration of the benzylic proton of product **46** was inverted compared to the one observed when the reaction was carried out using a π-acidic catalyst.

Substitued benzenes **47** were synthesized from allenyl allyl alcohols (as **48**, Scheme 17) in the presence of a protic acid.[33] Here, the catalyst had the dual role of activating the allene group and dehydrating the intermediate to eventually deliver an aromatized structure.



Scheme 17. Synthesis of polysubstituted benzenes from homoallylallenes.

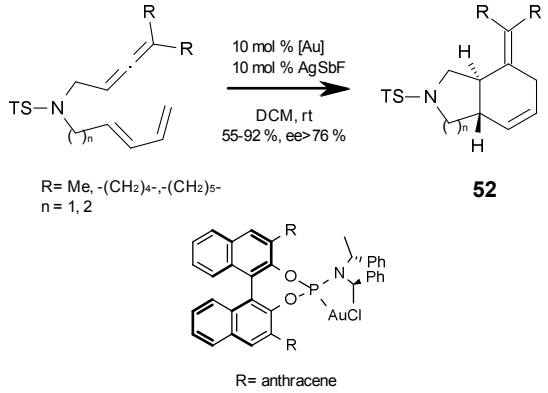
In 2007 Toste and co-workers developed the first transition-metal catalyzed cycloisomerization of 1,6-allenenes to the corresponding alkylidene-cyclobutanes (**49**, scheme 18).[34]



Scheme 18. Bicyclic frameworks from 1,6-allenenes via cationic gold catalysis.

The reaction was proposed to proceed through the activation of the allene to trigger the first cyclization leading to a vinylgold intermediate **50** possessing a stabilized benzylic carbocation. This complex smoothly went through a tandem cyclization/deauration thus creating the cyclobutane core from intermediate **51**. It was also possible to perform this gold-mediated [2 + 2] cycloaddition to access bicyclo-[3.2.0] structures in an enantioselective fashion using bimetallic gold complexes. Indeed, the use of a chiral digold(I)-biaryl-diphosphine complex as catalysts afforded products **49** with excellent enantioselectivities.

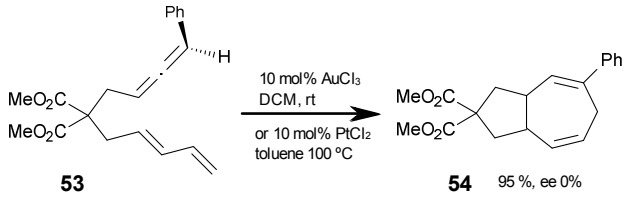
The group of Mascareñas reported an Au(I)-catalyzed cycloaddition of allenedienes, along with a highly asymmetric variant promoted by a chiral phosphoramidite-gold catalyst.[35] These reactions represent one of the first efficient applications of a carbophilic, monometallic Au(I) complex in an enantioselective manner (Scheme 19). Upon activation of the allene fragment, a [4+2] cycloaddition occurred and bicyclic products **52** were formed in good to excellent yields and enantioselectivities.



Scheme 19. Enantioselective activation of allendienes by a chiral Au(I) catalyst.

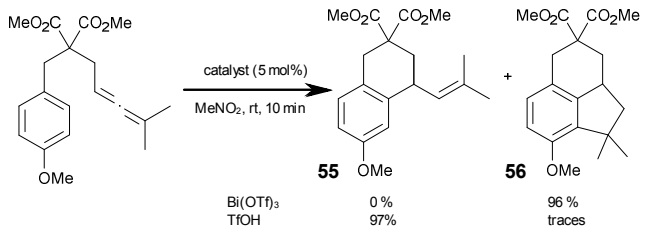
In 2010, Toste and co-workers reported an enantioselective gold(I)-catalyzed intramolecular [4+2]-cycloaddition of allenedienes.[36] The reactions enabled the asymmetric synthesis of *trans*-hexahydroindenes using a *C3* symmetric phosphite-gold(I) catalysts as Lewis acids.

Beside these remarkable examples of successful enantioselective processes, it is worth noting that challenges connected with this reactivity still exist. A meaningful example has been reported by the group of Trillo (Scheme 20).[37] It was indeed not possible to transfer the axial chirality of allenediene **53** to access enantioenriched bicyclic cycloheptadiene **54** in the presence of a Lewis acid catalyst (either using gold or platinum salts) despite the overall efficiency of the cyclization. These findings suggested that the activation of the allene delivered a perfectly planar (allylic) intermediate (corresponding to **1** in Scheme 1) that did not allow the transfer of chiral information. As mentioned in the introduction, it can be proposed that a similar outcome would have been obtained using a Brønsted acid, which could in principle form a similar type of planar intermediate. It is tempting to speculate that these findings can open the way for future developments using both strategies of electrophilic allene activation, for instance by using a chiral protic acid or a chiral counteranion when a Lewis acid catalyst is used.



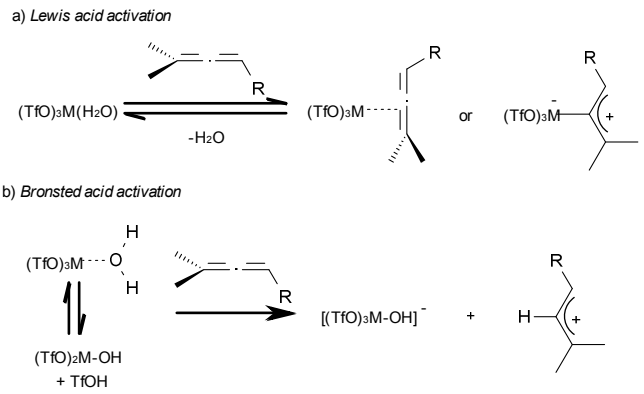
Scheme 20. Loss of chiral information in the cyclization of allenedyenes.

Intramolecular hydroarylation of allenes was achieved under very mild conditions using bismuth(III) triflate as catalyst (Scheme 21).[38] Aromatic rings can act as nucleophile for activated allenes and reaction conditions can ensure the selective formation of bicyclic product **55** or tricyclic derivatives such as **56**. Interestingly, the second formal aromatic C-H activation that delivered **56** did not occur using a Brønsted acid catalyst.



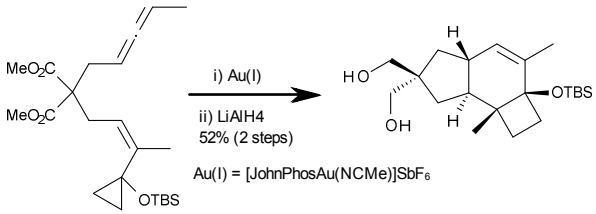
Scheme 21. Divergent reactivity of allenes by tuning reaction conditions.

Mechanistically, two distinct activation modes of the allene can be proposed for these cycloisomerizations. This example clearly shows once more how subtle factors can govern the outcome of sequences involving allenes. For instance, a purely Lewis-acidic based pathway has been envisaged. In this case, the electron-deficient metal coordinates the allene through either a slipped η^1 or η^2 interaction in equilibrium with the corresponding allyl cation in analogy with the activation mechanism previously proposed for gold catalysis (Scheme 22a). Alternatively, a protic acid such as TfOH can directly form an allyl cation upon addition on the allene group. Remarkably, the two pathways can coexist in this particular case. Indeed, Bismuth(III) triflate is generally obtained and therefore used in its hydrate form. Lewis acids are prone to coordination of electron-rich molecules to the electron deficient metal center. If these are protic species, the acidity may be greatly enhanced, and the system thus presents an induced Brønsted acidity (Scheme 22b).



Scheme 22. Comparison of competitive activation of allenes using $Bi(OTf)_3$.

A distinctive feature of Lewis acid catalysts compared to their Brønsted counterpart is observed using vinylcyclopropane-tethered allene derivatives. The group of Echavarren has been particularly active in this field and has developed methods to exploit the π-acidity of cationic gold complexes to activate the allene and then trigger subsequent ring extension of the cyclopropane ring to access complex, fused cyclobutanes in an elegant fashion. A similar reactivity has not been reported yet using a Brønsted acid. The synthetic relevance of this approach is witnessed for instance by the concise synthesis of the protoilludene core (Scheme 23).[39]



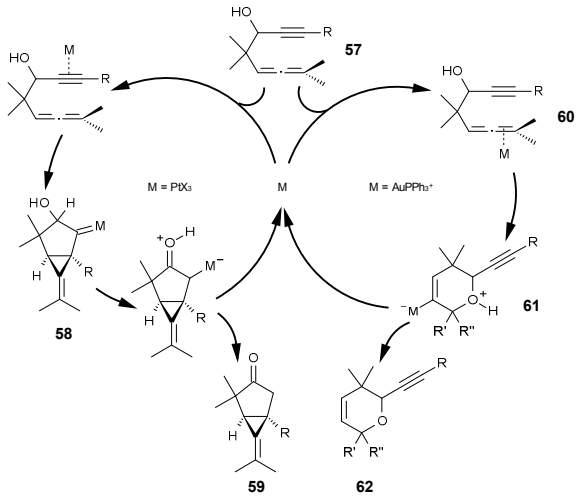
Scheme 23. Gold(I)-catalyzed allene-vinylcyclopropane cycloisomerization.

To conclude this section, it has to be mentioned that a vast literature exists on transition metal catalyzed cycloadditions of allenenes. These processes always involve the formal activation of the allene moiety and the transition metal catalysts used possess a certain Lewis-acid character. However, the behavior of allenes in these cascades is often that of an olefin that undergoes an oxidative cycloaddition on a metal center providing a metallacycle intermediate rather than a pure electrophilic activation. As this broad field exceeds by far the scope of the overview, we suggest a very recent review and references cited therein to acquire leading information on this reactivity.[40] To illustrate this subtle mechanistic difference, a meaningful examples have been reported by Mascareñas, further illustrating the divergent reactivity of 1,7-allenenes depending on the adopted transition metal catalysts. Different [4+2], [4+3] or [2+2+1] selective annulations can be achieved choosing among Rh, Ni, Au, or Pt catalysts. These mechanisms feature oxidative cycloaddition steps in the first two cases while sequences involving gold or platinum salts exploit the π-acidic character of these metals.[41]

Cyclisations of Allenynes

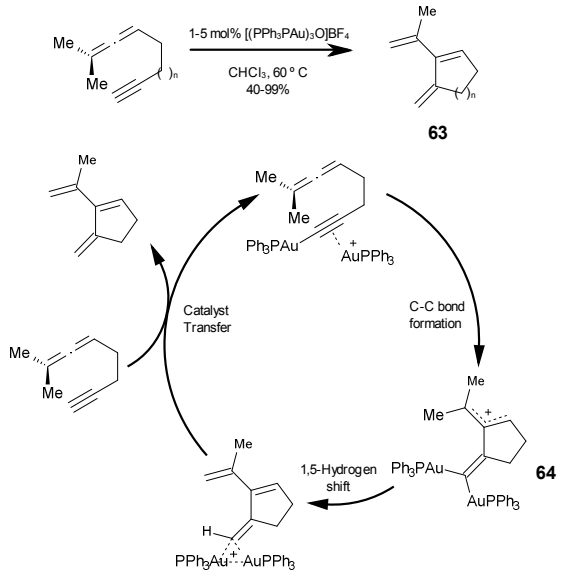
Electrophilic activation of allenes possessing a tethered alkyne group is mainly accomplished through transition metal catalysts, examples with protic Brønsted acids being scarce. In this section we will provide a brief overview of reactions involving the initial electrophilic activation of alkyne.

This apparently structural and electronic variation may however be seen as complementary opening up novel chemical opportunities. For example, in the presence of a platinum salt, initial coordination of the triple bond of 1,5-allenynes **57** (Scheme 24) was promoted, which followed by cyclopropanation of the less hindered part of the allene, provided carbenoic complex **58**.[42] This intermediate could then liberate bicyclic product **59** upon sequential 1,2-hydrogen shift/protodemetalation (Scheme 24, left). In contrast, the use of a cationic gold catalyst favored the initial electrophilic addition of the allene moiety (**60**, Scheme 24, right) and the subsequent nucleophilic attack of the propargylic alcohol provided vinylgold complex **61**. Dihydropyrane **62** was eventually generated *via* protodeauration.



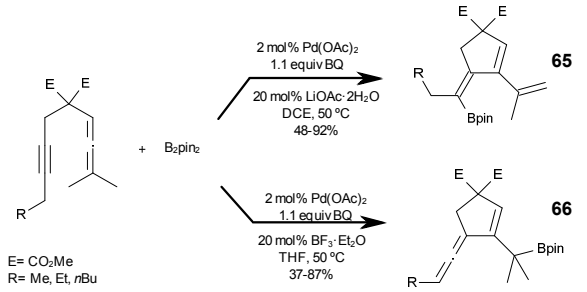
Scheme 24. Divergent pathways in the activation of 1,5-allenynes by Au(I)- and Pt(II)- catalysts.

Substituted carbocycles **63** could be selectively obtained under mild conditions using a trinuclear gold precatalyst (Scheme 25).[43] Many different mechanistic possibilities were proposed to rationalize this elegant cascade. A broad range of experiences supported the hypothesis that the sequence involved an initial π-acidic activation of the alkyne by Au(I) (rather than the allene) followed by the concomitant formation of bimetallic intermediate **64** upon replacement of the terminal acetylenic proton by a second cationic gold atom. This complex would then undergo tandem cyclization/1,5-hydrogen shift to afford **63**.



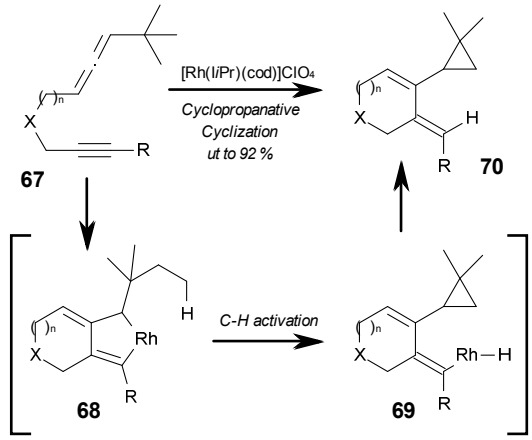
Scheme 25. Cyclisation of allenynes using multinuclear gold clusters.

Allenes can also be efficiently activated by Lewis-acid palladium(II) salts. For instance, Bäckvall has recently reported a highly selective tandem carbocyclization/borylation of 1,5-allenynes with diboron-bispinacolate in the presence of $Pd(OAc)_2$ as catalyst.[44] Addition of a stoichiometric oxidant was required to ensure the reoxidation of the metal at the end of these sequences, which were proposed to occur via initial activation of the allene by the electrophilic catalyst followed by cyclization and an eventual reductive borylation. Remarkably, by tuning reaction conditions, it was possible to selectively obtain either borylated trienes **65** or vinylallenes **66** (Scheme 26). In this case, better results were achieved upon addition of a second Lewis acid, such as $BF_3{\cdot}Et_2O$. By performing the reaction in acetic acid, the solvent itself could replace the boron derivative affording the acetoxylated analogue of vinylallene **66**.[45] In comparison to the borontrifluoride-cocatalyzed sequences, the presence of a Brønsted acid did not allow the formation of the triene derivative.



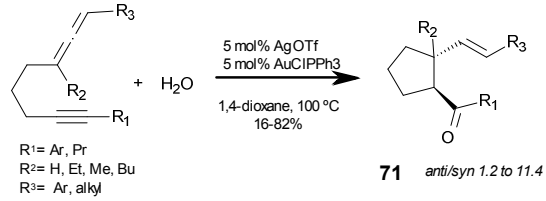
Scheme 26. Reactivity of allenynes via palladium catalysis.

Allenynes can undergo tandem cyclization/cyclopropanation in the presence of novel Rh(I) catalyst *via* a formal [2+2+2] cycloaddition.[46] Substrate **67** (Scheme 27) underwent oxidative cycloaddition to provide Rh(III) metallacycle **68** followed by C-H activation at the *tert*-butyl moiety to provide metalhydride **69** that readily generated the bicyclic product **70** upon reductive elimination.



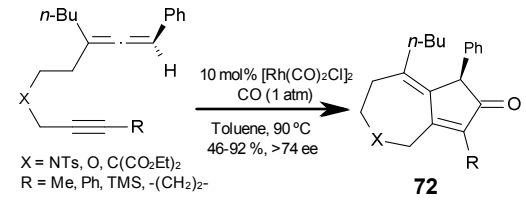
Scheme 27. Cyclization/cyclopropanation through C(sp3)-H bond activation.

A cationic gold catalyst was used to trigger the cyclization/formal hydration of allenynes to afford acylcyclopentanes **71** possessing a quaternary center (Scheme 28).[47] Depending on the substitution pattern of the substrate, good yields and diastereoselectivities could be achieved. On the basis of DFT calculations, the reaction was proposed to proceed through initial activation of the allene by the Lewis acid catalyst, 5-*exo*-*dig* cyclization followed by quenching the resulting carbocation with a molecule of water. Tautomerization of the enol intermediate delivered ketone **71**.



Scheme 28. Tandem cyclization/formal hydration of allenynes.

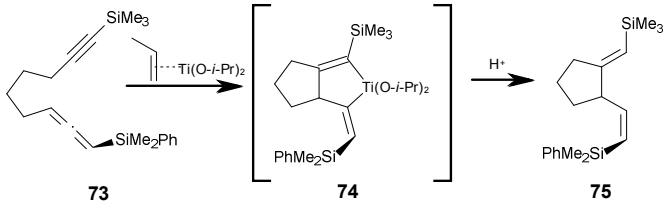
The use of transition metal catalysts allows to couple allene activation with other chemical processes. In the case of enynes, it is possible to access bicyclic cyclopentenones **72** via Rhodium catalysis (Scheme 29).[48] The reaction proceeded through oxidative cycloaddition to a Rh(III) metallacycle followed by CO insertion and final reductive elimination. By doing so, it was possible to efficiently transfer the axial chirality of an enantiopure substrate to produce **72**. As mentioned above, sequences involving oxidative cycloadditions of allenes with transition metals are beyond the scope of this review and were therefore just briefly emphasized.



Scheme 29. Cyclocarbonylation Reaction.

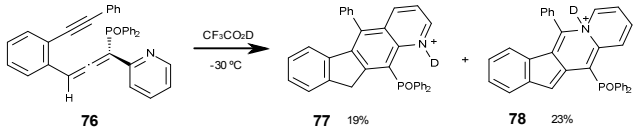
An interesting exception in the field has been reported in 1997 using titanium alcoholates (Scheme 30).[49] Allenynes **73** can

oxidatively add on titanium to provide intermediate titanacycle **74** in which the central carbon atom of the activated allene remains directly bound to the metal. Remarkably, the cyclization of optically active alleneynes led to the formation of the stereodefined 1,4-dienes **75** upon protonolysis. It is possible to terminate the process by reacting the titanacycle with different species including aldehydes, ketones and carbon monoxide. In all cases, products can be recovered with excellent ee's (80-86 %).. It is possible to control the geometry of the double bonds in products depending on the allene substitution. For instance, the bulky dimethylphenylsilyl group afforded exclusively the *Z*-alkene.



Scheme 30. Titaniummediated cyclization of optically active alleneyne.

Brønsted acid catalyzed cyclizations of allenynes have not extensively been studied as compared to their allenenes counterpart. One of the few examples includes an insightful NMR study of the Brønsted acid-catalyzed cyclization of allenyne **76** (Scheme 31).[50] Upon sequential allene activation/cyclization, the sequence could evolve either *via* electrophilic substitution/formal C-H activation delivering **77** or pyridine dearomatization in the case of **78**.



Scheme 31. Brønsted acid catalyzed cyclization of allenynes.

Conclusion

This brief description of allene activation by electrophiles presented a selection of the synthetic opportunities offered by both Lewis and Brønsted acid catalyses. The number and the quality of recent developments in this field clearly show the never-fading interest of chemists towards these versatile reagents, and we anticipate that additional chemical transformations remain to be discovered. Control of stereochemistry in enantioselective processes, design of dual catalytic systems to exploit the uniqueness of both transition metal- and organo-catalysis as well as the development of novel synthetic methods involving allenynes using Brønsted acid catalysts are just a few of the challenges awaiting creative solutions.

Acknowledgements

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Notes and references

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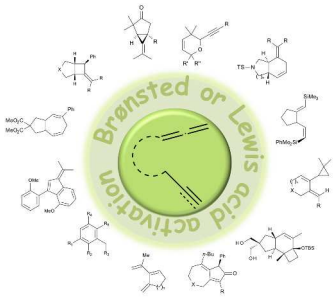

This review focuses on electrophilic activation of allenes by an acid. Key mechanistic features are presented together with recent synthetic applications.

Key learning points:

1) Owing to the perpendicular arrangement of their two π bonds, allenes exhibit unique features. Having a higher HOMO than alkynes, allenes are prone to react with mild electrophiles.

2) Allenes can be activated by Bronsted acids to generate the corresponding allyl cation, opening the way to cascade reactions in the presence of nucleophiles. Complex polycyclic structures can be readily accessed through this approach.

3) Reactions proceeding through planar allyl cationic intermediates cannot be performed in a stereoselective fashion. This limitation can be overcome using chiral auxiliaries embedded on the substrates or alternatively using transition metals with a Lewis acidic character.

4) Activation by Lewis acids can provide non-planar intermediates and thus, in contrast to Bronsted acids, preserves the chiral information from an enantioenriched allene to the final product.

5) Achiral and racemic allenes can also be used to access carbocycles in a stereoselective manner. Remarkable examples were already reported for electrophilic transition metals using tailor-made chiral ligands and recent developments of organocatalysis prompted the design of efficient chiral protic acids.

Bibliographies

Dr. Tatiana Cañeque was born in Madrid in 1980. She obtained her chemistry degree in 2004 at the University of Alcalá where she begun her Ph.D in Juan José Vaquero's group. She did two research visits at the Catholic University of Louvain under the supervision of Koen Clays to study NLO properties. In 2010 she completed her European doctorate discussing the Thesis "Palladium coupling processes on heteroaromatic cations: Synthesis and nonlinear optical properties of cationic chromophores". Since 2013 she's working in Max Malacria's group at ICSN and her interests include transition metal catalysis and total synthesis.

Giovanni Maestri got his MD from University of Parma in 2007 and made a research visit at UVA-Amsterdam with C. J. Elsevier. He later did his Ph.D. at Parma with Marta Catellani. In 2011 he begun a postdoc at UPMC with Louis Fensterbank and Emmanule Lacote and then followed Max Malacria at ICSN as post-doctoral researcher. In 2014 he moved back to University of Parma as assistant Professor. His main interests are catalytic synthesis, computational chemistry and all-metal aromaticity.

Max Malacria obtained his Ph.D. from the University of Aix-Marseille III with Pr. Marcel Bertrand. He was appointed Assistant in 1974 at the University of Lyon I with Pr. J. Goré. After almost two years as a postdoctoral fellow with Pr. K. P. C. Vollhardt at Berkeley, he went back to the University of Lyon as Maître de Conférences in 1983. In 1988 he was appointed Full Professor at the UPMC. In 1991 he was elected junior member of the Institut Universitaire de France and promoted to senior member in 2001. Since 2011 is director of the ICSN in Gif sur Yvette.

Fiona R. Truscott received a BSc/Msci in Natural Sciences from the University of Cambridge in 2008. She obtained her PhD in 2013 with Prof. Michael Willis at the University of Oxford in transition metal catalysed C-H functionalisation. She then moved to France to work at ICSN (Gif-sur-Yvette) as a postdoctoral fellow

Dr. Rodriguez performed graduate studies under the mentorship of M. Santelli (Marseille) and J. E. Baldwin (Oxford). During this time, he completed the total synthesis of several natural products, providing new ways to create complex molecular frameworks. He joined the University of Cambridge in November 2005 and was promoted to Senior Research Associate in 2009. His work carried out in the laboratories of S. Balasubramanian and S. P. Jackson led to the first evidence of the existence of G-quadruplex structures in human genes. In 2012, he was promoted with tenure to Chargé de Recherche at CNRS.