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Innovative Catalytic Protocols for the Ring-Closing Friedel–Crafts-Type Alkylation and Alkenylation of Arenes

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Over the past years an astonishing number of highly chemo- and regioselective intramolecular Friedel–Crafts (IMFC)-type alkylations of aromatic compounds have been described in the literature that allow remarkable synthetic shortcuts for the preparation of challenging aromatic compounds. In particular, both transition metal and conventional and unusual Lewis acids (LAs) have been described to promote ring-closing reactions even in the presence of polyfunctionalized cyclization precursors. Finally, the emerging field of catalytic enantioselective FC alkylations has recently concerned also intramolecular transformations both in the presence of chiral organic and organometallic promoters.

Index

1. Introduction

The synthesis of aromatic polyfunctionalized compounds represents an actual goal for numerous research groups due to their wide scope of applicability in the agrochemical as well as pharmaceutical fields. In particular, since the pioneering study by Charles Friedel and James M. Crafts,[1] many efforts have been devoted by the academic as well as industrial community toward the development of more environmentally friendly catalytic alkylation strategies featuring outstanding levels of chemo-, regio-, or even stereoselectivity. In this florid scenario, the intramolecular alkylation of aromatics has became a matter of increasing importance as it allows synthetically challenging polycyclic fused aromatic compounds to be obtained directly from inexpensive "low-energy" organic compounds. Moreover, catalytic alkylation processes involving unactivated C_{aryl}–H bonds rather than C–X (X = halide) analogs would dramatically increase the atom economy[2] of the whole reactions, with the concomitant use of milder experimental conditions.[3]

Although detailed mechanistic aspects for most of the processes described herein are still uncertain, intramolecular aromatic C–H alkylations can be conveniently gathered into two distinct catalytic strategies in which the catalyst alternatively actives the aromatic compound or the tethered electrophilic partner. In the first case, the intramolecular electrophilic metalation of arenes concerns the insertion of metal species in low oxidation states (usually transition metals are involved) into an sp^2-hybridized C–H bond to form highly reactive organometallic species that can be successfully trapped with appropriate electrophilic reagents (Scheme 1, a). On the other hand, the use of Lewis acids as promoters can be seen as a complementary approach to the former, with the activation event[4] involving the electrophilic species intimately linked to the arene (Scheme 1, b).

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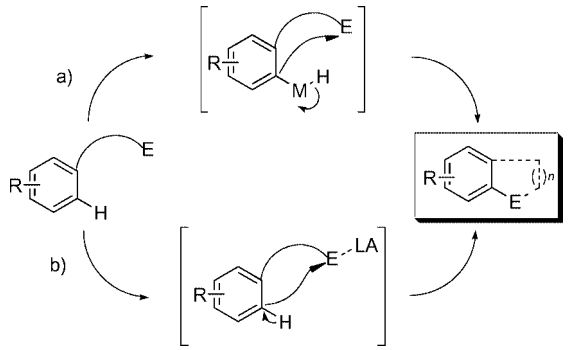
MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.



Scheme 1. Different strategies for the catalytic intramolecular alkylation of aromatic compounds.

It appears evident that both these approaches are valuable starting points for the design and development of innovative stereoselective versions. Here, despite the astonishing number of catalytic and enantioselective FC protocols that have appeared in the literature over the past decade, only a few of them concern highly enantioselective intramolecular strategies.[5,6] The following review article is meant to document the recent progresses achieved in the catalytic and stereoselective "intramolecular" aromatic alkylations of aromatic compounds and does not intend to provide a fully comprehensive treatise.

Due to the similarities in their chemical approach, related examples of intramolecular alkenylation of aromatic rings catalyzed by both π-acid transition metals and conventional LAs are described.[7] On the contrary, metal-catalyzed C_{sp^2}–C_{sp^2} cross-couplings starting from C(sp^2)–X (X = halide, OTf) will not be covered and the reader is referred to recent review articles[8] and monographs.[9] Similarly, annulation reactions that lead to polycyclic aromatic fused systems based on the use of two or more independent molecules will also not be treated.[10]

2. Catalytic Intramolecular Processes

The use of classical Lewis and Brønsted acids has found widespread application in the past in promoting FC reactions and continues to have considerable value due to their relative inexpensiveness and large availability.[11] Despite

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Prof. Achille Umani-Ronchi graduated in chemistry in 1960 from the University of Rome. He was an assistant at the Politecnico of Milano, Italy, from 1961 to 1969. He then became an Assistant Professor at the University of Bari with Professor Gianfranco Cainelli. He spent one year (1964–1965) as a postdoctoral fellow at the ETH in Zürich (Switzerland, Professor Duilio Arigoni) working on enzymatic reactions, and six months as a postdoctoral fellow at the University of Cambridge (Professor Sir Jack Lewis) working on organometallic chemistry. Since 1980 he has been a Full Professor of Organic Chemistry at the Faculty of Sciences of the University of Bologna, Italy. In 2002 he was the recipient of the Award of the Italian Chemical Society for his contributions to the field of organic synthesis. His research interests include the use of metals dispersed on graphite in organic synthesis, the development of enantioselective organometallic reactions, and the synthesis of biologically active compounds.

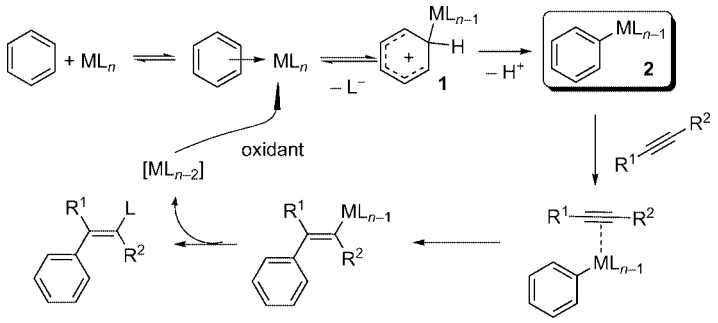


Figure 1. Tentative mechanistic pathway for the electrophilic metalation of aromatic C–H bonds.

these attributes, however, there are still limitations that stem from the use of stoichiometric amounts of additives that call for the use of new, milder, "fancy" soft LAs such as InX_3, BiX_3, $Re(OTf)_3$, and $AuCl_3$. These metal salts are capable of more-favorable product decomplexation, thereby allowing sub-stoichiometric amounts of additives to be successfully adopted.[12] From a mechanistic point of view, the activation of the electrophilic species by coordination of the LA is widely accepted to be the key step of the process.[13] However, there is an alternative reaction pathway that has been extensively investigated, proved, and exploited in the cycloalkenylation of arenes, namely C–H activation by a metal.[4,14] Since the initial electrophilic mercuriation discovered over one century ago,[15] many transition metals such as Pt, Au, Pd, and Rh have proved their effectiveness in promoting electrophilic aromatic metalations. The reaction course of the electrophilic metalation of aromatic C–H bonds has been well established: the initial coordination (η^2) of the metal to the arene leads to the formation of the key σ-aryl–metal complex (**2**), probably through electron-transfer processes and a Wheland-type intermediate (**1**; Figure 1). Such a mechanistic pathway generally concerns metals in high oxidation states, and the presence of electron-donating groups on the aromatic ring speeds-up the kinetics of the S_EAr process along with the high oxidation state of the metal.[16]

The organometallic species can easily undergo a carbometalation reaction with carbon–carbon double[17] and triple bonds (Figure 1). Under these conditions, the concomitant presence of a stoichiometric oxidant (i.e. formic acid, TFA) is indispensable in order to regenerate the catalytically active form of the metal species.

Mechanistically, the electrophilic metalation should not be confused with the oxidative addition of metals, predominantly in low oxidation states, into the C–H bonds of electron-poor aryl systems [Equation (1)].

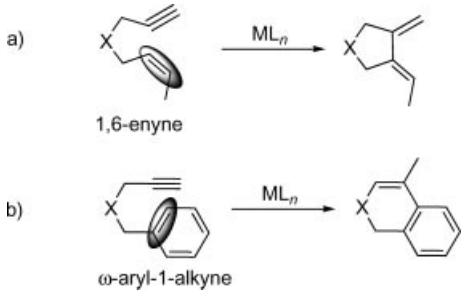
$$\begin{aligned} &\textit{oxidative addition} && RH + M^{n+} \longrightarrow R\text{–}\overset{H}{\underset{|}{M}}{}^{(n+2)+} \\ &\textit{electrophilic metalation} && RH + M^{n+} \longrightarrow R\text{–}M^{n+} + H^+ \end{aligned} \quad (1)$$

In the following sections we will collect some of the more relevant catalytic intramolecular FC alkylation and alkenylation processes by choosing the type of electrophilic framework as a discriminating factor.

2.1. Cyclization of Aryl Alkynes

2.1.1. Alkenylation by Alkyne Activation

In the last decade, alkenylation reactions have proved to be a valuable synthetic alternative to the Heck cross-coupling concerning C_{sp^2}(arene)–C_{sp^2} bond-forming processes. Among them, the en-yne cycloisomerization, also known as the Alder–ene reaction, was first described by Murai et al.[18] in 1996 and involves the quantitative atom-economical metal-catalyzed synthesis of cyclic compounds through the intramolecular rearrangements of 1,*n*-enynes (typically n = 6, 7; Scheme 2, a).[19] An extension of this protocol was subsequently described by replacing the ene counterpart with an aromatic ring. Under these conditions, the present strategy enabled the synthesis of phenanthrenes, dihydronaphthalenes, and other polycyclic fused aromatic systems in excellent yields (Scheme 2, b).



Scheme 2. Schematic representation of enyne metal-catalyzed cycloisomerizations.

Such processes, addressed also as FC alkenylations of arenes, took longer to be adequately developed in comparison to the analogous alkylations. In fact, *"... one major drawback from the direct FC alkenlylation of arenes is the alkyne polymerization ..."*.[20]

Mechanistically, although different rationales have been proposed that depend both on metal salts and reaction conditions, the interaction between the C–C triple bond and the catalyst is considered to be the key step during the nu-

cleophilic attack on the tethered alkyne moiety to give predominantly the 6-*endo-dig* product (Figure 2).

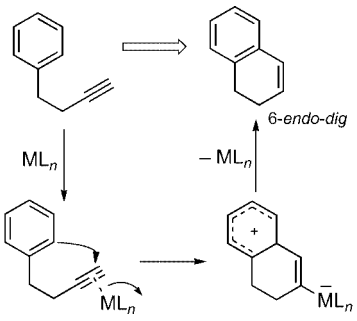
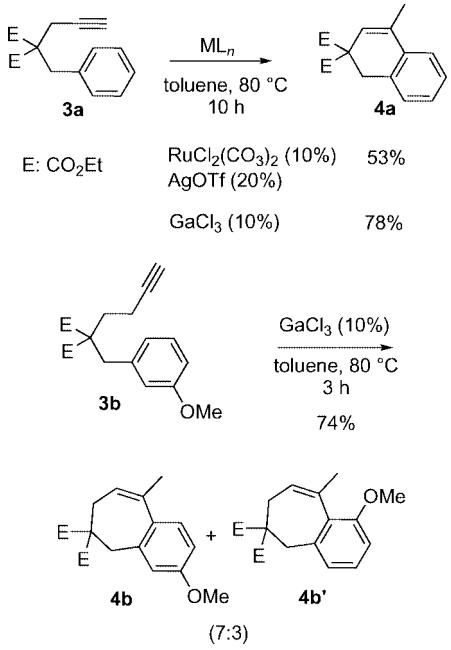


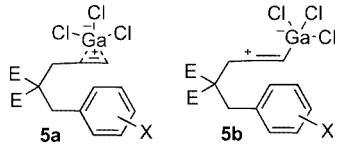
Figure 2. Tentative mechanism for the 6-*endo-dig* cycloalkenylation of alkyne arenes.

In particular, the high electron affinity of electrophilic late transition metals for π-systems and their excellent tolerance toward many hard functional groups suggest transition metal salts to be potentially effective catalysts for the cycloisomerization of alkynes. Among them, cationic Pt^{II} and Ru^{II} salts were initially found to be active in promoting the synthesis of dihydronaphthalenes and dihydrobenzocycloheptenes in moderate yields when electron-rich aromatic rings were employed.[21] For instance, the treatment of diethyl (phenylmethyl)-2-propynylpropanedioate (**3a**) with a catalytic amount of $[RuCl_2(CO_3)_2]$ (10%) and AgOTf (20%, halide sequestering agent) leads to the corresponding dihydronaphthalene **4a** in 53% isolated yield and high site selectivity (Scheme 3). This protocol was further expanded to unactivated arenes by using a catalytic amount of $GaCl_3$ (10%; 78% yield, Scheme 3).[22]

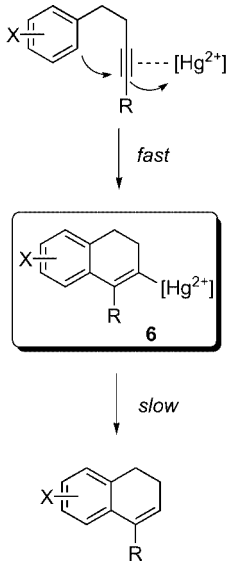


Scheme 3. Comparing the catalytic performances of metal salts in cycloisomerization processes.

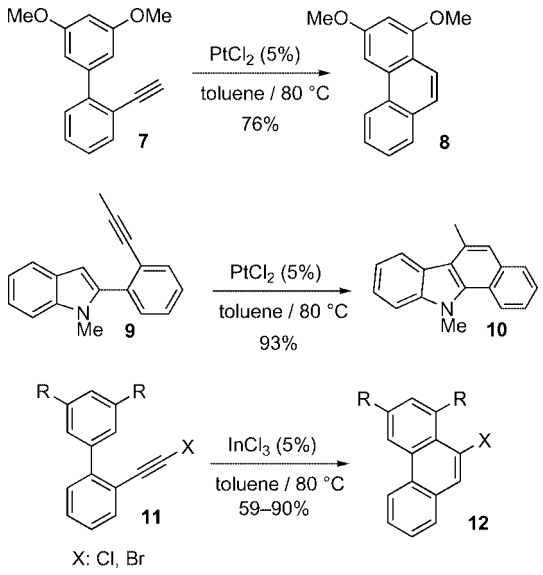
The milder reaction conditions required by the gallium catalyst in comparison to those with late-TMs allowed high site selectivity to be obtained. Moreover, beside the good functional-group tolerance proved by $GaCl_3$, the strategy furnished appreciable results also in the cycloisomerization of 6-aryl-1-alkynes **3b** to give dihydrobenzocycloheptenes **4b**, **4b′** in satisfactory yields. Finally, the authors proposed the formation of bridged- or open-type gallium complexes **5a**,**b** as active species during the whole mechanistic cycle.



Related to this study is the dihydronaphthalene synthesis promoted by $Hg(OTf)_2/(TMU)_n$ recently described by Nishizawa and co-workers.[23] This mercury-based catalytic system proved to be remarkably active even in low catalytic amounts (0.1% Hg/TMU, 1:3 ratio), promoting the cyclization of ω-arylalkynes to the corresponding 6-*endo* products with yields constantly higher then 95% (210 min reaction time). The isolation of the vinylmercury chloride **6** calls for the final protodemercuriation step to be the rate-limiting step of the whole catalytic cycle.



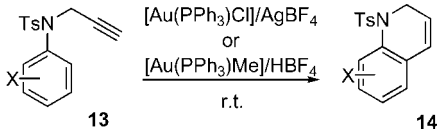
The synthetic approach exploited by Dankwardt[24] and later by Fürstner[25] for the synthesis of variously substituted phenanthrenes, helicenes and heteroarenes is conceptually analogous. The alkynylated biphenyl derivatives, which were synthesized by Suzuki cross-coupling reactions, smoothly underwent predominantly 6-*endo-dig* cyclization in the presence of $PtCl_2$ (5%, toluene, 80 °C) or in some cases $InCl_3$, $GaCl_3$, and $AuCl_3$. As a representative example, we report on the application of the protocol to the preparation of methoxyphenanthrene **8** (76% yield, 95:5 selectivity) and pharmacologically active benzo-fused carbazoles **10** (93% yield, selectivity > 95:5; Scheme 4).



Scheme 4. Platinum-catalyzed synthesis of phenanthrenes and heteroarenes by cycloisomerization.

The generality of this protocol was expanded to haloalkyne derivatives **11**, which were found to be poorly reactive under platinum catalysis. Here, although the key step of the synthesis of the aporphine-type alkaloids requires a stoichiometric amount of the indium(III) salt, in numerous cases a sub-stoichiometric amount of $InCl_3$ (5%) promoted the synthesis of 10-halophenanthrenes **12** in high yield (59–90%).[26]

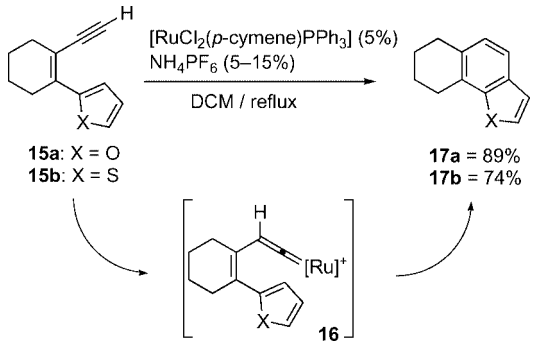
Very recently, Echavarren and co-workers have reported the effectiveness of Au^I salts in promoting the *endo*-selective hydroarylation of alkynes.[27] Here, the combination of $[Au(PPh_3)Cl]$ (3%) with $AgBF_4$ ($AgSbF_6$) or the use of cationic Au^I species formed in situ ($[Au(PPh_3)Me]/HBF_4$) guarantees the alkenylation of functionalized aryl alkynes **13** to give 1,2-dihydroquinolines **14** in high yield (Scheme 5).



Scheme 5. Synthesis of dihydroquinolines catalyzed by cationic gold catalysts.

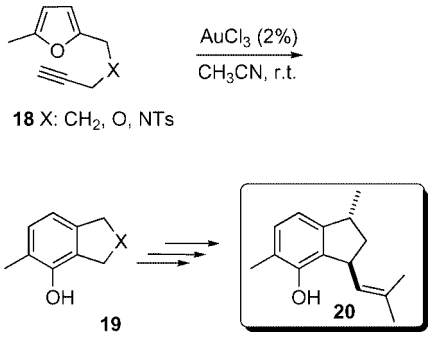
Generally, the protocol allows polycyclic compounds to be isolated in markedly milder conditions than those required by platinum catalysts.[28] Moreover, the authors carried out a theoretical investigation (DFT) of the reaction mechanism which showed a thermodynamic and kinetic preference for the 6-*endo*-*dig* mechanism.

An alternative mechanism was proposed earlier by Merlic and co-workers that describes the ruthenium-catalyzed 6π-electrocyclization of dienalkynes **15a**,**b** for the formation of benzofuran **17a** and benzothiophene **17b** derivatives via vinylidene intermediates **16** (Scheme 6).[29]



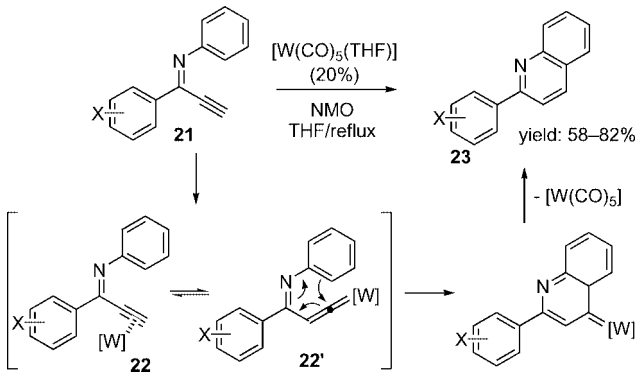
Scheme 6. Ru-catalyzed cyclizations of dienylalkenes.

A peculiar reactivity was demonstrated by furans in the intramolecular reaction with alkynes when both Au^I and Pt^{II} salts were employed as catalysts. In particular, Hashmi has reported the synthesis of substituted arenes **19** starting from **18** under mild conditions ($AuCl_3$, 2%, CH_3CN),[30a] with the reaction mechanism being an intramolecular [4 + 2] cycloaddition between the furan and the alkyne. Therefore, the gold-catalyzed reaction was employed in the multi-step synthesis of jungianol (**20**), allowing its synthesis to be shortened considerably (Scheme 7).[30b] Almost simultaneously, Echavarren and co-workers also highlighted the effectiveness of $PtCl_2$ in promoting such a transformation, which was proposed to take place by electrophilic aromatic substitution (platinum carbene intermediates).[31]



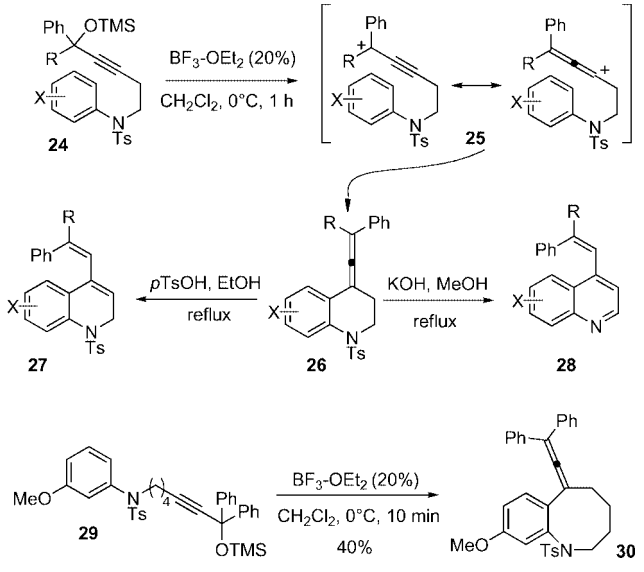
Scheme 7. Gold and platinum catalysis in the intramolecular reaction of furans and alkynes.

The synthesis of functionalized quinolines is another crucial target in several chemical fields such as pharmaceutical and materials science. A novel catalytic method for the construction of quinoline skeletons was described by Akiyama and co-workers. The authors reported the use of $[W(CO)_5$-(THF)] as an effective promoting agent (20%) for the electrocyclization of alkynyl imines **21** via tungsten carbene complexes **22′**. Analogously to the previous paper, a transient metallovinylidene is considered to be formed during the reaction course by [1,2]-hydrogen migration. Then, the final electrocyclization leads to the final target **23** and release of the catalytically active $[W(CO)_5]$ in solution (Scheme 8).[32]



Scheme 8. Alkynyl imines as valuable precursors for the tungsten-catalyzed synthesis of quinolines.

One of the few examples of the use of $BF_3{\cdot}Et_2O$ (20%) as a promoting agent in catalytic quantities is represented by an elegant approach recently reported by Ishikawa and Saito for the synthesis of quinolines and aza-heteroaromatic analogs.[33] The reaction course involves the formation of highly electrophilic allenyl cations **25** in situ starting from propargyl silyl ethers **24**. These intermediates smoothly undergo cyclization to form tetrahydroquinolines in good yields (higher than 90%) and high regioselectivity. Subsequent transformation into 1*H*-quinolines **27** or quinolines **28** can be easily performed by treating the allenyl compound under acidic or basic conditions, respectively (Scheme 9).



Scheme 9. Flexible synthesis of quinolines and analogous via in situ formed allenyl cations.

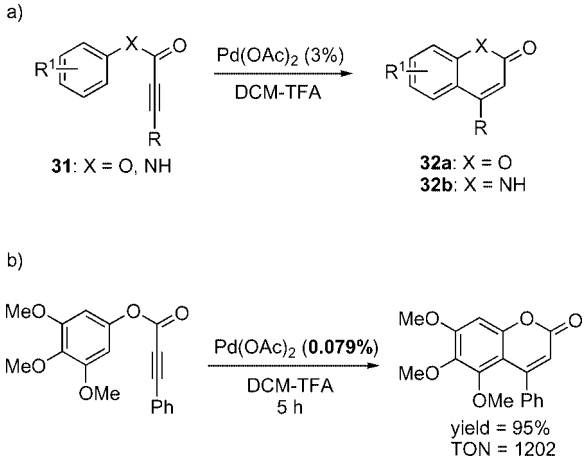
The scope of this protocol was further developed by applying the methodology to the synthesis of challenging eight-membered ring heterocycles **30**, as illustrated in Scheme 9. Although the yield dropped significantly to 40% in this case, the cyclization was complete in a very short reaction time (10 min), with reasonable conversions.

The carbocyclization of siloxyalkyne arenes was also reported in the presence of Brønsted acids. In particular, by generating highly reactive ketenium species in situ, the employment of a catalytic amount of $HNTf_2$ enabled the synthesis of variously substituted silyl enol ethers even in the presence of unactivated aromatic rings.[34]

In the field of LA-mediated alkenylations, Song, Lee, and co-workers very recently reported on the astonishing improvement of the catalytic activity of metal triflates when combined with hydrophobic ionic liquids ([bmim][PF_6], [bmim][SbF_6]) in catalyzing the synthesis of 4-substituted coumarins.[19] Indium, scandium, ytterbium, yttrium, and hafnium triflates proved their potentialities in inter- as well as intramolecular alkenylations, with the acceleration effect of the ionic liquid associated with its capability to stabilize the charged intermediates during the reaction course.

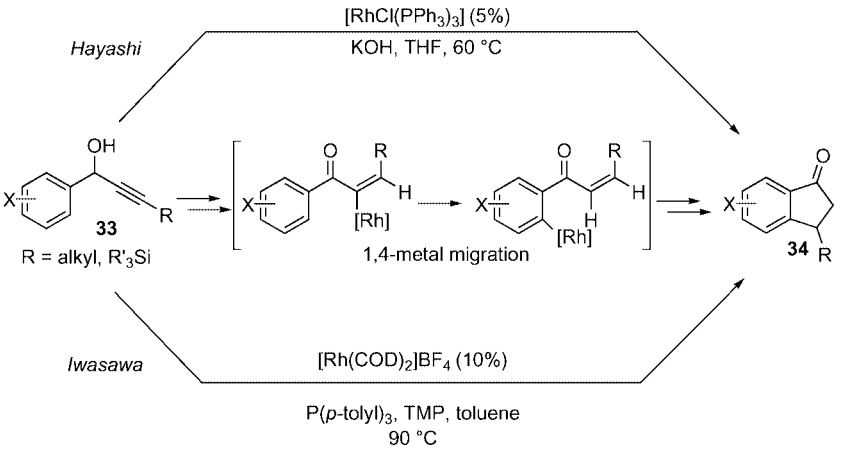
2.1.2. Alkenylation by Metal C–H Activation

Electrophilic metalation of aromatic C–H bonds was first reported by Fujiwara and co-workers[16] and applied to both intra- and intermolecular hydroarylation of alkynoates. In particular, the faster intramolecular version enabled the synthesis of coumarins **32a** and 2(1*H*)-quinolinones **32b** in excellent yields and high chemoselectivity in a *cis*-arylalkene synthesis starting from aryl alkynoates **29**. The use of $Pd(OAc)_2$ in combination with TFA as the catalytic system arose from a detailed screening of metal salts (catalytic activity decreases in the order $Pd^{II} > Pt^{II} > Ni^{II} > Rh^{II}$) as well as reaction conditions (Scheme 10, a).[35] In some cases, $PtCl_2$/2AgOAc was also efficient in the aforementioned cyclization. Several isotopic effect studies unambiguously proved the operating electrophilic metalation of the aryl ring. The spectacular turnover number [$Pd(OAc)_2$ < 0.1%, Scheme 10, b] showed by the Pd catalyst and the mild reaction conditions make this protocol a valuable synthetic tool in the chemical and pharmaceutical industries.



Scheme 10. Intramolecular hydroarylation of aryl alkynoates catalyzed by $Pd(OAc)_2$ in a TFA/CH_2Cl_2 solvent mixture.

Subsequent studies in this area were performed by He[36] and Sames,[37] who reported the use of highly electrophilic gold(III) and platinum(IV) salts in the hydroarylation of

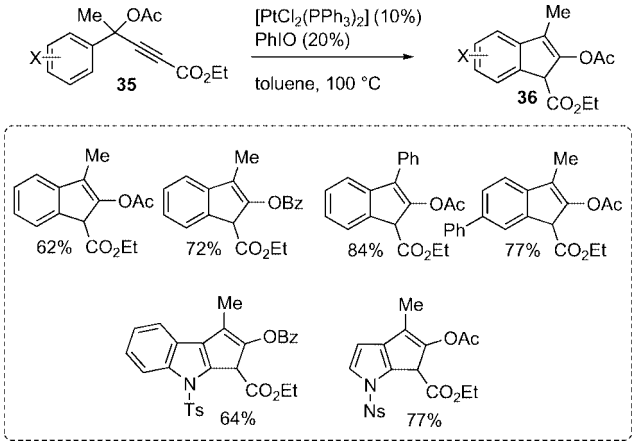


Scheme 11. Synthesis of substituted cyclopentanones by Rh^{I}-catalyzed cyclization of α-arylpropargyl alcohols.

aryl alkynoates (coumarins) and propargylic aryl ethers (chromenes),[38] respectively, even in the presence of unactivated aryl rings. A direct electrophilic metalation of the aromatic ring (assisted by the ethynyl coordination) is invoked in the mechanistic cycle leading to the corresponding arylgold(III) species. On the other hand, the high electrophilicity of the Pt^{IV} catalyst, in combination with its greater solubility in organic solvents compared to Pt^{II} analogs, allows for faster rates with the platinum(IV) salt with challenging substrates.

Propargylic alcohols are also important substrates for the synthesis of indene and indanone derivatives under mild reaction conditions. In this area, the results obtained independently by Hayashi[39] and Iwasawa,[40] who almost simultaneously investigated the activity of rhodium complexes in the cyclization of α-arylpropargyl alcohols **33**, are noteworthy. Both studies are based on the capability of rhodium complexes to undergo aromatic C–H insertion via 1,4-migration of alkenyl–metal species (Scheme 11).[41] In particular, both alkyl and trialkylsilyl propargyl alcohols **33** were smoothly cyclized to the corresponding substituted cyclopentanone **34** in high yields in the presence of Wilkinson's catalyst and $[Rh(COD)_2]BF_4$/phosphane complexes, respectively.

The activation of hydroxy groups as an acetate has allowed the straightforward synthesis of polyfunctionalized indenes **36** by pentaannulation reactions that proceed via Pt carbenoid intermediates.[42] The authors described the serendipity of the discovery that, despite the low conversions guaranteed by Pt^{II} salts, during the "TLC time" the complete and chemoselective formation of the desired indene product occurred (exposure to air).[43] From this evidence, Sarpong and co-workers deduced that the addition of an external oxidant to the reaction mixture could be beneficial for the final outcome. After a survey of conditions, 20% of PhIO turned out to be the optimal oxidising agent to combine with $[PtCl_2(PPh_3)_2]$ (10%) in the catalytic pentaannulation. A library of functionalized pentaannulated compounds was isolated with yields ranging from 62% to 84% (Scheme 12).

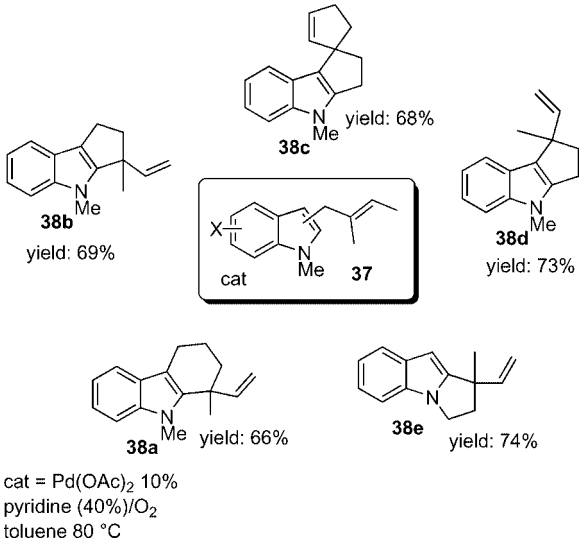


Scheme 12. Synthesis of functionalized indenes by Pt-catalyzed pentannulation.

2.2. Cyclization of Aryl Alkenes

Analogously to the cyclizations of aryl alkynes, C–C double bonds have also been shown to be valuable reagents for aromatic electrophilic substitutions. However, their use in catalytic alkylation processes has been developed to a lesser extent than the previously described cycloalkenylations. A breakthrough in this area of intense interest was reported by Stoltz and co-workers, who described the aerobic oxidative annulation of indoles catalyzed by Pd^{II}–pyridine complexes.[44] The use of atmospheric oxygen (1 atm) as stoichiometric reoxidant for the Pd^{0} guaranteed a remarkable mildness in the cyclization of both 2- and 3-substituted indoles (**37**; Scheme 13). The need for an external terminal oxidant came from the detection in the reaction product of a C–C double bond, indicating an operative β-hydride elimination. The electronic characteristics of the Pd complex are crucial for the positive transformation outcome. In particular, a compromise within electron-poor ligands must be found. In fact, while highly electron-deficient ligands are known to coordinate and to poorly stabilize the Pd metal, ligands that are too electron-rich partially quench its catalytic activity. Interestingly, these studies show that

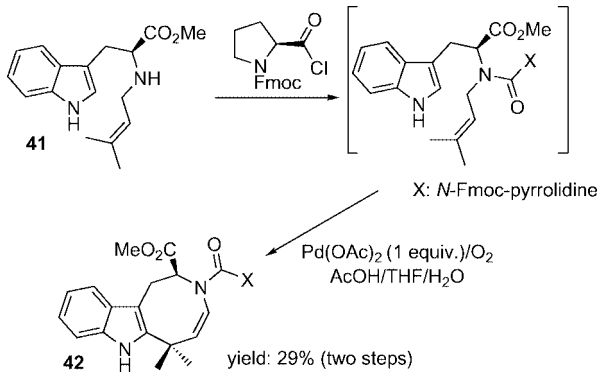
even unactivated C–C double bonds can act as electrophiles in the alkylation of arenes.



Scheme 13. Oxidative C–C bond-forming transformation mediated by Pd-py complexes.

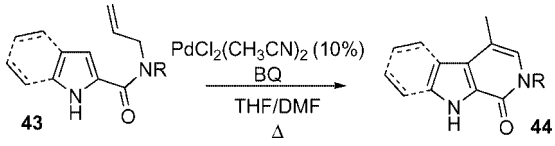
Widenhoefer and co-workers recently addressed their efforts to the synthesis of biologically relevant tetrahydrocarbazoles and tetrahydro-β-carbolinones in good yields and excellent chemoselectivity by cyclization and cyclization/carboalkoxylation of 2-(4-pentyl)indole derivatives **39** in the presence of platinum[45a] (2%) and palladium[45b] (5%) catalysts, respectively (Scheme 14). The degree of polyfunctionalization reached for **40b** in the cyclization/carboalkoxylation procedure is noteworthy. The protocol proceeds by a chemoselective 6-*endo*-trig ring-closure in the presence of stoichiometric amounts of Cu^{II} salts as oxidant for the final Pd^0 species.

A palladium-mediated intramolecular coupling between indole (C-2 position) and tethered unactivated olefins has also been employed by Corey and co-workers as the key step for the preparation of synthetically challenging indoloazocine tricyclic systems such as (+)-austamide (**42**). The optimal conditions involve the use of a mixture THF and H_2O as the solvent and a permanent atmosphere of O_2 (1 atm) to reoxidize the palladium in the catalytically active oxidation state (Scheme 15).[46]



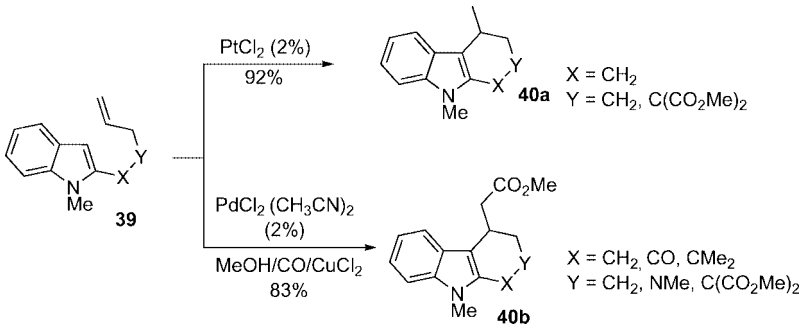
Scheme 15. Synthesis of dihydroindoloazocine by a Pd-catalyzed intramolecular regioselective alkylation of indole.

Continuing with the synthesis of nitrogen-containing heterocycles, Broggini and co-workers have quite recently described numerous versions of Pd-catalyzed intramolecular cyclizations,[47] among which the possibility to synthesize polycyclic indolyl and pyrrol derivatives **43** by oxidative palladium-catalyzed C–C forming annulations in the presence of unactivated olefin double bonds is noteworthy.[48] In this case, *p*-benzoquinone was found to be an effective re-oxidant for the Pd^0 species (Scheme 16).



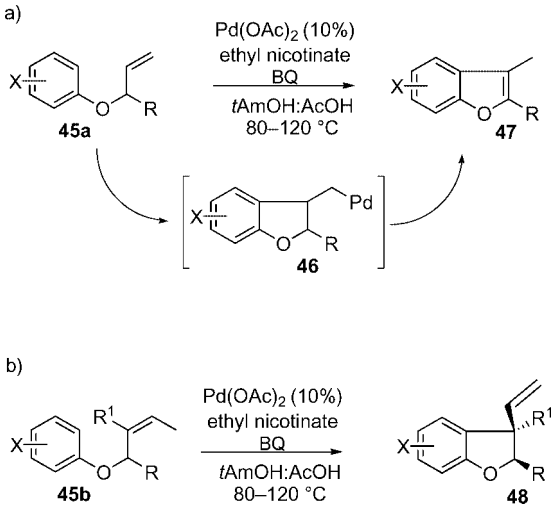
Scheme 16. Intramolecular oxidative Pd-catalyzed Heck coupling for the synthesis of polycyclic indole and pyrrole derivatives.

After the successful application of the intramolecular Fujiwara–Moritani/oxidative Heck reaction to the synthesis of polycyclic indoles (Scheme 13), Stoltz and co-workers highlighted the applicability of the Pd-catalyzed oxidative Heck-type coupling in the synthesis of functionalized benzofurans **47** and dihydrobenzofurans **48**.[49] The optimal reaction conditions concern the use of $Pd(OAc)_2$ (10%) combined with ethyl nicotinate (1:2 ratio) and benzoquinone (BQ) as the best oxidizing agent (1 equiv.), furnishing the corresponding benzofuran **47** in good yield (77%, Scheme 17, a). The reaction is believed to proceed via a Pd-catalyzed C–C bond forming process and β-elimination



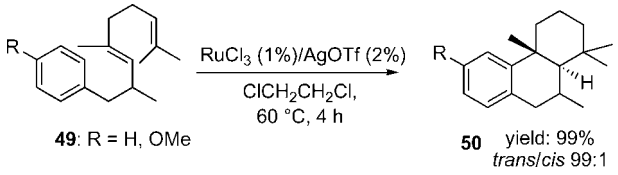
Scheme 14. Synthesis of polycyclic fused indoles by metal-catalyzed Friedel–Crafts alkylation of unactivated C–C double bonds.

followed by the re-aromatization step. Upon exploration of the generality of the oxidative cyclizations with the synthesis of a library of variously substituted benzofurans, the authors expanded the broadness of their strategy to the dihydrobenzofurans **48** starting from tri- and tetrasubstituted olefins **45b** (Scheme 17, b).



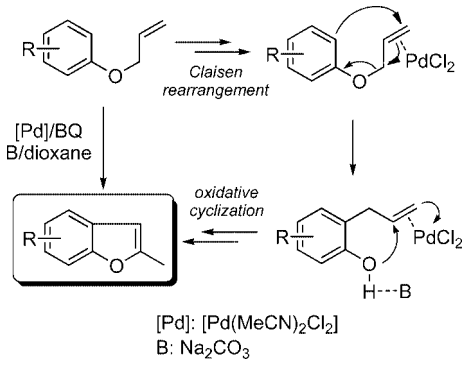
Scheme 17. Oxidative Heck-type coupling for the catalytic synthesis of benzofurans and dihydrobenzofurans.

After an impressive initial screening of metal salts and catalysts, Sames and co-workers identified an interesting lead in the $RuCl_3$/AgOTf system for the hydroarylation of a broad range of substrates such as hydronaphthalenes, hydrobenzofurans, hydrobenzopyrans, hydroquinolines, and hydrocarbazoles, almost simultaneously.[50] The protocol was finally successfully employed for the arene-polyene cyclization to give the corresponding tricyclic terpenoids **50** under mild conditions ($ClCH_2CH_2Cl$, 60 °C, 4 h) and in quantitative yield (99%, Scheme 18).



Scheme 18. Use of ruthenium-catalyzed hydroarylation of alkenes in the synthesis of tricyclic terpenoid **50**.

A direct one-pot synthesis of benzofurans and chromenes by a palladium-catalyzed cyclization of allyl and homoallyl aryl ethers was also described later by Youn and co-workers.[51] With a single catalytic species {i.e. $[PdCl_2(MeCN)_2]$/BQ}, the authors emphasized the synthetic utility of the tandem-Claisen rearrangement/catalyzed oxidative cyclization promoted by Pd^0 species.[52] The final formation of the aromatic benzofurans indicates that a β-hydride elimination is occurring during the reaction cycle, with the consequent need for a stoichiometric oxidant (BQ). Such a process, in fact, is supposed to be initiated by the activation of the olefin double bond through coordination with the Pd^{II} complex (Scheme 19).



Scheme 19. Pd-catalyzed tandem Claisen rearrangement/oxidative cyclization of aryl allyl ethers for the one-pot synthesis of benzofurans.

The heteroatom-directed C–H activation of the *ortho* site (directed orthometalation, DoM) in aromatic compounds is a well-known process[53] and numerous groups have used this approach to perform intermolecular aryl-alkene coupling under catalytic conditions.[54] Imines, ketones, esters, pyridines, and oxazolines are among the most widely employed directed metalation groups (DMG) in aromatic C–H activation. The high *ortho* regioselectivity obtained is believed to be ascribable to a precoordination of the directing group to the metal to give **52**, with subsequent insertion of this species into the adjacent C–H aromatic bond (Figure 3). Despite the tremendous benefits introduced by this approach, early investigations were limited in their applicability to terminal alkenes, which led to linear products only.

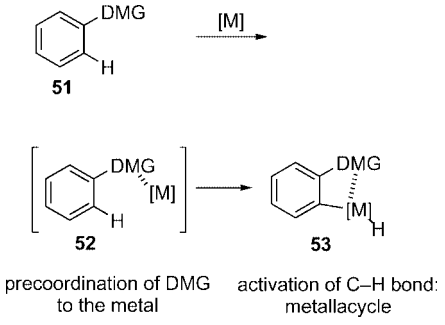
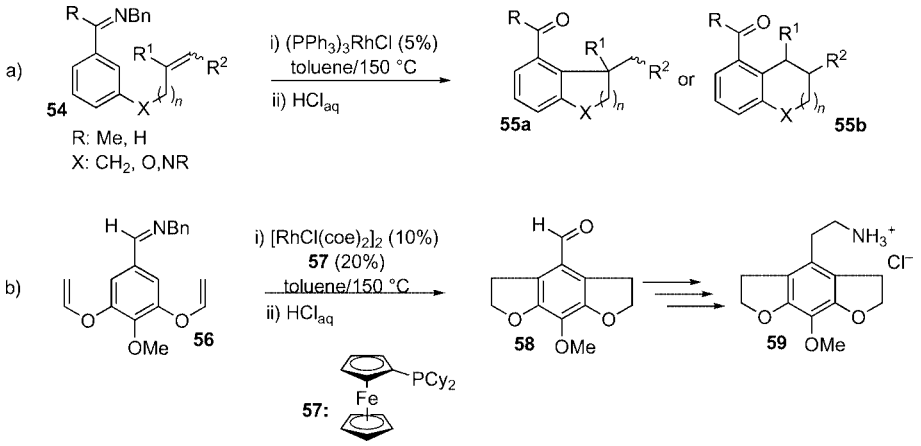


Figure 3. Schematic representation of directed orthometalation of substituted aromatic rings.

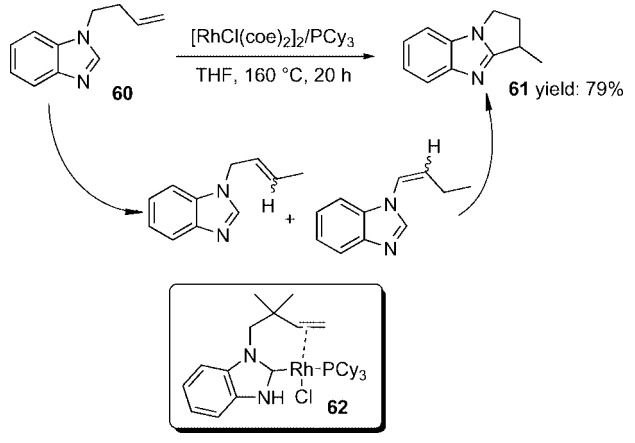
A significant improvement in the area is due to Ellman, Bergman, and co-workers, who described the first intramolecular annulation of aromatic imines with directed chelation-assisted C–H activation in the presence of internal *meta*-tethered olefins **54**.[55] Under optimal conditions, the use of a catalytic amount (5%) of Wilkinson's catalyst $[RhCl(PPh_3)_3]$ in toluene at 150 °C produced functionalized indanes, tetralanes, dihydroindoles, and dihydrobenzofurans in reasonable yields (25–85%, Scheme 20, a). The protocol was further developed with the purpose of carrying out challenging tandem cyclization reactions. After a brief survey of reaction parameters, the authors underlined the effectiveness of the $[RhCl(coe)_2]_2$/$FcPCy_2$ complex in promoting the tandem double C–H activation of the appropri-



Scheme 20. Rhodium-catalyzed arene–alkene coupling by imine-directed *ortho* C–H activation. Application to the synthesis of mescaline analogs.

ately designed benzyl imine **56**. The catalytic double annulation markedly shortened the synthetic route to polycyclic natural aromatic compounds such as the mescaline tetrahydrobis(benzofuran) analog **59** (Scheme 20, b).[56]

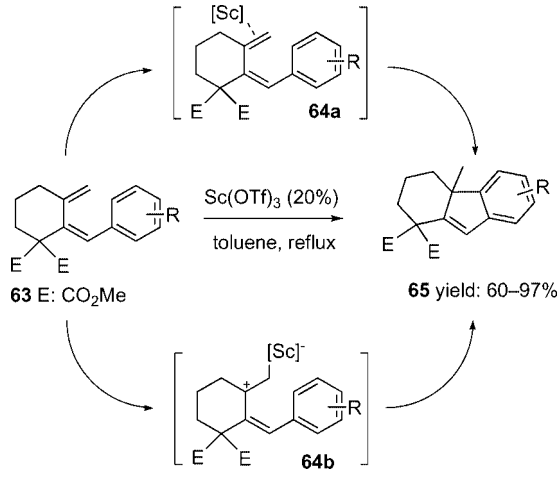
The $[RhCl(coe)_2]_2/PCy_3$ system has also found application in the regioselective intramolecular alkylation of *N*-tethered alkenylimidazole rings **60** to give annulated heterocycles in high yields (up to 79%, Scheme 21).[57a] However, the employment of air-sensitive catalysts and the need for high temperatures and long reaction times limited the applicability of such a strategy in large-scale productions. These aspects were later addressed and overcame by using microwave-assisted techniques (reaction time of less than 20 min versus several hours without microwaves) in the presence of the more stable Wilkinson's catalyst.[57b]



Scheme 21. Intramolecular alkylation of N-heterocycles via Rh-carbene complexes.

A detailed NMR investigation suggested an initial isomerization of the C–C double bond, with final conversion to the desired tricycle **61** by selective C–H activation at the position α to the nitrogen atom. Notably, an N-heterocyclic carbene complex **62** was isolated and crystallographically characterized as an intermediate of the intramolecular alkylation. Starting from this unexpected carbene species, a combined spectroscopic and theoretical investigation was conducted to clarify the crucial mechanistic steps of the process. The insertion of the coordinated alkenyl group into the Rh–C bond proved to be the rate-limiting step of the overall catalytic cycle.[58]

A different approach to the intramolecular aromatic alkylation was proposed by Balme and co-workers, who investigated the catalytic Friedel–Crafts cyclization of aryl dienes **63**.[59] Here, a series of 4a-methyltetrahydrofluorenes **65** were isolated in moderate to good yield (60–97%) by employing $Sc(OTf)_3$ (20%) in the cyclization of 1,3-bis-exocyclic dienes **63** (Scheme 22). Postulated intermediates of the process could be the electrophilically activated exomethylene species **64a** or the conjugate carbocation **64b** induced by the metal triflate.

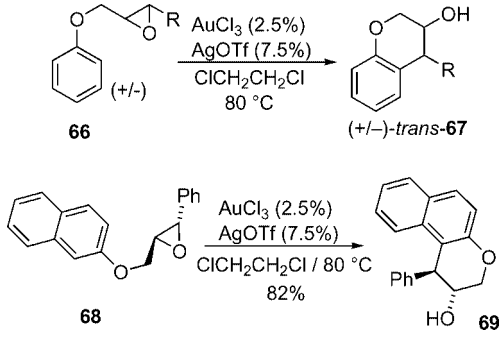


Scheme 22. Scandium triflate catalyzed intramolecular alkylation of arenes by cyclization of 1,3-bis-dienes.

Aryl-containing tricyclic compounds have also been synthesized by Pd-mediated coupling of silyl enol ethers and aromatic rings. In this study, Ihara and co-workers demonstrated the effectiveness of $Pd(OAc)_2$ as a catalyst for the intramolecular alkylation of arenes by insertion of the Pd–enol ether intermediate into the aryl double bond, followed by elimination of Pd^0.[60]

2.3. Ring-Opening of Epoxides

Epoxides are versatile electrophilic reagents that have found widespread employment in the synthesis of structurally complex polyfunctionalized molecules. In particular, despite their extensive use in intermolecular catalytic alkylations of aromatic compounds,[61] very little attention has been focused on catalytic and intramolecular cyclization of arylalkyl epoxides.[62] A breakthrough in this field was made by He and co-workers, who described the effectiveness of gold(III) salts in promoting the ring-opening of oxiranes by tethered electron-rich arenes.[63] The crucial role played by the $AuCl_3$ system in the mechanistic cycle was clearly verified by several control experiments performed in the absence of catalysts and in the presence of a range of LAs both in catalytic and stoichiometric amounts. Starting from variously functionalized arylalkyl epoxides **66** and employing three equivalents of AgOTf (based on gold) several 3-chromanols **67** were isolated in moderate to good yields (58–85%). Moreover, the protocol showed high stereospecificity when the ring-opening process was conducted with enantiomerically pure **68**. Under optimal conditions, the corresponding chromanol **69** was isolated in 82% yield as a single enantiomer, thus proving the operating S_N2-type mechanism of $AuCl_3$-mediated cyclic alkylation (Scheme 23).



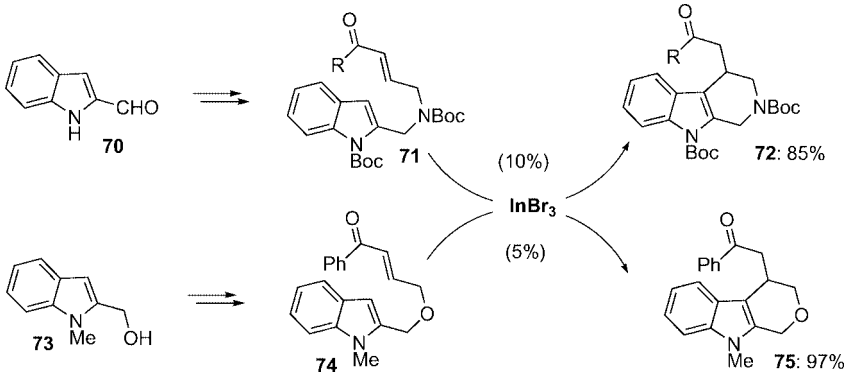
Scheme 23. Intramolecular aromatic-based ring-opening of epoxides catalyzed by $Au^{III}Cl$/AgOTf.

From a mechanistic point of view, the authors proposed two distinct pathways usually associated with Au-mediated aromatic alkylations, namely the formation of arylgold(III) intermediates[10] and the simple LA action of Au^{III} salts.[64]

2.4. Michael Additions

The conjugate addition of electron-rich aromatic systems to α,β-unsaturated carbonyl compounds has received much attention over the last decade as a straightforward synthetic shortcut to the chemo- and regioselective synthesis of functionalized aromatic systems. Its interest lies in the mildness of the reaction conditions and in the large number of known strategies (homogeneous as well as heterogeneous catalysis) for their accomplishment. However, despite this significant progress, very little has been reported concerning intramolecular aromatic alkylations via Michael-type additions (see Section 3 for some catalytic and stereoselective protocols).

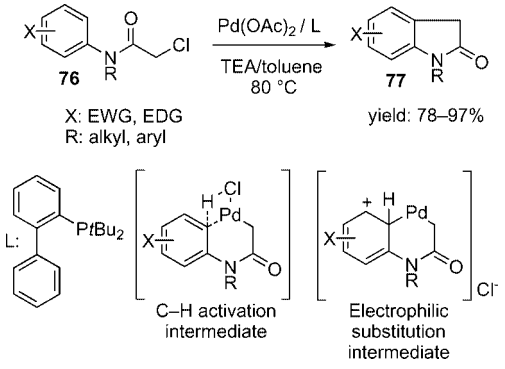
Due to our interest in the catalytic alkylation of indoles,[65] we envisaged the potential of an intramolecular Michael-type FC reaction for the synthesis of 4-substituted tetrahydro-β-carbolines **72** (THBC) and tetrahydropyrano[3,4-*b*]indoles **75**.[66] This approach involved the prior synthesis of the requisite indolyl enones **71**, **74**, which was possible in a few steps starting from readily available indole-2-carbaldehyde (**70**) and the corresponding *N*-Me-indolyl alcohol **73**. The employment of a catalytic amount of $InBr_3$ (5–10%) as the LA gave the desired cyclization products in high yield (85–97%), excellent chemoselectivity, and short reaction time (15–30 min, Scheme 24). Remarkably, the use of poorly heterophilic LAs,[67] such us indium salts, allowed the final annulation step to be performed in aqueous media as well, although longer reaction times were required for nearly complete conversion (12 h).



Scheme 24. $InBr_3$-catalyzed intramolecular Michael-type reaction as a practical route to the synthesis of tetrahydrocarboline and pyrazinoindole derivatives.

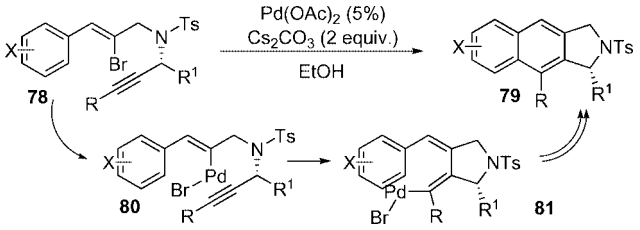
2.5. Use of Organic Halides as Electrophile Precursors

Beside the alkenylation reaction (Section 2.1), a valuable synthetic alternative to the Heck reaction for the formation of C_{aryl}–C_{aryl} and C_{aryl}–C_{alkyl} bonds would be the removal of the reactive functional group from the aromatic ring by embedding it in the tethered side-chain. This aspect was developed by Buchwald and co-workers, who described the direct synthesis of oxindoles **77** starting from α-chloroacetanilides **76** in the presence of $Pd(OAc)_2$ and (2-di-*tert*-butylphosphanyl)biphenyl (1% and 2%, respectively).[68] This method also allows the cyclic alkylation of challenging aromatic rings bearing highly electron-deficient groups (CF_3, NO_2), thereby furnishing a library of functionalized oxindoles in remarkable yields (78–97%). The oxidative addition of the Pd^0 species to the C–Cl bond is considered to be the initial step. Experimental proof for an intramolecular primary isotope effect (K_H/K_D = 4) is consistent with several mechanistic hypotheses, such as electrophilic substitution and "true" C–H activation (Scheme 25).



Scheme 25. Direct catalytic oxindole synthesis by Pd-catalyzed C–H functionalization of α-chloroacetanilides.

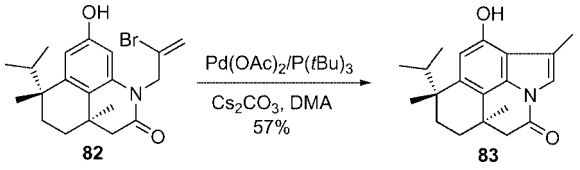
Functionalized bromoenynes **78** have recently been employed by Tanaka and co-workers in the Pd-catalyzed synthesis of optically active benzoisoindoles **79** in the first tandem bis-cyclization transformation.[69] In particular, when enantiomerically pure **78** was treated with $Pd(OAc)_2$ (5%) and Cs_2CO_3 in EtOH, a range of polyfused aryl-, indoyl-, and benzofuranyl-containing benzoisoindoles were isolated in moderate to good yields (39–74%, Scheme 26).



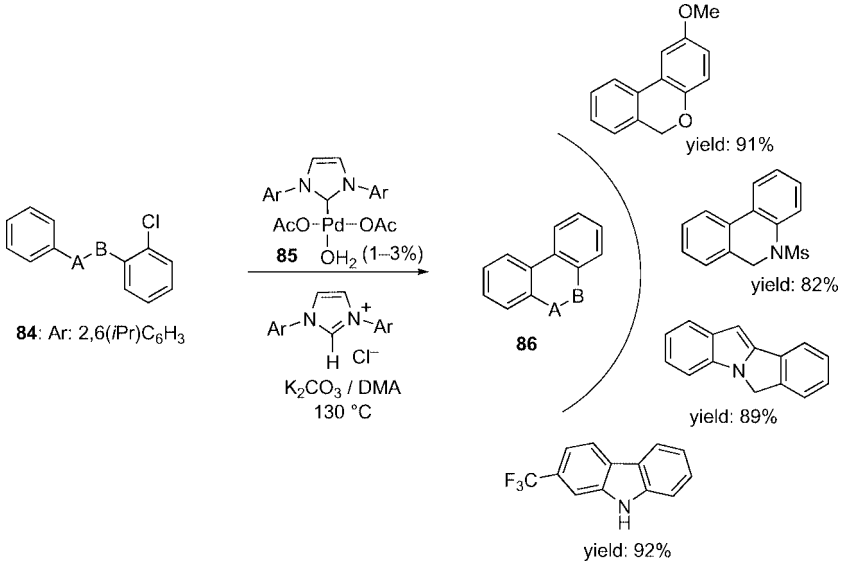
Scheme 26. Tandem bis-cyclization of bromoenynes catalyzed by $Pd(OAc)_2$.

Mechanistically, after the initial oxidative addition of the Pd^0 species to the C–Br bond (**80**) and subsequent carbopalladiaton of the C–C triple bond (**81**), the authors suggested three possible pathways for the final cyclization, namely: i) electrophilic attack of the aromatic ring on the Pd center, ii) oxidative addition of the aromatic C–H bond to the Pd-C intermediate, and iii) carbometalation of the arene followed by β-hydride elimination.

An elegant application of intramolecular Pd-catalyzed alkenylation coupling of arenes has been utilized by Sames and co-workers in the multi-step synthesis of Teleocidin B4 (**83**). In particular, treatment of the bromovinyl **82** with $Pd(OAc)_2$ (15%)/$P(tBu)_3$/Cs_2CO_3 led to the desired indole core **83** in 57% yield (Scheme 27).[70]



Scheme 27. Pd-catalyzed intramolecular alkenylation reactions of aromatic rings as the final step in the synthesis of teleocidin B4.



Scheme 28. Intramolecular hydroarylation of aromatic rings catalyzed by NHC-Pd complexes.

Fagnou and colleagues have demonstrated the unprecedented activity of N-heterocyclic carbene (NHC) ligands for the Pd-catalyzed intramolecular arylation of aromatic rings in the presence of aryl chlorides **84**.[71] In particular, both in situ generated and isolated NHC–palladium complexes **85** (1–3%) promote the synthesis of oxygen- and nitrogen-containing biaryls **86** in excellent yields in DMA at 130 °C. A 1:1 Pd/NHC ratio was demonstrated to be crucial to the reaction outcome as it allowed the competitive hydrohalogenation process to be minimized (<1% by GCMS). The reaction conditions as well as some selected examples are outlined in Scheme 28.

2.6. Nucleophilic Allylic Alkylation

In the last two decades of the 20th century nucleophilic allylic alkylation (Tsuji–Trost reaction) blossomed into a mature field as this reaction allows the synthesis of structurally complex molecules to be shortened markedly.[72] In particular, numerous challenging tertiary and quaternary carbon atoms can be obtained by coupling in situ generated η^3-allylpalladium species with soft nucleophiles.[73]

In this field, we have recently described the chemo- and regioselective cyclization of indolyl allyl carbonates **87** to give the corresponding THBCs **89** and hydropyrazinoindoles **90** in high yields (Scheme 29).

Particularly notable was the effect of the reaction conditions (base and solvent) on the final regiocontrol of the cyclization. In fact, while low coordinating media (CH_2Cl_2) combined with Li_2CO_3 led to exclusively C3-ring-closing allylic alkylation (91% yield, **89/90** > 50:1), the employment of highly coordinating solvents such as THF or DMF with an inorganic base bearing cations with a larger atomic radius drove the cyclization toward the predominant formation of the *N*-ring-closed compound (85% yield, **89/90** > 1:8).[74]

2.7. Pictet–Spengler Condensation

The acid-promoted annulation of amino arenes in the presence of carbonyl compounds is better known as the Pictet–Spengler (PS) condensation (Figure 4).[75] This process, known since 1911,[76] was initially applied to the synthesis of 1,2,3,4-tetrahydroisoquinolines **91** but was soon expanded also to the preparation of THBCs **92** through the replacement of benzene rings with tryptamine derivatives.

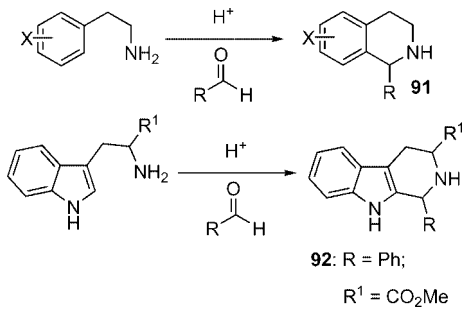
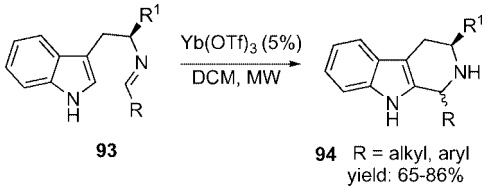


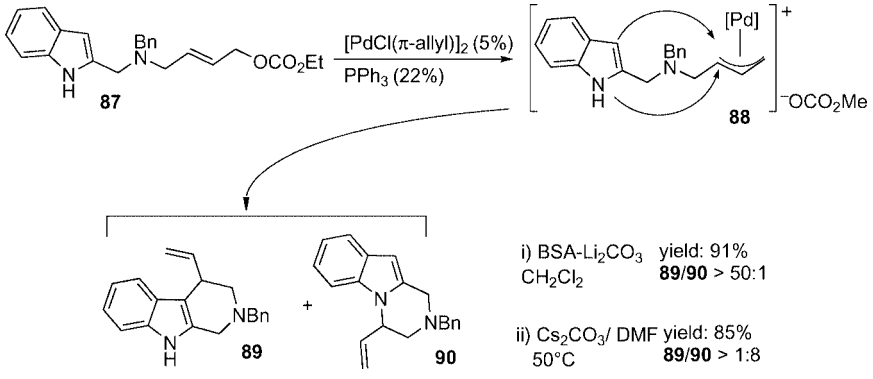
Figure 4. The Pictet–Spengler reaction.

Although the PS condensation is rightly associated with annulation reactions, in some cases the intramolecular FC alkylation occurs on the preformed starting carbonyl compounds by activation of the imine moiety. The great interest of the chemical community in this transformation lies both in the synthetic potentiality of the protocol and in the certainly improvable reaction conditions (temperature, loading of catalyst) to accomplish ring-closing processes on sensitive/labile electron-rich aromatic rings.[77]

Focusing on the synthesis of THBCs, Ganesan and coworkers have recently reported a valuable parallel screening approach for the discovery of effective LA catalysts for PS condensations.[78] From this study it appears that both aldehyde- and imine-selective LAs are effective in catalyzing the cyclization of the model aromatic imine **93** (R = Ph). Among them, $Yb(OTf)_3$ proved to be superior, allowing the loading of the catalyst to be significantly decreased (5 mol-%) when using microwave irradiation (Scheme 30).

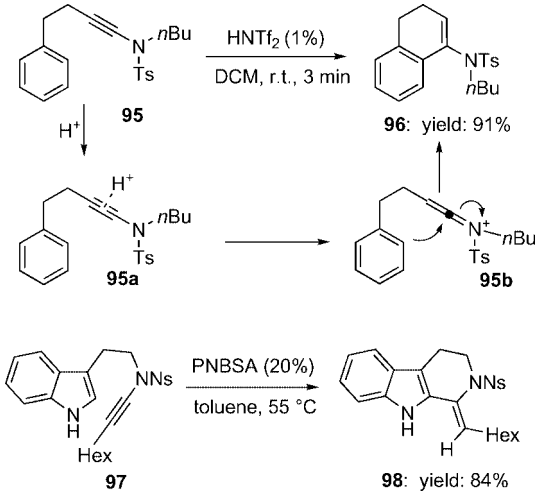


Scheme 30. Pictet–Spengler reaction catalyzed by $Yb(OTf)_3$.



Scheme 29. Use of catalytic nucleophilic allylic alkylations in the chemo- and regioselective synthesis of polycyclic fused indolyl-based compounds.

An unprecedented approach to the PS cyclization has been reported by Hsung and co-workers, who described the suitability of arene-ynamides **95** in the practical Brønsted acid catalyzed synthesis of polycyclic compounds.[79] The use of $HNTf_2$ (1%) and PNBSA (20%) proved to be superior both to conventional LAs as well as transition metal π-acids such as $PtCl_2$, $PtCl_4$, and $AgNTf_2$. In particular, the cyclization of C-tethered arene-ynamides **95** to give dihydroaminonaphthalenes **96** and THBCs **98** worked smoothly, giving rise to excellent yields within a few minutes. The current working hypothesis is that these PS cyclizations proceed via highly reactive keteniminum ions **95b** that undergo intramolecular nucleophilic attack by the aromatic ring (Scheme 31).



Scheme 31. Brønsted acid catalyzed ring-closing of arene ynamides.

2.8. Catalytic Aromatic Cyclizations onto Acyliminium Ions

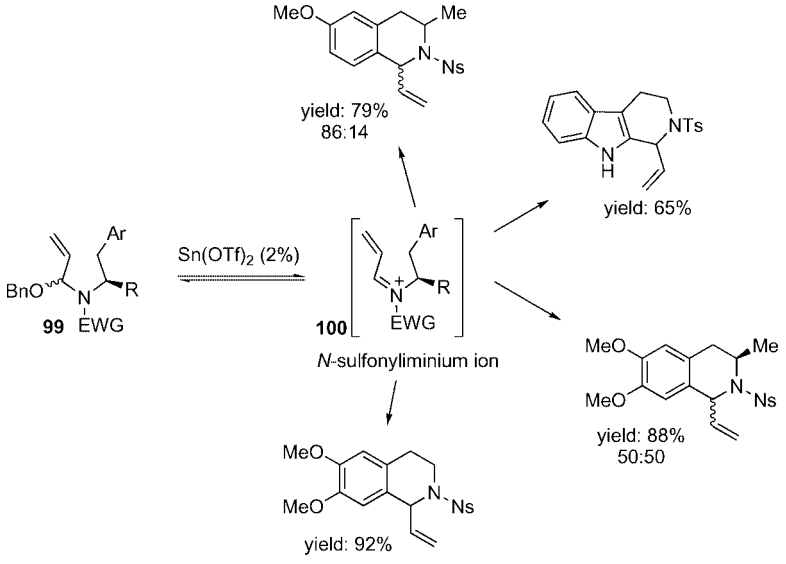
The in situ formation of carbocation species to trap aromatic rings by addition reactions is a widely used protocol for the construction of polycyclic aromatic systems. However, the use of stoichiometric amounts of Lewis or Brønsted acids are often required in order to guarantee reasonable conversions in acceptable times. Herein, allylic iminium ions are known to be valuable transient electrophilic species for both inter-[80] and intramolecular alkylation of aromatics.[81]

In this context, Hiemstra, Rutjes and co-workers very recently reported the use of low loadings of $Sn(OTf)_2$ (2%) as a catalyst for the formation of α-vinyl-substituted isoquinolines and β-carbolines in good yields via the allylic *N*-sulfonyliminium intermediate **100** (Scheme 32).[82]

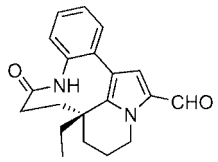
3. Catalytic Enantioselective Strategies

In a recent review, we stated that although there is no surprise in discovering that the FC alkylation reaction still offers numerous advantages in the synthesis of complex aromatic compounds after 128 years, we were intrigued by the fact, that "*... it has taken more than one century for asymmetric catalytic versions of this reaction to be developed ...*".[5c] This aspect reflects, to some extent, the challenges to move from stoichiometric to catalytic conditions, as well as chemo- and regioselectivity concerns.

Over the past five years, a great deal of effort has been dedicated to this topic by chemists, and this has resulted in the synthesis of polyfunctionalized aromatic compounds bearing benzylic stereocenters in a straightforward manner.[5] Of course, the utility of stereocontrolled FC processes for the synthesis of aromatic polycyclic fused systems would be greatly enhanced if performed intramolecularly. The potentiality of this approach has been adequately highlighted by Smith, Banwell, and co-workers,[83] who have described a survey of asymmetric strategies (i.e. chiral auxiliary and organic as well as organometallic chiral catalysts) for the asymmetric intramolecular alkylation of pyrroles as a key step for the synthesis of rhazinal (**101**).[84]

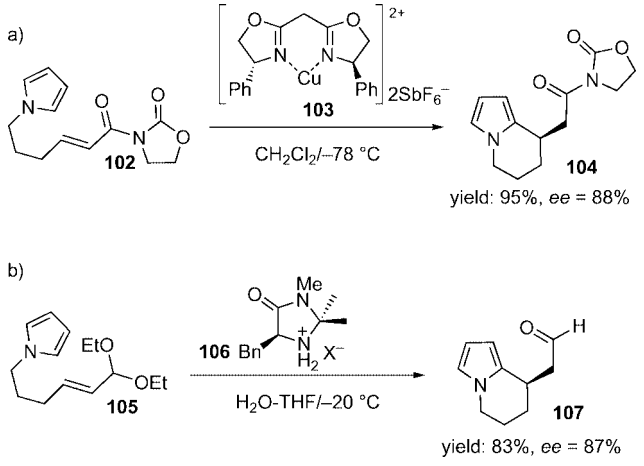


Scheme 32. Use of allyliminium ions as electrophiles for the intramolecular alkylation of aromatics.



101

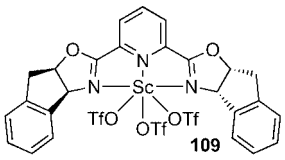
With particular regard to the catalytic processes, the sterecontrol achieved in the ring-closing reaction of pyrrole with achiral *N*-tethered Michael acceptors such as *N*-acyl-2-oxazolidinone **102** is noteworthy. The use of catalytic amounts of [Cu-(Ph-box)]$(SbF_6)_2$[85] (**103**) as the chiral LA led to the formation of **99** in 95% yield and 88% *ee* (Scheme 33, a). Moreover, the authors proved the suitability of the MacMillan chiral organocatalyst **106**[86] for metal-free stereoselective intramolecular alkylation of pyrroles with unsaturated acetals as the Michael acceptor **105**. When running the reaction in mixed organic-aqueous media (THF/H_2O) the cyclized product **107** was isolated in high yield (83–90%) and remarkable enantioselectivity (87%, Scheme 33, b).



Scheme 33. Organometallic a) and organic b) catalyzed enantioselective intramolecular alkylation of pyrrole.

The use of a pybox ligand combined with $Sc(OTf)_3$[87] has been described by Evans and co-workers in the synthesis of 1-functionalized tetrahydrocarbazoles **110** by an intramolecular Michael addition.[88] Here, the importance of 2-acyl imidazole as an easily removable two-site-binding auxiliary was underlined in order to guarantee a high level of enantioselectivity. In particular, **108** was cyclized to the corresponding **110** in quantitative yield and 97% *ee* (CH_3CN, MS, –40 °C, Scheme 34) in the presence of 2% of **109**.

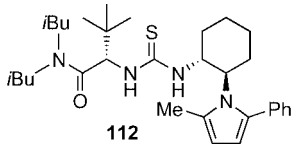
As we already mentioned in Section 2.7, the PS condensation is a well-known and valuable method for the one-pot synthesis of 1,2,3,4-tetrahydroisoquinolines and THBCs. Although several diastereoselective approaches, which frequently require stoichiometric amounts of acid promoters, have been described,[89] to date only one example of a catalytic and enantioselective PS condensation has appeared in the literature. Very recently, in fact, Jacobsen and co-



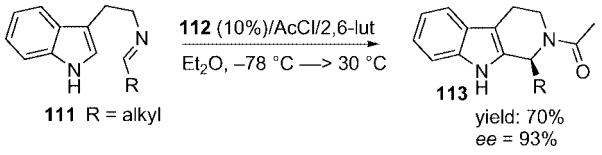
109

Scheme 34. Stereoselective alkylation of indoles by intramolecular Michael addition to 2-acyl imidazoles.

workers reported the effectiveness of a modulable family of chiral thioureas **112** in catalyzing the cyclization of both preformed and in situ obtained indolylimines **111**.[90] The working model involves an activation of the thiourea by formation of hydrogen-bonding interactions with the highly reactive *N*-acyliminium intermediate obtained by the addition of an acylating agent. This strategy provides access to 1-substituted-THBC **113** with 93% *ee*,[91] with the only limitation of an indolyl-aldoimine derived from aliphatic aldehydes (Scheme 35).



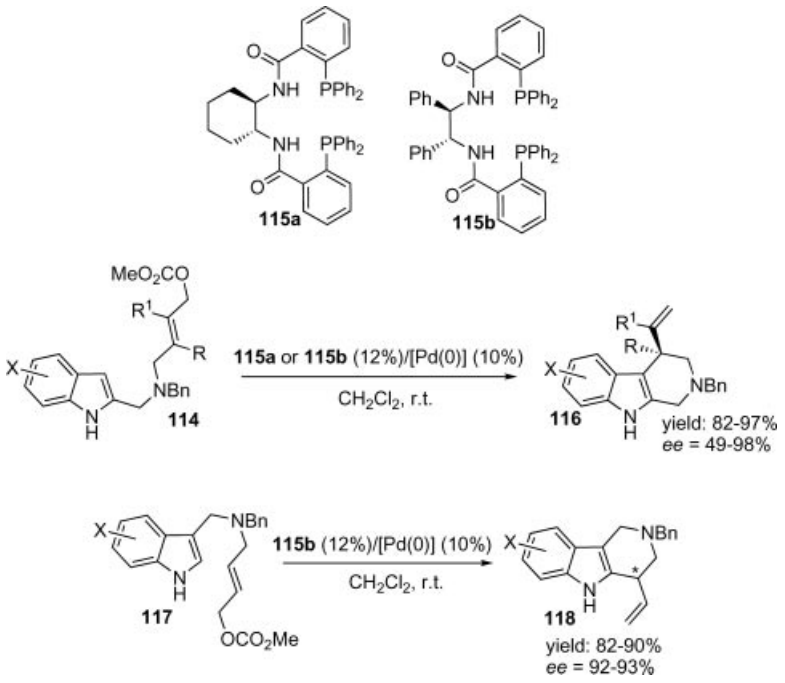
112



Scheme 35. Chiral thioureas as catalysts for the enantioselective PS condensation.

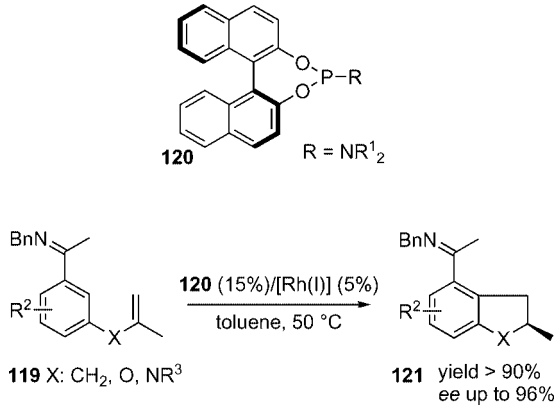
An alternative, and to some extent complementary, catalytic and stereoselective approach to the PS reaction has been developed recently in our laboratories.[92] This study is the result of our interest in the Pd-catalyzed allylic alkylation of indoles (see Section 2.6). In particular, by replacing the PPh_3 on palladium with a chiral ligand (i.e. Trost's ligands **115a**,**b**) we were able to obtain 4-substituted THBCs **116** with high regio- and stereoselectivity (*ee* = 82–97%). Remarkably, this protocol proved tolerant to substitutions both in the indole ring and in the amino side-chain, thus allowing even quaternary stereocenters (**116**: R = Me) to be obtained in 90% *ee* (Scheme 24). Moreover, the same strategy was employed for the first catalytic and stereoselective synthesis of tetrahydro-γ-carbolines **118** (*ee* up to 93%) simply by building up the carbonate chain in the C-3 position of the indole ring (Scheme 36).

A direct catalytic and enantioselective alkylation of arenes with unactivated carbon–carbon double bonds was pi-



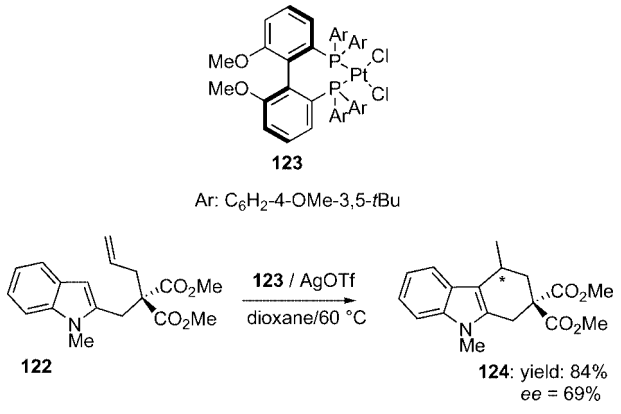
Scheme 36. Stereoselective synthesis of THGCs and THBCs by intramolecular AAA.

oneered by Ellman, Bergman, and co-workers.[93] Alkenes tethered in the *meta* position to aromatic imines **119** were efficiently coupled with the aromatic ring in the presence of chiral Rh catalysts containing monodentate phosphorus-based ligands. The optimal ligands (phosphoroamidites bearing BINOL as a chiral backbone) allowed the cyclization to be performed at a temperature 75 °C lower than the achiral version (with Wilkinson's catalyst, see Section 2.2), leading to a range of branched products **121** with excellent *ee* (up to 96%, Scheme 37).



Scheme 37. Direct Rh-catalyzed C–H bond activation in the stereoselective cyclization of aromatic imines.

Finally, promising levels of enantioselectivity were obtained by Widenhoefer and co-workers as a single example of the stereocontrolled synthesis of tetrahydrocarbazoles by intramolecular alkylation of indoles to a terminal alkene tethered in the 2-position (**122**).[45a] Here, the employment of a chiral mono-cationic bis(phosphane)platinum complex **123** furnished the corresponding ring-closed compound **124** in 84% yield and 69% *ee* (Scheme 38).



Scheme 38. Stereoselective platinum-catalyzed synthesis of tetrahydrocarbazoles by intramolecular indole alkene coupling.

4. Conclusions

Since the first realization of catalytic and stereoselective Friedel–Crafts alkylation of aromatics the interest in this area of study has recorded a continuous growth. Such a vibrant effort has produced valuable and practical intramolecular versions that have demonstrated their effectiveness for the construction of structurally complexes molecules. Both LAs, protonic acids, and π-acid transition metals have revealed their suitability to perform challenging C–C couplings among aromatic C–H bonds and even unactivated electrophilic partners.

In conclusion, although the selection of studies presented here stresses the remarkable state-of-the-art in intramolecular alkylation and alkenylation FC processes, the develop-

ment of new effective catalytic systems for practical stereoselective FC alkylations involving poorly reactive aromatic rings still remains a rewarding and intriguing challenge to be solved.

Abbreviations

AAA: asymmetric allylic alkylation; BINOL: 1,1′-bi-2-naphthol; bmim: butyl-3-methylimidazolium; BQ: 1,4-benzoquinone; DMA: *N*,*N*-dimethylacetamide; DMG: directed metalation group; DoM: directed orthometalation; FC: Friedel–Crafts; Fmoc: *N*-(9-fluorenylmethoxycarbonyl); IMFC: intramolecular Friedel–Crafts; LAs: Lewis acids; NMO: *N*-methylmorpholine *N*-oxide; Ns: nosyl, (4-nitrobenzenesulfonyl); PNBSA: *p*-nitrobenzenesulfonic acid; PS: Pictet–Spengler; RE: rare earth; *t*-Amyl-OH: 2-methyl-2-butanol; Tf: triflate, trifluoromethanesulfonate; THBC: tetrahydro-β-carboline; THGC: tetrahydro-γ-carboline; TM: transition metal; TMP: 2,2,6,6-tetramethylpiperidine; TMU: tetramethyl urea; Ts: tolyl-4-sulfonyl

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