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From Conventional to Sustainable Catalytic Approaches for Heterocycles Synthesis

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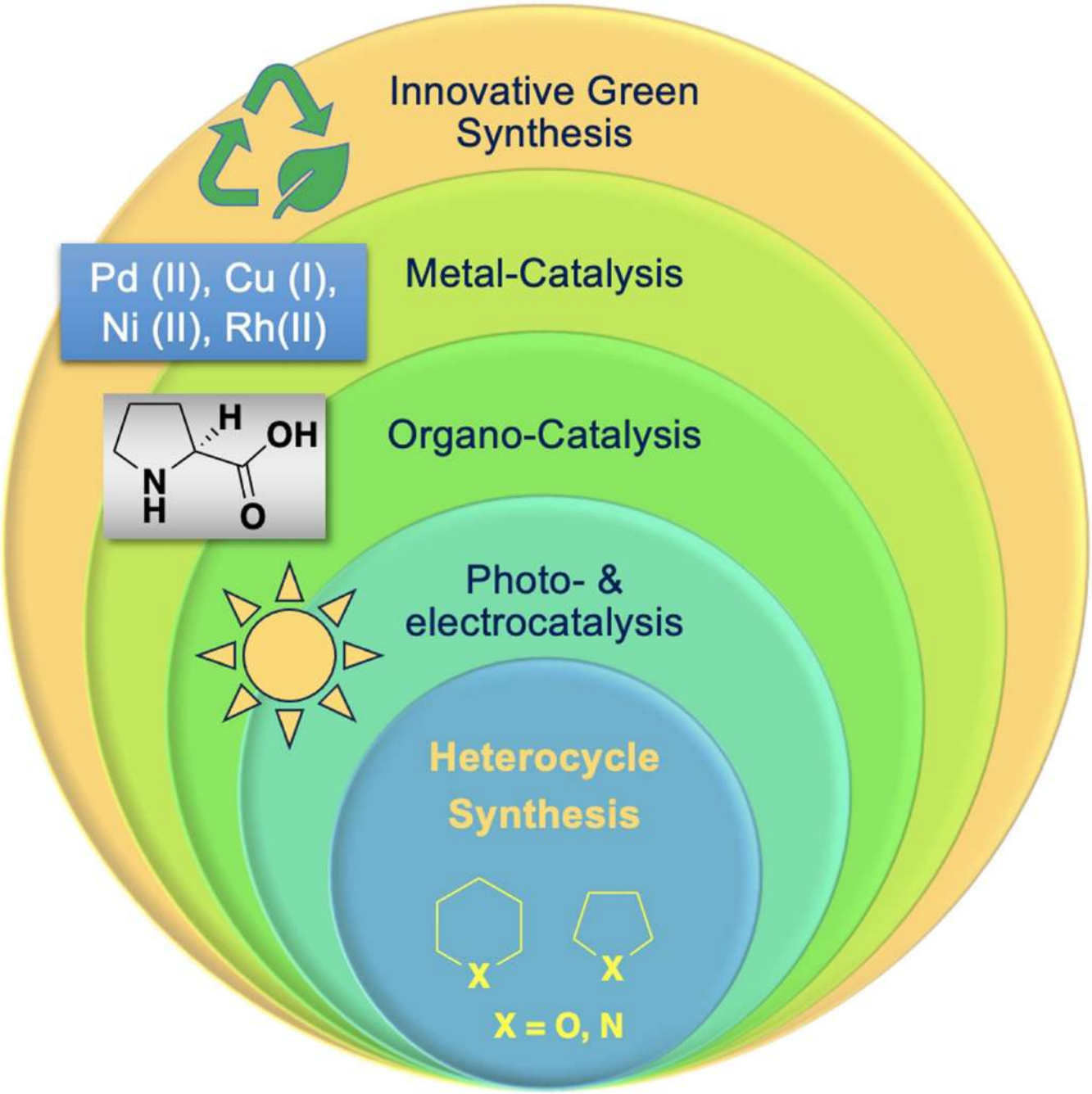

Synthesis of heterocyclic compounds is fundamental for all the research area in chemistry, from drug synthesis to material science. In this framework, catalysed synthetic methods are of great interest to effective reach such important building blocks. In this review, we will report on some selected examples from the last five years, of the major improvement in the field, focusing on the most important conventional catalytic systems, such as transition metals, organocatalysts, to more sustainable ones such as photocatalysts, iodine-catalysed reaction, electrochemical reactions and green innovative methods.

1. Introduction

Heterocycles are ubiquitous structures in all the fields of chemistry and therefore their synthesis is a hot topic since many years. In fact, heterocycles are fundamental building blocks in the field of drug design and discovery,[1] or for their obtainment;[2] for example, in 2021, 8 out of 20 top seller blockbuster drugs contain at least one heterocyclic active principle or a combination of different compounds, for a total of 11 compounds.[3] The structures are reported in Figure 1. Moreover, heterocycles are also key component of natural products,[4] catalysts[5] and building blocks in the field of material science.[6] Concerning synthetic strategies, many examples are reported in the literature, but we can rationalize them into three main approaches (see Figure 2): i) the construction of heterocycles from acyclic building blocks;[7] ii) from other heterocycles, also through rearrangement reactions;[8] iii) or through heterocycles functionalization.[9] The construction of a cycle from acyclic compounds (see route i on Figure 2) represents the main approach in this field, in fact here it will be discussed as the main approach for heterocycles synthesis. In this frame, different reaction's type can be involved, among many others, these methods could take advantage of the use of effective approaches such as Multi Component Reactions (MCR),[10] cascade or domino reactions,[11] dehydrogenative coupling[12] and formation of reactive intermediates such as carbene,[7d] or nitrogen-centered radicals (NCRs).[13] Rearrangement's reaction allow the obtainment of a heterocycle from the reaction of a different one (see route ii on Figure 2).[8b] Usually, these reactions are driven by the formation of a more stable system and are allowed by the presence of reactive site such as labile bonds with the heteroatom. The last approach is based on the introduction of a functional group (FG) on the already formed heterocycle, for example, through aromatic substitution (see route iii on Figure 2). Structure modification and fabrication of new heterocycles can be performed also through nucleophilic aromatic substitution of hydrogen with direct C–H bond functionalization without transition metals catalyst.[14]

All these synthetic approaches exploit the use of modern techniques, that also aimed to improve the sustainability of the synthetic approach, such as photochemistry,[15] electrochemistry,[16] micro-wave[17] or ultra-sound irradiation,[18] employing of ionic liquids as solvents.[19]

Considering the great importance of these compounds, the development of effective catalytic strategies represents a fundamental tool for the synthesis of heterocycles.[20] Indeed, the use of effective catalysts is a necessary issue to increase the sustainability of these synthetic processes and to convert them into greener approaches. In this field, many efforts were devoted to the development of catalysed asymmetric synthesis[21] and supported catalysts.[22] Moreover, the use of alternative solvents or reaction media, such as ionic liquids (IL), deep eutectic solvents (DES) or bio-based solvents, contributed to increase efficiency representing a substantial field improvement.

Here we will review on recent highlights from the literature regarding catalysed heterocyclic synthesis, focusing on recent years (2018–2022), and examining metal-catalysed reactions, organocatalysis, photocatalysis, iodine-mediate reactions and innovative green methods. Considering the extent of the topic, comprehensive analysis of the literature is out of the scope of this review, therefore, selected examples have been chosen based on their impact in the field, effectiveness or innovative sight. The demonstration of synthetic applications as well as the reaction mechanisms, will be discussed here.

2. Metal-based Catalysis

Catalysed synthesis of heterocycles mediated by metals or metal-complexes is, till date, one of the main research fields in chemistry.[23] The peculiar reactivity of many different metals allows yielding different reactive species that opens the way to effective catalytic processes. One of the main advantages of metal-catalysts is their effectiveness at low catalytic level, on the other hand, their use is often accompanied by some drawbacks such as their high costs, environmental toxicity or use of exotic ligands.

2.1. Palladium-based catalysts

Palladium is among the most studied metals for catalytic purposes, due to its versatility and effectiveness, as well as the peculiar reactivity, not accessible with conventional synthetic methods.

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Palladium catalysed synthesis of heterocycles is one of the main research areas extensively reviewed in the last years.[24] The major issue concerning the use of palladium is the cost of this metal, and the availability of different palladium sources such as $Pd(OAc)_2$, $Pd_2(dba)_3$ (dba = dibenzylideneacetone) or $PdCl_2$, more often employed. Other palladium sources such as PdI_2 or Pd/C,[25] were also investigated.

Among recent examples, Trost and Zuo proposed a novel Pd-catalyzed [3 + 2] spiroannulation reaction that easily yields [5,5] spirocyclic heterocycles **3** or **5** (Scheme 1).[26] Starting from azadiene **1**, the reaction outcome can be modulated by the nature of 1,3-dipole precursor, like vinylcyclopropanes **2** or vinylepoxides **4**, that forms different Pd-π-allyl intermediates **I**. The regioselectivity of the reaction is underlined by the nature of the ligand. In fact, combining vinyl derivatives **2** with (*R*)-SEGPOHOS, a selective cycloaddition at the exocyclic double bond of **1** (intermediate **II**), leads to intermediate **III** and then to spiro compounds **3** in good yields (64–91%, 15 examples) and excellent enantioselectivity (up to 99% ee). Limitation for $R_1 = CO_2$-t-Bu, $CO_2CH_2CF_3$ SO_2Ph were evidenced. Interestingly, combining the epoxide **4** and (*R*)-BINAP for the formation of the supposed Pd-π-allyl intermediate **I** (X=O), leads to spirooxazolidine **5**, also obtained in good yields (69–90%, 15 examples) and good enantioselectivity (up to 92% ee), but with a different regioselectivity involving the addition at C=N bond (**IV**) to furnish intermediate **V**. For both regiodivergent methods, $Pd_2(dba)_3$ was employed as catalyst and the structure of representative compounds **3** and **5** was resolved by means of X-ray.

Zhou and co-workers, reported an effective asymmetric palladium-catalyzed intramolecular Heck/Sonogashira reaction of amides **6** with terminal alkynes **7** (Scheme 2).[27] $Pd(OAc)_2$ was employed as catalyst source in combination with chiral sulfinamide phosphine ligand **8**, yielding to substituted chiral dihydroisoquinolin-1-one **9** bearing a propargyl-substituted quaternary stereocenter, in excellent yields, wide scope (68–99%, 60 examples) and excellent enantioselectivity (up to 99% ee). The reaction was further explored in terms of scale-up (on a gram-scale) and functionalization of derivatives **9**, revealing an excellent potential. Enantioselectivity was confirmed determining the

Carla Rizzo is Assistant Professor at University of Palermo since 2022. She received the PhD in Chemistry in 2016 at the University of Palermo, she spent research periods at QUILL, of the Queen's University of Belfast and at Georgetown University, Washington, DC, USA. She obtained several postdoctoral positions at the University of Palermo and, in 2017, she has been a visiting postdoctoral researcher at Durham University, working with Prof. J. W. Steed. Her research activity is mainly focused on the use of Green Solvents, Supramolecular Gels as well as new Biopolymer formation and functionalization.

Andrea Pace is Full Professor of Organic Chemistry at the University of Palermo. In 1997, he joined the research group of Prof. Nicolò Vivona working on heterocyclic chemistry. Tenured in 2000, between 2001 and 2003 he joined the group of Prof. Edward L. Clennan at the University of Wyoming where he started his studies on singlet oxygen chemistry in zeolites and fluorous environments. His current interests cover organic photochemistry and its environmental applications, the chemistry of fluorinated compounds, the synthesis and application of five-membered heterocycles as bioactive compounds and functional components in organic materials.

Ivana Pibiri is an Associate Professor of Organic Chemistry at Palermo University, where she obtained her MD in Chemistry in 1996, and PhD in Chemical Sciences in 2002. Her research interests cover the topics of medicinal chemistry and materials science, focusing on the synthesis of heterocyclic compounds and fluorinated functional materials, their reactivity and photochemistry. She is Lecturer of Chemistry of Organic Materials. She has received grants from the Italian Cystic Fibrosis Research Foundation, Italian Ministry of Research and University funding.

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Antonio Palumbo Piccionello is an Associate Professor of Organic Chemistry at Palermo University, where he graduated in Chemistry in 2003 and completed a PhD in Chemical Sciences in 2007. Research interests have covered the synthesis and photochemistry of heterocyclic compounds, the development of fluorinated oxygen-friendly media, as well as the synthesis of heterocyclic drugs. He was a member of the board of directors of the National Young Chemists Group of the Italian Chemical Society and received public funding and industrial grants.

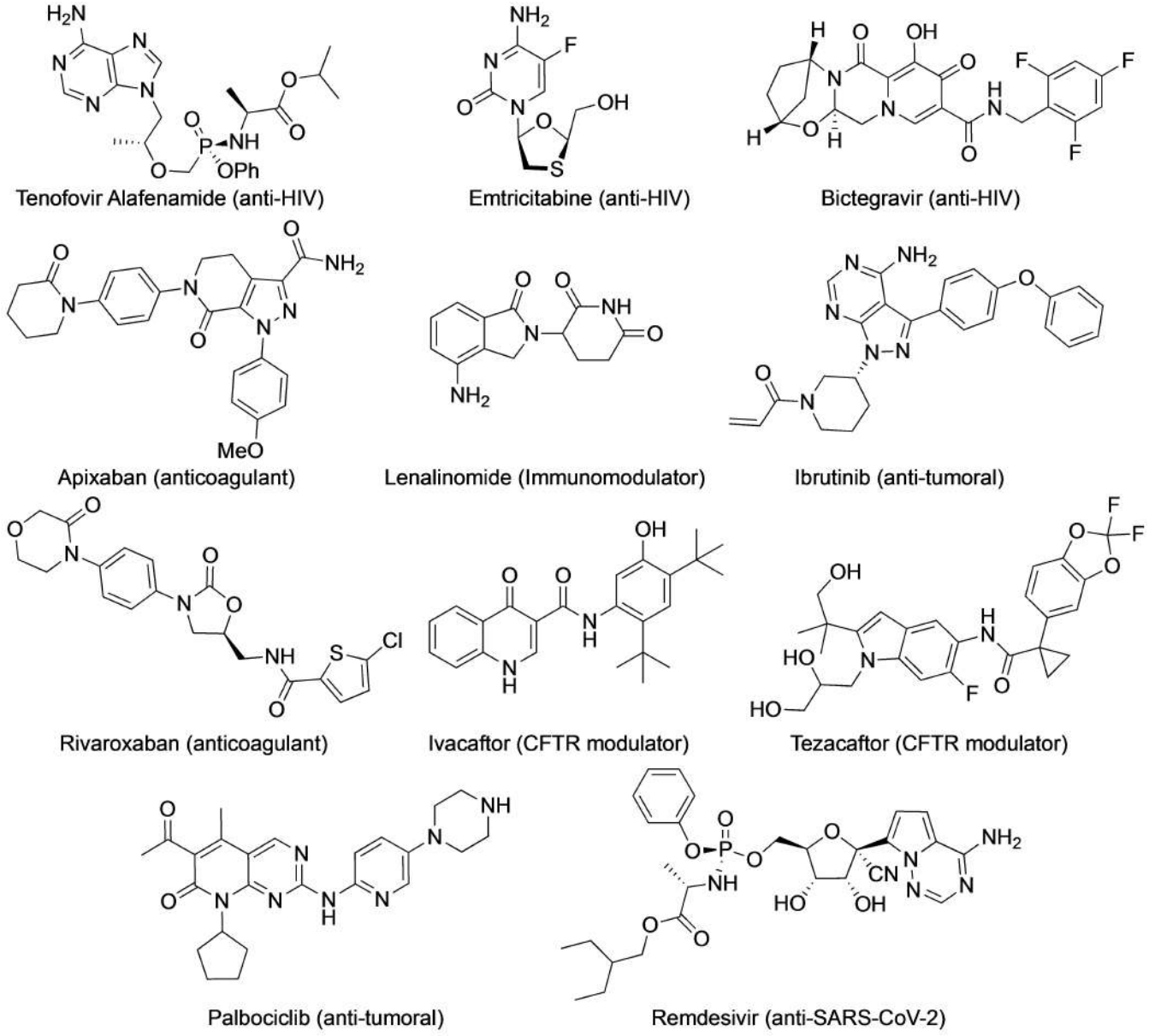
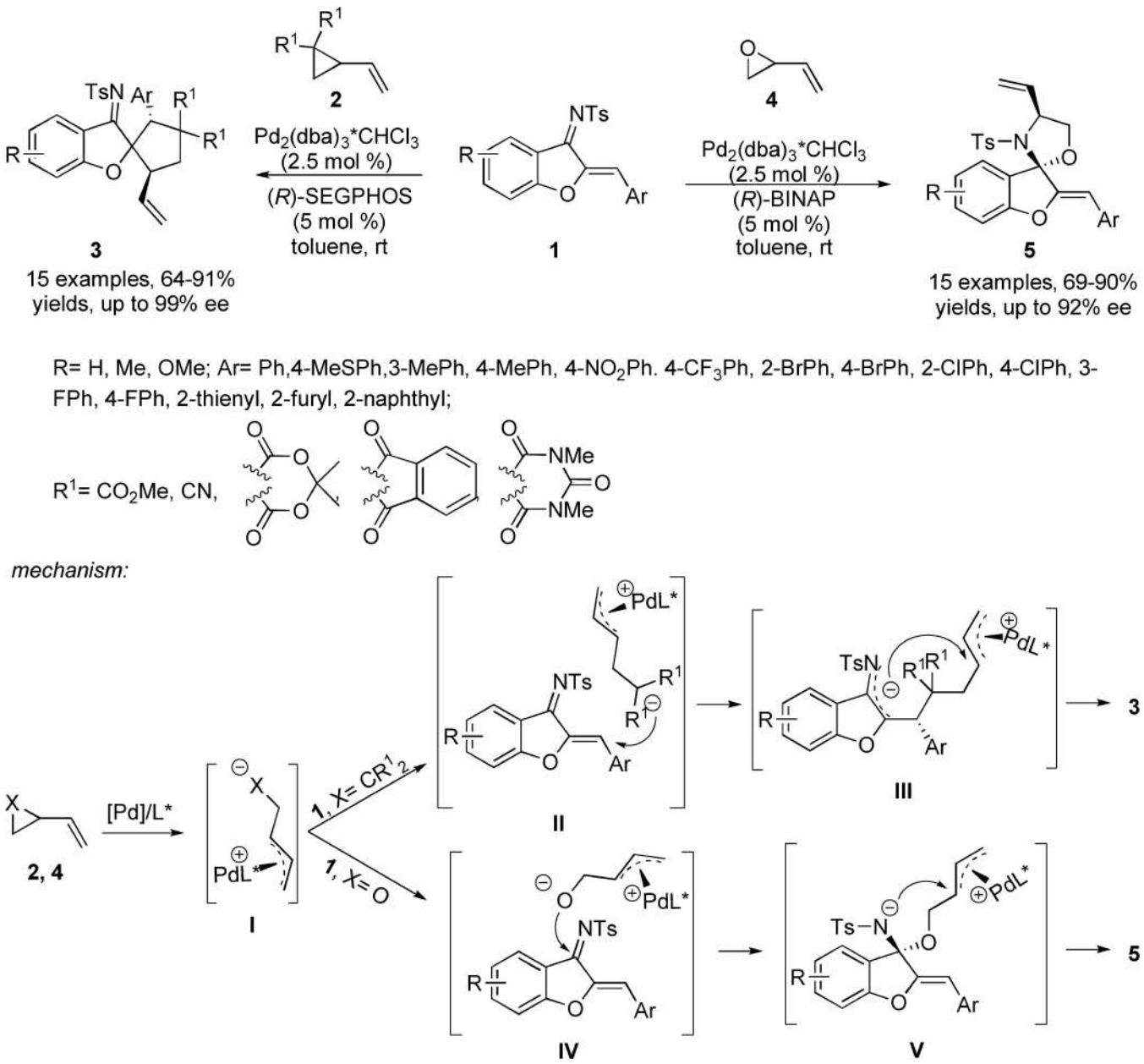


Figure 1. Structure of heterocyclic blockbuster drugs.[3]

absolute configuration of representative derivative **9** by single-crystal X-ray analysis.

The Zang's group presented for the first time chiral sulfinamide phosphine ligand **11** in combination with $Pd_2(dba)_3$ as catalytic system for an intramolecular hydroarylation of o-iodoaryl allyl ethers **10** by means of reductive Heck reactions (Scheme 3).[28] This highly enantioselective procedure (up to 95% ee) produces chiral 2,3-dihydrobenzofuran **12** with a broad scope (53 examples) and good to excellent yields (70–99%). The robustness and utility of this procedure was demonstrated with scale-up (gram scale) and through the synthesis of differently substituted CB2 receptor antagonists. Structure and chirality of the obtained products was demonstrated by means of X-ray diffraction. Moreover, compound *ent*-**12** was synthesized, using a ligand with opposite configuration.

The spirooxindole compounds **15** (Scheme 4i) or **17** (Scheme 4ii) were obtained from acyclic amides **13** or **16**, respectively, through a one-pot palladium-catalyzed asymmetric Heck/carbonylative lactonization or lactamization sequence.[29] The catalytic system composed by $Pd_2(dba)_3$ and chiral phosphine ligand **14** produces lactones **15** (9 examples) and lactams **17** (22 examples) in good to high yields (51–93%, 70–99%, respectively) with good to excellent enantioselectivities (up to 99% ee). Some limitations for N protecting group (R^2=H, Bn, Boc, Ts, Bz) were evidenced. The methodology was applied to gram scale synthesis and to the obtainment of the alkaloid coixspirolactam A, also allowing elucidation of its absolute config-



Scheme 1. Scheme and mechanism of spiroannulation reaction.[26]

uration for the first time, and to the asymmetric synthesis of an CRTH2 receptor antagonist. The reaction outcome was rationalized through an oxidative addition of the catalyst to furnish intermediate **I**, followed by carbo-metallation to give **II** with the quaternary stereocenter. Final products were obtained by means of CO insertion and cyclization through nucleophilic attack of the X atom.

2.2. Copper-based catalysts

Copper catalysed reactions in heterocyclic chemistry are widely studied due to the ready accessibility of this metal and its low cost.[30]

The main application of Cu(I) catalytic system is for the click reaction toward 1,2,3-triazoles, one of the key reactions awarded with Nobel prize 2022. Nevertheless, these reactions will not be discussed here.[1e,31] Concerning recent literature, Hong and co-worker demonstrated an efficient asymmetric Cu(I)-catalyzed cascade cyclization/[1,2]-Stevens-type rearrangement of acyclic precursors **18** to chiral chromeno[3,4-c]pyrroles **21** in presence of bisoxazoline ligands **19**/**20** (Scheme 5).[32] Chiral products **21** were obtained in moderate to good yields and wide scope (39–86%, 60 examples with some unreactive entries for R^2=Cy) but with excellent enantioselectivity (up to 99% ee). Notably, this method could be highlighted for the atom-economy and for the formation of quaternary carbon

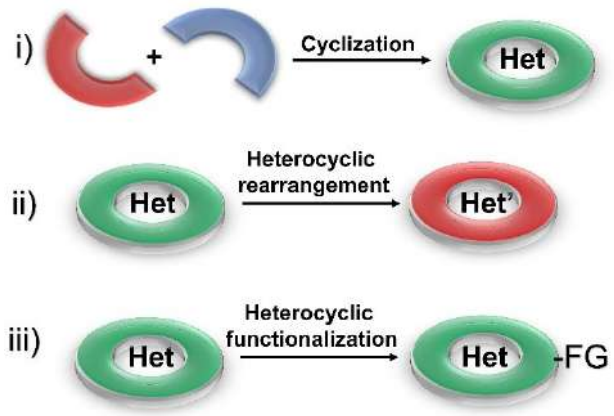
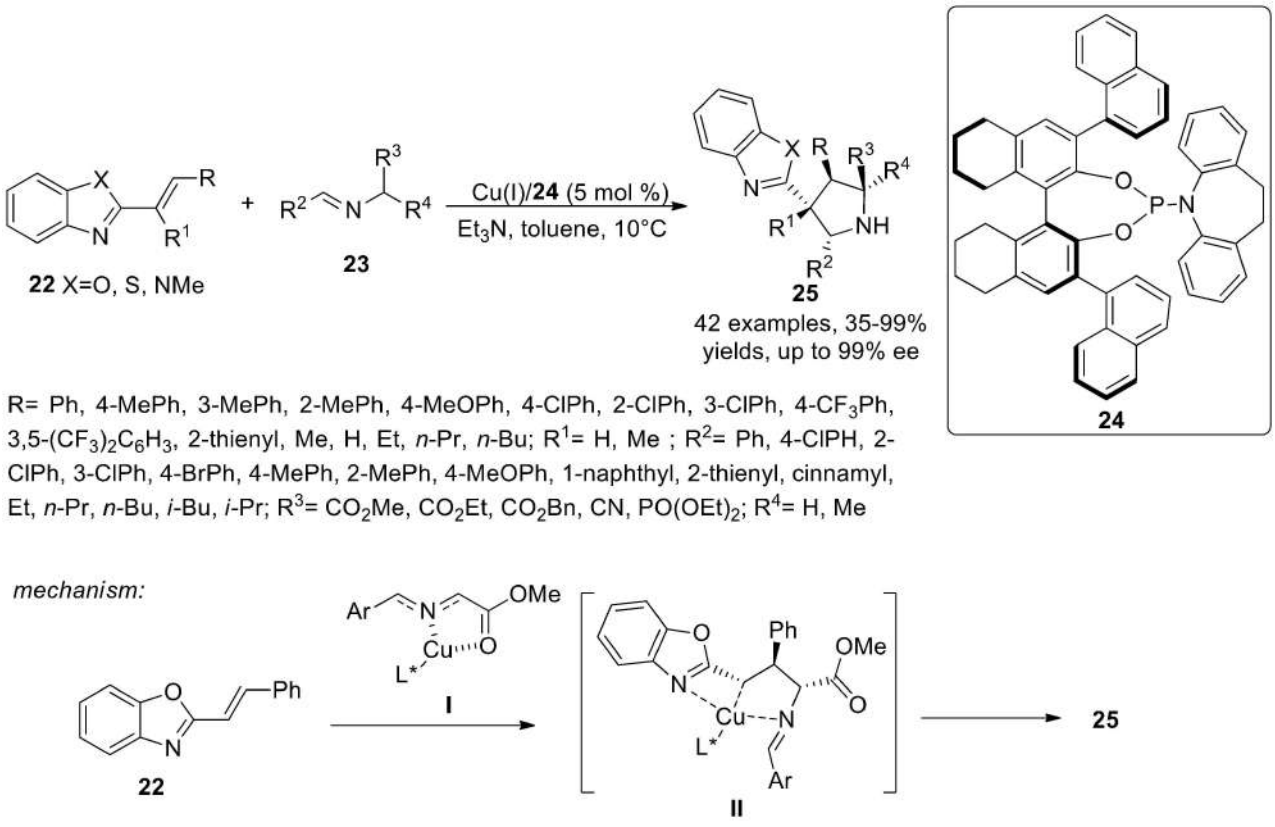


Figure 2. Representative strategies for heterocyclic synthesis: i) the construction of heterocycles from acyclic building blocks;[7] ii) from other heterocycles, also through rearrangement reactions;[8] iii) or through heterocycles functionalization.[9]

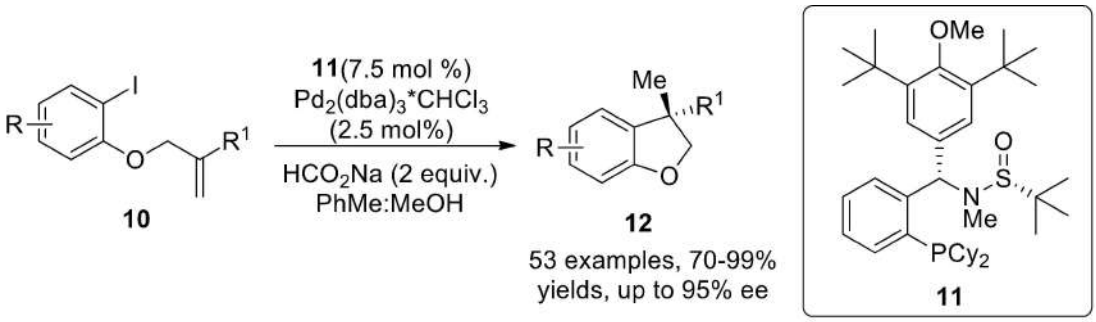
stereocenter also with the Si–C bond through the first asymmetric formal carbene insertion into silyl ethers. The reaction was further explored by means of preparative scale experiments and mechanistic investigations at computational level and using deuterated substrates. The catalyst binds the N–C≡C triple bond (intermediate **I**) allowing activation toward nucleophilic attack of the propargyl moiety and yielding to vinyl-cation **II**. Intramolecular nucleophilic attack from the –OR[1] moiety led to oxonium ylide **III**, which undergoes to [1,2]-Stevens-type rearrangement to key chiral intermediate **IV**. Final products **21** were obtained through aromatization and catalyst's release (**IV**→**V**→**VI**).

Chang et al., reported the asimmetric Cu(I)-catalyzed 1,3-dipolar cycloaddition of alkenylheterocycles 22 with azomethine ylides 23 employing ligand 24, a phosphoramidite with triple homoaxial chirality (Scheme 6).[33] Chiral pyrrolidines 25, containing multiple chiral centers, were successfully obtained (35–99% yields, 42 examples) with good selectivity (up to 99% ee). Interestingly, the nature and the steric hindrance of the heterocycle linked to dipolarophiles 22 determine a chirality switch of pyrrolidine products, explained by extensive density functional theory (DFT) calculations. Computational studies further support the stepwise addition of azomethine ylide complex **I** to give intermediate **II** and then final pyrrolidine compounds, with great control of the stereochemistry induced by the ligand.

Synergistic Cu(I)/Ir(I) catalyst system, was employed for cascade reaction of indolyl allylic carbonates with aldimine esters **27** by Wang's group (Scheme 7 and 8). Tetrahydro-γ-carbolines **30** were obtained starting from 2-substituted indole **26** and ligand **28** and **29** through an allylation reaction, between complex **I** and **II**, followed by an iso-Pictet-Spengler cyclization of intermediate **III** (Scheme 7).[34]



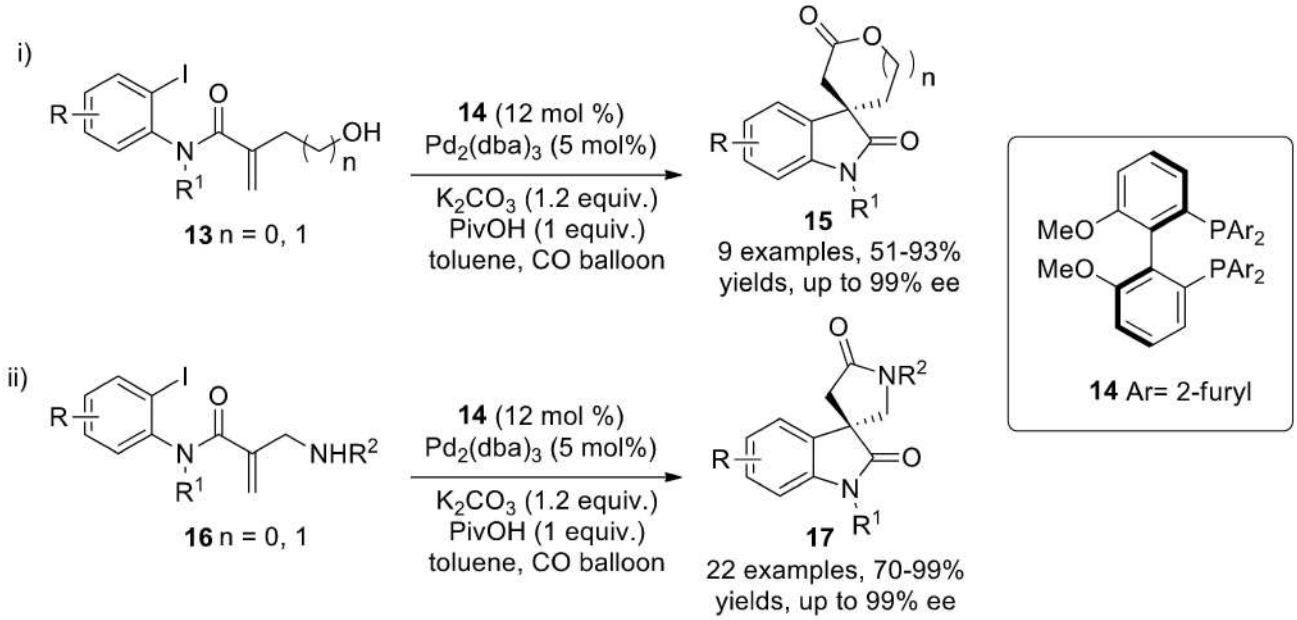
Scheme 2. Scheme of asymmetric palladium-catalyzed intramolecular Heck/Sonogashira reaction.[27]



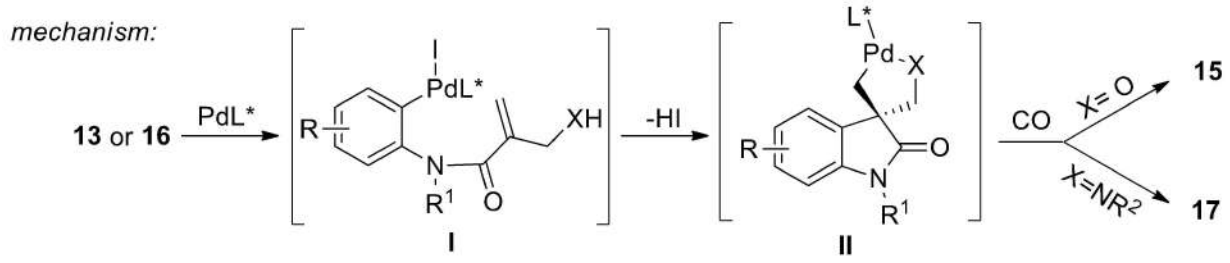
R= H, Me, t-Bu, Ph, CMe_2Ph, F, Cl, NO_2, 4,5-Me_2, 1-Br-5-Me,

R^1= Et, *n*-Pr, *n*-Bu, *n*-C_5H_{11}, *i*-Pr, *t*-Bu, CH_2R^2 where R^2= Ph, 4-FPh, 4-ClPh, 4-CF_3Ph, 4-CO_2EtPh, 4-MePh, 3-MePh, 2-MePh, 4-MeOPh, 3-MeOPh, 2-MeOPh, 3-NO_2Ph, 3,5-Me_2-C_6H_3, 3,5-$(MeO)_2$Ph, 3,5-Ph_2-Ph, 3,5-F_2-Ph, 3,4,5-F_3-Ph, 1-naphthyl, 2-naphthyl, 2-(benzo[*d*][1,3]dioxol-5-yl), pyrenyl, 2-thienyl, 2-(dibenzo[*b*,*d*]thiophen-3-yl), 9-methyl-9*H*-carbazol-2-yl, O-3,5-Me_2Ph, 3-(piperidine-1-carbonyl).

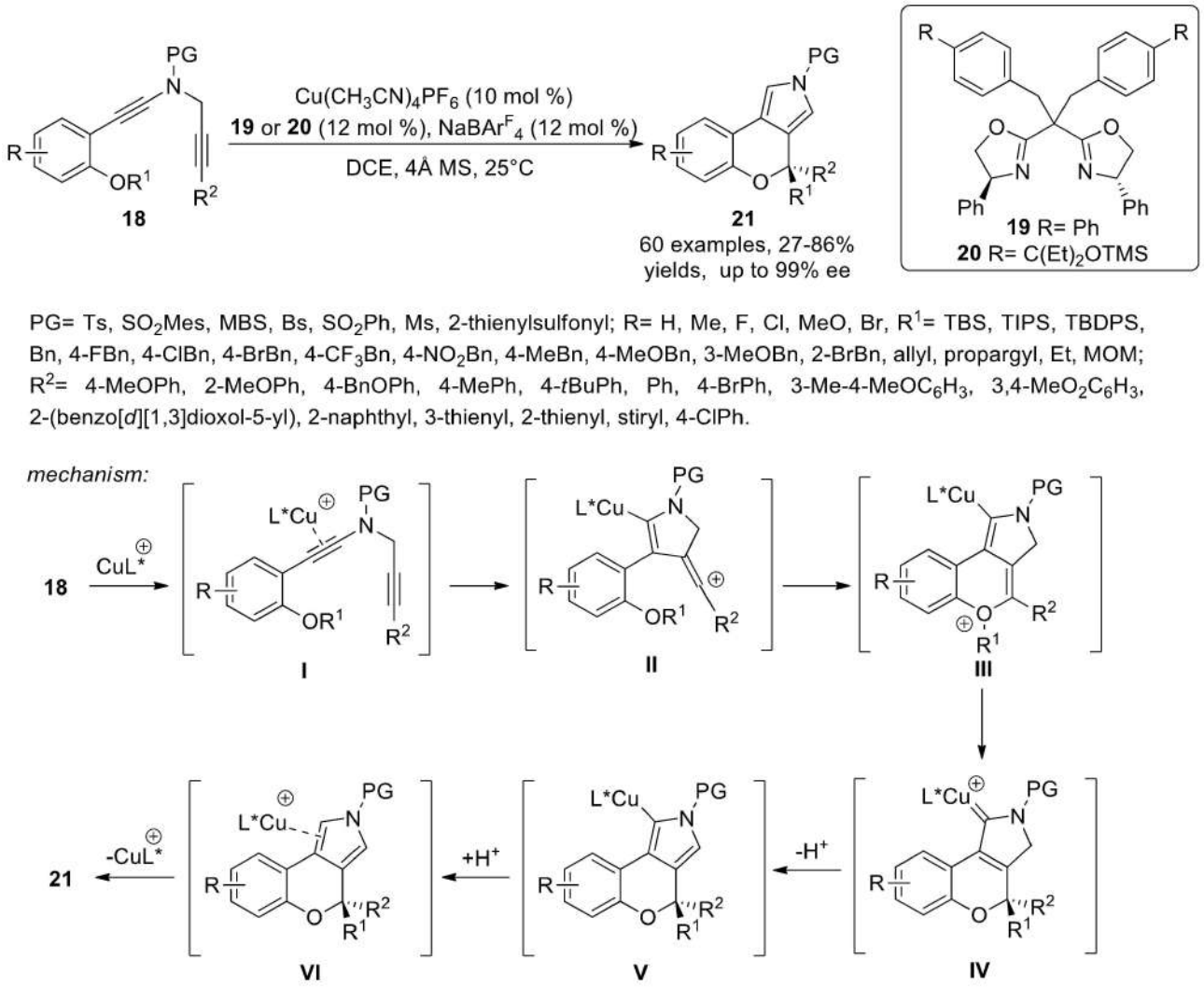
Scheme 3. Scheme of intramolecular hydroarylation of o-iodoaryl allyl ethers.[28]



R= H, 4-Me, 5-Me, 4-F, 4-Cl, 4-MeO, 4-CF_3; R^1= Me, Bn, PMB; R^2= Ph, 1-naphthyl, 4-tBuPh, 4-MeOPh, 2-MeOPh, 4-FPh, 4-MePh, 2-MePh, 4-CNPh, 4-CF_3Ph, 1,1'-biphenyl, 3,5-$Me_2C_6H_3$



Scheme 4. Scheme and mechanism of asymmetric Heck/carbonylative lactonization or lactamization sequence.[29]



Scheme 5. Scheme and mechanism of asymmetric cyclization.[32]

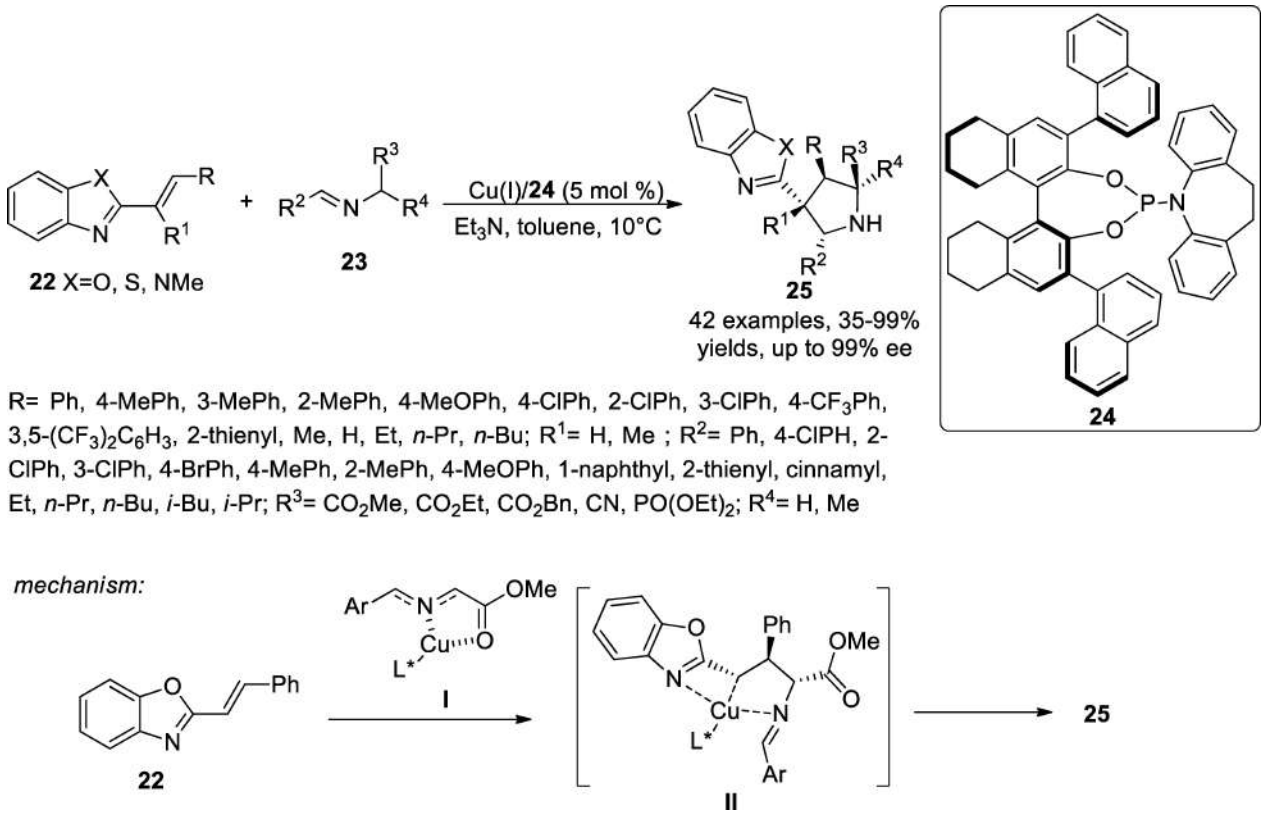
The cascade reaction was effective to reach carbolines **30** (34 examples, 75–99% yields, with up to 99% ee). The stereodivergency of the process was demonstrated by control experiments with ligand presenting different chirality, yielding to a precise control of the carboline chiral centres, toward the obtainment of different diastereoisomers with high selectivity. Also, scale-up and further elaboration of the carboline core were reported.

The same research group also reported an asymmetric cycloaddition of azomethine ylides **27** with 4-substituted indolyl allylic carbonates **31** for the construction of azepino-[3,4,5-cd]-indoles **33** with the synergistic Cu(I)/Ir(I) catalyst system, in the presence of ligand **28** and phosphoramidite **32** (Scheme 8).[35] The fused seven-membered ring is formed by cascade asymmetric allylic alkylation, between complex **I** and **II**, followed by intramolecular Friedel–Crafts reaction of intermediate **III**, mediated by $Zn(OTf)_2$ (see **TS** scheme 8), furnishing a series of azepino [3,4,5-cd]-indoles **33** in moderate yields and stereoselectivity (34 examples, 44–70% yields, 97–99% ee). The stereocontrol of the reaction over the three chiral centers was experimentally demonstrated and supported by DFT calculations.

2.3. Nickel-based catalysts

Nickel is widely employed for its catalytic activity, in particular, toward cross-coupling and C–C bond forming reactions, representing sometime a less expensive alternative to palladium.[23c] Nickel salts and complexes such as $Ni(acac)_2$ (acac = acetylacetonate), $NiBr_2(DME)$ (DME = ethylene glycol dimethyl ether) or $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) are widely used.

Recently, it was reported the first example of Ni-catalysed and ligand-controlled dicarbofunctionalization of amide/esters **34** with alkenes **35** for the regiodivergent synthesis of five-membered benzo-fused lactams **37** or six-membered benzo-fused derivatives **39** (Scheme 9).[36] Reaction divergency is mediated by the ligand, in fact, in both cases intermediate **I** was formed through Ni-catalyst oxida-



Scheme 6. Scheme and mechanism of asimmetric 1,3-dipolar cycloaddition.[33]

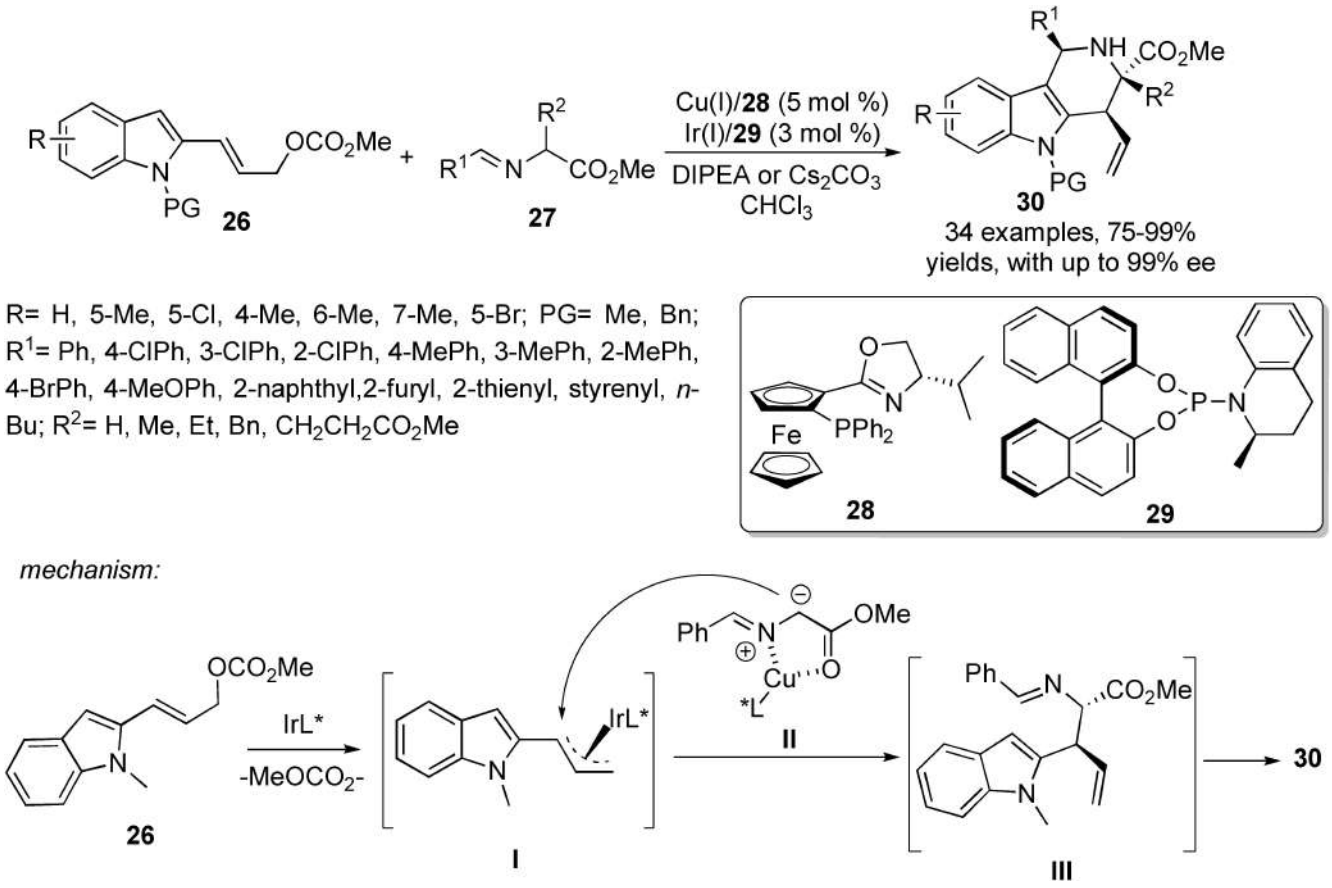
tive addition; when performed in the presence of chiral oxazoline **36**, a 5-exo cyclization/cross-couplings process, to intermediate **II** and **III**, was favored yielding indole-2-ones **37** in low to good yields and enantioselectivity (46 examples, 19–83% yields, up to 98% ee). Employing 2,2′-bipyridine ligand **38**, a novel 6-endo-selective cyclization/cross-coupling to intermediate **IV** and **V** was highlighted, leading to 3,4-dihydroquinolin-2-ones, or oxygenated analogues, **39** with wide scope and generally good yields (58 examples, 32–92% yields). The proposed methodology allows yielding different heterocycles bearing a quaternary carbon center and the synthetic value for the obtainment of alkaloid scaffolds or bioactive compound was explored.

Wu and co-workers designed the new bidentate chiral imidazoline ligand **42** (named Quinim) for Ni-catalyzed reductive cross-coupling reaction of carbamoyl chlorides **40** with alkyl iodide **41** to yield chiral pyrrolidinone **43** (Scheme 10).[37] Pyrrolidinones **43** were obtained, at low temperature and with excess Mn as reducing agent, with broad substrate scope (43 examples, 35–90%), despite some limitations (R=Ts; R^1=Me, for example) and high enantiomeric excess (up to 96% ee). Determination of the absolute configuration was accomplished by means of crystallography, while synthetic utility of products **43** was demonstrated by conversion into other pyrrolidinones or γ-amino-acids. From a mechanistic point of view, the reactivity was rationalized through the initial formation of Ni(0)-carbamoyl intermediate **I**, under reductive conditions, which undergoes intramolecular migratory insertion into the double bond for the formation, on the enantio-determining step, of cyclic intermediate **II**. After Mn-mediated reduction to intermediate **III**, a single electron transfer (SET) from iodide **41**, forming alkyl radical (see **IV**), allows coupling (see **V**). Reductive elimination of the latter intermediate, finally yields to pyrrolidinones **43**.

Similarly, *N*-aryl carbamoyl compounds **44** undergo to a Ni-catalysed reductive carbo-acylation with alkyl iodides **45** to furnish enantiomeric indole-2-ones **47** utilizing chiral ligand **46** (Scheme 11).[38] Indole-2-ones **47** with a quaternary carbon-center were synthesized with very broad scope and generally good to excellent yields (73 examples, 45–94% yields); enantioselectivity is good (up to 89% ee) but was limited by the nature of the R^1 group (ee = 63–65% for Et or *i*-Pr). The reaction mechanism resembles Ni-mediated carbo-acylation on scheme 10, with the formation of chiral center on intermediate **II** after migratory insertion from **I**. Mn(0)-mediated reduction and SET from the alky iodide **45**, generate intermediates **III** and **IV**, respectively. Also in this case reaction was completed after radical coupling to **V** and final reductive-elimination of Ni-catalyst.

2.4. Rhodium-based catalysts

Rhodium is a noble metal widely used for its catalytic activity in the automotive industry. In the recent years many



Scheme 7. Scheme and mechanism of allylation reaction followed by an iso-Pictet-Spengler cyclization of intermediate **III**.[34]

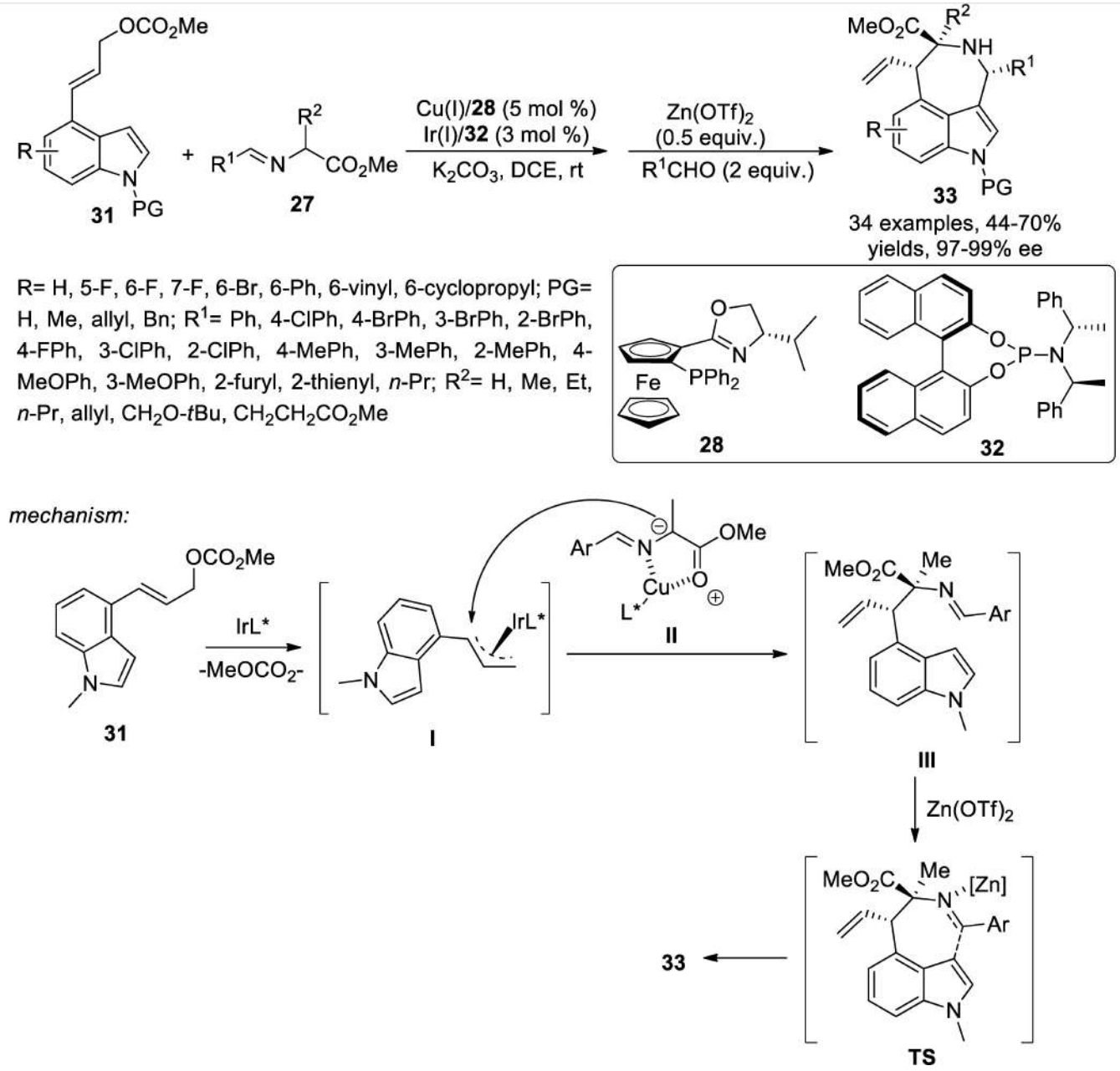
applications toward the synthesis of heterocycles were reported.[39] Rh-catalysed reaction of bicyclic aziridine **48** with diazo-ketones **49** occurs with aziridinium ylides as key intermediates for the synthesis of nine-membered ring compounds **50** or dehydromorpholines **51** (Scheme 12).[40] This reaction was deeply investigated by means of DFT calculations and temperature or the nature of the diazo-ketone **49**, precursor of the Rh-carbene **I**, strongly influences the outcome of the reaction through intermediate **II**, yielding dehydromorpholines **51** (route b) when R^2 is an acyl-group (14 examples, 29–58% yields), on the other hand, nine-membered compounds **50** are preferred (route b) when R^2 is not an acyl group (R^2=H, Me, Ph CN, 4 examples, 68–98%). The rotational barrier of the C–N bond on **II** is a key factor on the thermodynamic control of the reaction. The proposed reactivity is limited in scope and yields but deserve more studies considering that enable the obtainment of highly complex heterocycles.

Hassan and co-workers efficiently designed an artificial metalloenzyme (ArM) embedding a Rh cyclopentadienyl (Cp) catalyst in the active site of a wild-type monomeric streptavidin (wt-mSav) that consent to perform the asymmetric synthesis of δ-lactams **54** via a tandem C–H activation and [4 + 2] annulation from acrylamides **52** and styrenes **53** (Scheme 13).[41] Combination of the cyclopentadienyl Rh(III) catalyst with biotin (Cp^{Biotin}), allows the formation of mSav, instead of its tetrameric form, thus favoring the inserting of the complex and modification of the catalytic site of the enzyme to perform a non-natural transformation. Under optimized conditions, different chiral δ-lactams **54** were obtained (24 examples, 8–99% yield, up to 97% ee) but efficiency is strongly affected by the nature of R group (low yield for R=OEt, PMP). After activation of the catalyst by acetate from the buffer, acrylamide was metalated into **I**, which yields intermediate **II** through a concerted C–H activation. Formation of seven-membered rhodacycle **IV** by means of carbo-metallation into styrene is preceded by coordination of the alkene into **III**. The final N–O bond insertion to **V**, followed by elimination of the Rh(III) catalyst, yields to the chiral compound **54**.

Final products **54** were also readily converted into biologically relevant compounds.

2.5. Catalysts containing other metals

Iron catalysts are largely employed for heterocyclic synthesis as iron is the second most abundant metal in the earth's crust and it has been considered as the ideal choice for catalyst development in chemical transformations being

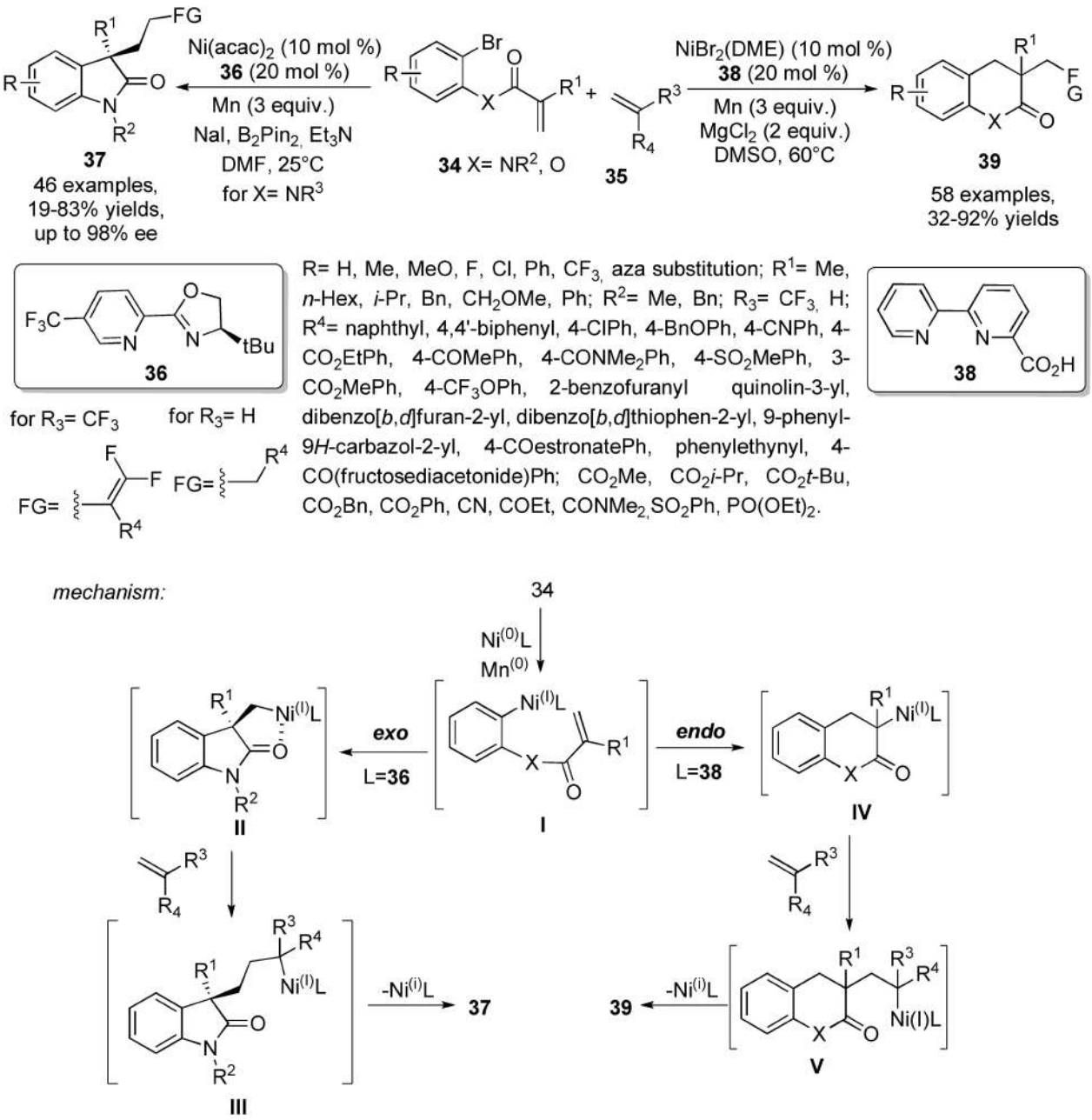


Scheme 8. Scheme and mechanism of asymmetric cycloaddition reaction[35]

cheap and low toxic.[23a,42] An interesting application of Fe-catalysed reactions rely on the use of Phthalocyanine-Fe(III)Cl (PcFe(III)Cl) for the synthesis of γ-lactams **56** starting from dioxazolones **55**, through a radical pathway (Scheme 14).[43] The presented system is highly robust and effective, giving compounds **56** (18 examples, 47–99% yields), under aerobic conditions and with high turnover numbers (TON), up to 47000. The suggested mechanism was investigated by means of DFT studies as well as through tests with deuterated derivatives. It's suggested an initial coordination of dioxazolone **55** to catalyst (**I**), thus inducing decarboxylation to radical **II**.

Hydrogen atom abstraction (**III**) and radical rebound to intermediate **IV** complete the cycle with the releasing of the lactam product.

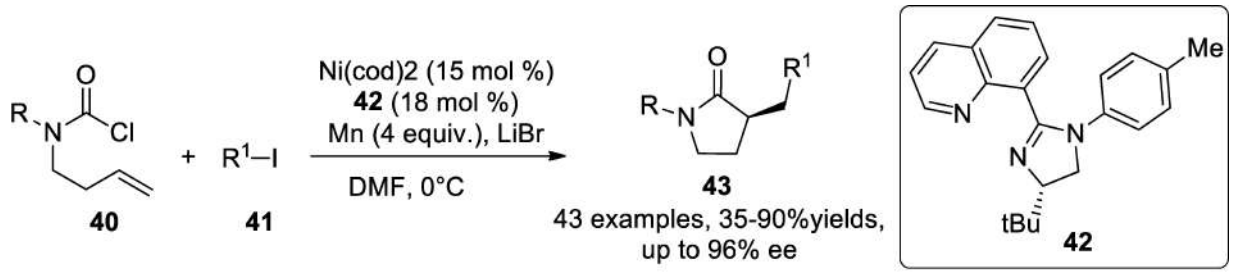
In recent years gold catalysis is readily expanding due to the formation of imino gold carbene complexes, that allows the synthesis of various heterocycles.[44] In this context, Tian et al. developed a catalyst-mediated synthesis of acylindoles **59** and quinoline derivatives **60**/**61** from ynamides **58**, via imino gold carbene intermediates generated from benzisoxazoles **57** (Scheme 15).[45] Picolinate Au(III)-catalyst (Pic-$AuCl_2$) yields to 6-acylindoles **59** with good scope and selectivity (37 examples, 35–99% yields), 5-acylindoles were obtained in some cases when position 6 of the indole ring



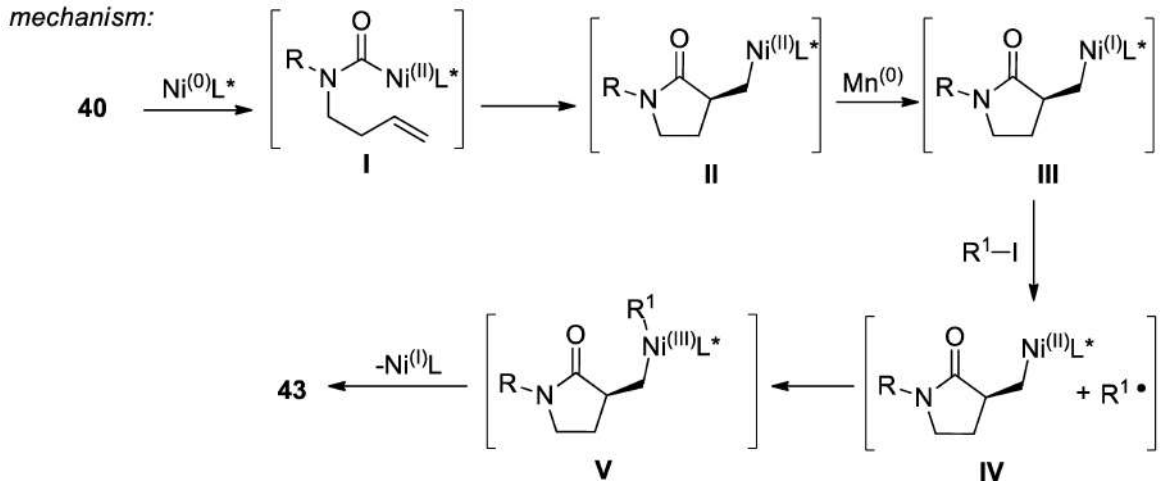
Scheme 9. Scheme and mechanism of dicarbofunctionalization of amide/esters with alkenes.[36]

was blocked by another substituent. Otherwise, with the JohnPhos ligand, gold(I) catalyst brings a carbene/carbonyl addition to quinoline epoxides **60**, which in turn could rearrange into 3-hydroxylquinolines **61**, depending on reaction conditions (20 examples, 48–97 % yields). Products structures were also confirmed by X-ray data and the method was also applied to reactions at a gram scale. Interestingly, limitation to reach the final products is evidenced, for both processes, when an alkyl group is directly linked to the ynamine moiety (R^3=$(CH_2)_3$Ph). A computational DFT study deeply explained this unprecedent reactivity. In particular, some features of the catalyst were evidenced for the reaction outcome. In fact, while both Au-catalyst can produce key intermediate **III** (through ynamide coordination to **I** followed by nucleophilic attack of the benzisoxazole moiety and ring-opening of **II**) only Au(I) can effectively catalyze the nucleophilic attack of the carbonyl oxygen to seven-membered intermediate **IV** (route a). On the other hand, in presence of Au(III) the preferred pathway (route b) take place from nucleophilic attack of the aryl ring to intermediate **V**. The final indoles **59** were obtained after acyl-migration reaction in representative derivative **VI** and deauration mediated by the formation of **V**.

In the search of green method for the synthesis of heterocycles, effective Iridium complexes **63a–b** enable yielding quinoxaline **65**, benzimidazole **67** and quinazolines



R= Bn, Ph, 4-MeOPh, 2-naphthyl, 4,4'-biphenyl, 3-ClPh, 4-MeOBn, 4-CF_3Bn, 4-*t*-BuBn, 4-CF_3OBn, 4-FBn, 4-ClBn, 2-BrBn, furan-2-ylmethyl, *n*-Bu, phenethyl, 3,4-dimethoxyphenethyl, CH_2CO_2Me, $CH_2CH_2CO_2Me$, 2-(1-methyl-1*H*-indol-3-yl)ethyl, dehydroabietyl. R_1= $(CH_2)_6CH_3$, Et, *i*-Bu, $(CH_2)_6CH_3$, $(CH_2)_2$*i*-Pr,$(CH_2)_{11}CH_3$, $(CH_2)_6Cl$, $(CH_2)_3OTBS$, $(CH_2)_4OAc$, $(CH_2)_3CF_3$, $(CH_2)_2C_4F_9$, 3,7-dimethyloct-6-en-1-yl, $(CH_2)_{10}CONBn_2$, $(CH_2)_{10}COOMe$, $(CH_2)_8OPh$-4-CHO, $(CH_2)_8OPh$-4-CN, $(CH_2)_8SPh$-4-Cl, $(CH_2)_5BPin$, $(CH_2)_{10}$-(5-bromo-indol-1-yl), $(CH_2)_4N(CO)_2C_6H_4$,



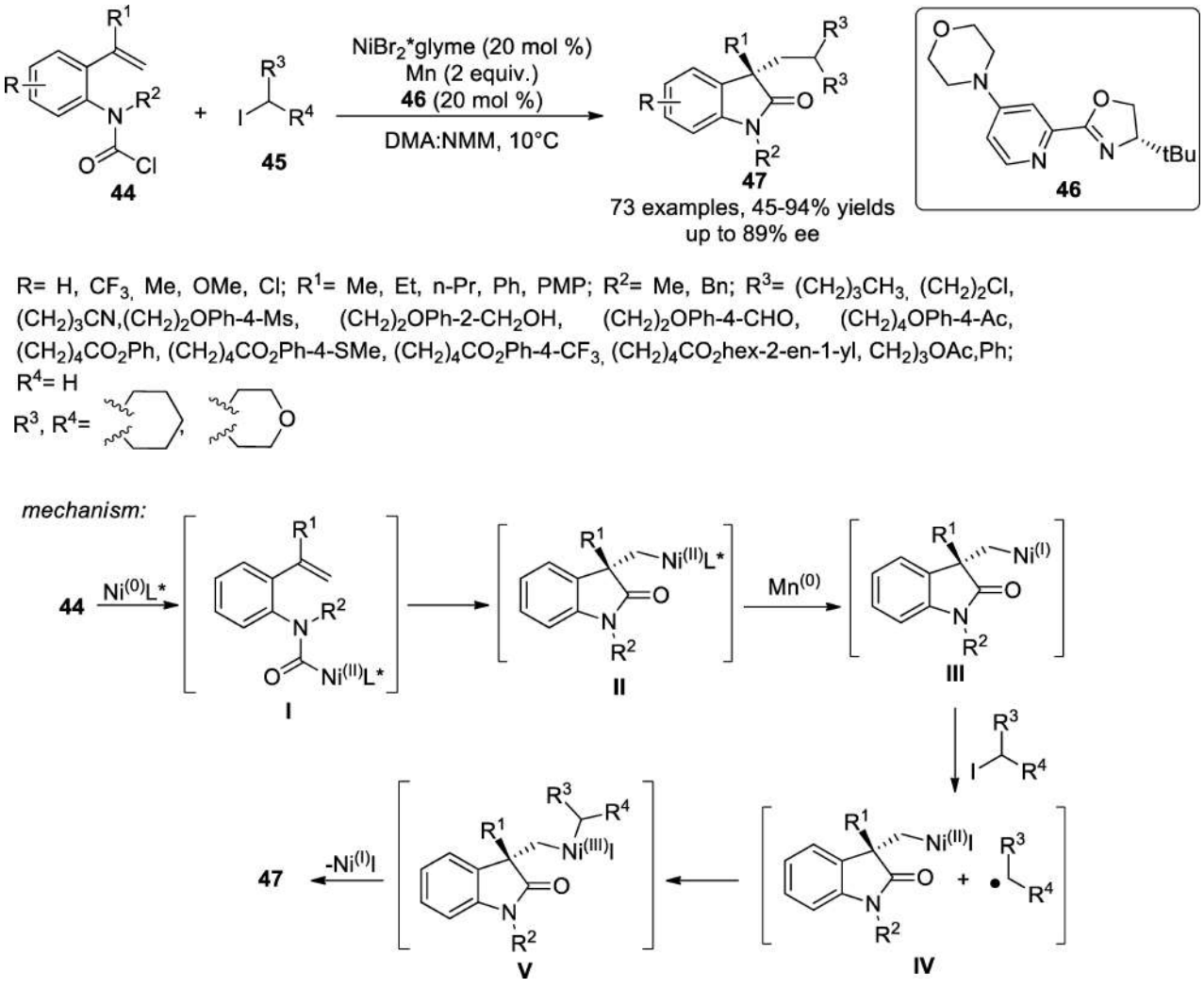
Scheme 10. Scheme and mechanism of the reductive cross-coupling reaction of carbamoyl chlorides with alkyl iodide.[37]

69 in water (Scheme 16).[46] Quinoxalines **65** (25 examples, 62–92% yields) were obtained from *o*-phenylendiamines or *o*-nitroanilines **62** under air using glycols **64**. Notably, starting from nitroamines **62** (X=NO_2) higher yields were obtained (Scheme 16i). Benzimidazoles **67** (14 examples, 41–87% yields) were efficiently obtained from diamines **62** with primary alcohols **66**, avoiding the use of any base, but requiring inert atmosphere. Similarly, quinazolines **69** (11 examples, 60–94% yields) can be obtained under the same conditions as above from diamines **68** (Scheme 16ii).

Synthesis at preparative scale, of different substrates and pharmaceutically relevant compounds, was accomplished, revealing the robustness of the proposed method. DFT calculations supported the formation of an Ir—H intermediate complex that drives the dehydrogenative coupling to desired heterocycles. The process is representatively discussed for the reaction of the glycols **64**, were their initial oxidation into **I** is accompanied by the condensation with nitro-anilines to furnish intermediate **II**. At this stage concurrent NO_2 reduction and alcohol oxidation yield to intermediate **III** that readily cyclizes into quinoxaline **65**.

Similarly, a phosphine free Mn-mediated reaction, catalysed by complex **71**, to give quinoxalines **65**, benzothiazoles **73** and quinolines **76**, via acceptorless dehydrogenative coupling (ADC), was reported (Scheme 17i–iii).[47] In details, o-diamines 70 were reacted with diols **64**, with the presence of catalytic KOH and under solvent-free conditions, to furnish **65** in fair to good yields (21 examples, 52–85% yields), this method could be also extended for pyrazines. Under the same conditions, primary alcohols **66** were coupled with o-amino-thiophenols **72** yielding efficiently benzothiazoles 73 (15 examples, 69–87% yields). The same reaction could be applied to the synthesis of quinolines **76** (15 examples, 58–86% yields) starting from 2-aminobenzyl alcohols 74 and secondary alcohols **77**, with a small excess of tBuOK as base. The method well tolerates different functional groups and could take advantage of the use of a tridentate Mn(I) complex (X-ray given) avoiding the use of phosphine ligands.

Ruthenium-based catalysts are generally related to ring-closing metathesis (RCM) reactions.[48] An unprecedent intramolecular C—H amidation of dioxazolones **77** to prepare



Scheme 11. Scheme and mechanism of reductive carbo-acylation with alkyl iodides.[38]

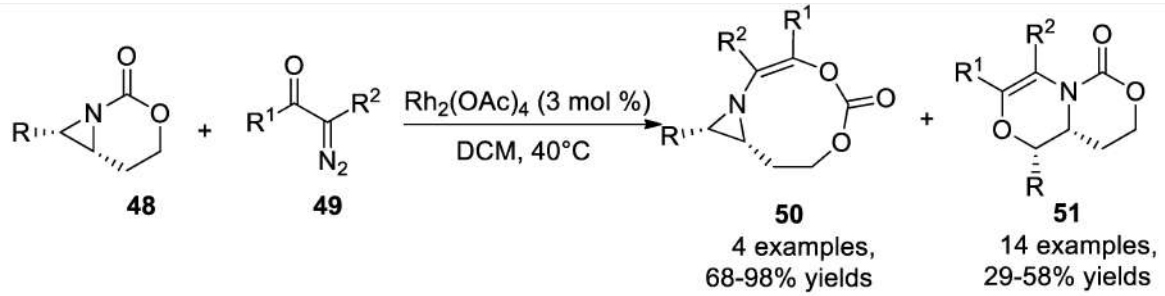
chiral γ-lactams **79** was disclosed by using a new class of chiral cyclometalated ruthenium catalysts, such as **78**, bearing two phenanthrolinium ligands (Scheme 18).[49]

The reaction proceeds smoothly giving chiral lactams **79** with good yields, with few exceptions, and good stereoselectivity (16 examples, 14–99% yields, up to 98% ee). The protocol was applied to a gram scale synthesis of chiral products and tested for the synthesis of natural products such as (–)-isoretronecanol and (–)-heliotridane. Catalytic activity of Ru-complex was explored in terms of catalyst loadings (down to 0.005 mol% with up to 11200 TON), lowering of undesired Curtius-type rearrangement by-products and also by means of DFT calculations. All these data suggest that binding of the dioxazolone to the Ru-catalyst induces decarboxylation of complex **I** to yield ruthenium-imido intermediate **II**. Subsequent concerted H abstraction and C–N bond formation (**TS**) of the nitrene-like intermediate **III**, followed by catalyst release, give lactams **79** in a stereo-controlled fashion.

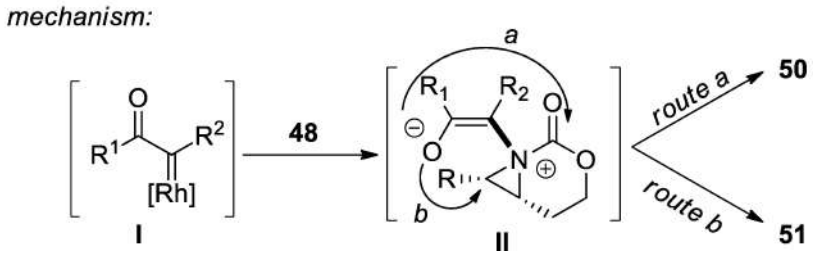
Finally, Cobalt-mediated reactions are widely employed for the catalysed synthesis of heterocycles.[50] Hirata and co-workers developed an asymmetric synthesis of chiral benzothiadiazine-1-oxides **83** from sulfoximines **80** and dioxazolones **81** through combination of an achiral Cp*Co(III) catalyst (Cp* = pentamethylcyclopentadienyl) and the binaphthyl chiral carboxylic acid **82**, via enantioselective C–H bond cleavage (Scheme 19).[51] The procedure gives benzothiadiazine-1-oxides **83** through a robust protocol that tolerate different functional groups and furnish high enantioselectivity (26 examples, 43–96% yields, up to 96% ee).

3. Organocatalysis

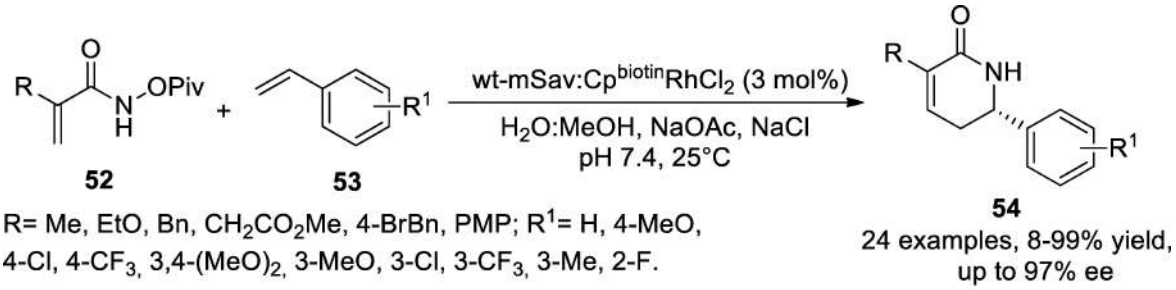
Organocatalysis is a young, but well consolidated, research field that has been awarded with Nobel prize in 2021, confirming its cutting-edge importance in chemistry. Also in



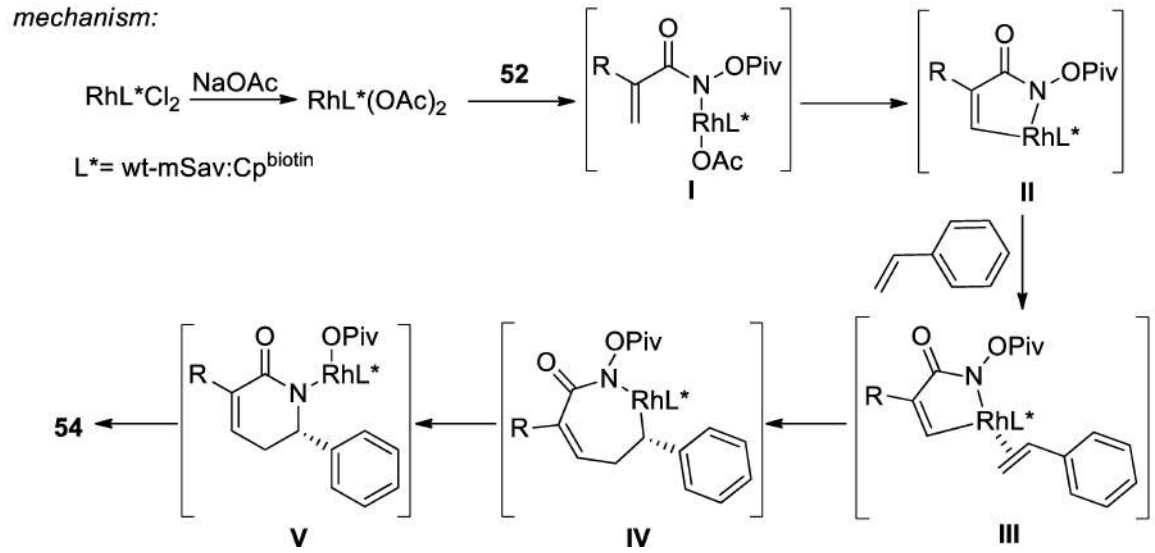
R= Et, *n*-Bu, $(CH_2)_3Cl$, *i*-Pr, Bn; R^1= Me, Ph, 4-ClPh, 3-ClPh, 2-ClPh, 4-MeOPh, 3-MeOPh, 2-MeOPh; R^2=Ac, CO_2Me, CN, H



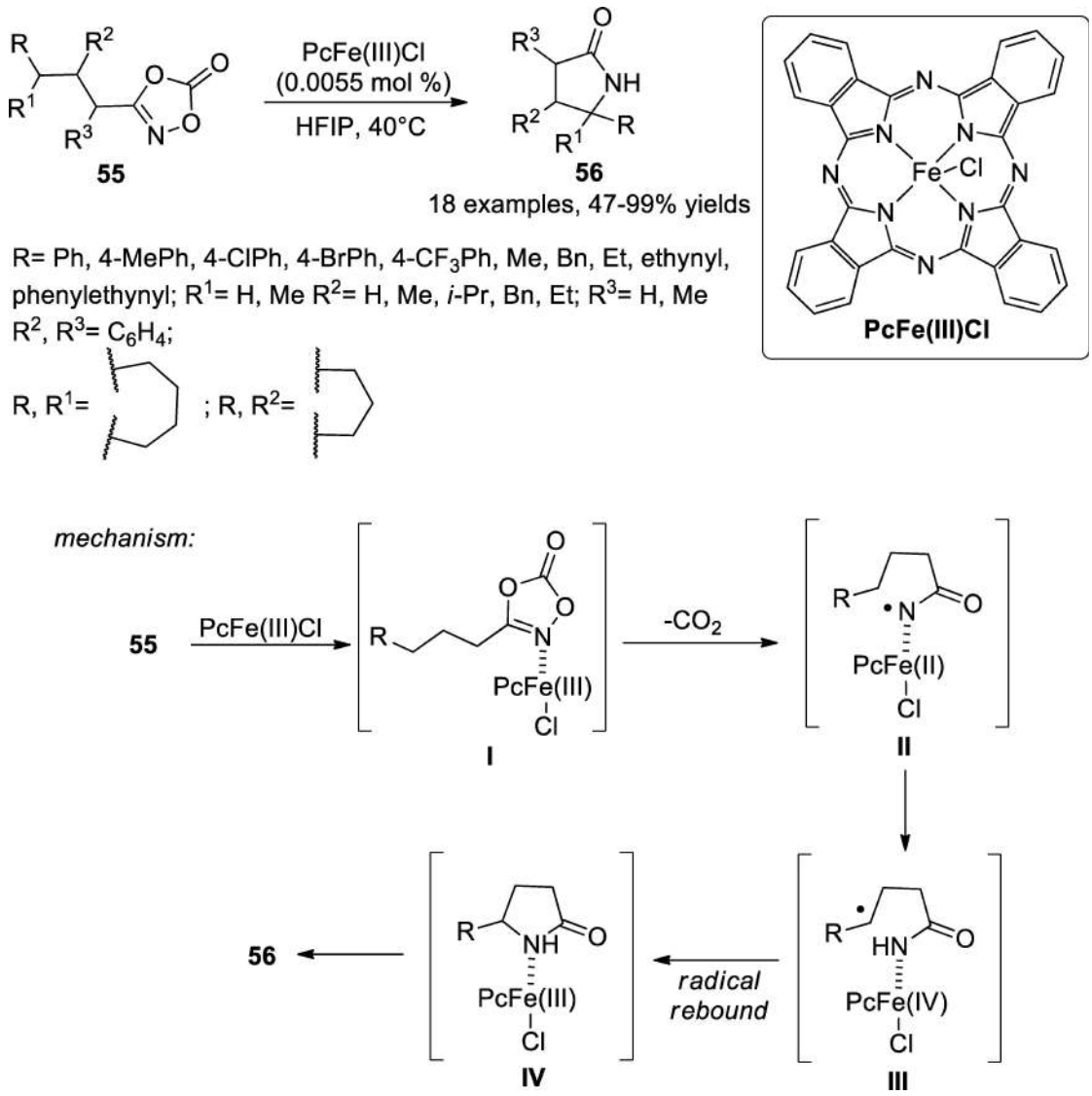
Scheme 12. Scheme and mechanism of of bicyclic aziridine reaction.[40]



R= Me, EtO, Bn, CH_2CO_2Me, 4-BrBn, PMP; R^1= H, 4-MeO, 4-Cl, 4-CF_3, 3,4-$(MeO)_2$, 3-MeO, 3-Cl, 3-CF_3, 3-Me, 2-F.



Scheme 13. Scheme and mechanism of tandem C–H activation and [4 + 2] annulation from acrylamides and styrenes.[41]



Scheme 14. Reaction scheme and mechanism of the synthesis of γ-lactams through a radical pathway.[43]

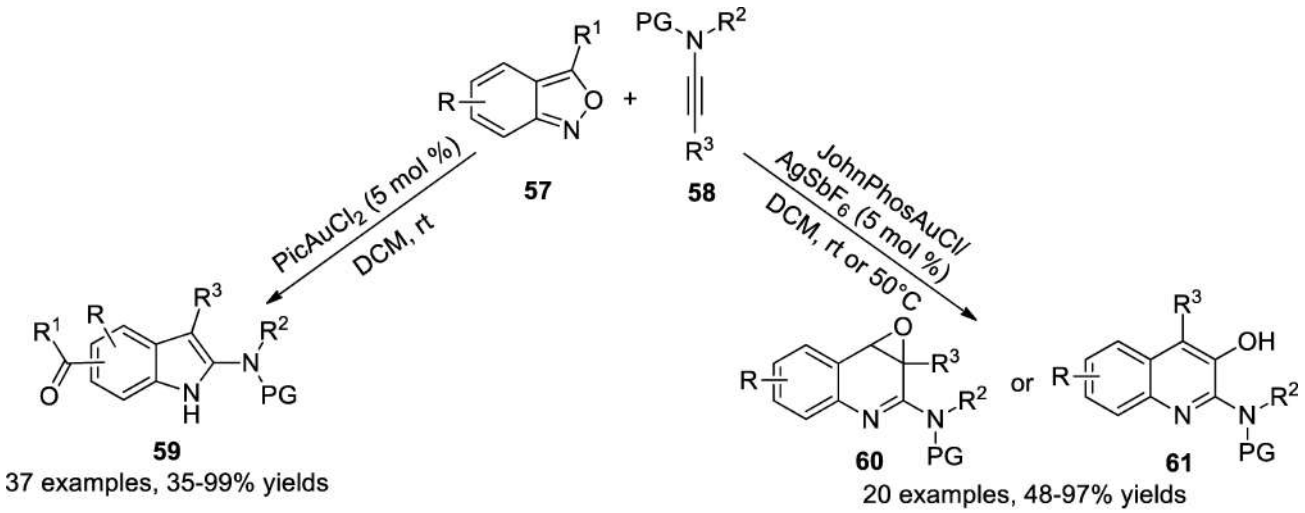
the field of heterocyclic synthesis organo-catalytic systems revealed their utility and widespread applications.[52]

Chiral phosphoric acids (CPA) are widely appreciated as catalytic platform for developing heterocyclic compounds efficiently.[53] As recent example, CPA **86** is an effective organocatalyst for an asymmetric Paal–Knorr reaction between *N*-aminoindole **84** and diketones **85** to afford axial chirality around N–N bond of *N*-pyrrolylindoles **87** in high yields and selectivity (29 examples, 60–98% yield, up to 96% ee) (Scheme 20i).[54]

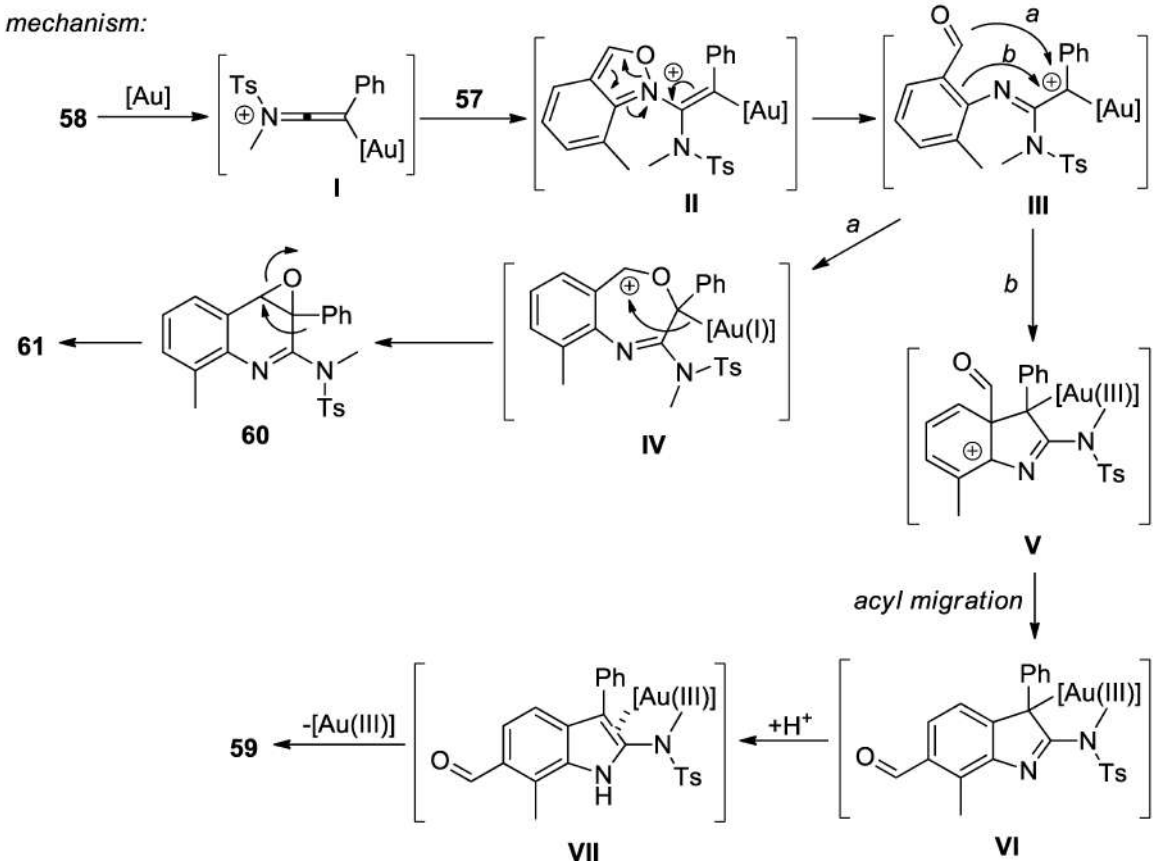
This method can also efficiently make available axially chiral bispyrroles **89** (24 examples, 41–98% yields, up to 97% ee) from aminopyrroles **88** (Scheme 20ii). Formation of the products is mediated by CPA catalyst since the formation of intermediate imine **I** and its isomerization into enamine **II**. The cyclization into chiral intermediate **III** represents the key intermediate for the, from center to axial, chirality transfer due to dehydration to aromatic product.

Interestingly, these chiral heterocycles can be obtained on one-mol scale and easily converted into chiral organocatalysts for (2+4) cyclization. Finally, some **87**/**89** derivatives also display cytotoxic activity in the micromolar range against cancer cells.

CPA **91** allows the first metal-free protocol for the cyclization of ynamides **90** into axially chiral *N*-arylindoles **92** (Scheme 21).[55] *N*-arylindoles **92** were obtained in excellent yields and enantioselectivity (27 examples, 87–99% yields, up to 98% ee). Hydrophosphoryloxylation of ynamide **90** produces enamide **I**. Interestingly, reaction's monitoring by means of MS evidenced the existence of intermediate **I**. Then, **I** go through the intramolecular substitution to protonated intermediate **II**. The method was scaled-up and chiral indoles **92** were further functionalised producing, in turn, an organocatalysts for representative asymmetric MCR or ligands for asymmetric Pd-catalysed allylic alkylation.

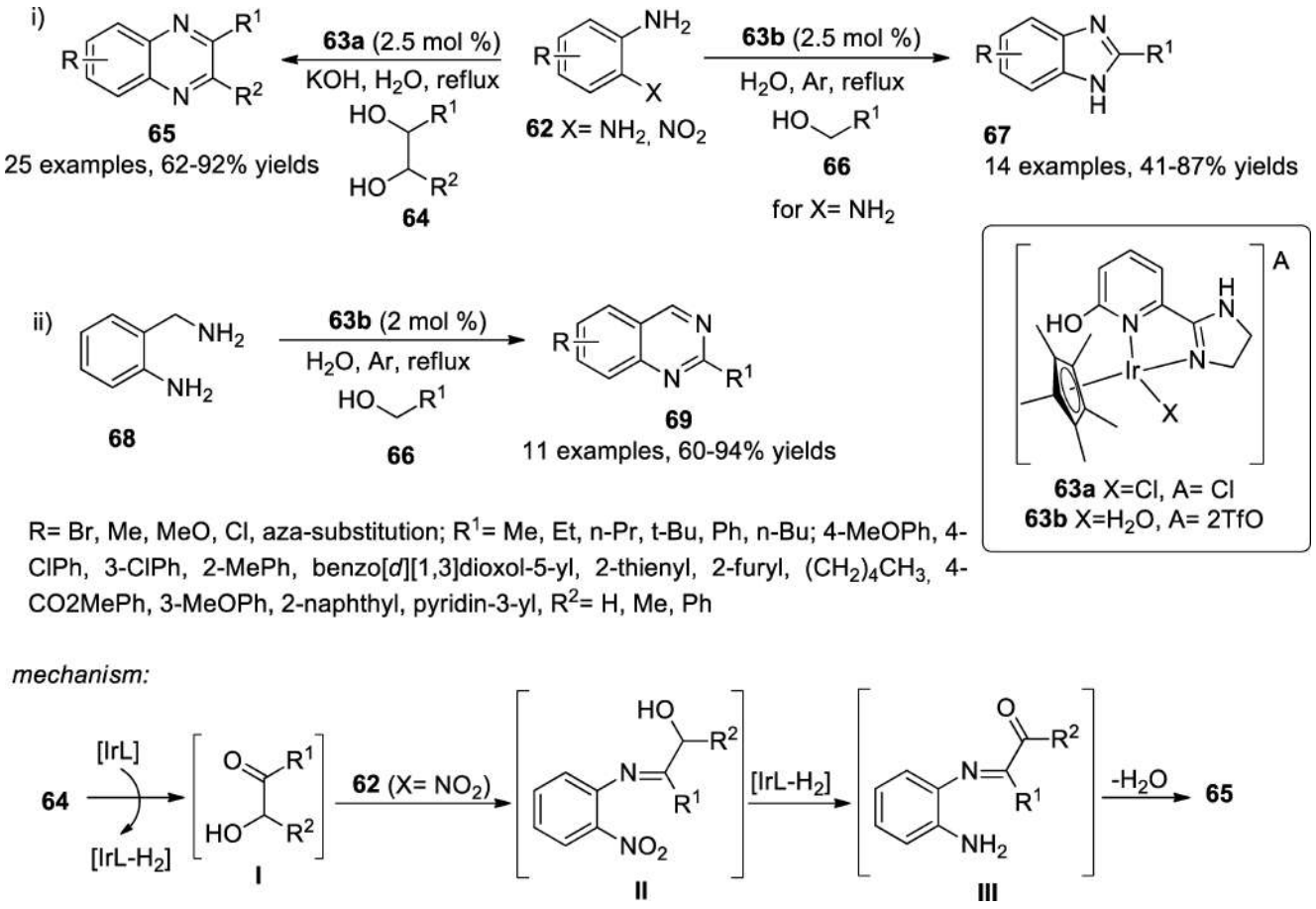


R= Me, Br, Cl, OMe; R^1= H, Me; R^2= Me, Et, n-Bu, i-Bu, Bn, Ph, 3-MePh, 4-MePh, 4-MeOPh, 3-ClPh, 4-MeBn; R^3= Ph, 4-ClPh, 4-MePh, 4-*t*-BuPh, 4-EtOPh, 4-BrPh, 3,5-$(MeO)_2C_6H_3$, 4-FPh, 4-CF_3Ph, 3-MePh, 3-ClPh, 2-FPh, 3-thienyl, $(CH_2)_3$Ph; PG= Ts, Ms, SO_2Ph, Ns,



Scheme 15. Reaction scheme and mechanism for the synthesis of acylindoles and quinoline derivatives.[45]

Xia et al., demonstrated the first organocatalytic addition of carbazoles **94** or indoles **97** to azonaphthalenes **93** for the synthesis of novel chiral *N*-arylcarbazole **96** or *N*-arylindoles **99**, respectively (Scheme 22).[56] Catalyst **95** assists the formation of atropisomeric **96** with broad substrate scope and good yields (26 examples 51–97% yields, up to 96% ee), similarly indoles **99** were obtained in fair to good yields (10 examples 46–93% yields, up to 99% ee) and under mild conditions using brominated catalyst **98**. CPA mediates nucleophilic attack through hydrogen-bond activation, as showed in **TS**, to chiral



Scheme 16. Scheme and mechanism of green method for the synthesis of heterocycles with Iridium complexes.[46]

intermediate **I**, while re-aromatization induces central to axial chirality transfer.

Obtained atropisomers were converted into ligands for asymmetric Pd-catalysed allylic alkylation or organocatalysed asymmetric MCR of phosphorus ylide with imine and formaldehyde. In both cases, good selectivity was demonstrated. The obtained compounds were also envisaged as potentially interesting for organic light emitting diodes (OLED) design.

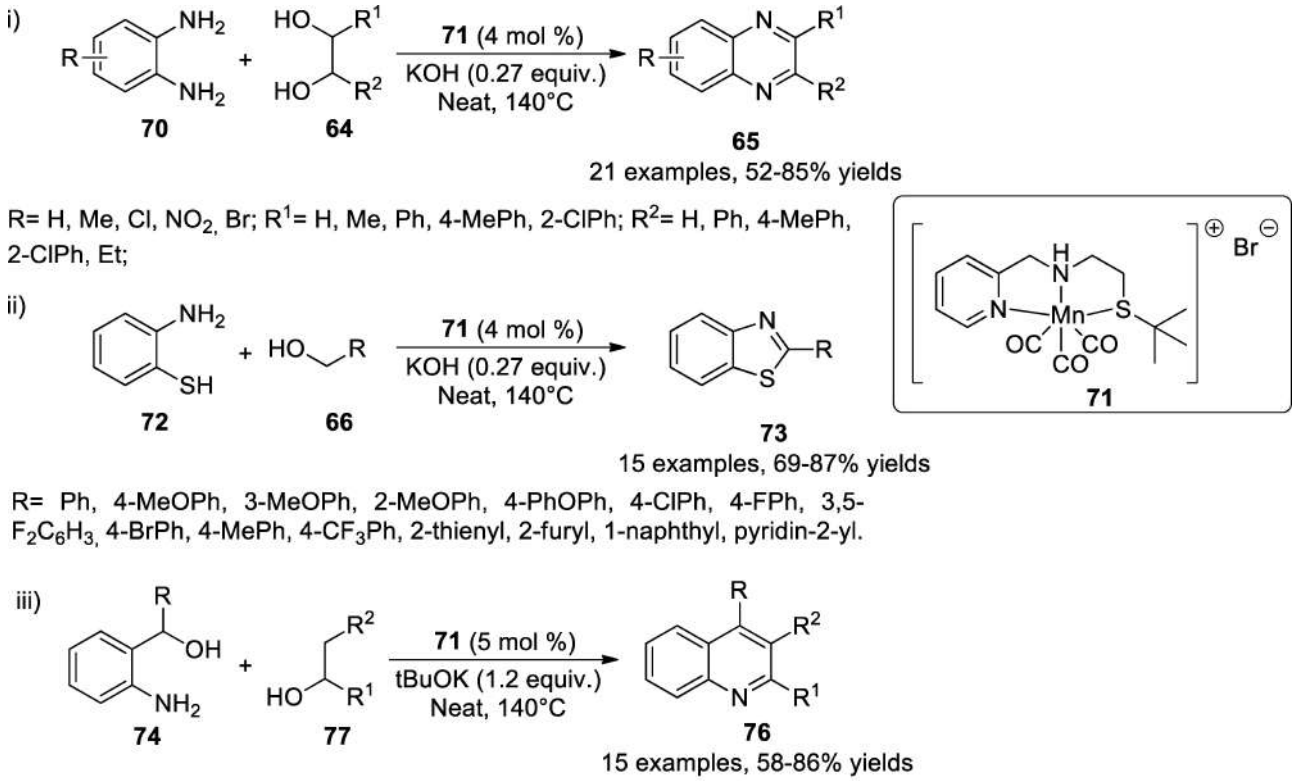
CPA catalyst **102** mediates a stepwise (4 + 3) cycloaddition of 3-indolylmethanols **100** with diene **101** to produce 6-aminotetrahydrocyclohepta[b]indoles **103** enantio- and diastereoselectively (Scheme 23).[57] The tricyclic products **103** were produced with good yield and excellent stereoselectivity (21 examples, 31–86% yields, >98:2 dr and up to 98% ee) under mild conditions. The procedure could be easily scaled-up and obtained compounds further functionalised, thus opening the way to natural cyclohepta-[b]indole products.

Highly hindered CPA **105** can efficiently catalyze the intramolecular cyclization of racemic 2-amido benzyl alcohols **104** into asymmetric (*S*)-benzoxazines **106** through kinetic resolution, thus giving resolved (*R*)-alcohols **104** (Scheme 24).[58] Benzyl alcohols **104** (also secondary) reacted with broad scope and were resolved with high selectivity (31 examples, yield near 50%, up to 96% ee). Absolute configurations were assigned to resolved **104** and heterocycles **106** by means of X-ray.

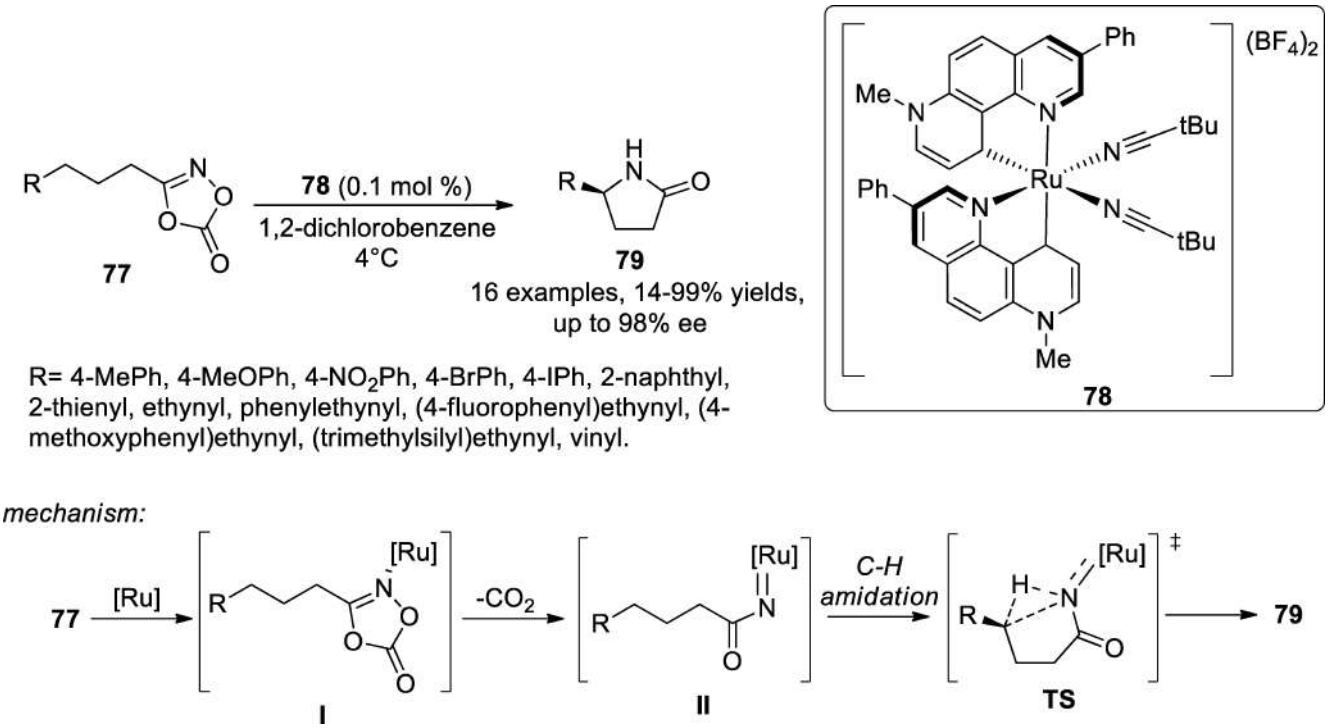
Gram-scale reaction and further synthetic elaboration of obtained compounds was employed to demonstrate the importance of this method to obtain pharmaceutically relevant chiral heterocycles.

The mechanism was also elucidated through experiments with substrate labelled with ^{18}O at the amide bond, revealing that the catalyst activates the amide moiety as electrophilic centre, as unlabelled **106** were obtained. Plausible reaction mechanism via dual H-bond activation is illustrated in Scheme 24.

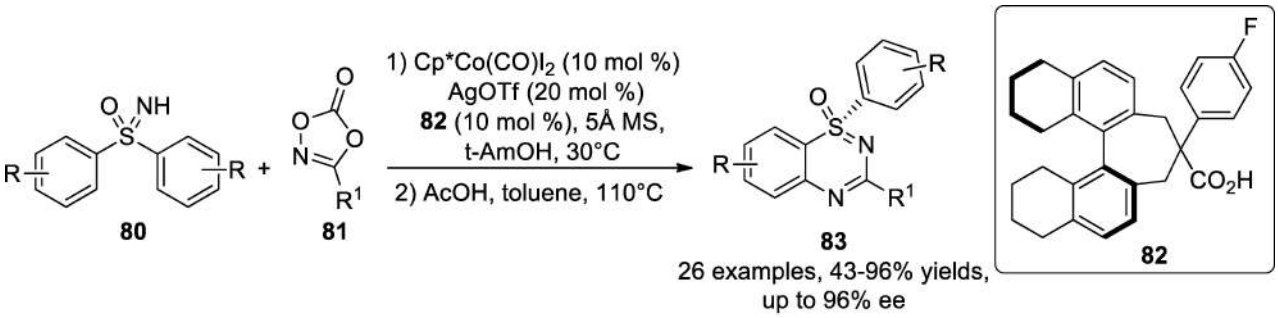
Kretzschmar et al., claimed the first asymmetric intramolecular Aza–Diels–Alder reactions (ADARs) of ortho-quinone methide imine, generated from dienophile-tethered compounds **107** by a chiral phosphoric amide **108**, to yield quinolizidines **109** or oxazinoquinolines **110** (Scheme 25).[59] The reaction occurs under mild conditions (no additive, RT) and complex polycyclic *N*-heterocycles can be obtained easily. In particular, quinozilidines **109** can be obtained with *cis* diastereoselectivity and good enantioselectivity (14 examples, 68–95% yields, up to 82% ee). Conversely, oxazinoquinolines **110** were obtained with a *trans* diastereoselectivity and similar reaction outcome



Scheme 17. Reaction scheme for a phosphine free Mn-mediated reaction proceeding via dehydrogenative coupling (ADC).[47]



Scheme 18. Scheme and mechanism of intramolecular C–H amidation of dioxazolones.[49]



R= H, 4-F, 4-Cl, 4-Br, 4-Ac, 4-Me, 4-*t*Bu, 4-OMe, 3-Cl, 3-Me, 2-F, 2-Me; R^1= Ph, 4-FPh, 4-CF_3-Ph, 4-MeOPh, 3-MePh, 2-MePh, 3,5-$Me_2C_6H_3$, 2-naphthyl, 2-thienyl, 3-thienyl, Me, heptyl, stiryl.

Scheme 19. Reaction scheme of asymmetric synthesis of chiral benzothiadiazine-1-oxides.[51]

(10 examples, 65–95% yield, up to 90% ee). The method also works in a three-component domino reaction where **107** were formed and subsequently converted into ortho-quinone methide imine intermediates to perform an ADAR. Large-scale synthesis was performed and further elaboration of the obtained compounds to yield highly substituted tetrahydroquinolines was reported.

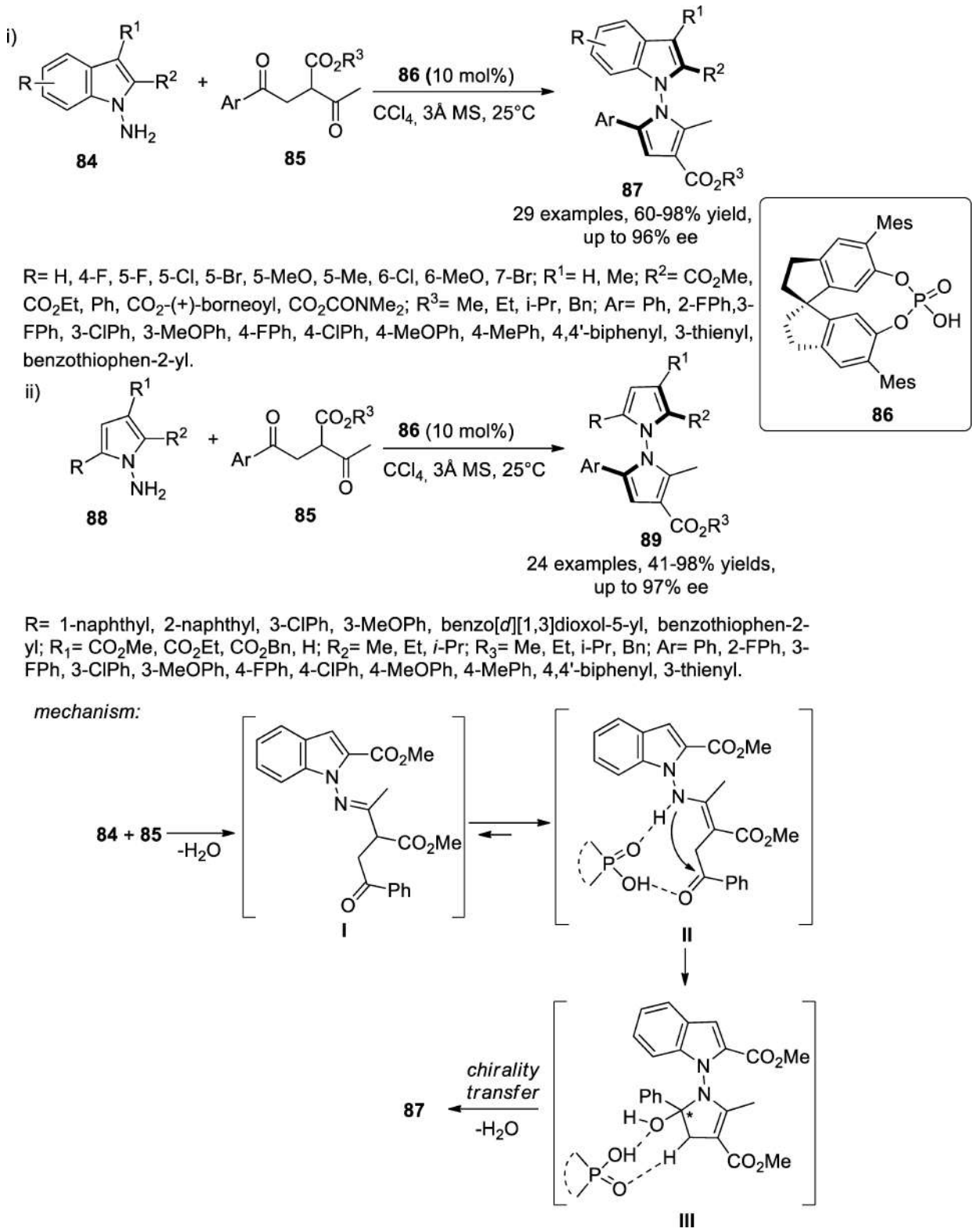
The List's group demonstrated the catalytic activity of chiral imidodiphosphorimidate **113** toward the obtainment of highly substituted chiral *O*-heterocycles **114**, tetrahydrofurans (n = 0) or pyrans (n = 1), via two steps enantioselective nucleophilic additions of silylenolether **112** to dicarbonylic compounds **111** (Scheme 26).[60] Different tetrahydrofurans **114**, 2,2,5-trisubstituted or 2,2,5,5-tetrasubstituted depending by the nature of the nucleophile (Nu=H, Me, allyl, CH_2CO_2Me, from Et_3SiH, Me_3Al, allyltrimethylsilane, **113**, respectively) and by the dicarbonylic compound **111** (ketoaldehyde or diketone), were obtained with good yield and selectivity (16 examples, 58–94% yield, up to 99% ee). Application to pyran synthesis was demonstrated but poorly explored (2 examples, 75–76% yield, up to 97%). Furthermore, the synthesis of the side chain of natural product anhydroharringtonine was reported as example of the synthetic utility of this approach.

For the first time, tetrahydro-β-carbolines **115** were successfully rearranged into chiral spirooxindoles **117**, through oxidative action of *N*-iodosuccinimide (NIS), mediated by CPA **116** (Scheme 27I).[61] Tetrahydro-β-carbolines **115** were efficiently reacted under mild conditions (13 examples 67–97% yields, up to 99% ee) and this protocol has been applied to an efficient synthesis of alkaloid (–)-horsfiline in few steps and avoiding the use of chiral auxiliaries. The same approach, but with a different CPA catalyst **119**, was also employed for the oxidative rearrangement of tetrahydropyranoindoles **118** to tetrahydrofuranyl-sprooxindoles **120** (6 examples 72–90% yields, up to 87% ee) (Scheme 27II). Structure and absolute configurations for both products series were demonstrated by means of X-ray analysis, while mechanistic investigations allowed isolation of one reaction intermediate and revealed that the catalyst activity was linked to its dynamic kinetic resolution, as depicted in Scheme 27.

Xu and co-workers, designed the first organocatalytic, metal and Brønsted acid free, asymmetric Conia-ene-type carbocyclization of arylsulfonylprotected ynamide **121**, using proline-based catalyst **122** (Scheme 28).[62] This method allows the efficient synthesis of different alkaloids skeleton just changing reaction's condition. In fact, morphans **123** were efficiently obtained using $PhCF_3$ as solvent at 80 °C, showing excellent enantioselectivity (24 examples, 61–97% yields, up to 97% ee). Compound *ent*-**123** was yielded as well using the enantiomer of catalyst **122**. Moving to a different solvent system, *t*-BuOH:H_2O mixture, cycloisomerization of alkylsulfonyl-protected ynamide cyclohexanones **121**, lead to the normorphans **124** as the main products with high enantioselectivity (9 examples, 51–92% yields, up to 90% ee). Structure and stereochemistry of obtained compounds was demonstrated trough X-ray data, while DFT calculations were used to explain regioselectivity and enantioselectivity of the reaction (depicted in Scheme 28). The newly synthesized morphans and normorphans show cytotoxic effects against a panel of cancer cells, revealing that morphans exhibited significant cytotoxic effects.

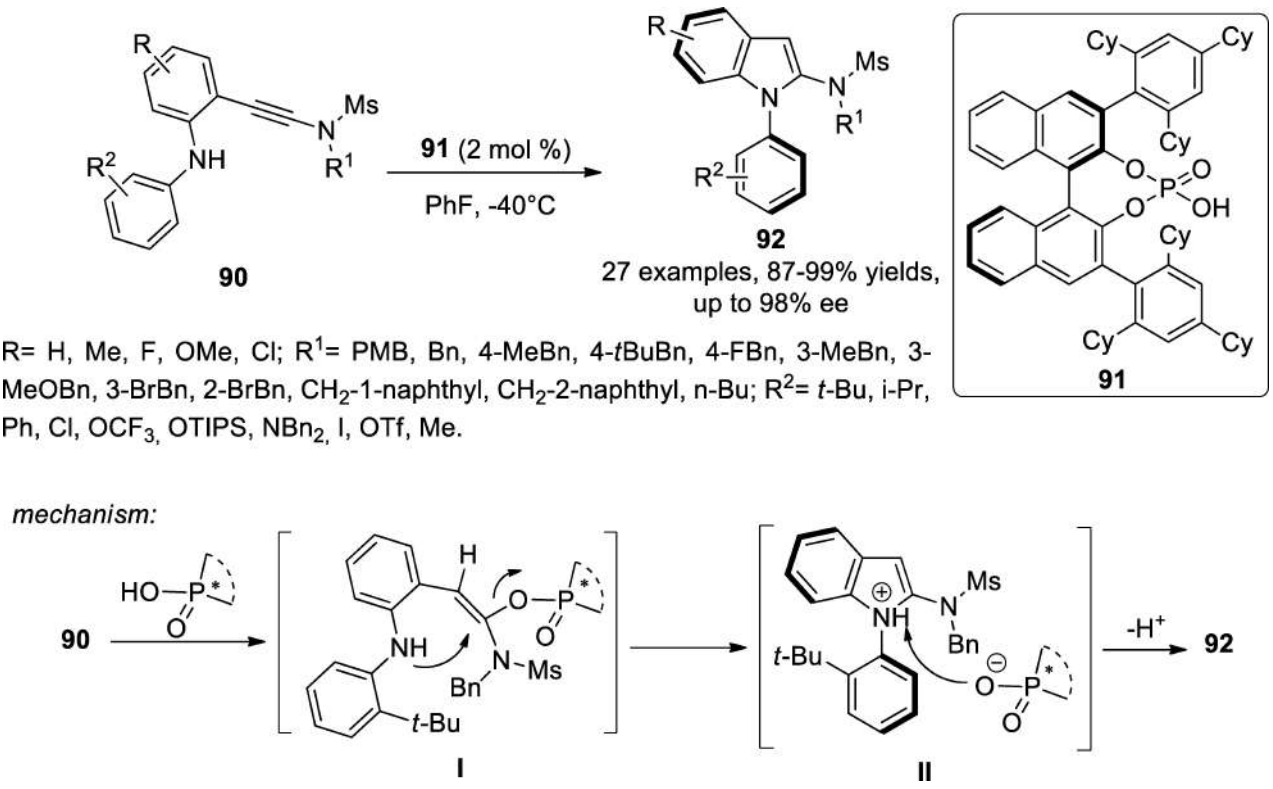
L-proline was efficiently employed as catalyst for a domino three component reaction of carbonyl compounds (aldehydes **127** or isatins **129**) with nitriles **126** and kojic acid **125** under ultrasound irradiation (Scheme 29).[63] This mild and green approach was used to obtain amino-substituted dihydropyrano[3,2-b]pyrans **128** (14 examples, 90–98% yields), and spiro indoline-3,40-pyrano[3,2-b]pyrans **130** (10 examples, 88–98% yields). This Green protocol was positively evaluated in terms of Atom Economy (AE), Reaction Mass Efficiency (RME), Atom efficiency, E-factor, Process Mass Intensity (PMI), and Carbon Efficiency (CE). Nevertheless, despite the use of a chiral catalyst, no enantioselectivity was reported, neither measured.

Thiourea Cinchona alkaloid derivative **132** was used as catalyst for the conversion of racemic 3,4-dihydro-2*H*-pyrroles **131**, into atropoisomeric 3-arylpyrrole **133** and resolved (+)-3,4-dihydro-2*H*-pyrroles **131** (Scheme 30).[64]



Scheme 20. Scheme and mechanism of asymmetric Paal–Knorr reaction.[54]

Racemic pyrroles **131**, readily obtained from nitroalkenes with α-isocyanoacetates, are considered as intermediates of the Barton–Zard reaction and were kinetically resolved into **133** and (+)-**131** with high efficiency (16 examples, up to 56% conversion, selectivity factor range 19–153, and up to 98% ee). The resolved (+)-**131** underwent to aromatization into *ent*-**133**, with the enantiomer of catalyst **132**, in excellent to quantitative yields. Under these conditions ee



Scheme 21. Scheme and mechanism for the cyclization of ynamides **90** into axially chiral *N*-arylindoles **92** (Scheme 21).[55]

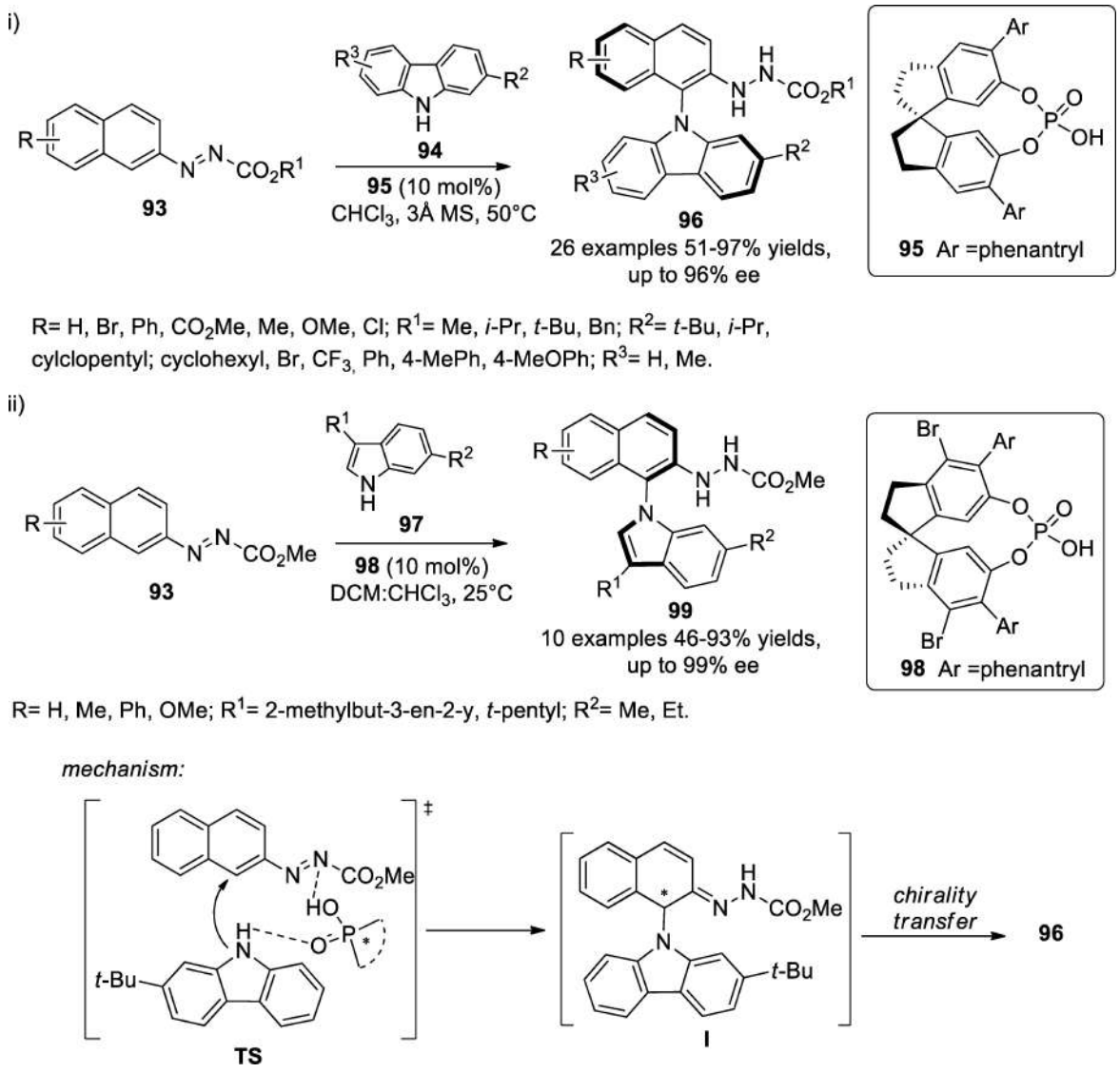
of the starting material was maintained, revealing that the catalyst mediates a chirality transfer of the central-to-axial type. Mechanistic studies also suggest that this catalyst could mediate the aromatization process through an unprecedented sequence involving a *syn* elimination of HNO_2 (see Scheme 30), in contrast to the well-accepted Barton–Zard mechanism.

Chiral cinchona-squaramide derivative **136** catalyses the first example of asymmetric intramolecular aza-Michael addition, from Michael acceptors **134** with tosylamide **135** for the synthesis of dihydroisoquinolines **137** (Scheme 31).[65] Broad scope and selectivity were demonstrated, also with different Michael acceptor frameworks on **134** (29 examples, 31–90% yields, up to >99% ee). The catalyst could also be recycled and oxidation of **137** could lead to different rings comprised a new tetracyclic core with retained enantioselectivity. Hypothesized mechanism is depicted in Scheme 31.

Commercial phosphine HypPhos **139**, was used as asymmetric catalyst for the first Staudinger–aza-Wittig reaction and desymmetrization of ketones **138** into chiral indanopiperidine **140** (Scheme 32).[66] This reaction occurs at room temperature and provide high yields (30 examples, 85–99% yields, up to 99% ee) even on multigram scales (2.5 g) of indanopiperidine **140** with a chiral quaternary center. Structure of products was demonstrated trough X-ray data, while the mechanism was supported by DFT calculations. Notably, HypPhos **139** is recycled trough the catalytic cycle as its phosphine oxide is reduced *in situ* by phenylsilane and 2-nitrobenzoic acid. The products of this reaction were employed for the synthesis of a *N*-methyl-D-aspartate receptor (NMDAR) antagonist demonstrating the potential use of compounds **140** for the synthesis of new drugs.

The chalcogen bonded catalyst **143** enable the cyclization of indoles **141** with three molecules of β-ketoaldehydes **142** leading to the formation of 6*H*-azepino[1,2-a]indole **144** as an unprecedent example of chalcogen-chalcogen bond catalysis (Scheme 33).[67] Tricyclic products **144** were efficiently obtained under mild conditions (30 examples, 40–81% yields). Structure of compounds **144** was demonstrated by means of X-ray and a stepwise mechanism was proposed (see Scheme 33), with an unprecedent activation, through Se—O interactions, of the carbonyl groups of **142** toward enolization, aldol reaction and Michael addition.

The polydopamine (PDA) acts as an amine oxidase mimic to catalyse the reaction of diamine **73** or anthranilamide **147** with primary amines **144**/**146** in water to produce quinoxalines **145**, benzimidazoles **67**, or quinazolinones **148**, under aerobic conditions (Scheme 34).[68] The proposed protocol could be employed for robust synthesis of quinoxalines **145** (10 examples, 71–85% yields), benzimidazoles **67** (15 examples, 52–92% yields) and quinazolinones **148** (4 examples, 61–72% yields, no reaction for R = 4-CF_3). The catalytic activity of PDA was linked to the catechol-quinone moieties that activate amines **144** or **146** which form intermediate imino adducts with **73** or **146**. A final oxidative cyclization, mediated by oxygen, is supposed to be the final



Scheme 22. Scheme and mechanism for the synthesis of novel chiral *N*-arylcarbazole or *N*-arylindoles.[56]

step for *N*-heterocycles obtainment. PDA can be reused for three cycles without loss of catalytic activity and can also be supported on Fe_3O_4 nanoparticles. The suggested mechanism is illustrated in Scheme 34.

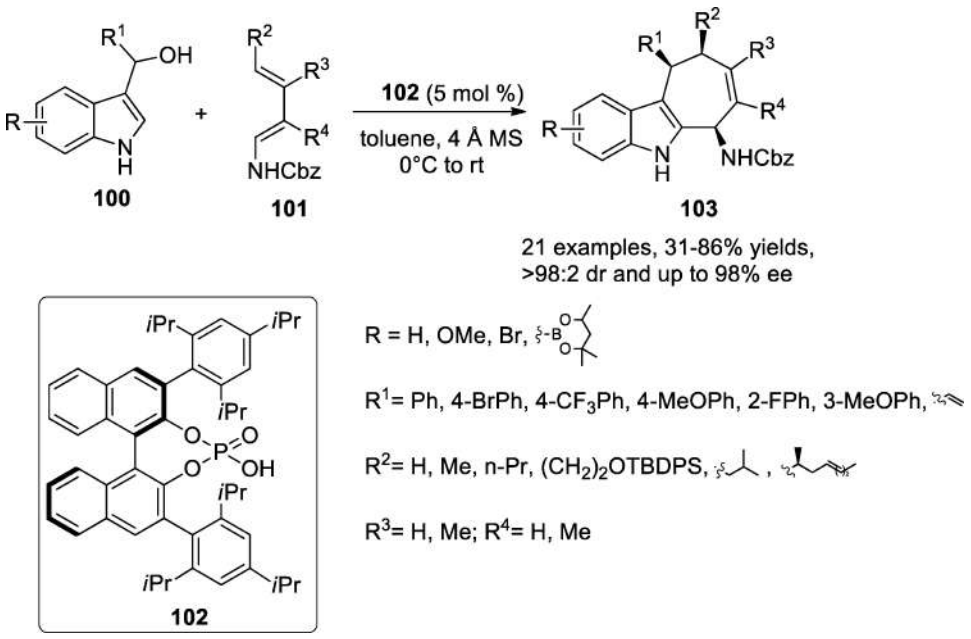
Chiral *N*-Heterocyclic carbene (NHC) **151** was explored for the unprecedent enantioselective aza-benzoin reaction of aldehydes **150** with 2*H*-azirines **149** to chiral acylaziridines **152** (Scheme 35).[69] A wide range of corresponding chiral aziridines were obtained with a broad scope at room temperature and in good yields and selectivity (34 examples, 48–97% yields, up to 98% ee). The NHC catalyst drives the umpolung of the aldehyde to enables asymmetric nucleophilic attack at the azirine C=N. The chiral aziridines obtained with this procedure were characterized with X-ray to determine absolute configuration and converted into other relevant chiral compounds.

Borate anion **154** was investigated for the first time for its ability to catalyse the diastereoselective oxidative cascade cyclization of chiral *N*-propargyl ynamides **153**/**157** into polycyclic *N*-heterocycles **156**/**159** (Scheme 36I–II).[70]

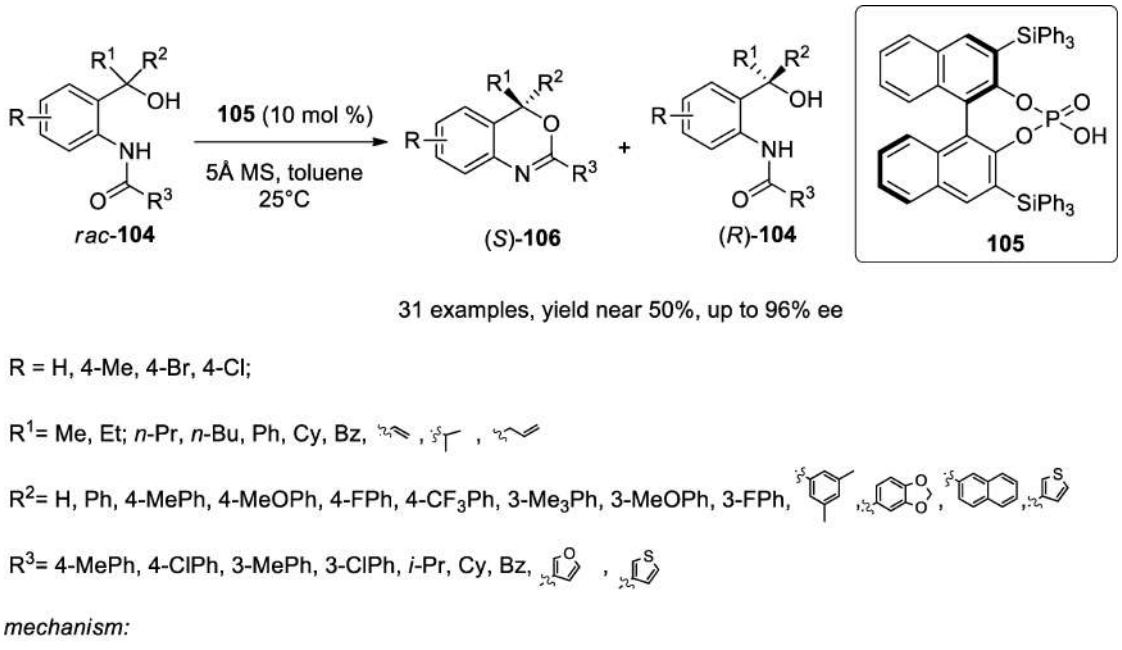
The final compounds were obtained in a diastereoselective fashion, using pyridine *N*-oxides as oxidant, in an efficient manner (18 examples, 36–84% yields, up to 99% ee for **156**; 12 examples, 65–81% yields, up to 99% ee for **159**). This metal-free process proceeds through a Lewis acid-catalyzed SN2′ pathway and resemble the catalytic activity of gold. Diastereo- and enantioselectivity was demonstrated by means of X-ray. The reaction can be scaled-up to one gram and the obtained compound can easily converted into other medicinally relevant bioactive polycyclic compounds.

4. Photocatalytic synthesis

Light-induced photocatalytic systems including transition-metal-catalyzed methods have been established as versatile

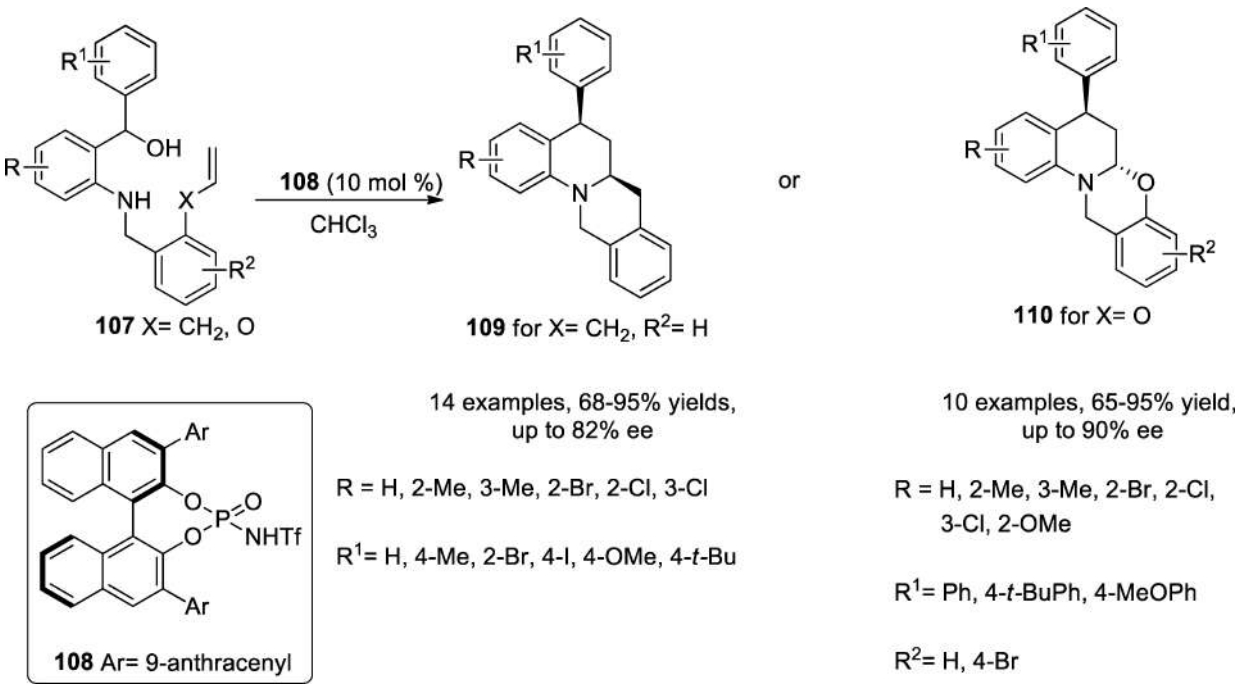


Scheme 23. Reaction scheme of a stepwise (4 + 3) cycloaddition of 3-indolylmethanols with diene.[57]

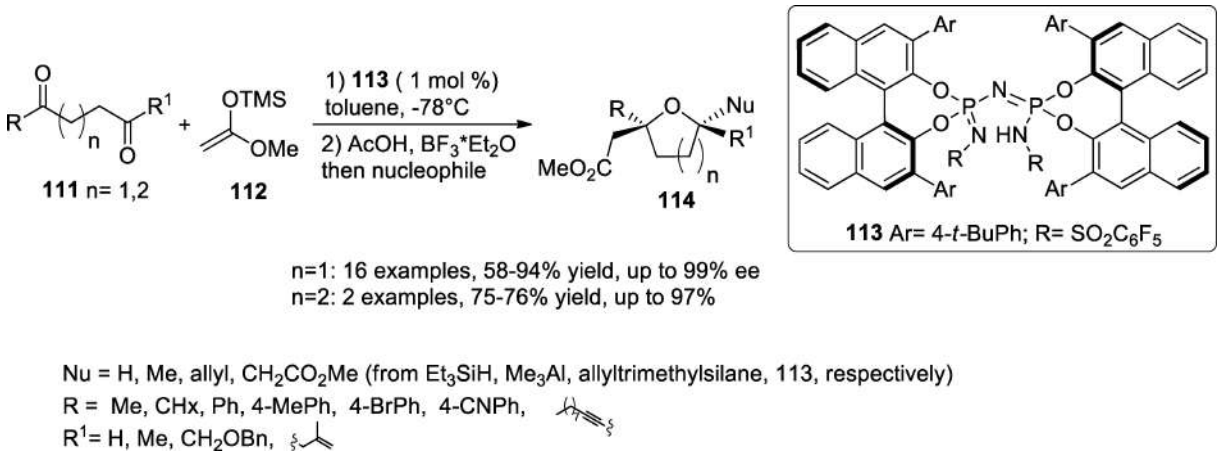


Scheme 24. Scheme and mechanism of the intramolecular cyclization of racemic 2-amido benzyl alcohols.[58]

and sustainable approaches for the synthesis of value-added molecules.[71] For example, in the synthesis of nitrogen containing heterocycles, nitrenes can be considered as promising synthons. Their construction, unfortunately, requires the use of hazardous and expensive transition metal catalysts, high temperatures, harsh conditions, so discouraging their employment.



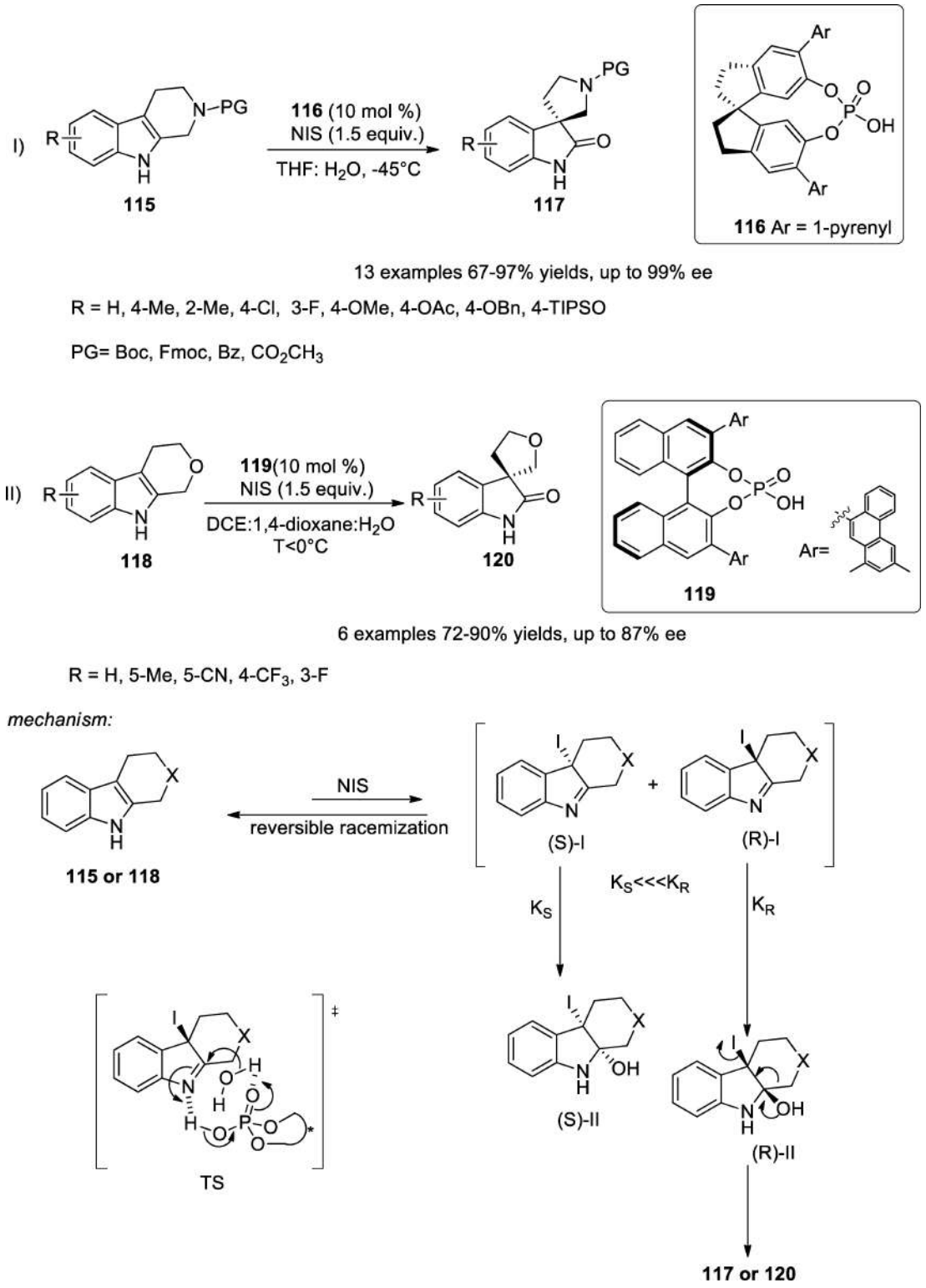
Scheme 25. Reaction scheme of asymmetric intramolecular Aza–Diels–Alder of ortho-quinone methide imine.[59]



Scheme 26. Reaction scheme of enantioselective nucleophilic additions of silylenolether to dicarbonylic compounds.[60]

Recently, an elegant green synthesis of carbazoles, making use of nitrene as intermediates, has been reported:[72] intramolecular C–H amination reaction exploiting ortho-substituted aryl sulfilimines **161** as new generation intermediates, instead of the classic azides, iminoiodanes, azirines. Sulfilimines **161** are easily prepared starting from the corresponding anilines **160** with Martin's sulfurane (Scheme 37). The decomposition of aryl sulfinimines affording the carbazoles **162**, although efficiently conducted by rhodium catalysts, is brilliantly realized by exploiting UV light in mild conditions. The study compares different catalysts, different solvents and light sources, concluding that best performance is obtained in THF and blue LEDs as light source, leading to carbazoles **162** in quantitative yield. The study also demonstrates the wide scope of this protocol (21 examples) and scalability of the process in the efficient gram-scale synthesis of Clausine C, a natural product possessing antibiotic activity.

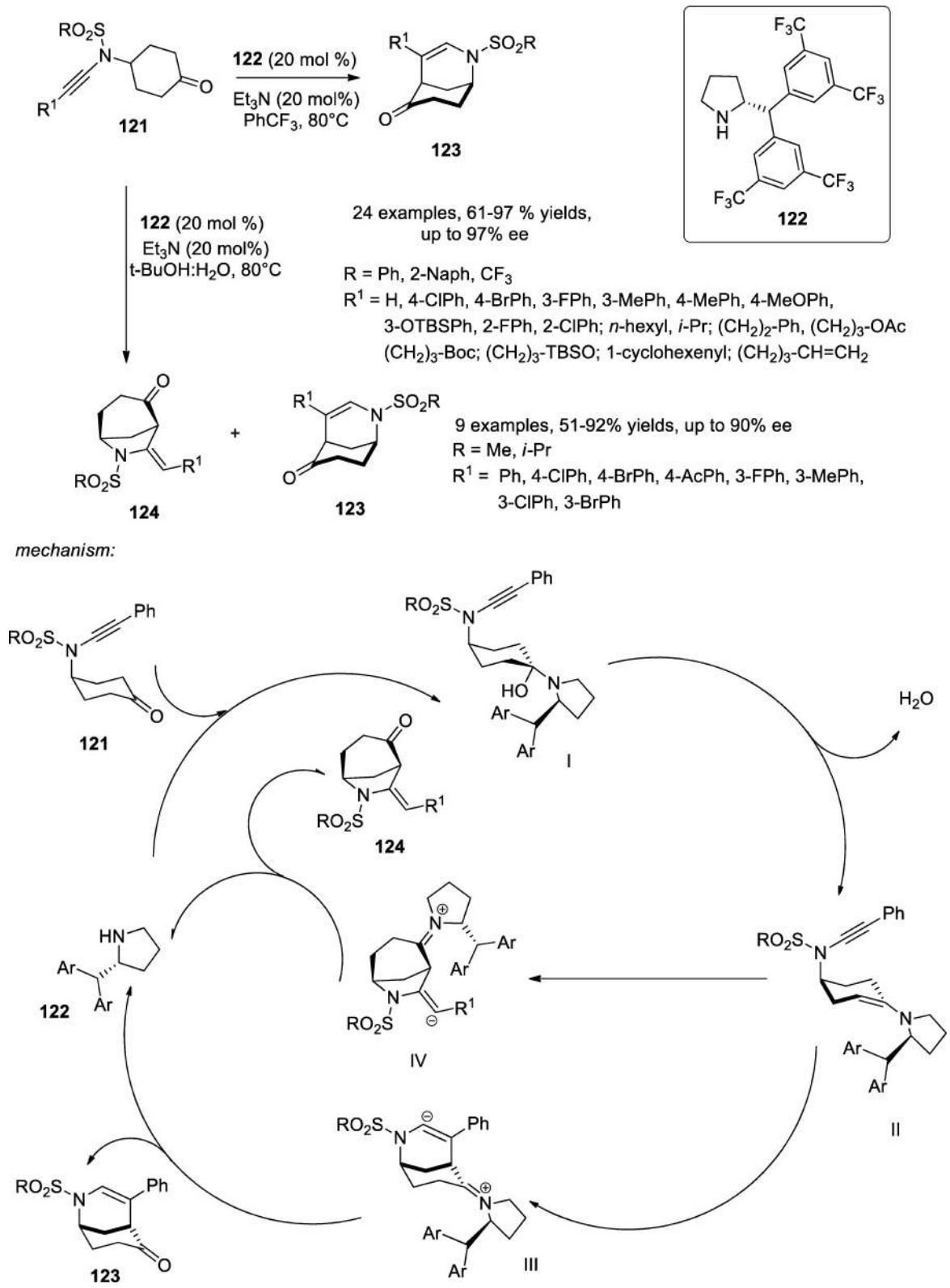
Metal- and oxidant-free conditions have been developed for visible-light-enabled biomimetic tandem aza-6π electrocyclization to pyridines **165** followed by a Minisci-type reaction (Scheme 38). This method, at room temperature, allows to obtain diverse polysubstituted picolinaldehydes **166** with high efficacy, selectivity, and good functional group tolerance, so to be exploited for the synthesis of several drug analogues and natural products. Ortho-position selective C–H formylation on pyridine rings drives to useful synthetic building block and could deliver to unsymmetrical



Scheme 27. Scheme and mechanism of tetrahydro-β-carbolines rearrangement into chiral spirooxindoles.[61]

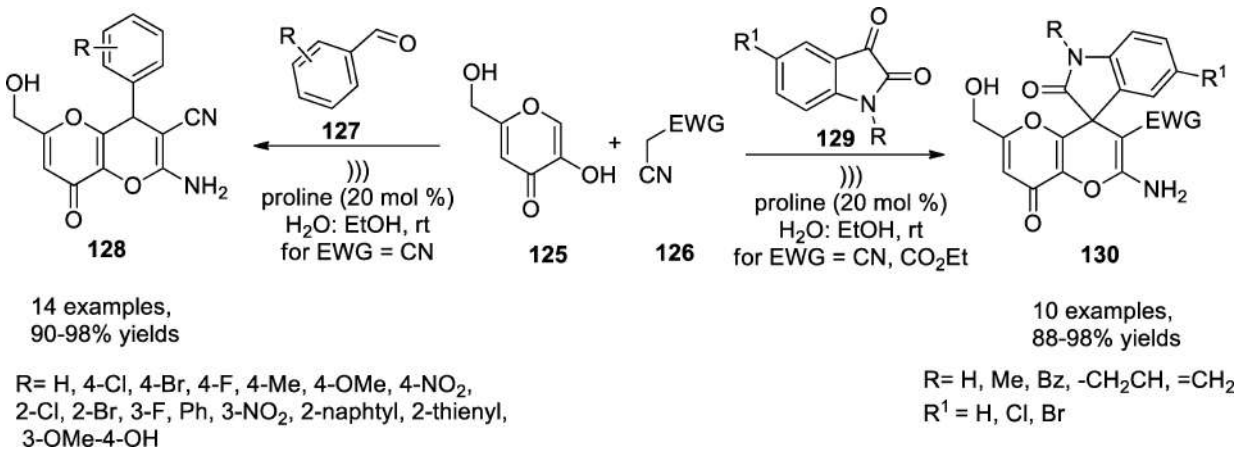
2,2′-bipyridine type ligands, so providing environmentally benign and sustainable mild conditions for facile late-stage modifications of drug analogues and construction of diverse *N*-heterocycles.[73]

Another cascade (sulfonation/cyclization) metal free photocatalityc protocol makes use of blue light at room temperature, glycol as a green solvent, and 9-mesityl-10-methylacridinium perchlorate (Acr-MesClO$_4$) as catalyst to synthesize sulfone-containing heterocycles including oxin-

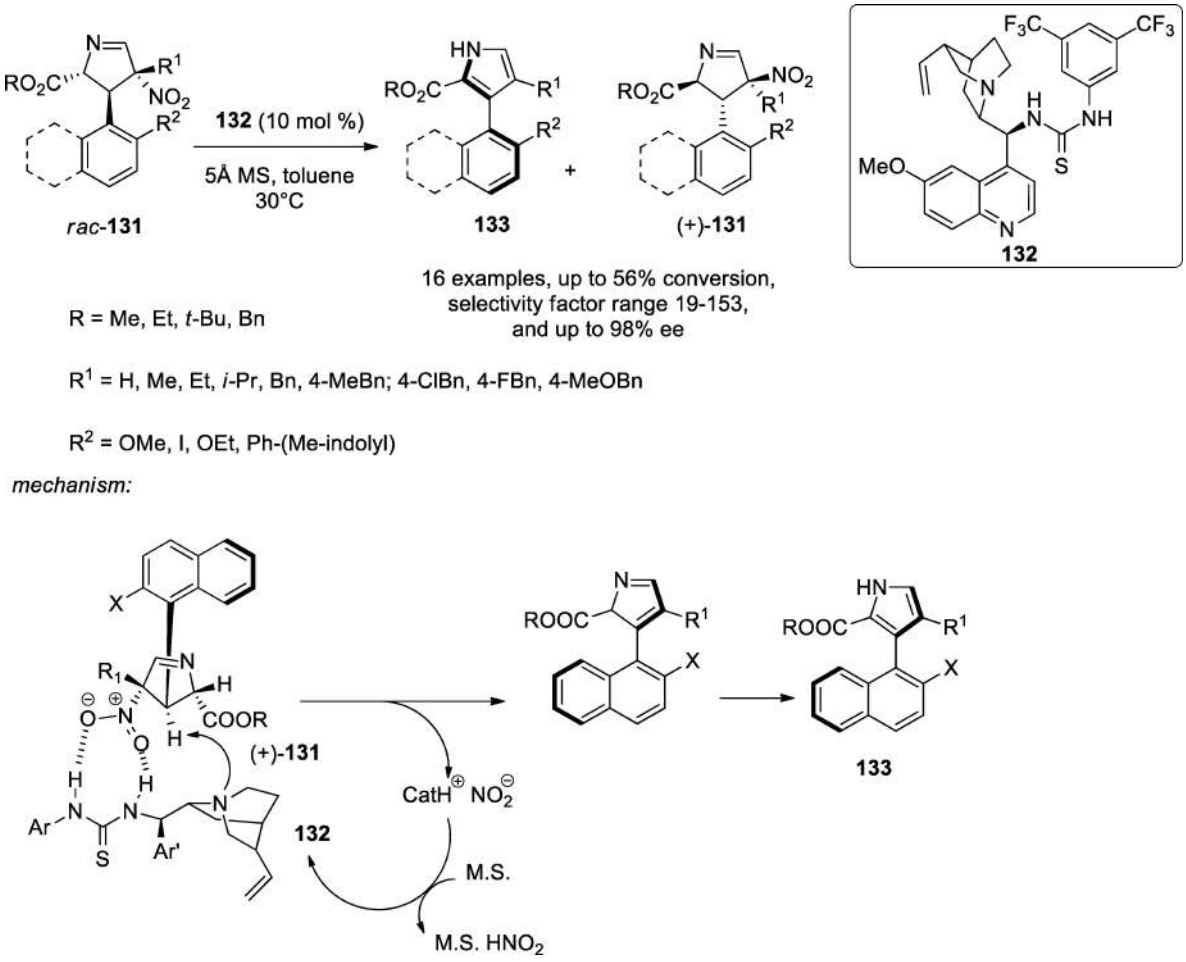


Scheme 28. Scheme and mechanism of asymmetric Conia-ene-type carbocyclization of arylsulfonylprotected ynamide.[62]

doles **168**, thioflavones **169**, and quinoline-2,4(1*H*,3*H*)-diones **170** (Scheme 39). The authors suggest that the polar solvent ethylene glycol act by stabilizing the ionic intermediates in the reactions.[74] The mechanism describing the cyclization via S.E.T. is depicted in Scheme 39.

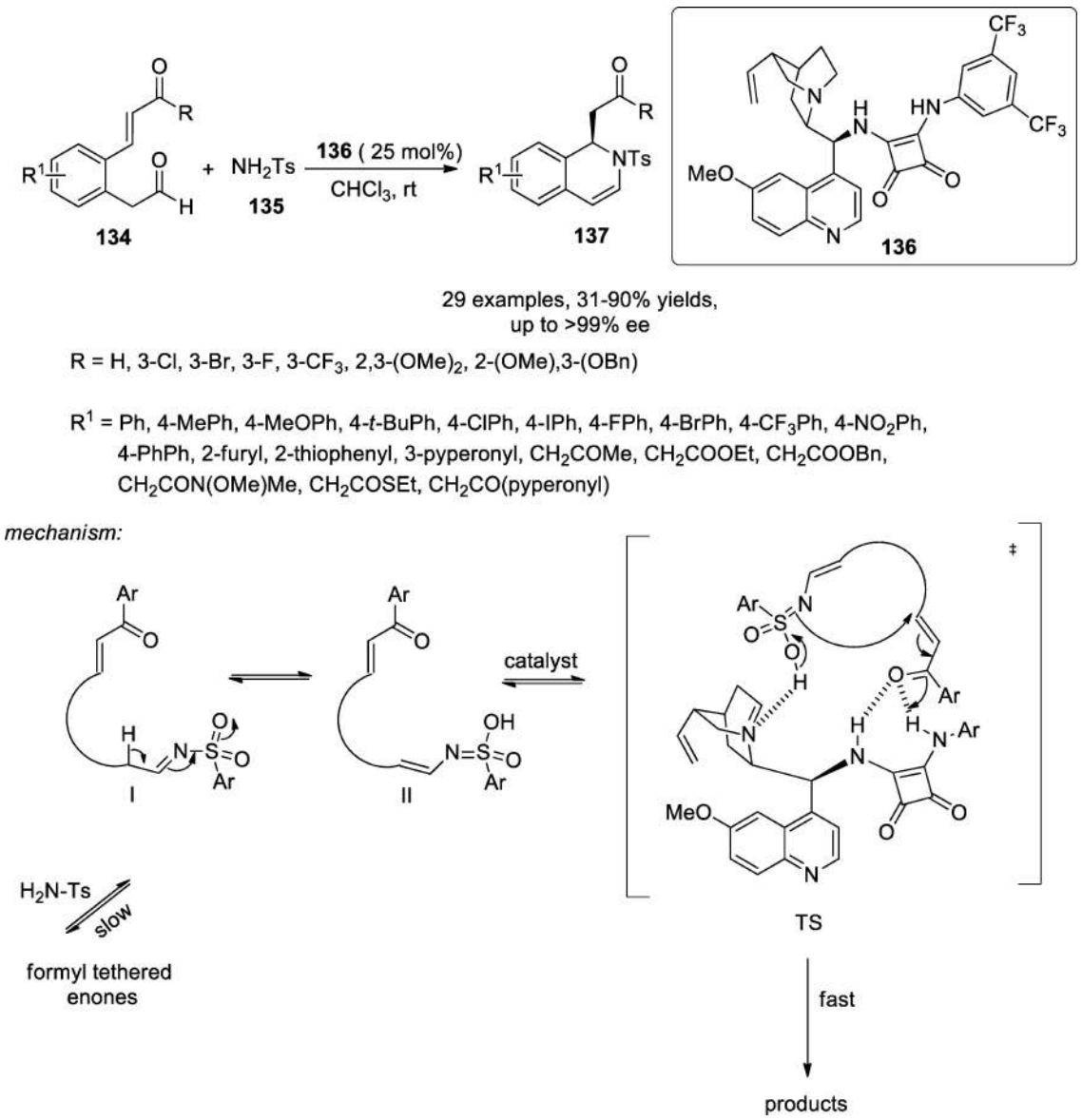


Scheme 29. Reaction scheme of domino three component reaction of carbonyl compounds with nitriles and kojic acid under ultrasound irradiation.[63]

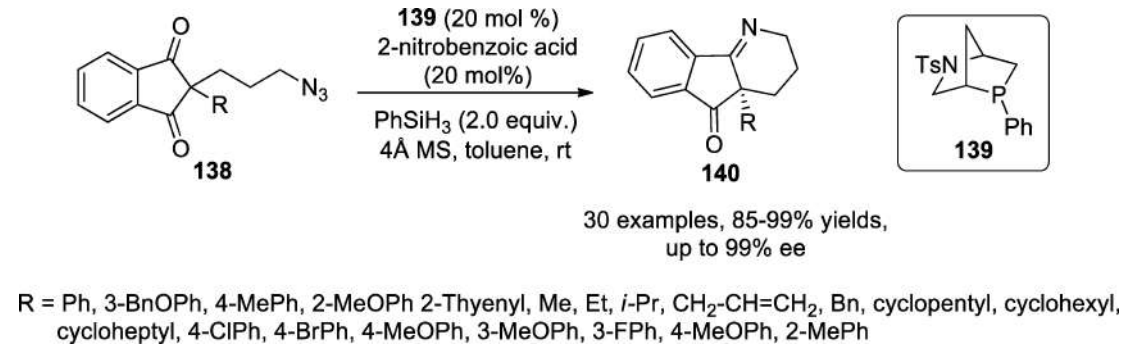


Scheme 30. Scheme and mechanism of the conversion of racemic 3,4-dihydro-2*H*-pyrroles into atropoisomeric 3-arylpyrrole and resolved (+)-3,4-dihydro-2*H*-pyrroles.[64]

An interesting green approach to indole derivatives has been suggested, exploiting both photocatalytic and biocatalytic steps in a sequence. The photocatalytic steps involves iodo-anilines **171** and $[Ir(dtbbpy)(ppy)_2]PF_6$ or $[Ir[dF(CF_3)ppy]_2(dtbbpy)]PF_6$ (where dtbbpy is for di-terbutylbipyridine; ppy is for phenylpyridine, $dF(CF_3)ppy$ is for difluoro, trifluoromethyl phenylpyridine) as Ir-photoinitiator (Scheme 40), exploiting blue LED to obtain the cyclized acetyl-indolines. These, in turn, undergo hydrolysis by HCl to give indolines **172**, that were converted into aromatic

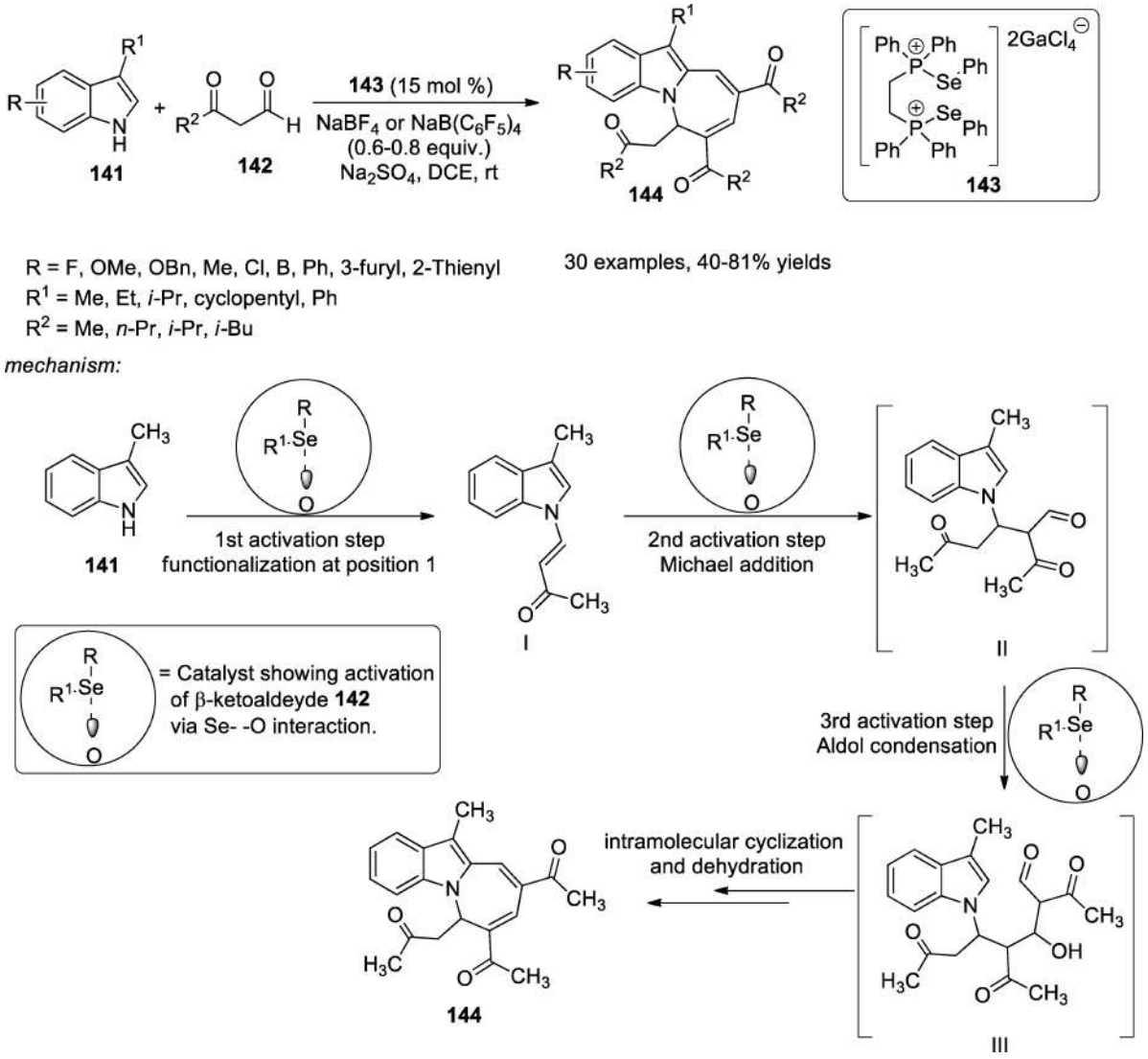


Scheme 31. Scheme and mechanism of asymmetric intramolecular aza-Michael addition.[65]



Scheme 32. Reaction scheme Staudinger–aza–Wittig reaction and desymmetrization of ketones into chiral indanopiperidine.[66]

indoles **173** by monoamine oxidase (MAO) enzymes, enzymes by FAD dependent pathway (depicted in Scheme 40), with excellent efficiency conversion and yields, under mild reaction conditions.[75]



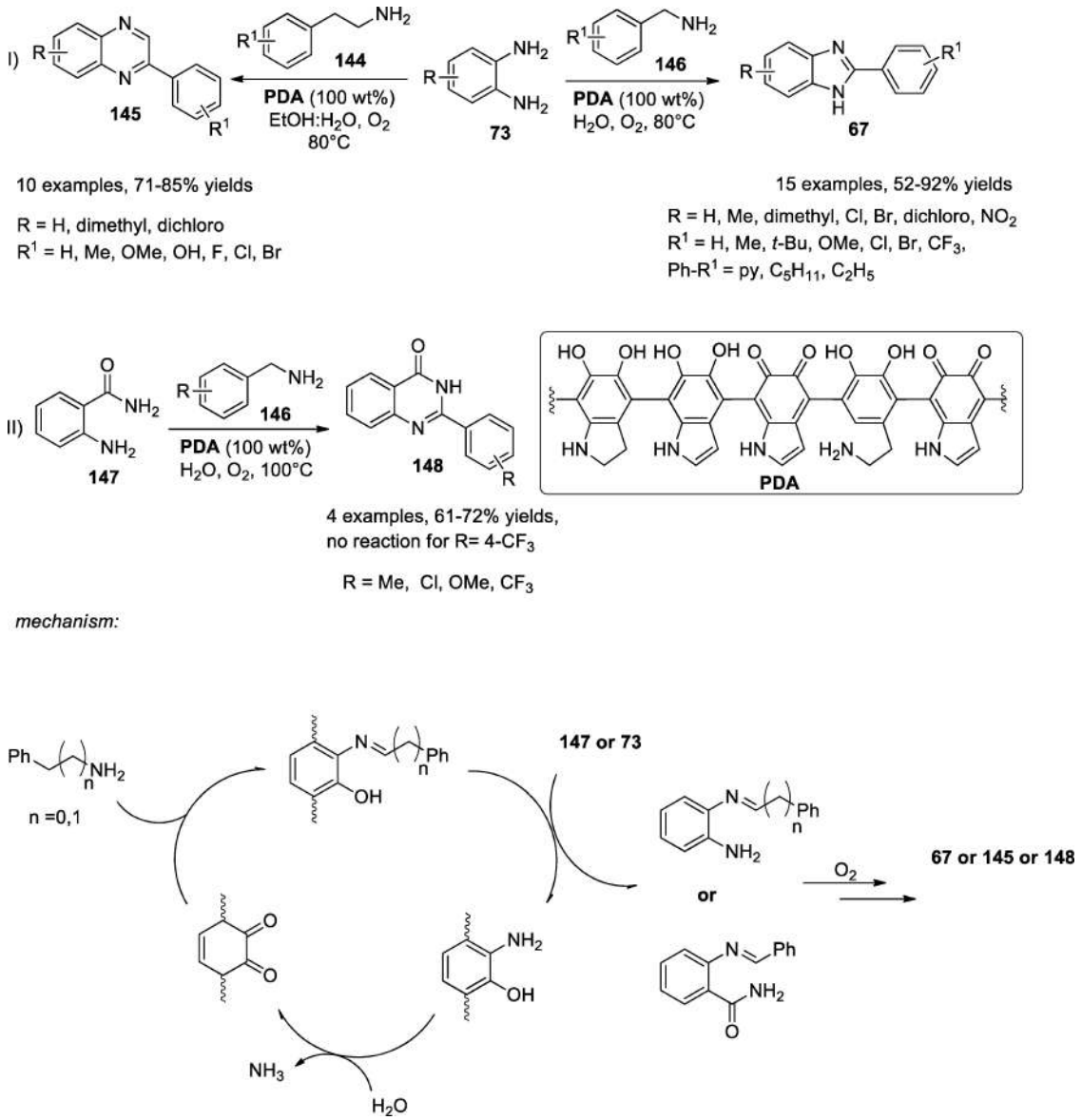
Scheme 33. Scheme and mechanism of indole cyclization reaction.[67]

Ir photocalyst, in particular Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6, has been used under continuous flow conditions in the preparation one-step of saturated *N*-heterocycles **176** (e.g. morpholines, piperazines, thiomorpholines, oxazepanes, diazepanes, substituted pyrrolidines, piperidines), making use of Tin amine protocol (SnAP) reagents **174** and aldehydes **175** (Scheme 41). This protocol, despite not offering higher yields, shows some advantages over the customary use of stochiometric copper complex: it has exceptionally broad substrate scope, tolerates the presence of aromatic heterocycles as well as unprotected functional groups. The continuous flow method makes easier reaction scale-up as well as simplified reaction workup.[76] The redox mediated mechanism is sketched in Scheme 41.

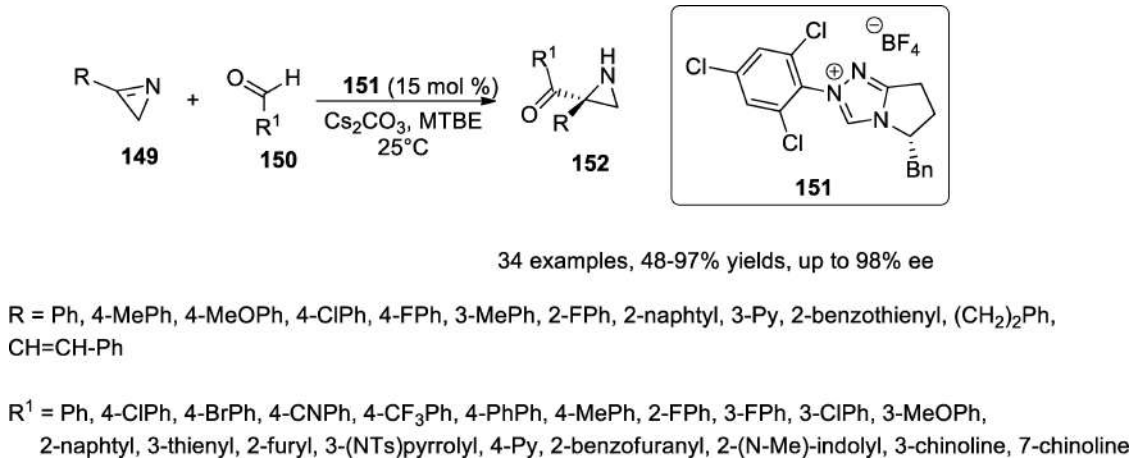
Photocatalysis is suggested also for oxidative dehydrogenation steps. Hence, saturated *N*-heterocycles **177** can be aromatized by an interesting procedure (Scheme 42), exploiting highly efficient and stable semiconductor Nb_2O_5 nanorods with oxygen vacancies as photocatalyst, fluorescent lamps as light source, mild conditions such as room temperature. This procedure showed good tolerance of functional groups and efficiency in terms of turnover (the catalyst was stable and could be reused up to 10 times with negligible loss in activity) and good to excellent yields even applicable to gram-scale synthesis.[77]

The mechanism of the oxidative dehydrogenation has been investigated by computational approach and suggests that oxygen vacancies are responsible for the photoelectrochemical properties and adsorption capacity of both molecular O_2 and substrates, boosting the photocatalytic activity.

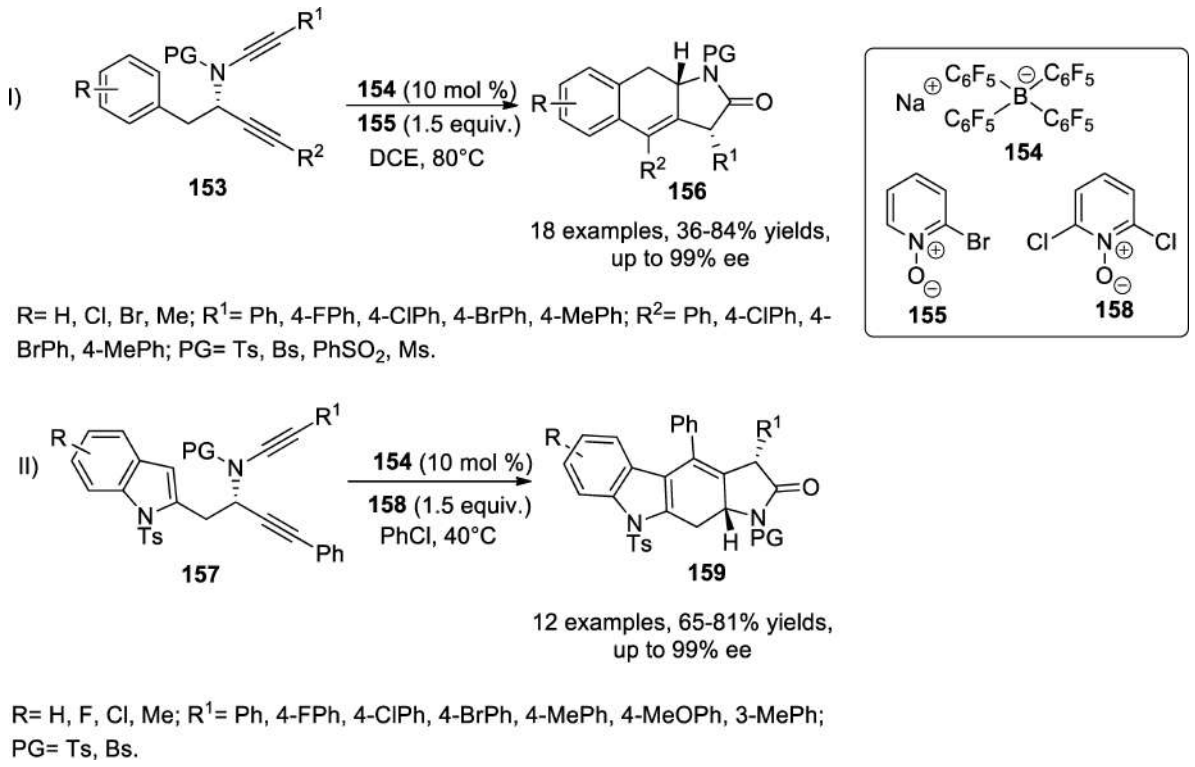
The same kind of synthesis of *N*-heterocycles by oxidative dehydrogenation has already been proposed previously, exploiting atomically dispersed manganese sites anchored onto conjugated tris-triazine units of graphitic carbon nitride as a bioinspired photocatalyst (Mn1/tri-CN) taking inspirations from metalloenzymes. In this case oxygen activation on the primary coordination sphere of atomic



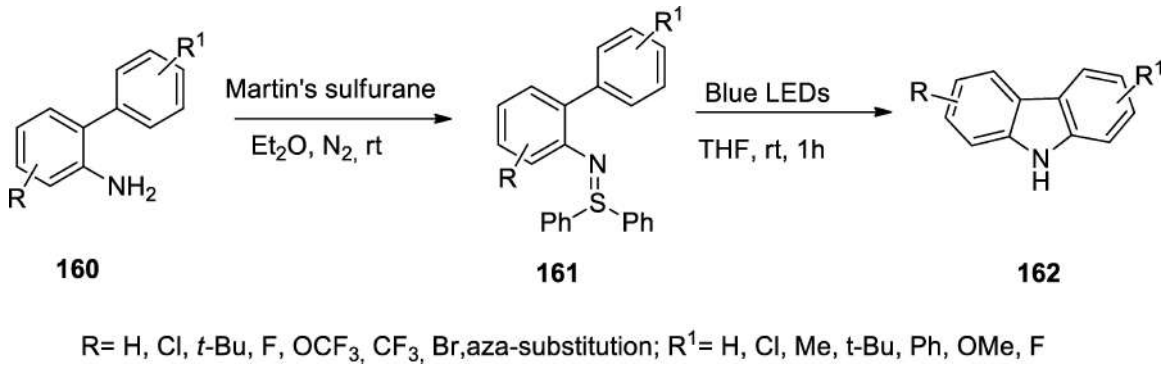
Scheme 34. Scheme and mechanism of the reaction of diamine or anthranilamide with primary amines in under aerobic conditions (Scheme 34).[68]



Scheme 35. Scheme of the enantioselective aza-benzoin reaction of aldehydes with 2*H*-azirines.[69]



Scheme 36. Scheme of diastereoselective oxidative cascade cyclization of chiral *N*-propargyl ynamides into polycyclic *N*-heterocycles.[70]

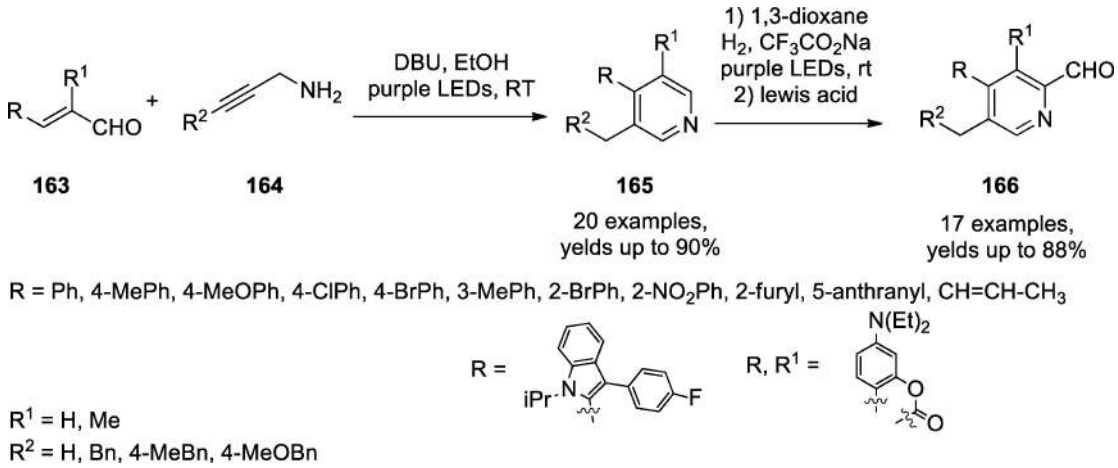


Scheme 37. Scheme of intramolecular C–H amination reaction exploiting ortho-substituted aryl sulfilimines as new generation intermediates.[72]

Mn–N2 sites and substrate adsorption by π-π stacking interactions on tri-*s*-triazine units, mimicking the secondary coordination sphere, synergistically contribute to high-efficiency electron transfer mediating photocatalytic oxidation reactions. The process has shown wide substrate scope, mild reaction conditions such as visible-light, room temperature and raw air atmosphere, and excellent performances.[78]

Very interestingly, a recent paper reports a direct, simple and environmentally friendly approach to pyridines through one-pot thermo-photocatalytic approach using a novel POM-modified MOF.[79] In this work, a new type of porous material, PCN-222, was synthesized by combining a porphyrin-based ligand and zirconium chloride with the help of TFA and BA modulators. This material was then modified with a POM, $H_3PW_{12}O_{40}$, resulting in a novel porous POM@PCN-222. This modified material exhibited excellent photocatalytic activity in the synthesis of pyridines **180**, from 1,4-dihydropryridines intermediates through a pseudo four-component reaction between aldehydes **127**, methyl acetoacetate **179**, and ammonium acetate (Scheme 43). The composite material showed improved catalytic performance compared to the unmodified materials, due to the synergistic effect between the MOF and the POM. Additionally, the strong interaction between PCN-222 and POM prevented POM leaching during the reaction, allowing for the composite to remain highly active for up to three reaction runs.

Among photosensitizers applied to the photocatalyzed synthesis of heterocycles, cercosporin is a perylenequino-



Scheme 38. Scheme of visible-light-enabled biomimetic tandem aza-6π electrocyclization followed by a Minisci-type reaction.[73]

noid pigment with excellent properties of photosensitization, easily produced by endophytic fungus *Cercospora sp.* JNU001 strain via microbial fermentation. It has been reported a new method exploiting cercosporin and visible light under mild conditions to catalyse the synthesis of 1,4,5,6-tetrahydropyridazines **183** and 1,2,3-thiadiazoles **184** with good regioselectivity and functional-group compatibility (except for R = pyridin-2-yl), showing a nice example of combination of microbial fermentation and organic photocatalysis for the construction of nitrogen-containing heterocycles (Scheme 44).[80]

5. Electrochemical reactions

Among synthetic green processes, organic electrochemistry is an interesting path to explore, as by exploiting low voltage electrical current avoids the use of potentially unsafe redox reagents.

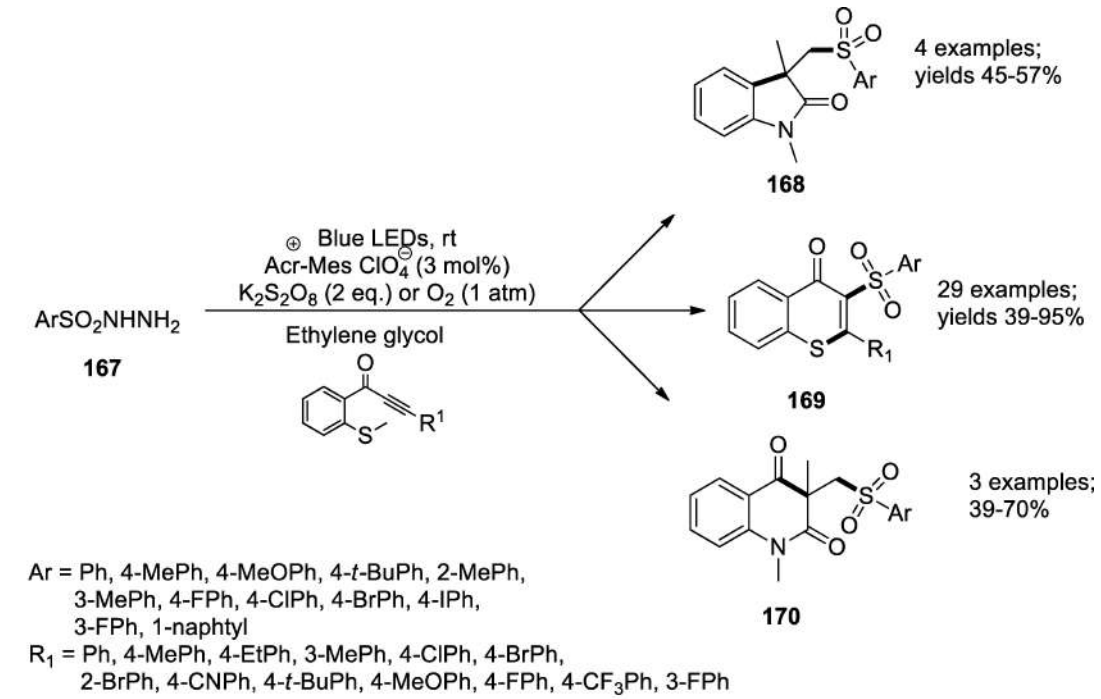
In the construction of *N*-heterocycles, classical oxidation reactions are a key step to achieve cleaving of C–C bonds and insertion of heteroatoms into alkenes and alkynes. In this context, the electrochemical dehydrogenation reaction (Scheme 45) is a convenient route to achieve oxidative bond formation, in the absence of external oxidants, with cathodic hydrogen evolution,[81] with the great advantage of atom and step economy; moreover, this path would permit high tolerance toward the presence of oxidation-labile functional group (Fg).

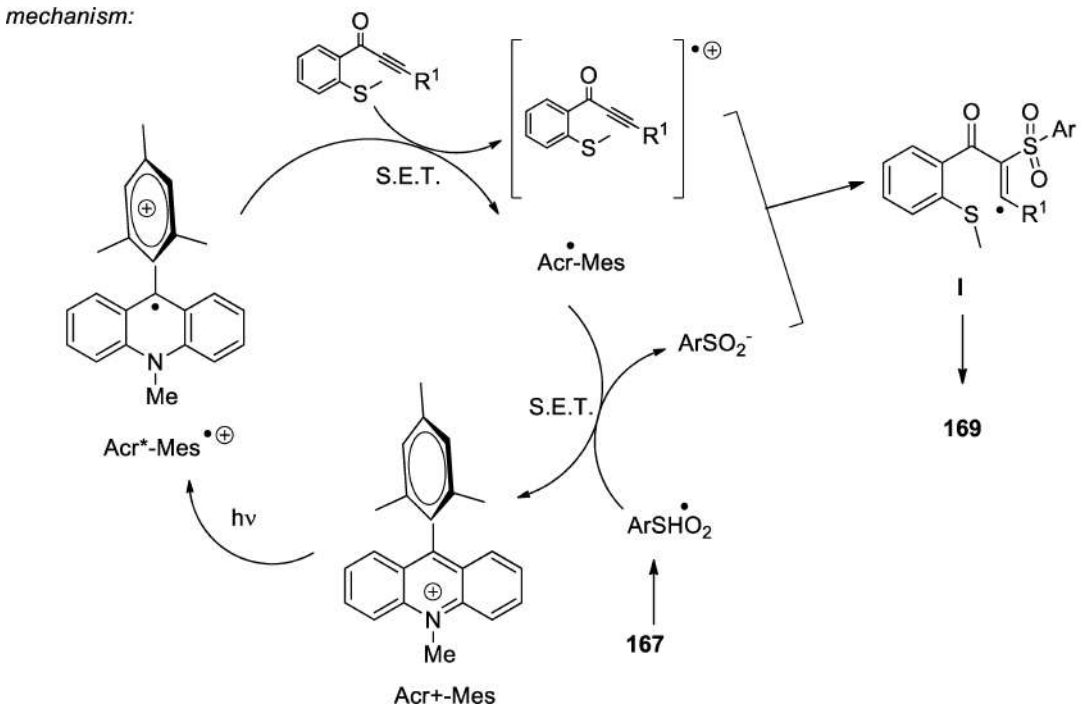
Reaction condition optimization widen the scope of this electrochemical protocol to various heterocyclic scaffolds. Moreover, experimental observation allows to hypothesize a possible reaction mechanism that involves anodic oxidation of alkene and proceeds via electrochemical aziridination and ring rearrangement.

As another peculiar example, an electrochemical radical cyclization cascade has been employed to prepare fused benzoheterocycles **188** (Scheme 46).[82] In particular, benzimidazolones and benzoxazolones, key heterocyclic cores in drugs (e.g. droperidol, pimozide, domperidone, and chlorzoxazone) have been constructed as fused bicyclic scaffold in a single step from arylamine-tethered 1,5-enynes **187**. This electrochemical protocol, making use of reticulated vitreous carbon (RVC) as anode and platinum plate cathode, allows to obtain diverse substitution patterns and complete regiocontrol.

The proposed mechanistic pathway suggests the occurrence of a radical cyclization cascade leading to the formation of the bicyclic scaffold of the benzoheterocycle product. First, the arylamine **187** is anodically oxidized and deprotonated to give an amidyl radical **I**, which then undergoes cyclization to afford a vinyl radical **II**. Intramolecular cyclization of **II** results in the formation of intermediate **III**. Alternatively, **II** can generate an exocylic radical **IV**, which can subsequently be converted into **III** via a tricyclic radical intermediate **V** (Scheme 46). Radical **III** next undergoes single-electron transfer oxidation, followed by deprotonation, to afford another intermediate, which after dehydrogenation affords final benzo-fused heterocyclic product. The electrons gathered at the anode travel to the cathode and combine with protons to produce H_2. As a result, no electron and proton acceptors are needed.

Electrochemical green approach has been proposed also to obtain fluorinated heterocycles, object of growing interest in recent years, especially due to their application in pharmaceuticals.[1b,h] An interesting example is the environmentally friendly synthesis developed to provide tri- and difluoroalkylation of vinyl azides **189/191** and electrochemical radical cyclization and dearomatization by using $RfSO_2Na$ ($Rf=CF_3$, CF_2H) as fluoroalkylating agent (Scheme 47).[83] In the proposed mechanism, the trifluoromethyl radical is generated via electrochemical anodic oxidation and reacts with vinyl azide **189** to produce the iminyl radical intermediate **I**. Subsequently, intermediate **I** underwent homolytic aromatic substitution to give radical **II** which is electrochemical anodic oxidized to form cation intermediate **III**. **III** finally deprotonated to give the desired product **190** and hydrogen.

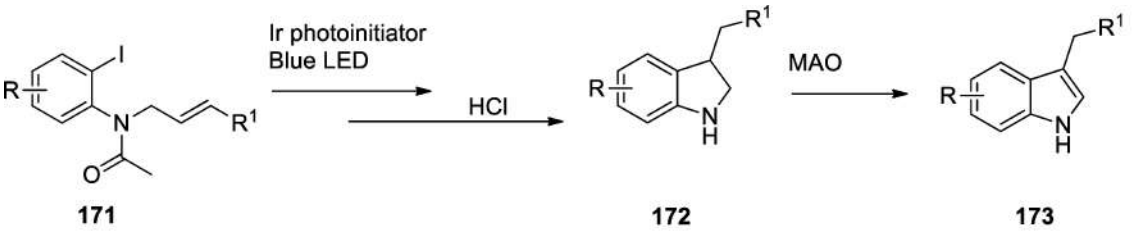


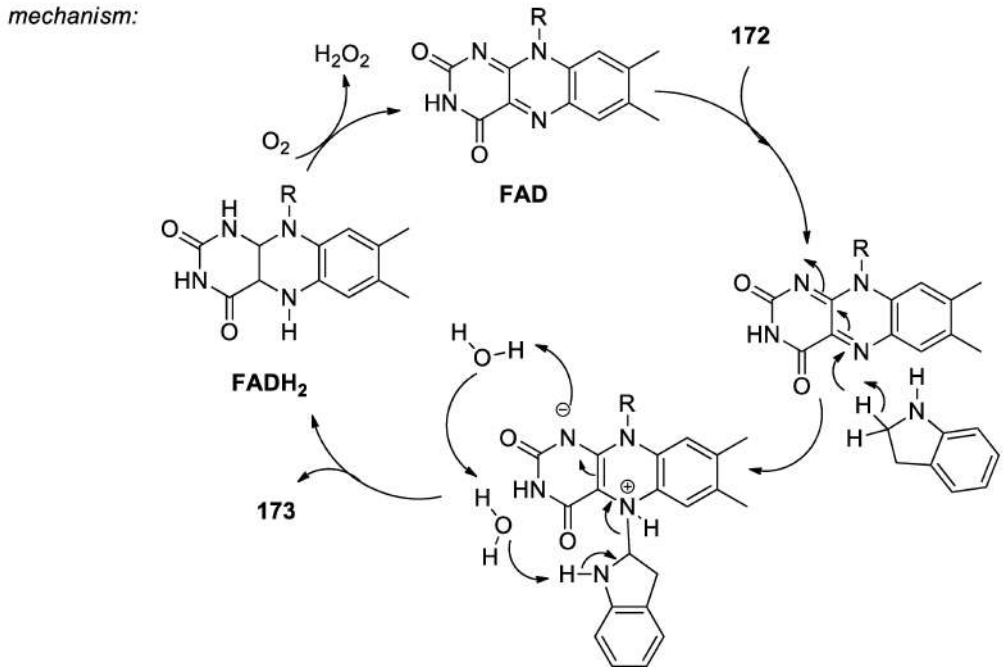


Scheme 39. Scheme and mechanism of cascade sulfonation/cyclization metal free photocatalityc reaction.[74]

6. Iodine mediated synthesis

Molecular iodine demonstrated be as an efficient cyclization agent, for this reason it has been increasingly applied as catalyst in heterocyclic synthesis, allowing to replace transition metal catalysts. The catalytic ability of iodine in numerous oxidative transformations leads to the formation of new C–O, C–N, and C–C bonds in organic compounds.[84] Iodine mediates especially intramolecular amination and amidation reactions but it can give access to several cyclization reactions.

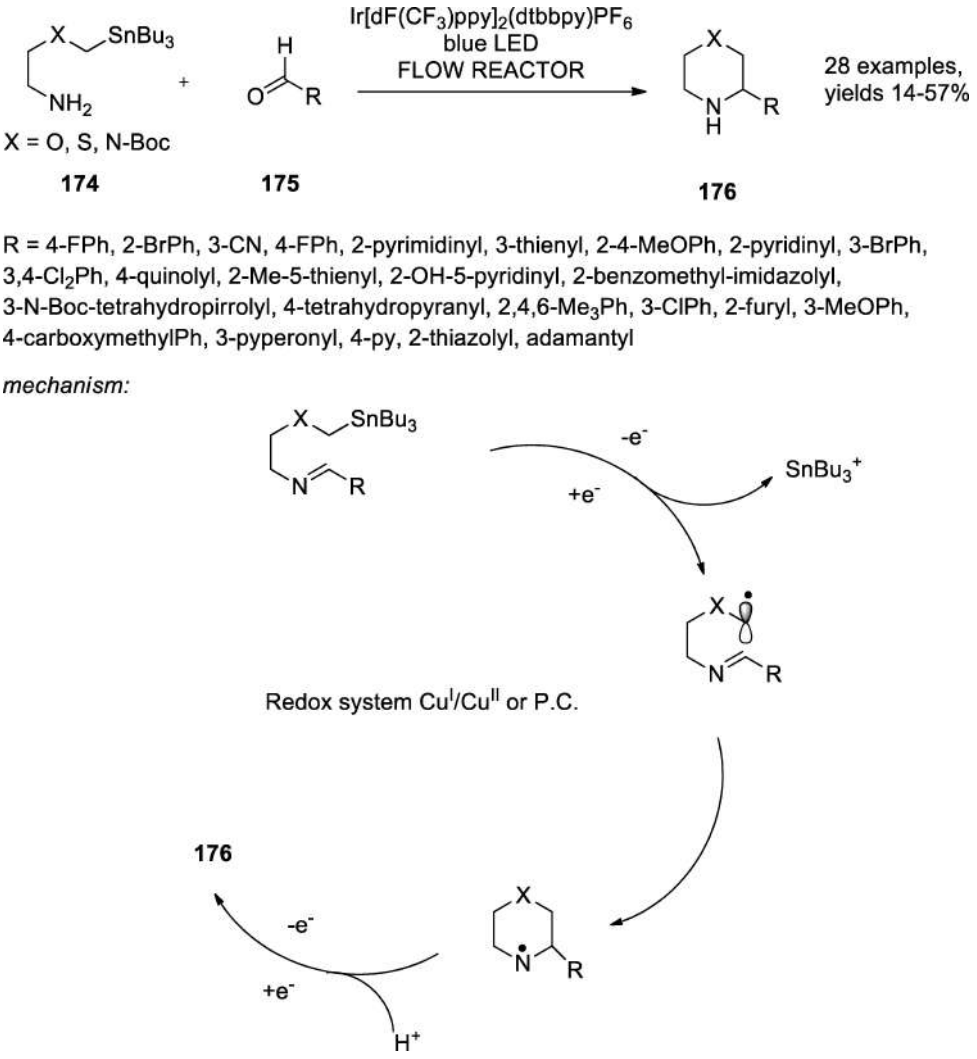




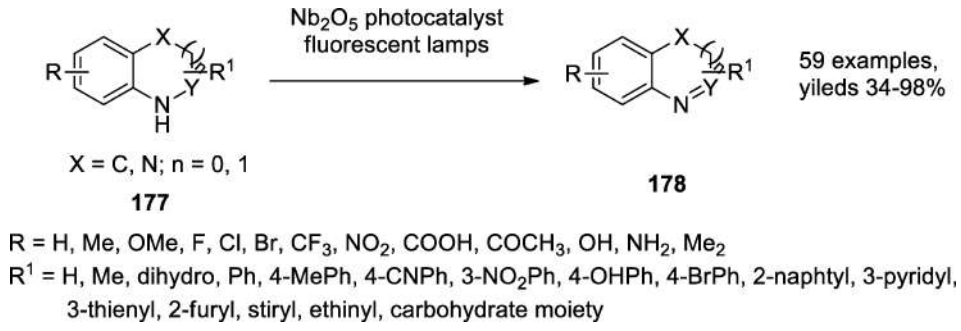
Scheme 40. Scheme and mechanism of photocatalytic and biocatalytic steps green approach to indole derivatives synthesis.[75]

Pyrrolidine rings can be synthesized thanks to amination reactions catalysed by a metal-free procedure in presence of iodine (Scheme 48).[85] Sequential intermolecular and intramolecular amination of aliphatic C–H bonds were performed trough an iodine-catalyzed process, showing preference for secondary methylene positions over tertiary methine groups and for more hydridic C–H bonds over acidic ones. For example, when mesylamide **194** (R= methanesulfonyl) was employed as nitrogen source, the intermolecular C–H amination, proceeded regioselectively at the benzylic position. The subsequent intramolecular ring closure provided pyrrolidines **196** (Scheme 48I). In addition to the sequential reactions, the one-pot reaction can be carried out with good results also using different nitrogen sources. The tandem C–H amination reaction was also successfully employed for the synthesis of an anticonvulsant and anesthetic agent MK-801 **199** (R=H), presenting a pyrrolidine ring (Scheme 48II). Also, the reaction can occur in two steps or directly in a single batch.

Following a similar approach, 4-aryl-2-quinolone derivatives **201** have been synthesized under metal-free conditions via iodine-mediated intramolecular C–H amidation of 3,3-diarylacryl amides **200** (Scheme 49). This procedure allows to overcome the regioisomeric product formation and E/Z isomerization associated with classical metal-mediated synthesis, as the direction of the cyclization in the selected metal-free conditions is governed by preferred proximity of the amide group in the Z-substrate. The nature of substituents in the aryl rings did not influence the outcome of the reaction, while the presence of a diarylalkene moiety was necessary to yield the desired product. The intramolecular amidation was performed on several substrates leading to very good yields (17 examples yield up to 87% yields) and involved the in situ generation of hypoiodous acid. The mechanism proposed involved the radical species **II** formed from homolytic cleavage of the iodo-derived intermediate **I**. Radical **II** may undergo addition to aryl ring and in the highly redox environment, the newly



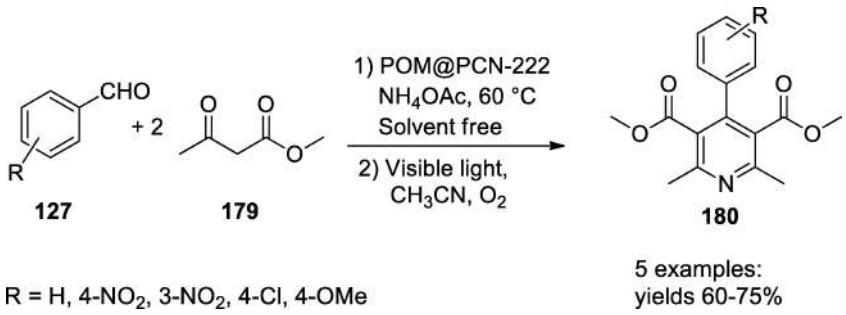
Scheme 41. Scheme and mechanism of continuous flow conditions in the preparation one-step of saturated *N*-heterocycles.[76]



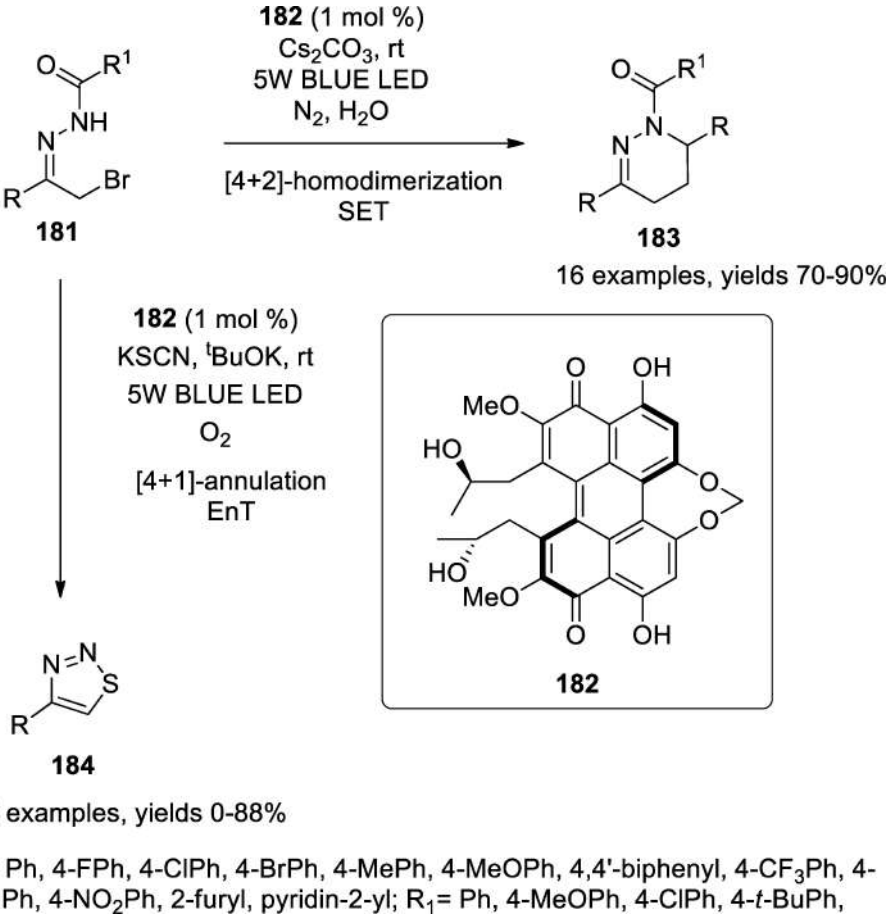
Scheme 42. Scheme of reaction for the oxidative dehydrogenation of saturated *N*-heterocycles with fluorescent lamps.[77]

formed radical **III** may undergo oxidation to cation **IV**, resonance stabilised to **V**. Base-mediated loss of proton leads to overall C(sp^2)-H amidation. Oxidative regeneration of iodine may continue the catalytic cycle.[86]

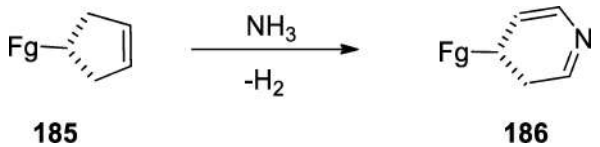
Molecular iodine also promoted the synthesis of pyrrolo-[1,2-a]quinoxalines **204** and quinazolin-4-ones **206** using *N*,*N*-dimethylformamide (DMF) as carbon synthon (Scheme 50).[87] Satisfactory yields were obtained (47 examples afford from 50% to 89% yields) and scale up conditions were applied without decrease in yield, providing potential application of the methodology in the pharmaceutical industry. *N*-acyl and *N*-methyl pathways (Scheme 50) were proposed as possible mechanisms. In the *N*-acyl pathway, iodine working as a Lewis acid allows the formation of an



Scheme 43. Reaction scheme for the synthesis of pyridines through a pseudo four-component reaction.[79]



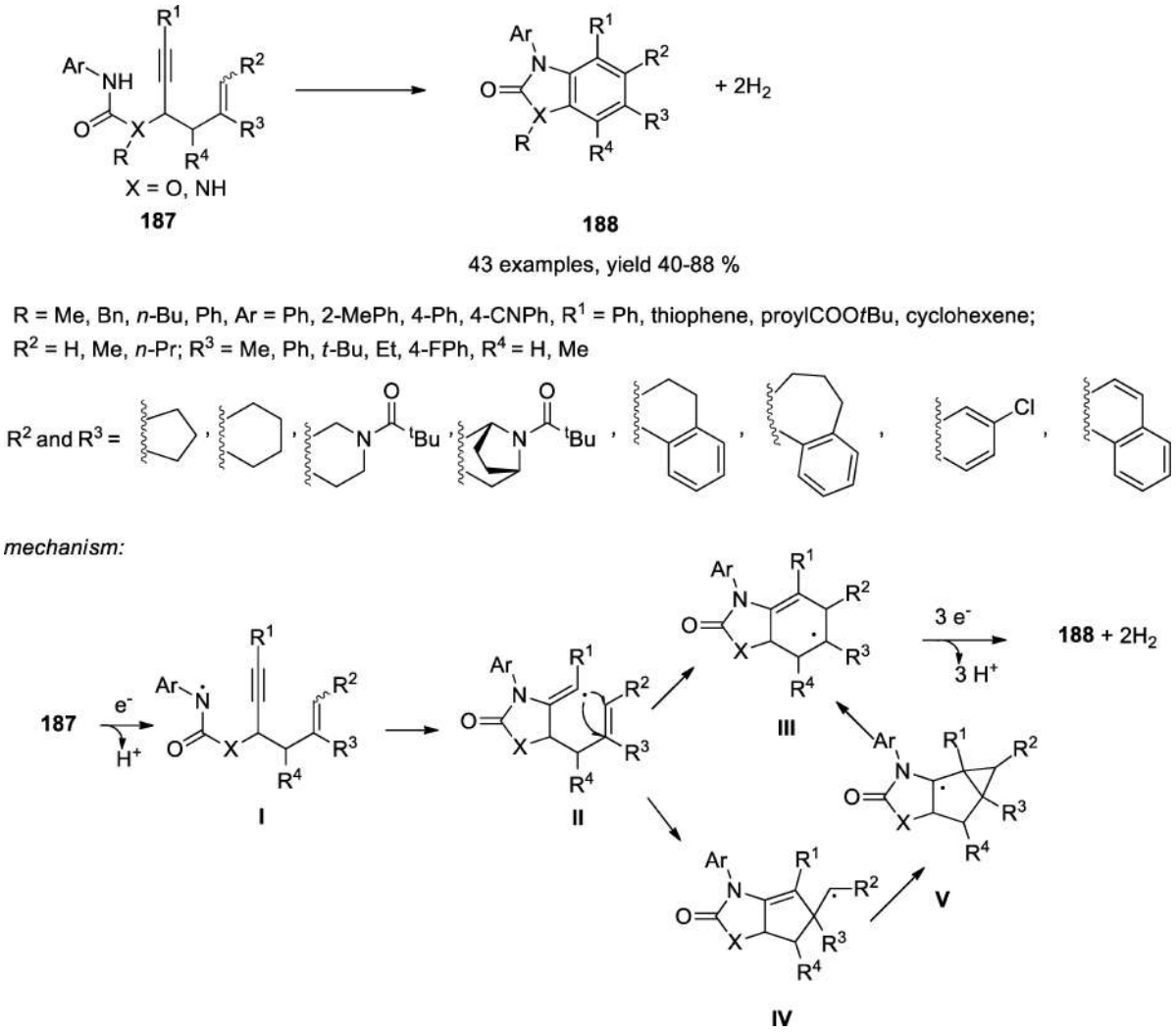
Scheme 44. Reaction scheme for the synthesis of 1,4,5,6-tetrahydropyridazines and 1,2,3-thiadiazoles.[80]



Scheme 45. Reaction scheme for the electrochemical dehydrogenation.[81]

imine structure **I** which undergoes to intramolecular cyclization. In the N-methyl pathway, DMF reacted with iodine to form a quaternary ammonium ion and an iodine anion, which interacted with **205** to give intermediate **II**. Then, *N*-methyl formamide left and the imine structure **III** was formed. Finally, intramolecular cyclization and oxidation took place to give rise to the desired products.

Taking advantage from the amination reaction occurring in presence of molecular iodine, a three-component reaction has been fine tuned for the synthesis of 3-aroylimidazo-[1,2-a]-*N*-heterocycles **210** from aryl ketones **208** and 2-amino-*N*-heterocycles **207** using dimethyl sulfoxide **209** as methylene donor (Scheme 51). The reaction was catalyzed by I_2 in the presence of $K_2S_2O_8$ giving rise to the desired products in moderate to good yields (14 examples yield from 50% to 74% yields). In general, aryl ketones bearing

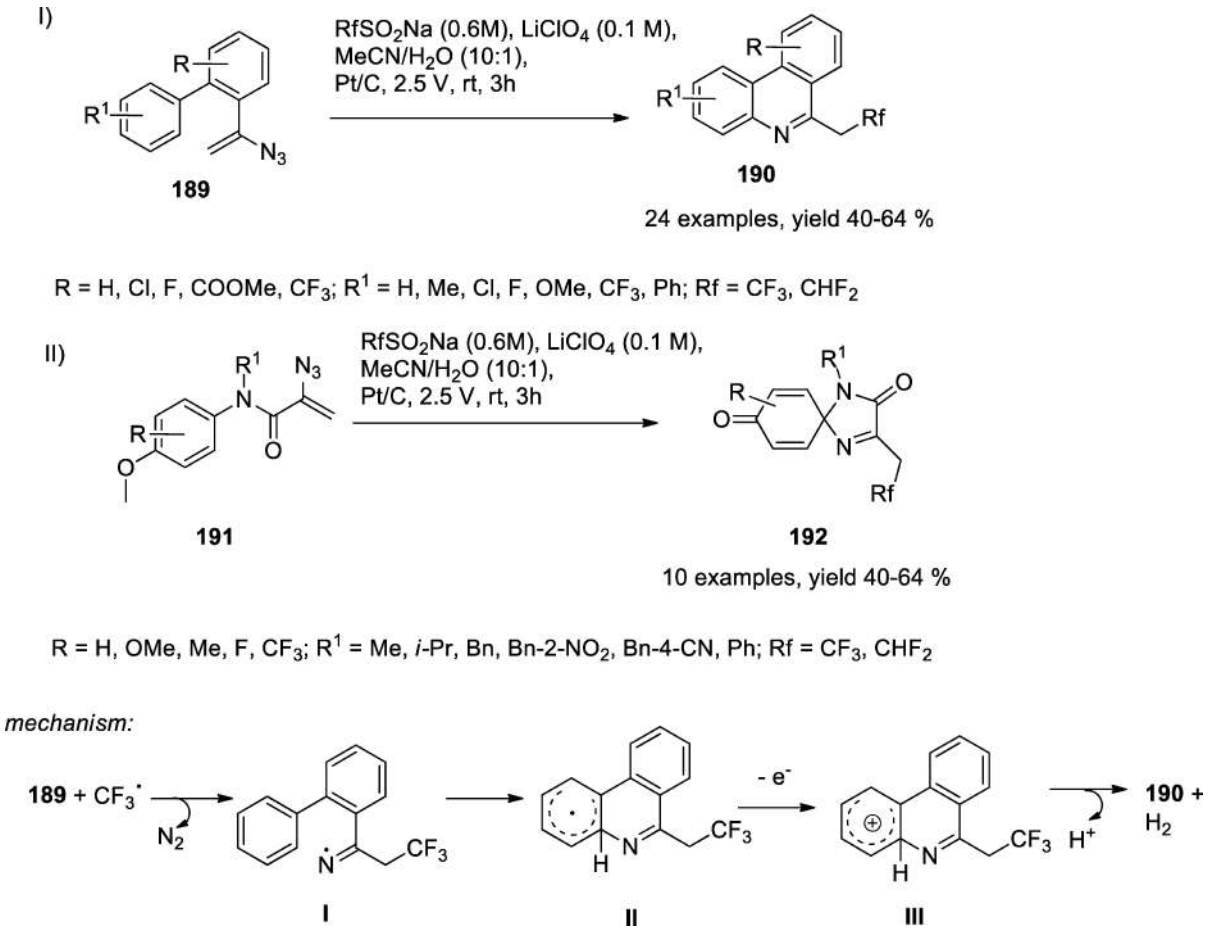


Scheme 46. Scheme and mechanism of electrochemical radical cyclization cascade to prepare fused benzoheterocycles.[82]

electron-withdrawing groups provided higher yields than ketones bearing electron-donating ones. The product did not form when para-hydroxyl acetophenone was used as substrate. On the other hand, the position of the substituent group on the phenyl ring significantly influenced the yield.[88] Mechanistic insight shows that 2-aminopyridine (**207**) reacts with the sulfenium ion, previously formed between DMSO and $K_2S_2O_8$, to give intermediate **I**. Then a coupling of the intermediate **II** with acetophenone occurs and the resulting compound **III** is reacted with I_2 to afford intermediate **IV**, which after cyclization and oxidation gives rise to product **210**.

This protocol was also employed for the synthesis of (7-methoxyimidazo[1,2-a]pyridine-3-yl)(3,4,5-trimethoxyphenyl) methanone, an anticancer drug candidate leading to 61% yield, interestingly higher and more efficient than the three-step reaction methodology previously reported yielding only 20% of the product.[89] The one-pot synthesis, thus, increase the access to biologically active 3-aroylimidazo-[1,2-a]-*N*-heterocycles with various substitution patterns.

Iodine has been used as catalyst also for the synthesis of 4-sulfonyl pyrazoles **213** obtained from *N*,*N*-dimethylenaminones **211** and tosylhydrazine **212** as starting materials. The pyrazole formation occurred via the tandem C(sp^2)-H sulfonylation and the pyrazole annulation under metal-free conditions (Scheme 52).[90] The reaction was performed in presence of tert-butyl hydroxyperoxide (TBHP), molecular iodine and $NaHCO_3$. Once fixed the optimal experimental conditions a full substrate scope of enaminones and sulfonyl hydrazines was carried out allowing the access to several pyrazole derivatives obtained with moderate to high yields (26 examples yield 52% to 88% yields). In particular, the enaminones with electron withdrawing group on phenyl structure afforded products with lower yields. When alkyl based enaminone was employed, however, no target product was synthesized. On the other hand, the nature of hydrazine substituents did not significantly affected yields. Mechanistic insights show that I_2-catalyzed free radical C–H sulfonylation of enaminone takes place giving rise to the sulfenylated enaminone intermediate **I**. Subsequently, the



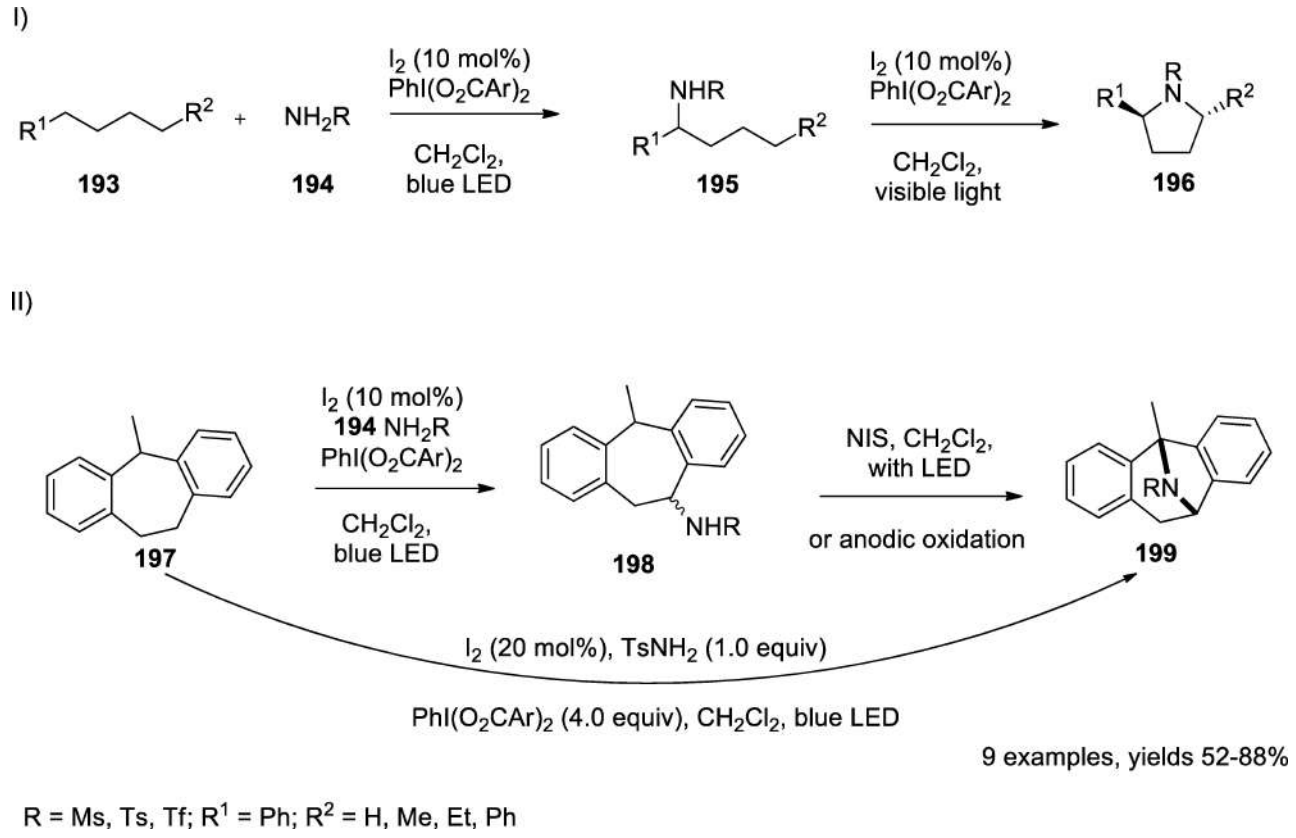
Scheme 47. Scheme and mechanism for the electrochemical synthesis of fluorinated heterocycles.[83]

transamination of the *N*,*N*-dimethyl amino group in **I** with tosyl hydrazine occurs and affords intermediate **II**. The internal nucleophilic addition of the nitrogen to the ketone carbonyl leads to the formation of pyrazoline intermediate **III** which can isomerize and for loss of water gives the product.

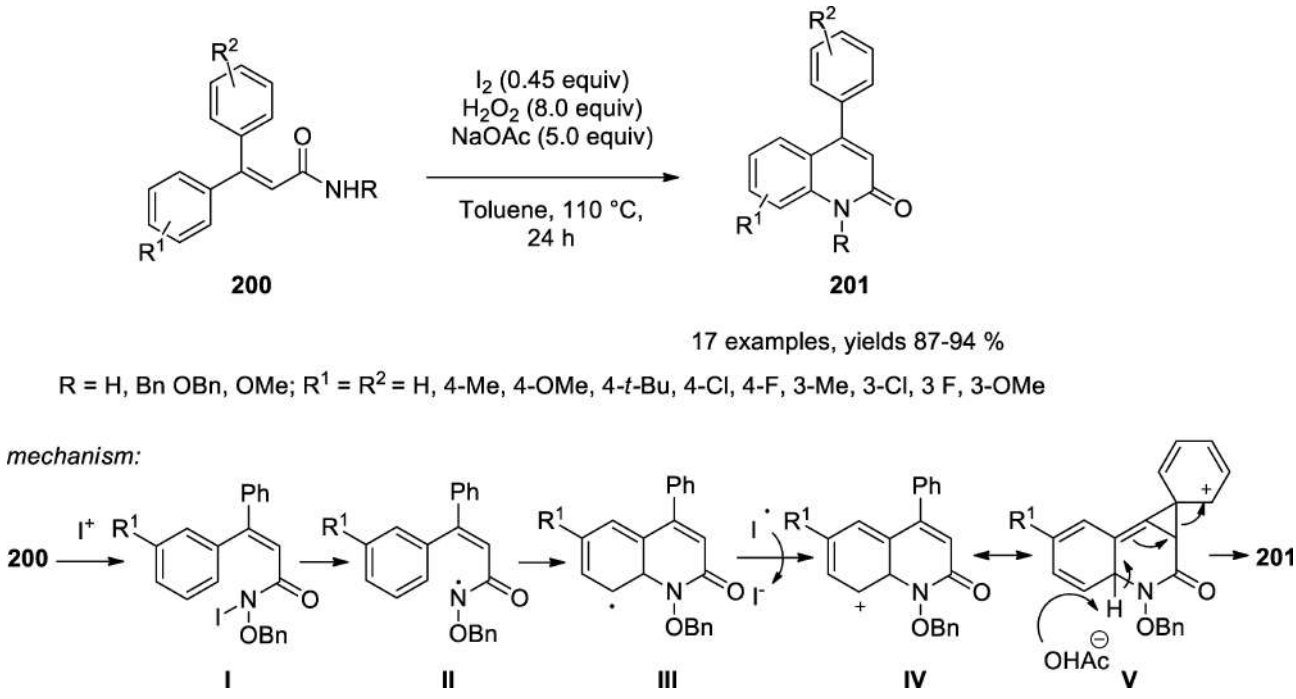
Iodine-catalysed reactions have been performed also for the cyclization and the O/S exchange of acrylamides **214** with tetramethylthiuram disulfide (TMTD) **215** in one step to achieve quinolino-2-thiones derivatives **216** (Scheme 53). Iodine proved to be indispensable for the outcome of the reaction, facilitating the conversion of TMTD to a reactive intermediate and the cyclization of acrylamides in *N*-heterocyclic skeletons. The metal-free reaction occurred just in one step and proved to be efficient with moderate to high yields (22 examples yield from 45% to 91% yields). A radicalic mechanism, in which radical **I** favors a 6-endo-trig attack that results in the formation of radical II is proposed to explain the outcome of reaction. This methodology allows to have an easy access to diversely substituted quinolino-2-thiones **216**, extremely important for their diverse bioactivity and that are usually synthesized only through several synthetic steps and with transitional metals catalysts.[91]

Iodine$^{I/III}$ catalysis has also recently emerged for the design of stereochemically defined bioisosteres and it was employed for the synthesis of isochromans fluorinated analogs **219** (Scheme 54). Iodine catalysis is performed with iodoresocinol-based catalyst **218**, Selectfluor® was selected as the oxidant and pyridine·HF complex as a nucleophilic fluoride source. This would generate the requisite ArIF2 species in situ. Thus, iodine catalysis allowed the alkene activation/fluorination sequence of 2-vinylbenzaldehydes **217** and triggered the cyclization after formation of a transient oxocarbenium ion **I**. So, novel fluoroisochromans **219** can be produced with high levels of stereoselectivity (up to > 95:5 dr and 94% ee) in a one-pot synthesis. The so obtained isochromans were further utilized for the synthesis of a fluorinated analog of the highly selective D_4 receptor antagonist Sonepiprazole.[92]

Finally, iodine catalysis has been used also for thiophene synthesis. Several substituted thiophenes **221**/**224** were obtained via metal-free dehydration and sulfur cyclization of alkynols **220**, **222** or **223** with elemental sulfur (S_8) in moderate to good yields (49 examples afforded from 60 to 90% yield), (Scheme 55). The hypothesized mechanism for the sulfur cyclization reaction begins with the initial activation of the hydroxyl group with HI produced from I_2

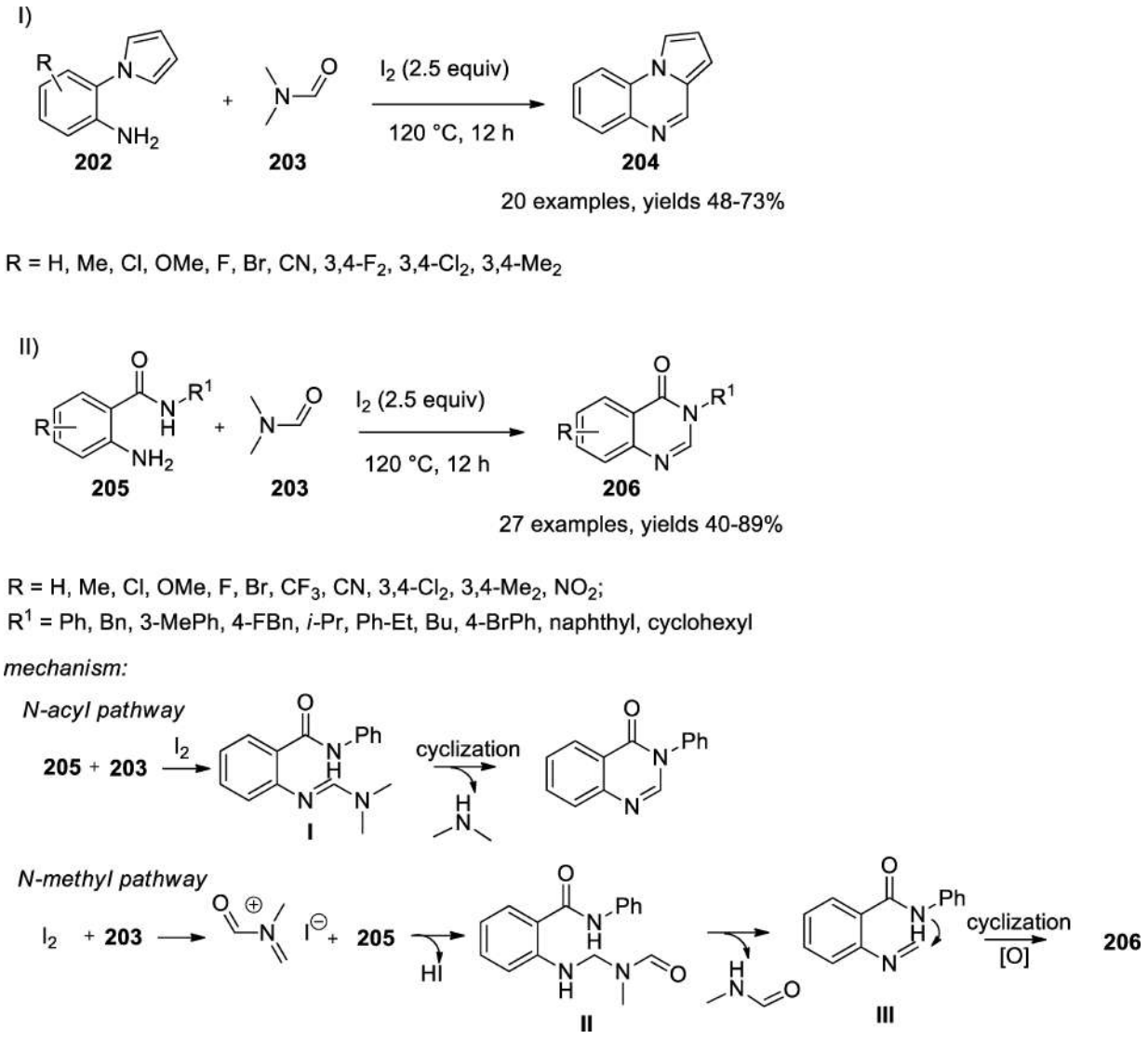


Scheme 48. Reaction scheme for the synthesis of pyrrolidine rings through amination reactions.[85]



Scheme 49. Scheme and mechanism of intramolecular C–H amidation of 3,3-diarylacryl amides.[86]

that give the propargyl carbocation intermediate **I**, which after dehydrogenation process leads to alkenyne intermediate II. Then, trisulfur radical anion ($S_3^{\bullet-}$) adds to the C–C triple bond of **II** to generate the alkenyl radical **III**, which



Scheme 50. Scheme and mechanism for the synthesis of pyrrolo[1,2-a]quinoxalines and quinazolin-4-ones.[87]

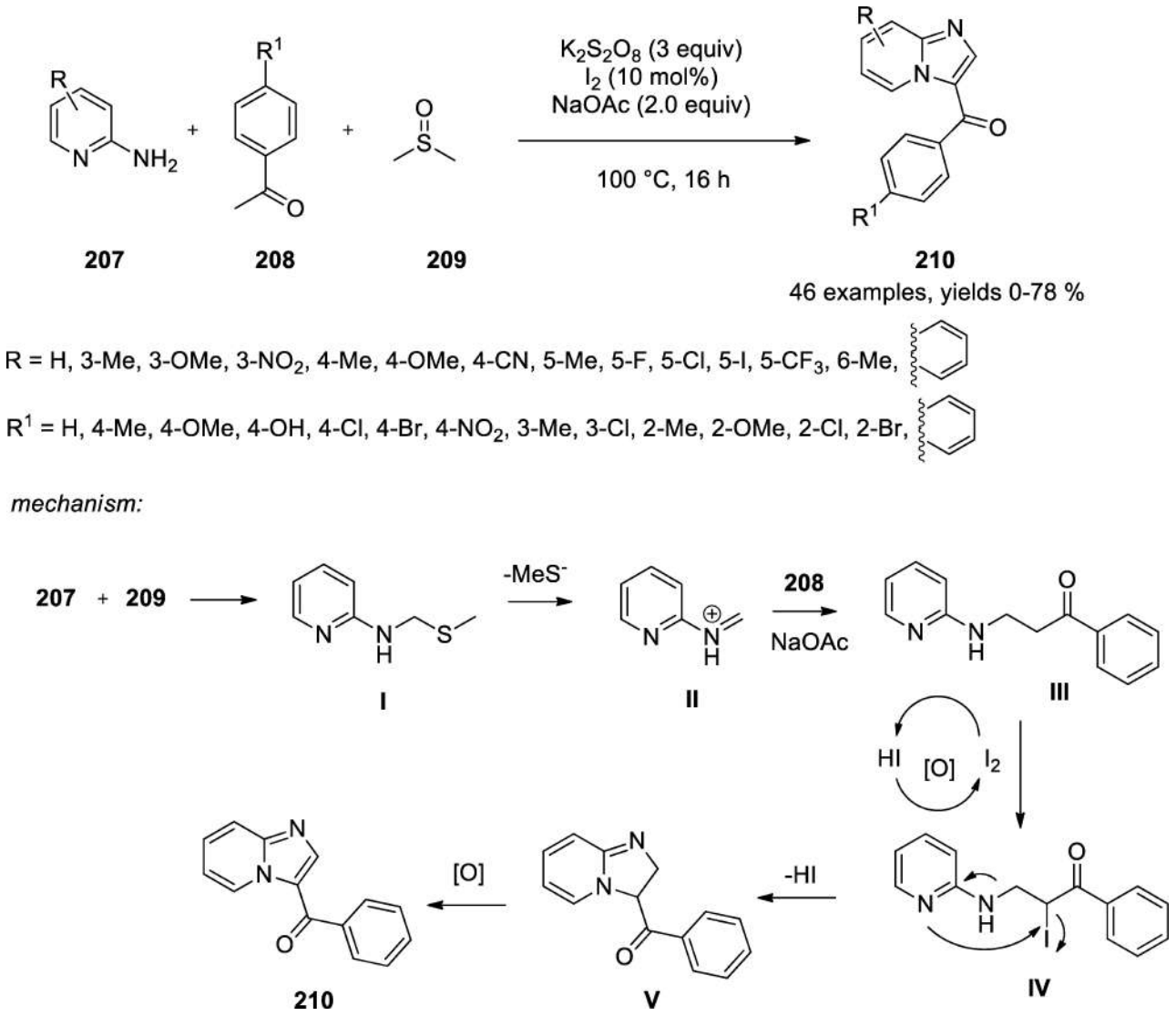
then undergoes intramolecular 1,3-hydrogen migration to obtain another intermediate that after intramolecular radical coupling gives the product and release $S_2^{\bullet-}$ species. This approach provides the base-free generation of a trisulfur radical anion and its addition to alkynes as an initiator, broadening the applications of this radical in the synthesis of sulfur-containing heterocycles.[93]

7. Innovative "green" synthesis

In the last years, in addition to the efficiency in terms of reaction yield and purity of the product, a particular attention to the global environmental impact of the reactions has been devoted and a list of green chemistry principles has been drawn up.

Considering that most heterocycle synthesis requires heavy metal catalysts or toxic solvents, some alternative synthetic strategies have been proposed. Among them the use of ionic liquids as solvents or catalysts is one of the most followed approaches. Ionic liquids (ILs) are organic salts presenting melting temperature below 100 °C, negligible vapour pressure and flammability.[94] The combination of several cations and anions awards also high tunability to ILs. These features allow a comprehensive use of this class of compounds in several synthetic processes.[95]

For example, imidazolium ILs with basic anions, such as acetate, have been reported as efficient reaction media for the synthesis of some oxazolidinones **228** (Scheme 56).[96] IL together with $AgNO_3$ is the catalytic system for the synthesis of the selected heterocycles, the reaction proceeded through the atom-economical three component reactions of 2-aminoethanols **225**, CO_2 and propargyl alcohols **227**. The best reaction conditions have been tested and a different catalytic ability has been observed in dependence of IL cation and anion, with the most basic IL anion favoring the



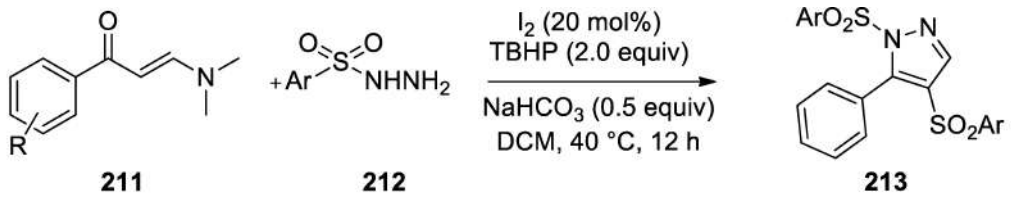
Scheme 51. Scheme and mechanism of a three-component amination reaction for the synthesis of 3-aroylimidazo[1,2-a]-*N*-heterocycles.[89]

outcome of the reaction. The substrate scope revealed yields of heterocycle > 90% in 10 out of 11 examples. Mechanistic insights revealed the active role in catalysis of IL, as the imidazolium cation was the source for the production of two active adducts of *N*-heterocyclic carbene with CO_2 and Ag, respectively formed in the two steps of the reaction (Scheme 56). Indeed, three component reactions of propargyl alcohols, CO_2, and 2-aminoethanols are cascade reactions, proceeding firstly with the cyclization between CO_2 and propargyl alcohols and subsequently the carbonate intermediate reacts with 2-aminoethanols to give the final oxazolidinones and hydroxyl ketones through the nucleophilic ring opening reaction. It has been proven that the higher catalytic efficiency of the Ag/IL system is due to the formation of adduct 2, more active than free Ag^+.

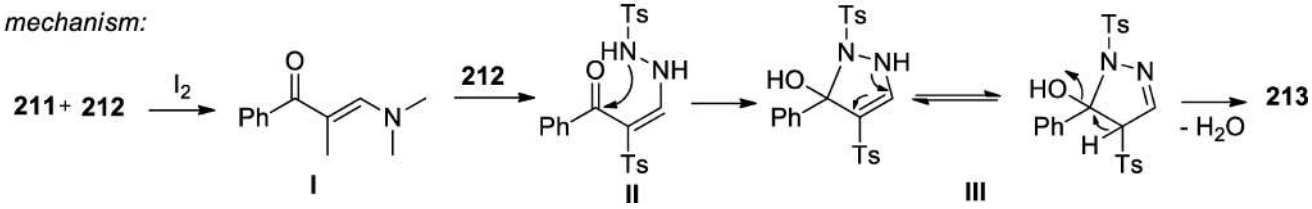
A great efficiency of the catalytic system with a low loading of metal catalyst has been reported. In addition, the catalytic system can be recycled up to five cycles without any relevant loss in efficiency. Green metric parameters evaluated the overall impact of the reaction as greener and more sustainable than the one of other Ag-catalyzed systems.

Mechanistic insights revealed the active role in catalysis of IL, as the imidazolium cation was the source for the production of two active adducts of *N*-heterocyclic carbene with CO_2 and Ag, respectively formed in the two steps of the reaction (Scheme 56).

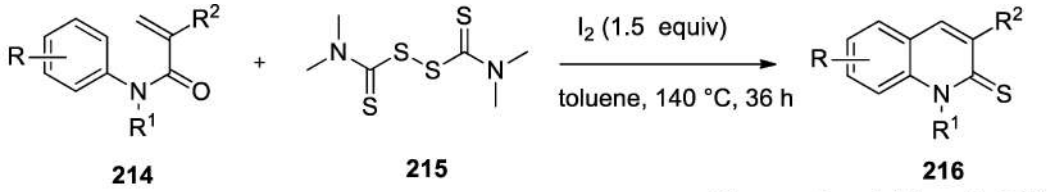
A dicationic piperidinium IL **233** owning the double function of solvent and catalyst was applied for another one-pot three component reaction leading to the formation of some triazolo-pyrimidine **234** under mild conditions (Scheme 57).[97] The desired products were afforded in 73–94% isolated yield within 120–150 min. Nature of substituents strongly influenced yields as electron-withdrawing groups gave a higher yield within shorter reaction times than electron-donating substituents in the same positions.



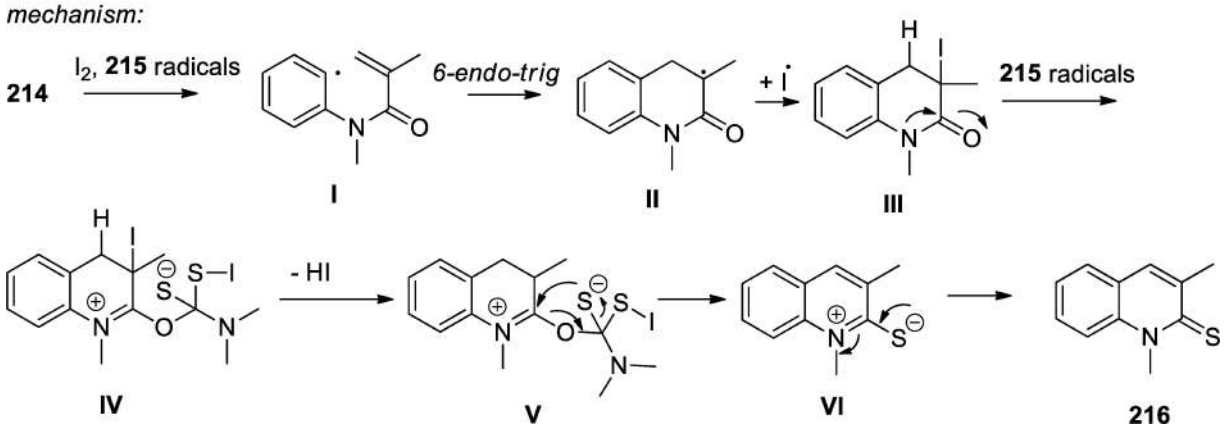
R = H, 4-Me, 4-Cl, 4-OMe, 4-F, 4-Br, 4-NMe_2, 2-Me, 3-Me, 3-Cl, 3-NO_2, 3,4-Cl_2, 3,4-OMe_2,
Ar = Ts, Ph, 4-MeOPh, 4-FPh, 4-ClPh, 4-BrPh, 2-ClPh, 3,5-Cl_2Ph.



Scheme 52. Scheme and mechanism for the synthesis of pyrazole via the tandem C(sp^2)–H sulfonylation and the pyrazole annulation under metal-free conditions.[90]



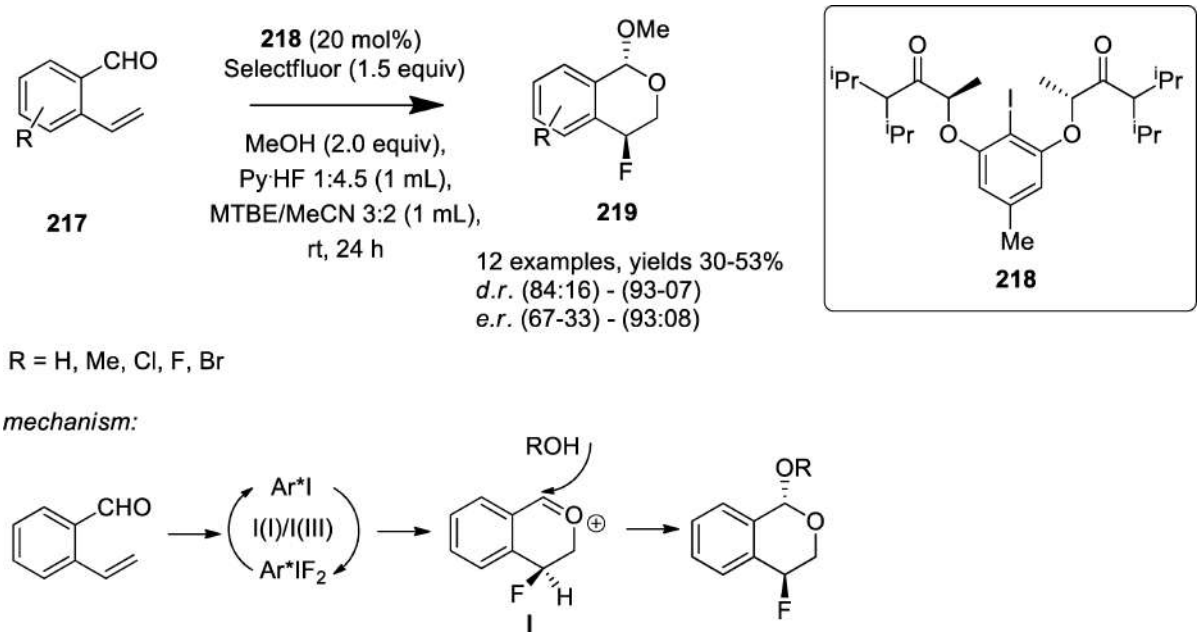
R = H, 4-Me, 4-Et, 4-*i*-Pr, 4-*t*-Bu, 4-F, 4-Cl, 4-Br, 4-CN, 4-OMe, 4-OEt, 3-Cl, 3-Br, 3-CF_3, 3-Ph, 3-COPh, 2-Me, 2-F, 2-Br;
R^1 = Me, Ph; R^2 = Me, Ph



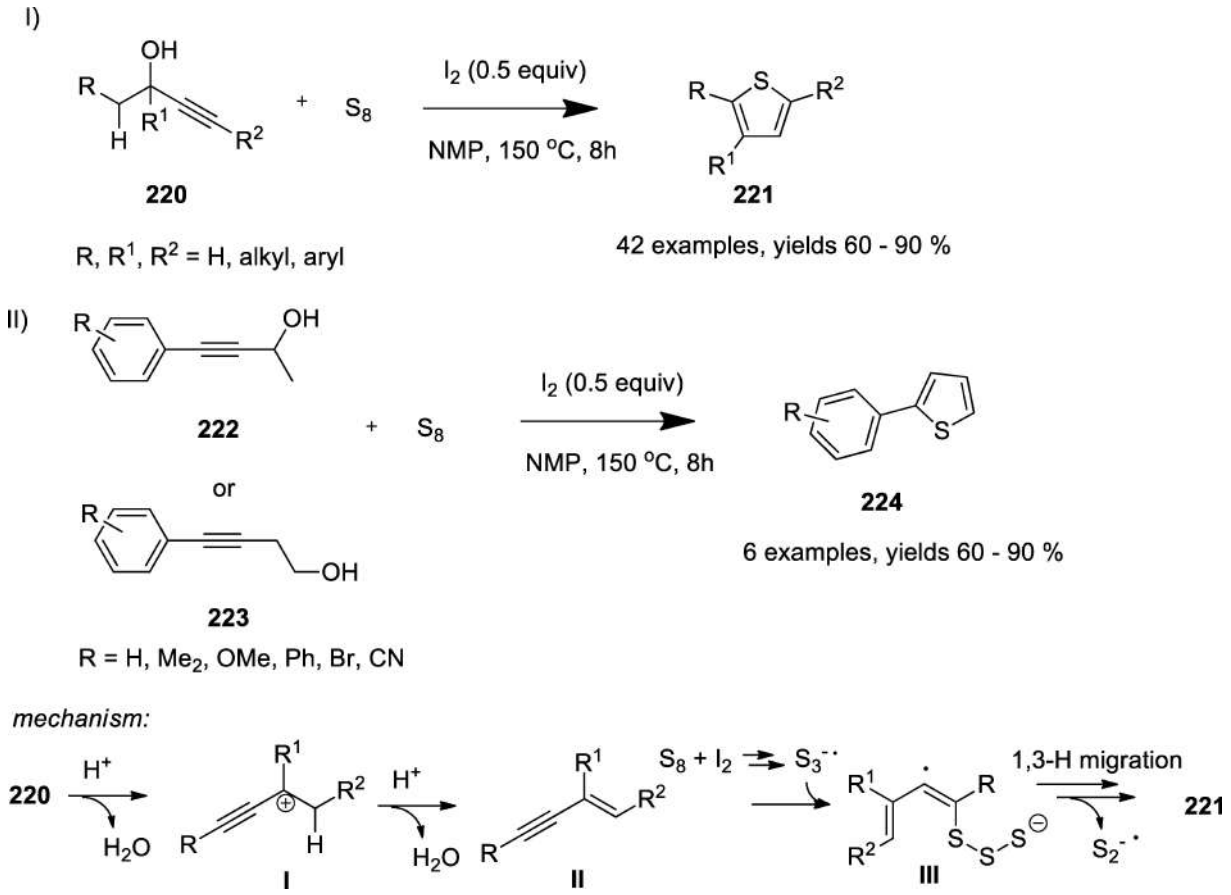
Scheme 53. Scheme and mechanism for the cyclization and the O/S exchange of acrylamides with tetramethylthiuram disulfide.[91]

The substituents at the para-position of the aromatic aldehydes gave higher yields than the same substituents at the meta- or ortho-positions. The IL was retrieved and reused several times without reducing its catalytic efficiency. In the proposed mechanism, the IL catalyzes the reaction activating aldehyde **231** and ethylcyanoacetate **232** through hydrogen bond formation. In addition it can also promote the dehydration step (Scheme 57).

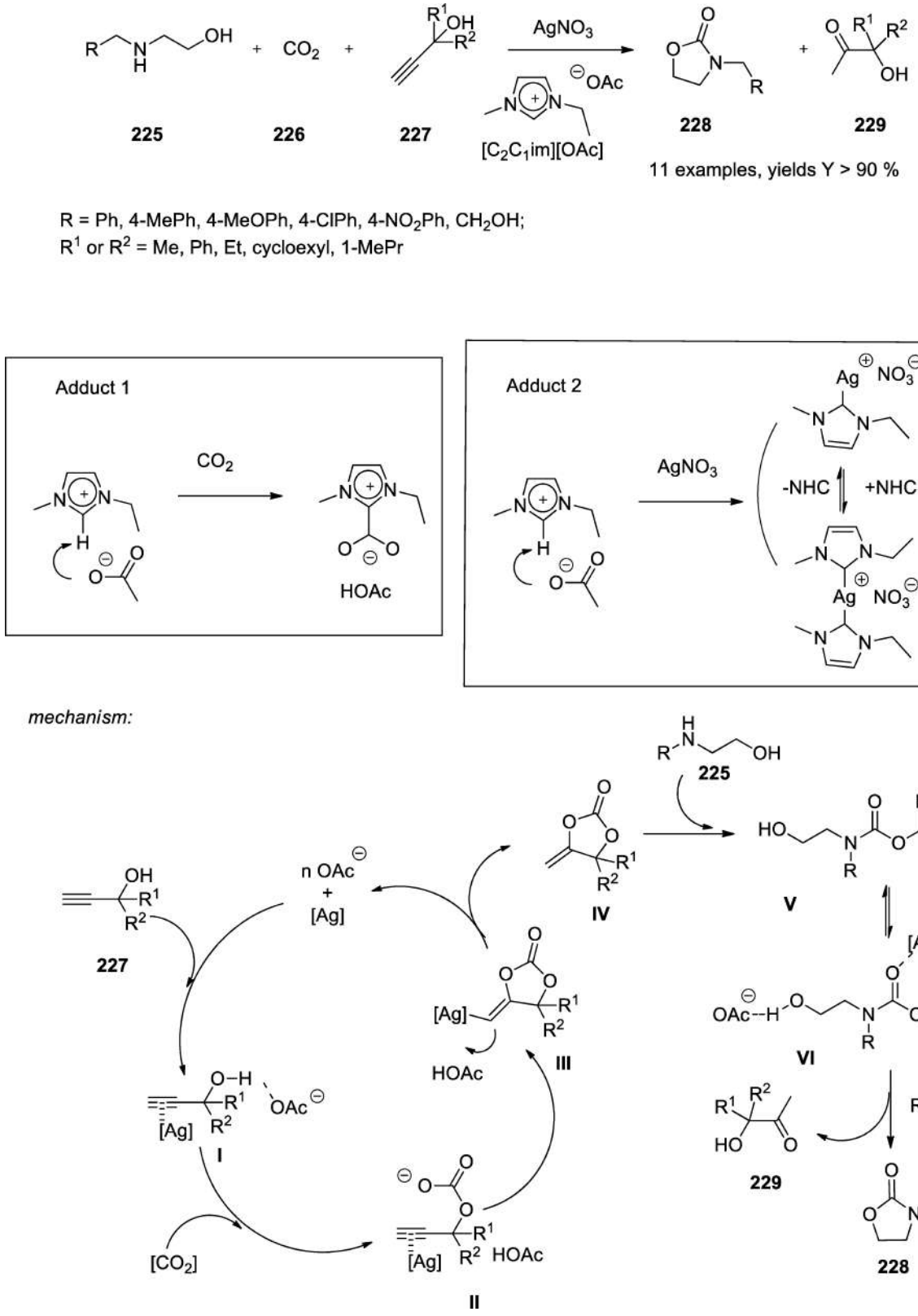
On the other hand, acidic piridinium molten salts **238** were used as catalysts for the synthesis of six membered O-



Scheme 54. Scheme and mechanism for the synthesis of isochromans fluorinated analogs.[92]



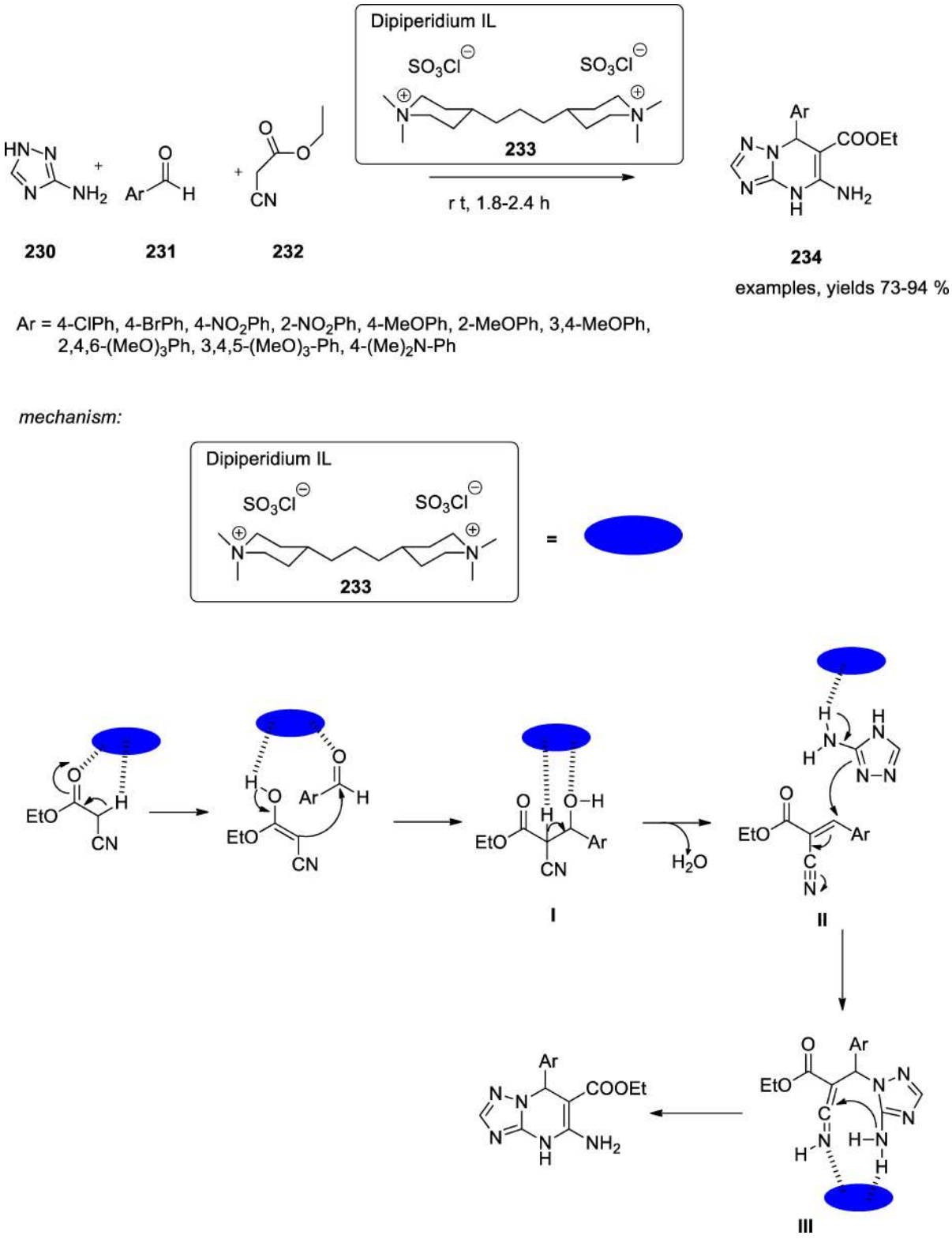
Scheme 55. Scheme and mechanism for thiophenes synthesis obtained via metal-free dehydration and sulfur cyclization of alkynols.[93]



Scheme 56. Scheme and mechanism for the synthesis of some oxazolidinones in ILs.[96]

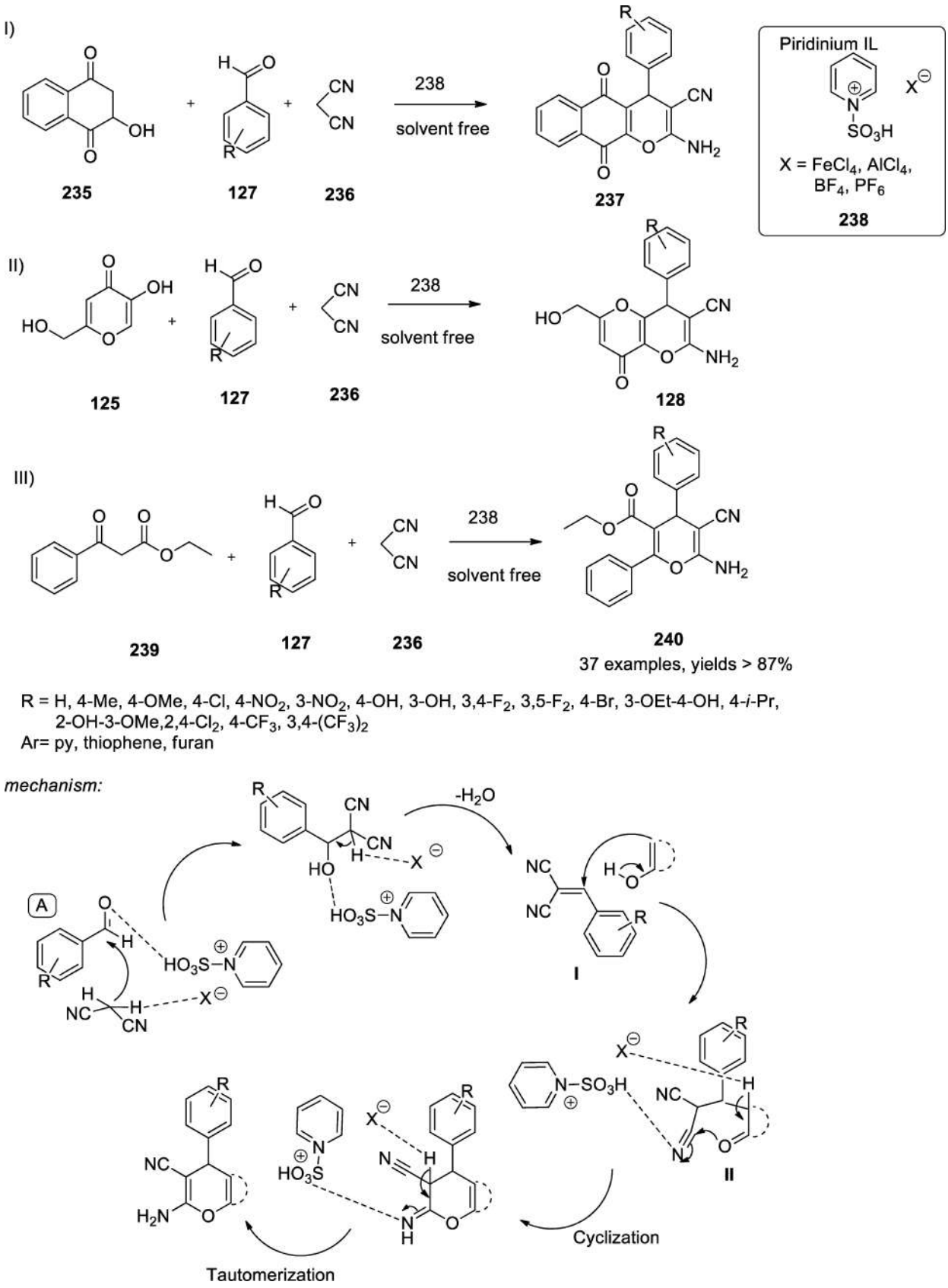
heterocyclic compounds such as 2-amino-4*H*-chromene **237**, 2-amino-4,8-dihydropyrano **128** and 2-amino-4H-pyrans **240** under solvent free conditions (Scheme 58).[98]

According to the proposed mechanism, the acidic site of the catalyst initially activated aldehyde, that subsequently reacted with malonitrile to afford the first intermediate **I**. **I**

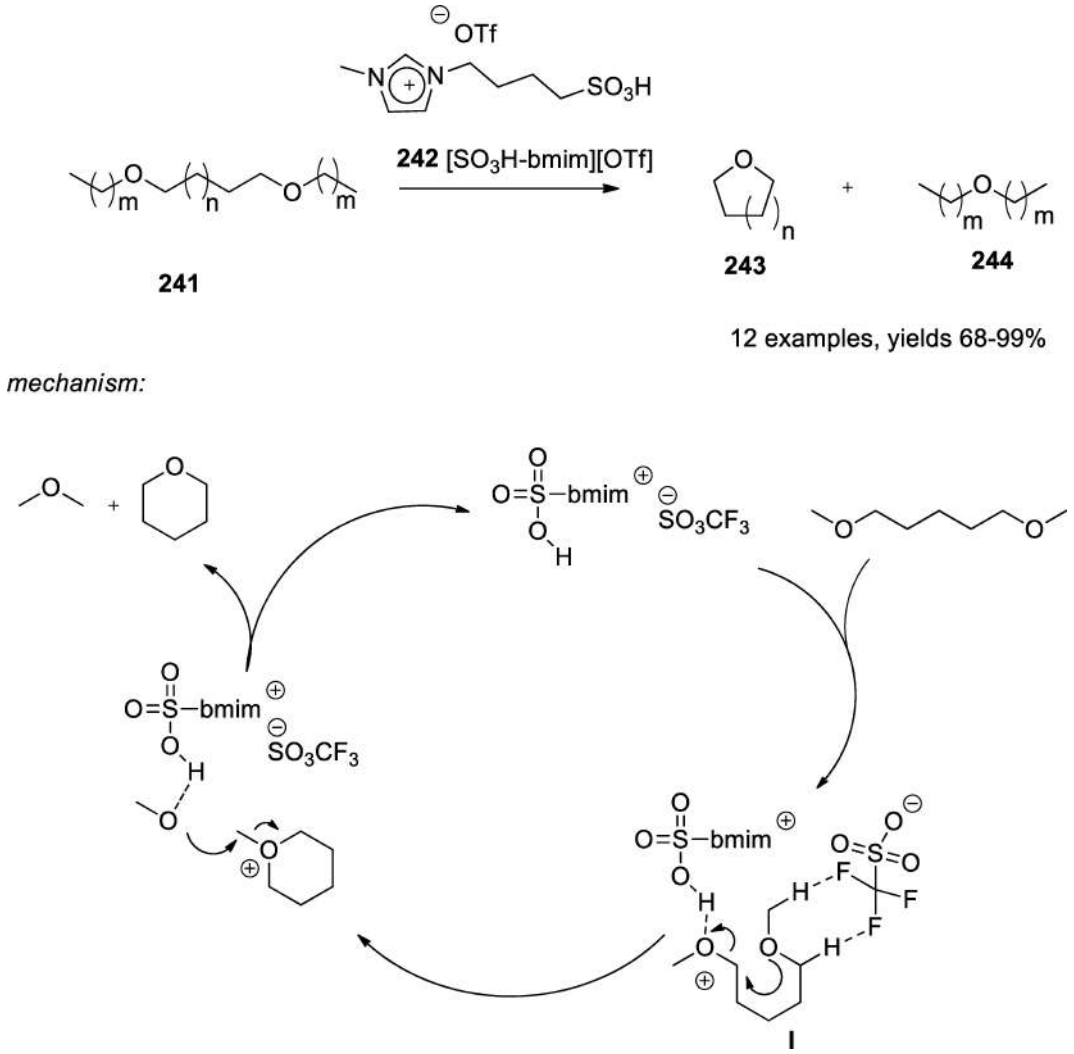


Scheme 57. Scheme and mechanism for the one-pot three component reaction leading to the formation of some triazolo-pyrimidine under mild conditions.[97]

reacted as Michael acceptor with nucleophilic substrate to give intermediate **II**, which afforded the desired product after cyclization and tautomerization (Scheme 58). Once again IL can be reused several times without any loss in efficiency, mild reaction conditions and higher efficiency, aldehydes with electron withdrawing groups afforded the desired products with high yields and low reaction times in compared to the electron releasing ones (37 examples with



Scheme 58. Scheme and mechanism for the synthesis of six membered O-heterocyclic compounds under solvent free conditions.[98]

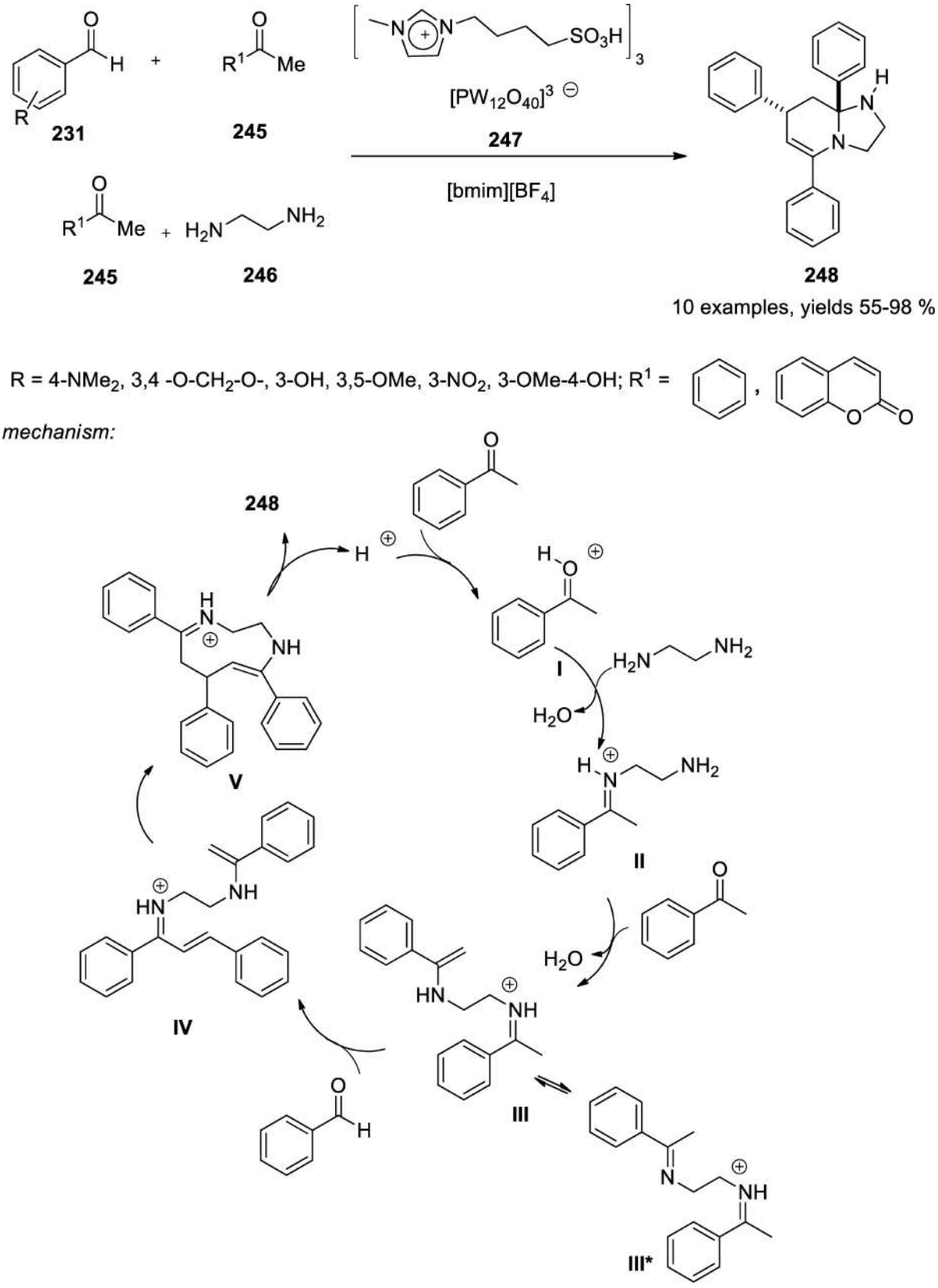


Scheme 59. Scheme and mechanism for the synthesis of a series of tetrahydrofurans and tetrahydropyrans using IL-based biphasic system.[99]

yields > 87 %). Good results were reached using IL as catalyst in comparison with literature reports about the same reaction (see Scheme 29 for comparison).

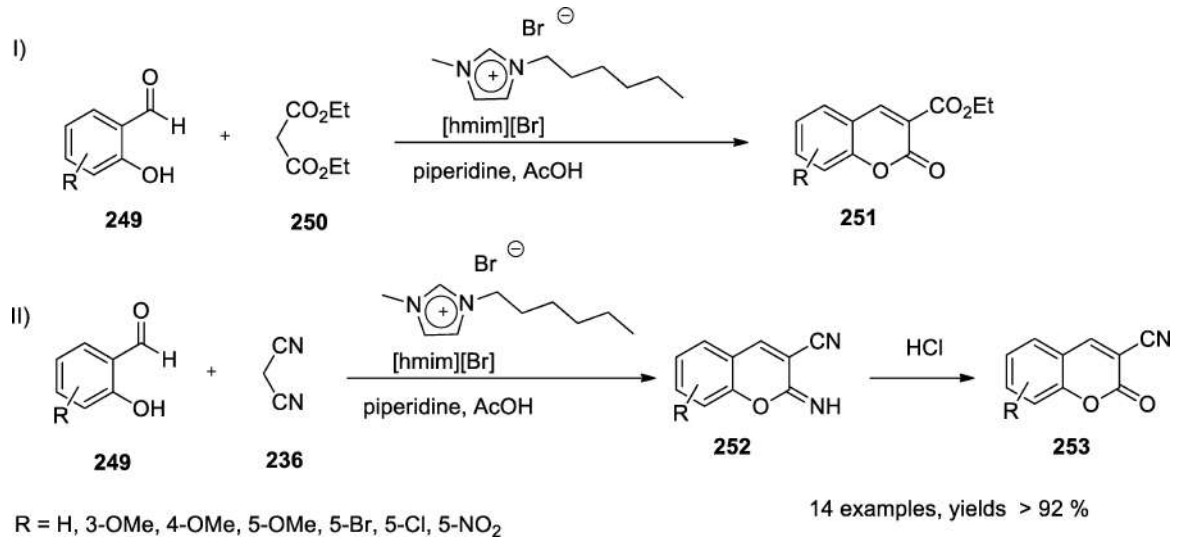
Instead, an IL-based biphasic system allows the obtainment of a series of tetrahydrofurans and tetrahydropyrans **243** in excellent yields and in large scale using a metal-free protocol (Scheme 59).[99] In particular, acid imidazolium IL **242**, [SO_3H-bmim][OTf], proved to be the best IL in catalyzing the ring closing reaction avoiding the use of Lewis acids usually involved in this metathesis reaction. An interface effect played an important role in mediating the reaction rate due to the immiscibility between the products and the IL catalyst, thus the products can be spontaneously separated. The combination of DFT calculation and experimental analysis, once again proved the importance of hydrogen bond formation between IL and reactants. The combination of DFT calculation and experimental analysis, once again proved the importance of hydrogen bond formation between IL and reactants. Scheme 59 shows the proposed reaction mechanism in which the ether is activated from IL through H-bonds formation. Then, the C atom attached to the activated O atom is attacked by the other O atom, providing the cyclic oxonium intermediate and [SO_3H-bmim]-OMe complex. Finally, the oxonium intermediate is demethylated by [SO_3H-bmim]-OMe, generating O-heterocycles and dimethylether. At the end of the cycle IL is completely regenerated for new catalytic tests.

Acidic imidazolium task-specific IL **247** has been applied also as catalysts for the synthesis of 10 new hexahydroimidazo[1,2-a] pyridine derivatives **248** exclusively in the trans configuration and in a short reaction times (Scheme 60). A greener efficient multicomponent methodology was developed to have a rapid access to new heterocyclic derivatives. 1-butyl-3-methylimidazolium tetrafluoroborate IL [bmim][BF_4] was proved as the best reaction medium and 5 mol% acidic catalyst at 70 °C allowed to obtain products in only 60 min. In addition, two concurrent possible mechanisms of reaction were proposed thanks to the use of a charge tag strategy in combination with ESI(+)-MS/MS investigations. One of them involves the acetophe-



Scheme 60. Scheme and mechanism for the synthesis of hexahydroimidazo[1,2-a]pyridine derivatives using acidic imidazolium task-specific IL.[100]

none protonation giving intermediate **I** which reacts with ethylenediamine to form **II**. Another acetophenone molecule is then condensed affording **III**. The aldehyde is next incorporated to give intermediate **IV** which through an



Scheme 61. Scheme of reaction for the synthesis of a series of coumarin derivatives in IL.[101]

intramolecular enamine reaction is converted into the final adduct (Scheme 60). The incorporation of coumarin scaffolds in the structure of one of the heterocyclic compounds allowed its use as bioimaging agent, revealing an incorporation preference in mitochondria.[100]

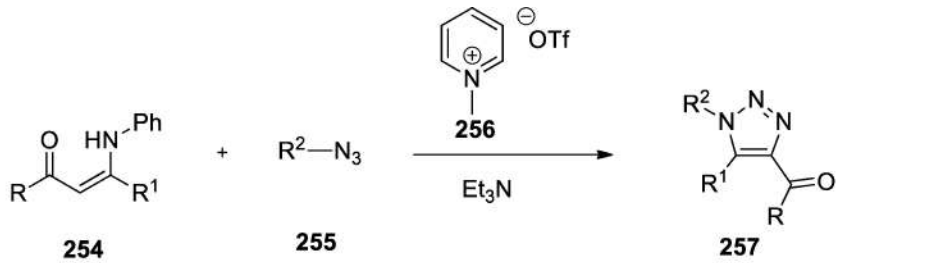
One of the most common and used IL namely 1-hexyl-3-methyl imidazolium bromide [hmim][Br] has been applied for the synthesis of a series of coumarin derivatives **251**/**253** (Scheme 61). The IL allowed to reach excellent yields using mild reaction conditions in a one-pot procedure, in addition the easy work-up and purification process were some of the advantages of this method. The reactions proceed very fast in the presence of ionic liquid at room temperature while in conventional solvents higher temperature was required to reach the same results and formation of by-products was observed as well.[101]

It has been proved that the presence of IL such as 1-methyl pyridinium trifluoromethanesulfonate **256** is needed to allow the outcome of the reaction for the synthesis of 1,4,5-trisubstituted-1,2,3-triazoles **257** with complete regioselectivity starting from aryl azides **255** and enaminones **254** (Scheme 62). The combination of DFT calculation and experimental data revealed that is a cascade reaction in which Huisgen's concerted asynchronous 1,3-dipolar cycloaddition is followed by elimination of aniline through a favored retro-aza-Michael reaction. Two transition states can be formed corresponding to the two possible isomers that can be obtained before product formation. In addition, it seems that the activation by water of the cycloaddition and the cascade process are pushed on by the base-promoted elimination.

The formation of triazoles using the same experimental condition is not observed in conventional organic solvents, *i.e.* dioxane or toluene, and in absence of triethylamine as base catalyst. The proposed methodology allows to reach the final heterocycles using an easy procedure, low reaction times, complete regioselectivity with no formation of by-products.[102]

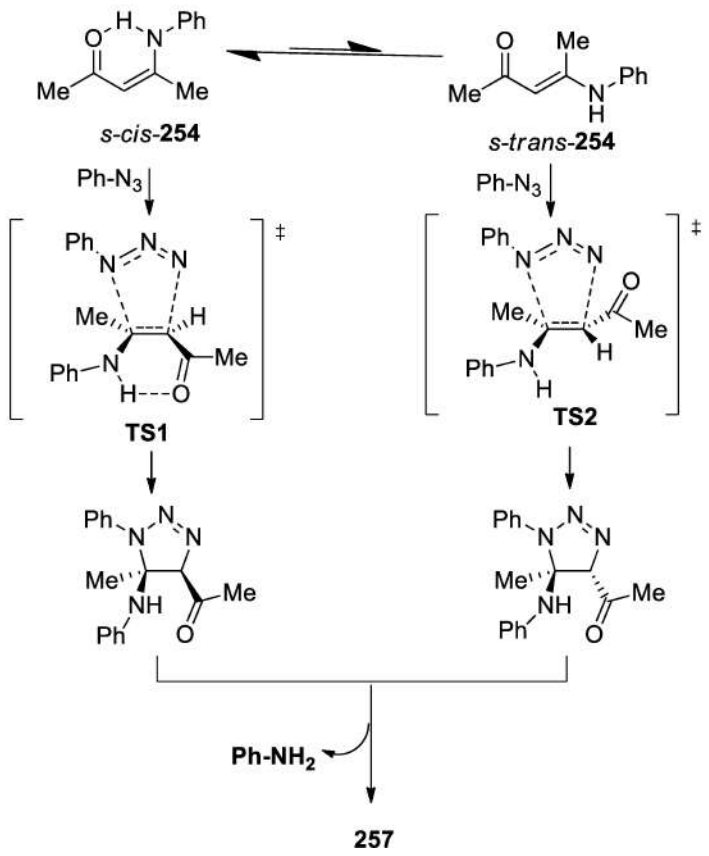
The oxidative cyclocondensation towards 2,3-disubstituted quinazolinones **260** occurs as well only using ILs as reaction media, while just traces or low yields of the products are obtained in conventional solvents (Scheme 63).[103] In particular, 1-butyl-3-methylimidazolium ILs were used, and the role of IL anion has been also investigated revealing the best performance for tetrafluoroborate. After reaching quinazolinones **260**, ILs can be recycled. Mechanistic studies shed lights on hydrogen bond interactions between IL cation and substrate. The reaction presumably proceeds through the formation of the *N*-benzyl-o-aminobenzamide **I**, that reacts with **III**, generated in situ due to the auto-oxidation of **259**, affording intermediate **IV**. Intramolecular tandem cyclocondensation-oxidation via **V** produces the final product.

Deep eutectic salts (DESs) have recently conquered, in addition to ILs, the definition of "green solvents" thanks to their properties such as the low volatility and no flammability, as well as they can be obtained simply mixing a hydrogen bond donor and one acceptor molecules.[104] In this context, some benzoxazole-pyrrolidinone heterocyclic compounds **265** were synthesized using substituted benzylamines **263** and 2-aminophenol **264** under ultrasonic irradiation in the presence of DES (Scheme 64). The most efficient DES was prepared by using an eutectic mixture of urea and a synthesized glycine-derived ionic liquid (carboxymethanamonium chloride).[105] The synthesis of the heterocyclic compounds required two synthetic steps: the first one performed in water with the aid of microwave irradiation (MW) and second one in DES with sonication. The developed method showed great advantages in terms of high productivity, short reaction time, and simple processing. Moreover, DES was easily separated from reaction mixtures and was recycled for multiple reactions. As well as in the case of



R and R^1 = Me, Et, Ph; R^2 = Ph, Bn, 3-FPh, 4-NO_2Ph, 4-ClPh, 4-MePh, 4-OMePh

mechanism:



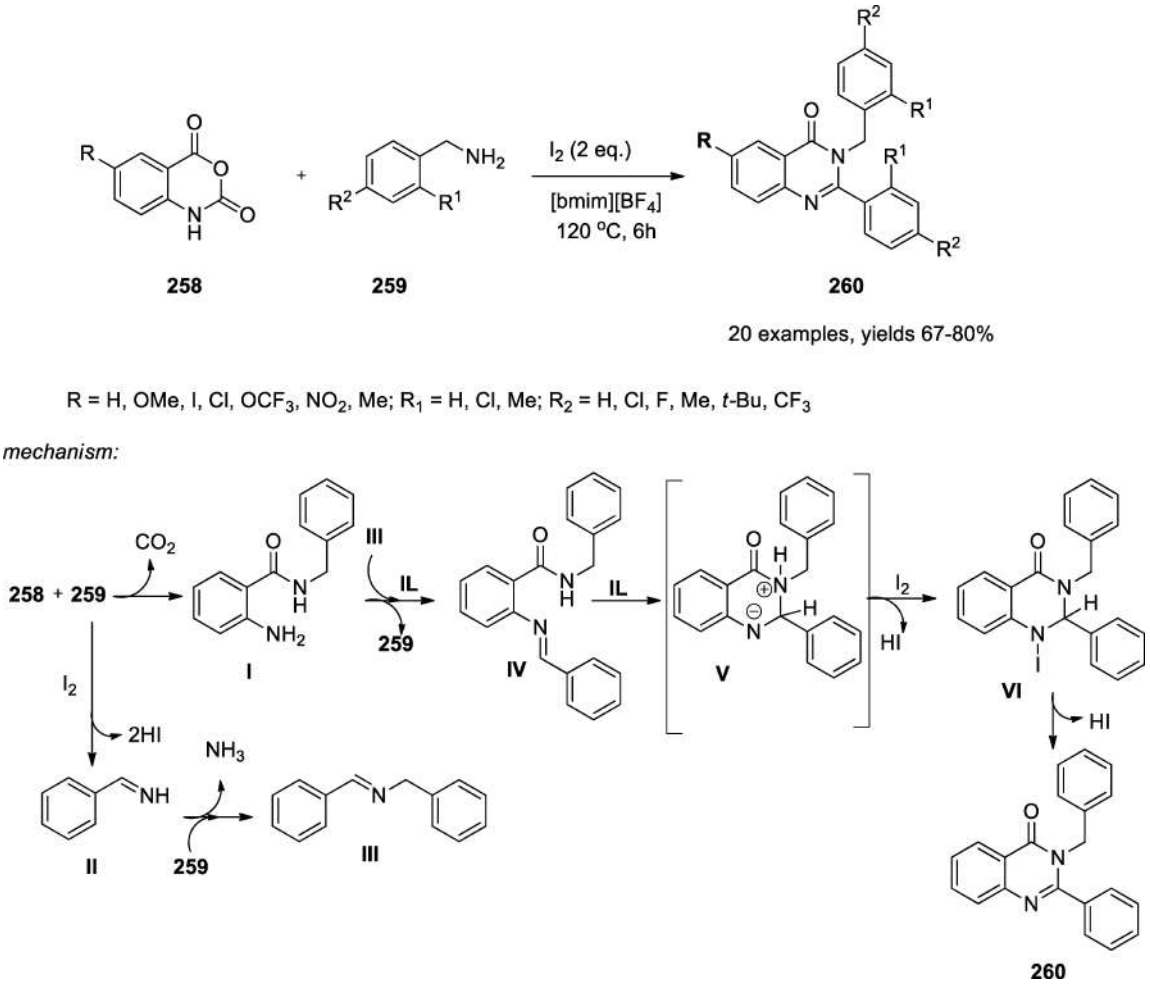
Scheme 62. Scheme and mechanism for the synthesis of 1,4,5-trisubstituted-1,2,3-triazoles.[102]

some ILs, DES own the double function of solvent and catalyst.

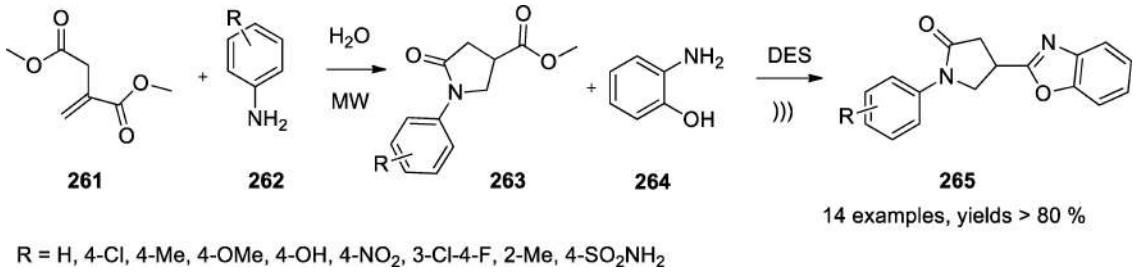
Another synthetical and environmentally friendly approach is the mechanochemical one, used for the van Leusen pyrrole synthesis with base catalysts. The process leads to 3,4-disubstitued pyrroles **268** in moderate to excellent yields (Scheme 65)[106] The developed protocol established the reaction between toluenesulfonylmethyl isocyanide **266** and chalcone **267** in the presence of a base. The reactants were milled in the presence of three balls (7 mm in ø) for 90 min at 30 Hz. The procedure allows to obtain good yields and is compatible with a range of electron-withdrawing groups and can also be applied to the synthesis of oxazoles. However, the attempt to extend the protocol to porphyrin synthesis was not successful.

8. Summary and Outlook

Heterocyclic chemistry is a fundamental topic in organic chemistry and in all related research areas spanning from medicinal chemistry to material science. In order to facilitate the expansion of this research field, it is extremely important that efficient synthetic methods are continuously developed. In this context, the catalytic synthesis has advanced the field of



Scheme 63. Scheme and mechanism for the oxidative cyclocondensation towards 2,3-disubstituted quinazolinones.[103]



Scheme 64. Reaction scheme for the synthesis of benzoxazole-pyrrolidinone heterocyclic compounds under ultrasonic irradiation and in DES.[105]

heterocyclic chemistry by pushing the boundaries of efficiency and complexity, leading to the successful production of new drugs and complex natural products in recent years, paying attention also to the sustainability of the entire synthetic process. Here we showed some selected examples of all the main studied catalytic systems, highlighting some recent results that could move further the field and open the way to new chemical spaces for many different applications.

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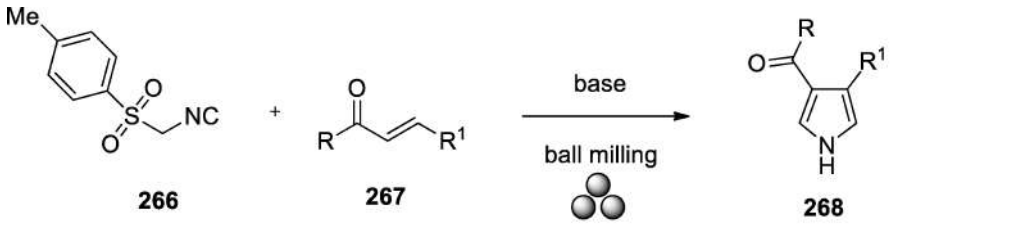

Scheme 65. Reaction scheme for the van Leusen pyrrole synthesis in mechanochemical conditions.[106]

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: catalysis · green synthesis · heterocycles · organocatalysis · synthesis · transition metals · photocatalysis

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