Review

Synthesis of Nitrogen Containing Heterocyclic Scaffolds through Sequential Reactions of Aminoalkynes with Carbonyls

Antonio Arcadi [1,*], Valerio Morlacci [1], and Laura Palombi [1]

[1] Dipartimento di Scienze Fisiche e Chimiche, Università degli Studi dell'Aquila, Via Vetoio, 67100 Coppito (L'Aquila), Italia.
E-mail: antonio.arcadi@univaq.it. E-mail: valerio.morlacci@graduate.univaq.it; E-mail: laura.palombi@univaq.it.
* Correspondence: Author to whom correspondence should be addressed.

Abstract: Sequential reactions of aminoalkynes represent a powerful tool to easily assembly biologically important polyfunctionalized nitrogen heterocyclic scaffolds. Metal catalysis often plays a key role in terms of selectivity, efficiency, atom economy and green chemistry of these sequential approaches. This review examines the existing literature on the applications of reactions of aminoalkynes with carbonyls which are emerging for their synthetic potential. Aspect concerning the features of the starting reagents, the catalytic systems, alternative reaction conditions and the pathways as well as the possible intermediates are provided.

Keywords: Sequential Reactions; Aminolkynes; Heterocycles; Metal catalysis

1. Introduction

Aminoalkynes are bifunctional derivatives which can undergo a diverse array of transformations. They offer sequential reactions with an electrophile and a nucleophile and are ideal for cascade reactions. Sequential reactions represent a powerful tool to build up simple or more complex polyfunctionalized organic scaffolds from readily available reagents with high efficiency, selectivity, and atom economy [1-3]. Recently, applications of sequential reactions of aminoalkynes represent a very active research field in organic synthesis and medicinal chemistry. In particular, sequential reactions of β-, γ-, and δ-aminoalkynes to afford a variety heterocyclic scaffolds were explored. Inactivated alkynes moieties are not very reactive toward nucleophiles. Their behaviour changes by activation of the C-C triple bond by a metal catalyst. Various biologically important nitrogen heterocycles were directly synthesized in an easy way by means of intramolecular hydroamination of aminoalkynes in the presence several transition metal as well as lanthanide catalysts. [4-5] The aptitude to form π- and σ-complexes can help for the choice of catalysts for the desired transformations when bi- or polyfunctional substrates are involved [6]. The reaction of γ- and δ-aminoalkynes with sulfonyl azides in the presence of $Ru_3(CO)_{12}$ catalyst efficiently afforded led cyclic amidines of relevance in medicinal and coordination chemistry as well as materials science. [7] The gold(I)-catalyzed tandem cyclization of γ-aminoalkynes with alkynes in water afforded diversely substituted pyrrolo[1,2-a]quinolines. [8] Zhou *et al*. extended this reaction using less active terminal amidoalkynes in similar conditions. [9] The CuCl-catalyzed cascade transformation of internal β-aminoalkynes with alkynes under microwave irradiation gave diversely substituted tetrahydropyrrolo[1,2-*a*]quinolines. [10] An intramolecular gold-catalyzed hydroamination/aza-Diels-Alder tandem process of β-/γ-aminoalkynes with high regio and diastereoselectivity and up to almost complete chemoselectivity showed great efficiency in a one-pot approach to the complex nitrogen heterocyclic derivatives of medicinal importance such as the one-step synthesis of incargranine B aglycone and (±)-seneciobipyrrolidine (I). [11] Fañanás, Rodríguez, and co-workers described

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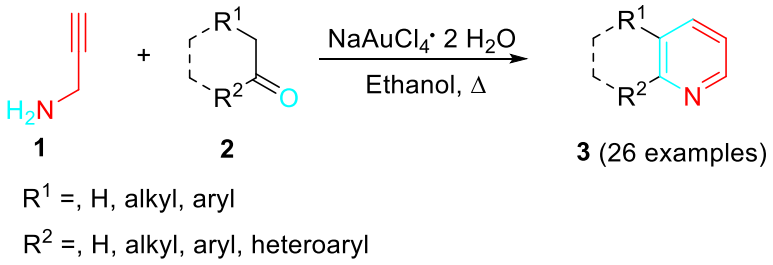
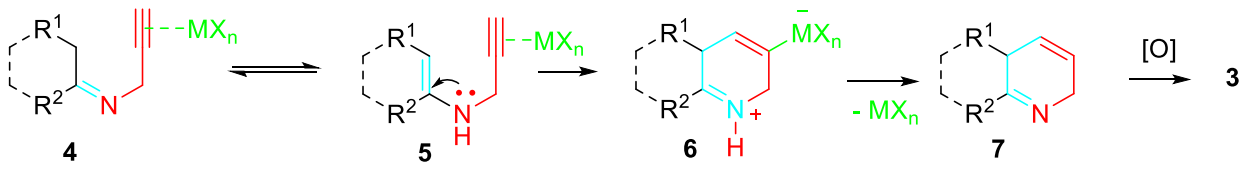
the preparation of complex pyrrolidines from readily available *N*-Boc-derived β-aminoalkynes and alkenes or alkynes through relay actions of Pt^{II} or Brønsted acids. [12-13] The reaction of α-aminoalkynes with carbon monoxide and selenium yielded 5-alkylideneselenazolin-2-ones stereoselectively via cycloaddition of *in situ* generated carbamoselenoates to the carbon-carbon triple bond. β-Aminoalkyne also afforded the corresponding six-membered selenium-containing heterocycle with the aid of CuI. [14] An operationally simple palladium-catalyzed intramolecular hydroaminocarbonylation of a variety of aminoalkynes directly provided a viable approach to a variety of valuable seven- and eight-membered lactams with high chemoselectivity and regioselectivity. [15] A sequential heterogeneous PtI_2-catalyzed hydration of δ-aminoalkynes followed by intramolecular cyclization and intermolecular addition as well as ring-expansion cascade reaction with another electron-deficient alkynes was developed for the synthesis of various eight-membered nitrogen heterocycles in excellent yields under mild reaction conditions. The simple PtI_2 could be easily recycled. [16] Moreover, a PtI_2-catalyzed formal three-component cascade cycloaddition reactions between γ-aminoalkynes and electron-deficient alkynes gave highly functionalized cyclohexadiene-*b*-pyrrolidines in good yields.[17] Finally, among the domino and multicomponent processes that involve aminoalkynes, their cascade reactions with carbonyl derivatives stand out as a highly versatile tool to build up libraries of nitrogen-containing heterocyclic scaffolds with diversity and molecular complexity. This review will examine the literature on this last topic and is organized according to the structure of the aminoalkyne substrate. Aspects concerning the features of the catalytic systems, the substrate scope, insight into the reactions pathways, possible intermediates as well as alternative conditions are discussed.

2. Sequential Reactions of α-Aminoalkynes (Propargylamines) with Carbonyls

Propargylic amine derivatives represent useful α-aminoalkynes building blocks for the construction of nitrogen containing heterocyclic scaffolds through their sequential reactions with carbonyls. The gold-catalyzed reaction of propargylamine **1** with dialkyl acyclic/cyclic ketones, methyl, aryl/heteroaryl ketones and aldehydes bearing α-hydrogens **2** allowed a simple approach to pyridines **3** through a sequential amination / cyclization / aromatization cascade (Scheme 1). [18]



Scheme 1. The catalyst was envisaged to promote both the amination of carbonyl compounds **2** and the regioselective *6-endo-dig* cyclization of the *N*-propargylenamine (*N*-propargyldienamine) intermediate **5**. (Scheme 2).



Scheme 2. Transition metal-catalyzed sequential amination/cyclization/aromatization reaction.

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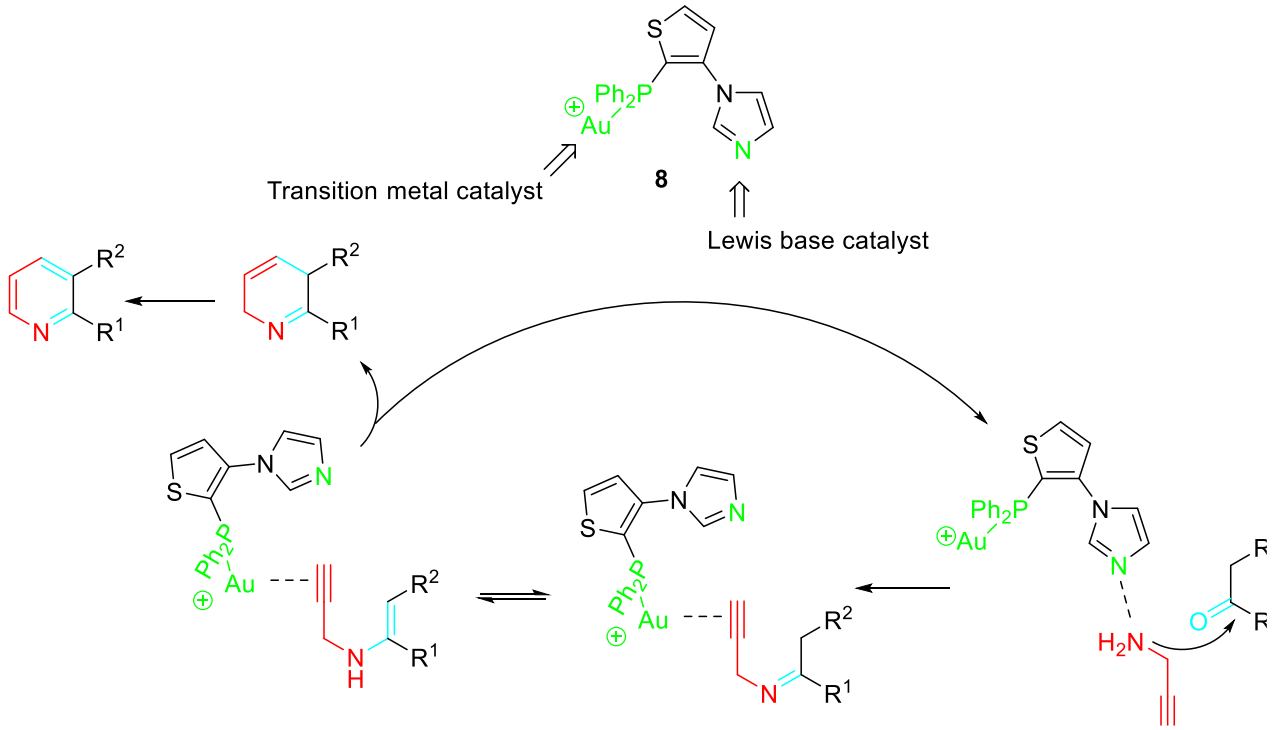
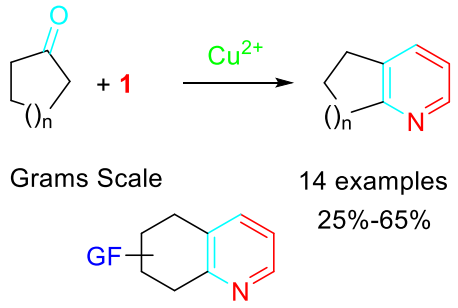
A variety of catalysts were tested in the reaction of **1** with **2**. In particular, $NaAuCl_4{\cdot}2H_2O$ resulted a highly efficient catalyst. Moreover, Au **8** were synthesized and applied as efficient bi-functional catalysts. It was found that imidazolyl group acted as a Lewis base to catalyze the condensation of carbonyl compounds with propargylamine to form the imino intermediate, and the involved Au^+-complex species activated the alkynyl moiety to give the dehydropyridine derivative which underwent auto-oxidation reaction to afford the target pyridines (Scheme 3). [19]



Scheme 3. Sequential reactions of carbonyl compounds and propargylamine catalyzed by Au-complex **8.**

Copper salts were also effective catalysts in the reaction of cyclic ketones with propargylamine and the highest product yields were observed in i-PrOH in the presence of 5.0 mol % $CuCl_2$ in air. Decreased yields among cyclic ketones were observed in the following order: six-membered ≫ eight-membered > five-membered ~ seven-membered. However, the inexpensiveness of the catalyst and the tolerance to a wide number of protective functional groups in the ketone make the procedure very suitable for large scale preparation of fused pyridines. (Scheme 4). [20]



Scheme 4. Cu-catalyzed pyridine synthesis from cyclic ketones and propargylamine.

Selective aspects of the reaction of steroidal carbonyls with propargylamine were investigated. According to the results, the regioselective pyridine fusion to the cyclic

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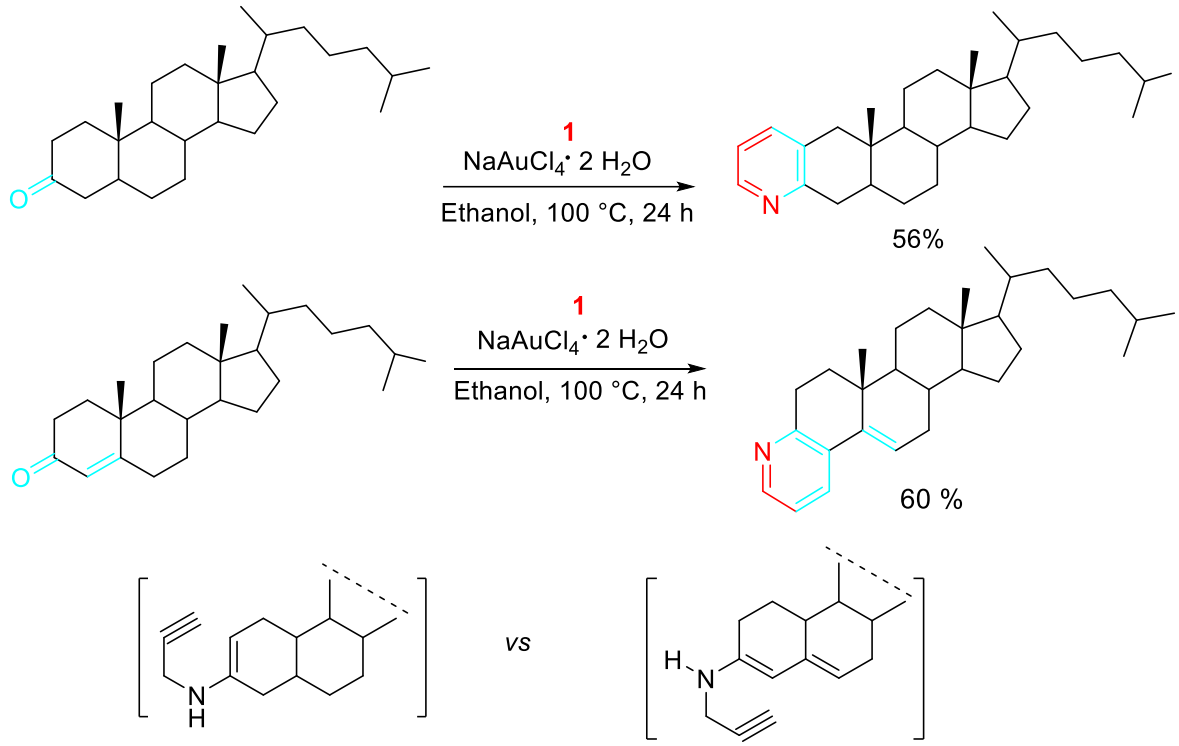
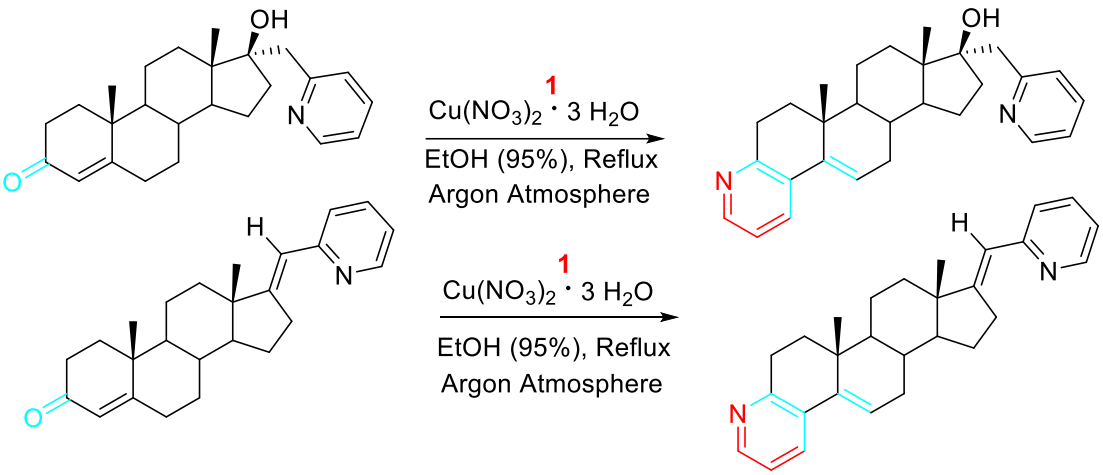
skeleton was addressed by suitable choice between the substrate bearing a saturated or conjugated carbonyl group (Scheme 5). [18]



Scheme 5. Linear *vs* angular steroidal pyridines.

Analogously, new A-ring pyridine fused androstanes in 17a-homo-17-oxa (D-homo lactone), 17*α*-picolyl or 17(E)-picolinylidene series were obtained by reacting 4-en-3-one or 4-ene-3,6-dione D-modified androstane derivatives with propargylamine under the presence of a Cu(II) catalyst, and evaluated for potential anticancer activity in vitro (Scheme 6). [21]



Scheme 6. Copper-catalyzed synthesis of A-ring fused pyridine D-modified androstane derivatives.

Similarly, the efficient synthesis of pyridine rings fused to the 3,4-positions of the steroid nucleus was described via the Cu(II)-catalyzed reaction of propargylamine with 17β-hydroxyandrost-4-en-3-one, 17α-methyl-17β-hydroxyandrost-4-en-3-one, 17β-

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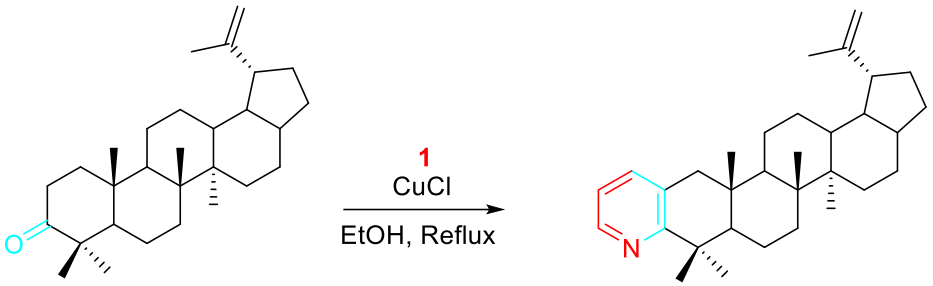
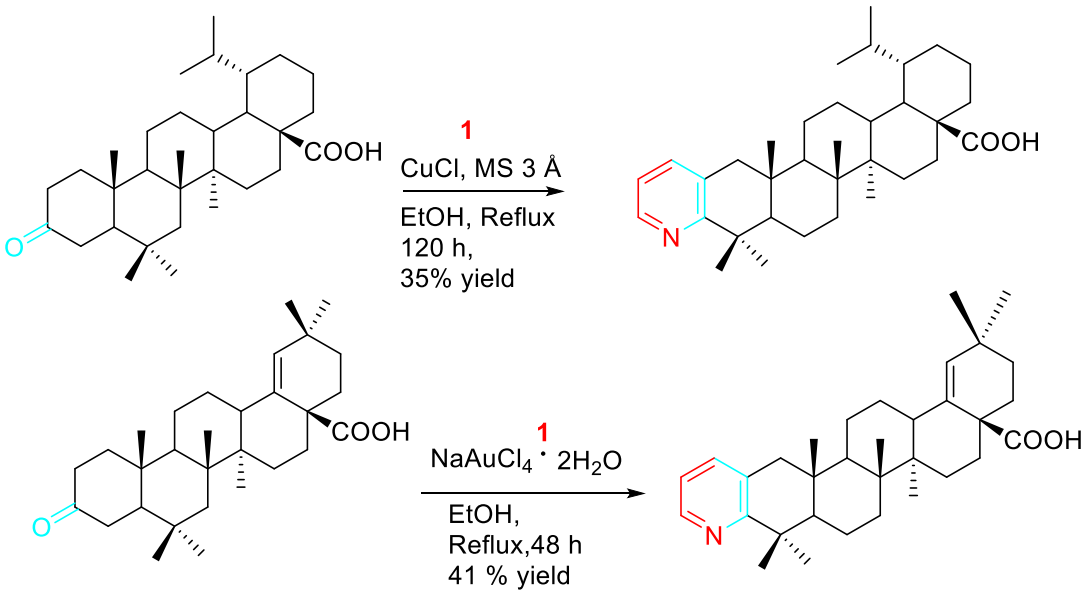
hydroxyestr-4-en-3-one. [22] The procedure was also applied to the synthesis of heterocyclic betulin derivatives (Scheme 7). [23-24]



Scheme 7. Copper-catalyzed synthesis of betulin derivatives.

Optimization of the synthesis of steroidal pyridines was tried by prolonging the reaction time and varying the catalyst loading. In some cases the use of $NaAuCl_4 \cdot 2H_2O$ instead of CuCl and the addition of activated molecular sieves to the reaction mixture led to significant improvement (Scheme 8). [25]



Scheme 8. Optimization of the synthesis of relevant steroidal pyridines.

Several other applications of the methodology accomplished the preparation of significant scaffolds. Indeed, the chemical synthesis of highly potent and acid-stable inhibitors of hedgehog signaling carbacyclopamine analog **11** was reported. The gold-catalyzed amination/annulation/aromatization sequence applied to the inseparable mixture of the mixture of the isomers **9** and **10** regioselectively furnished, after removal of the *tert*-butyldimethylsilyl ether (tetrabutylammonium fluoride, THF, 25 °C), carbacyclopamine analog **11** in 36% overall yield for the two steps. (Scheme 9). [26]

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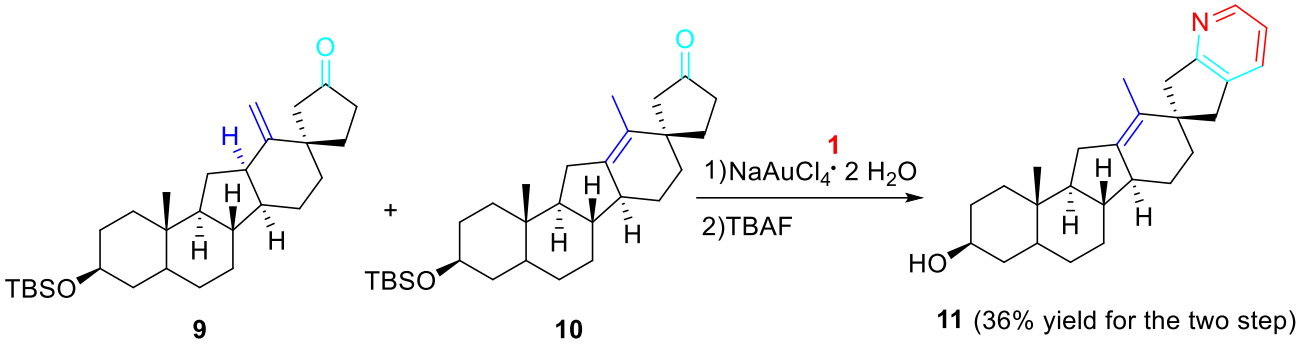
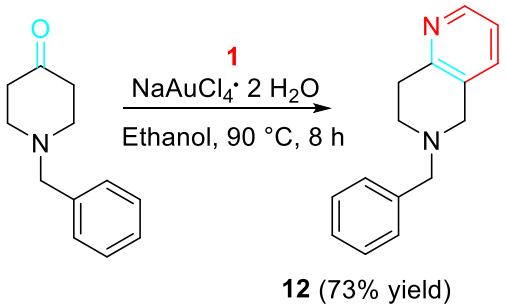


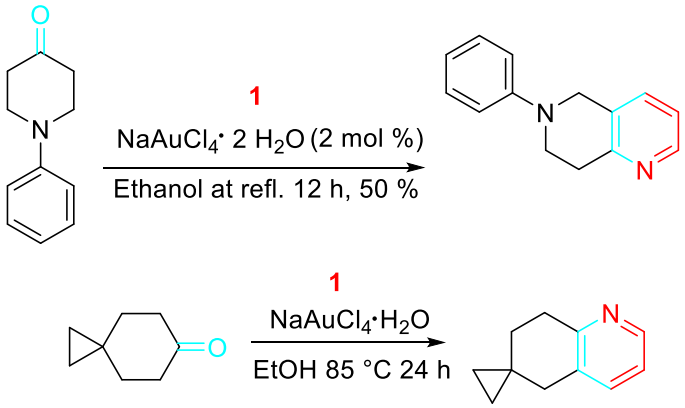
Scheme 9. Gold-catalyzed synthesis of the carbacycloamine analog **11**.

Furthermore, the gold-catalyzed reaction of 1-benzylpiperidin-4-one with propargylamine efficiently afforded the potassium channel modulator 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthirine **12** (Scheme 10). [27]



Scheme 10. Gold-catalyzed synthesis of the potassium channel modulator **12**.

The methodology was extended to the synthesis of Wnt signal path inhibitors. (Scheme 11). [28-29]



Scheme 11. Synthesis of Wnt signal path inhibitors.

The gold-catalyzed synthesis of BAY-298, a nanomolar small molecule (SMOL) hLH-R antagonist reducing sex hormone levels in vivo was described (Scheme 12). [30]

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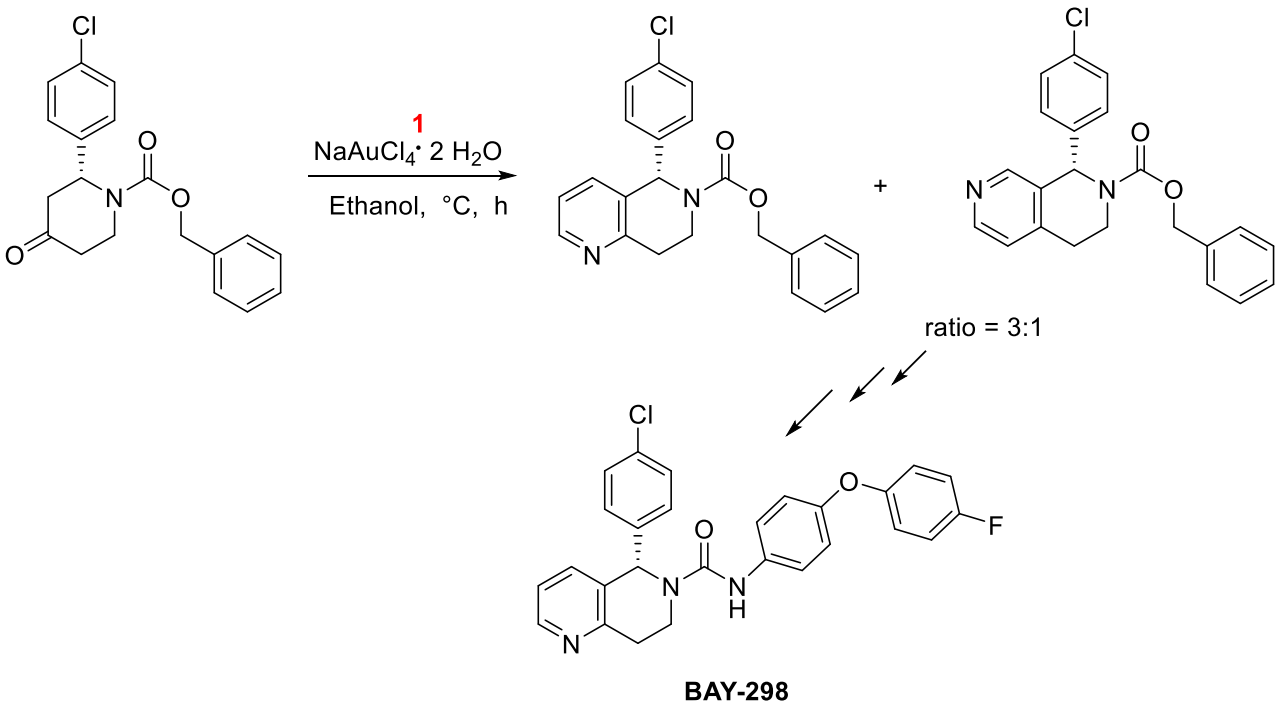
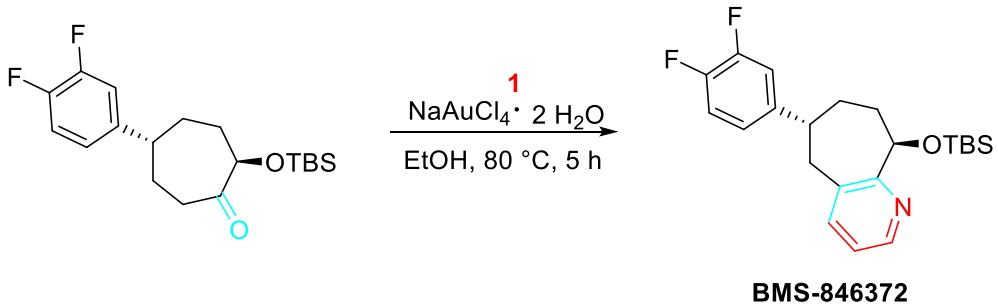


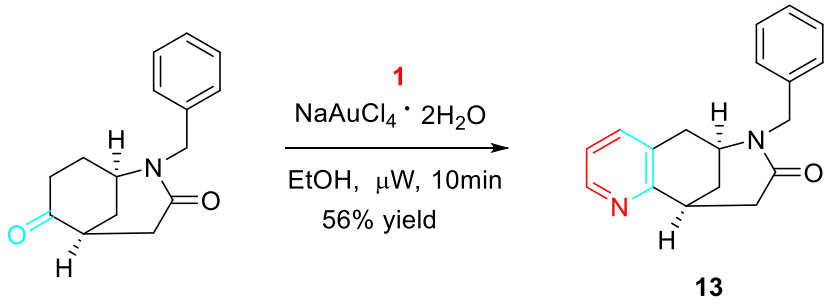
Scheme 12. Gold-catalyzed synthesis of BAY-298.

Moreover, the gold-catalyzed sequential process of condensation/cyclization/aromatization procedure was extended as the key step for the preparation of BMS-846372, a potent and orally active human CGRP receptor antagonist employed for the migraine therapy (Scheme 13). [31]



Scheme 13. Synthesis of BMS-846372.

The methodology resulted, also, a viable tool obtain aryl and heteroaryl derivatives of benzomorphanes **13** pharmacologically active as inhibitors of 11 ß-hydroxysteroid dehydrogenase (HSD) 1 (Scheme 14). [32]



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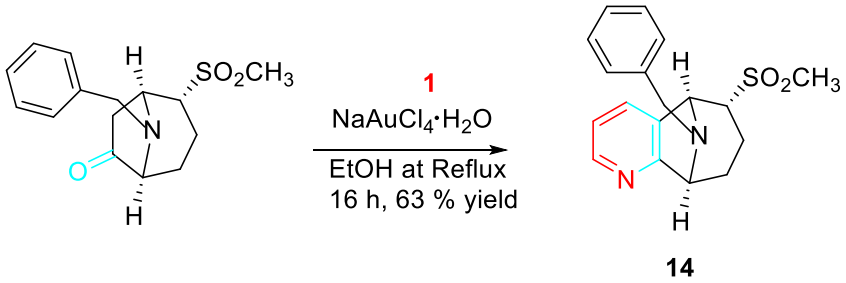
Scheme 14. Gold-catalyzed synthesis of the benzomorphane derivative **13**.

The synthetic approach had yielded a number of scaffolds suitable for the design of performance-diverse screening libraries (Scheme 15). [33]



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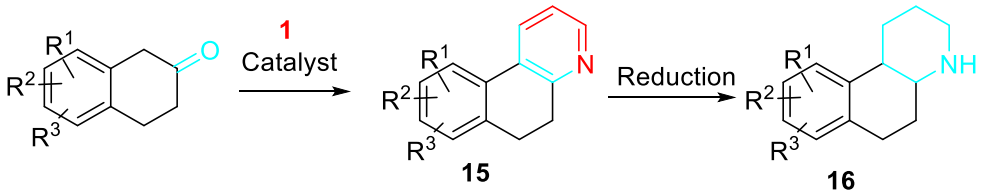
Scheme 15. Gold-catalyzed synthesis of the tropane-related scaffold **14**.

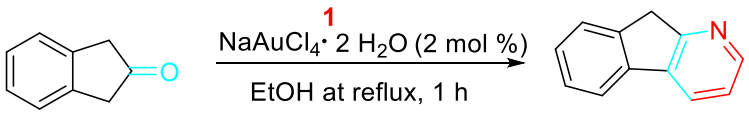
The reaction of 2-tetralones and propargylamine in the presence of complexes of gold or copper, preferably $NaAuCl_4$ and CuC1 was employed to synthesize octahydro-benzoquinoline derivatives **16** as inhibitors of 11β-hydroxysteroid dehydrogenase for the treatment of metabolic disorders like metabolic syndrome, diabetes, obesity, and dyslipidemia. The reaction is usually run in alcohols at temperatures of 20 to 120° C through conventional heating or microwave irradiation. The resulting pyridine was re-duced transformed to the corresponding piperidine (Scheme 16). [34]



15 **16**

Scheme 16. Synthesis of 11β-hydroxysteroid dehydrogenase inhibitors.

The sequential gold-catalyzed condensation/annulation reaction of the 1,3-dihyrdo-*2H*-inden-2-one with the propargylamine provided the corresponding *9H*-indeno[2,1-b]pyridine **17** as the ligand for the synthesis of an olefin polymerization catalyst (Scheme 17). [35]



17 (52%)

Scheme 17. Gold-catalyzed synthesis of the ligand **17**.

The gold(III)-catalyzed reaction of simple β-ketoesters with propargylamines achieved the synthesis of potentially bioactive 2,5-dihydropyridines **18** in satisfactory yields (Scheme 18). [36]

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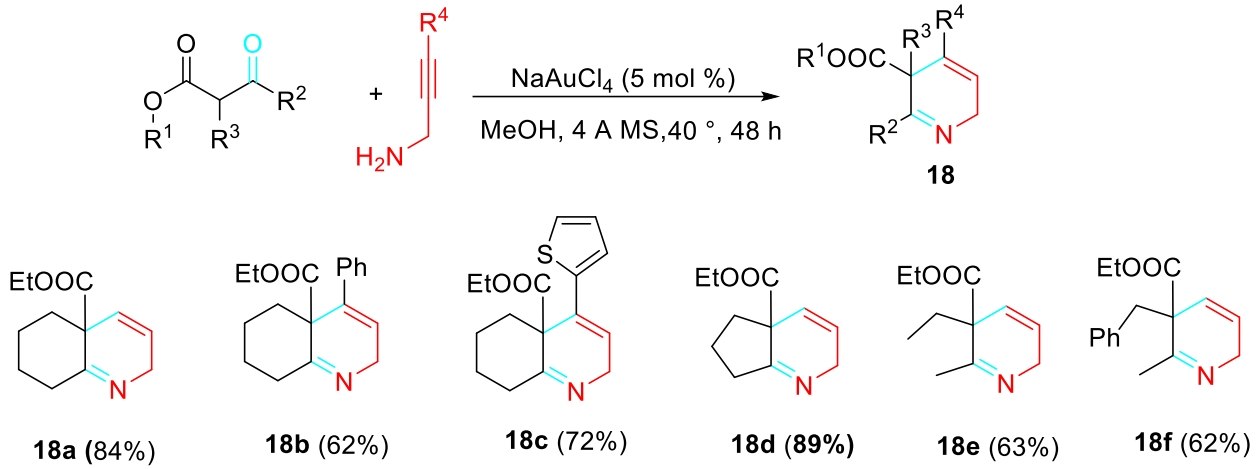
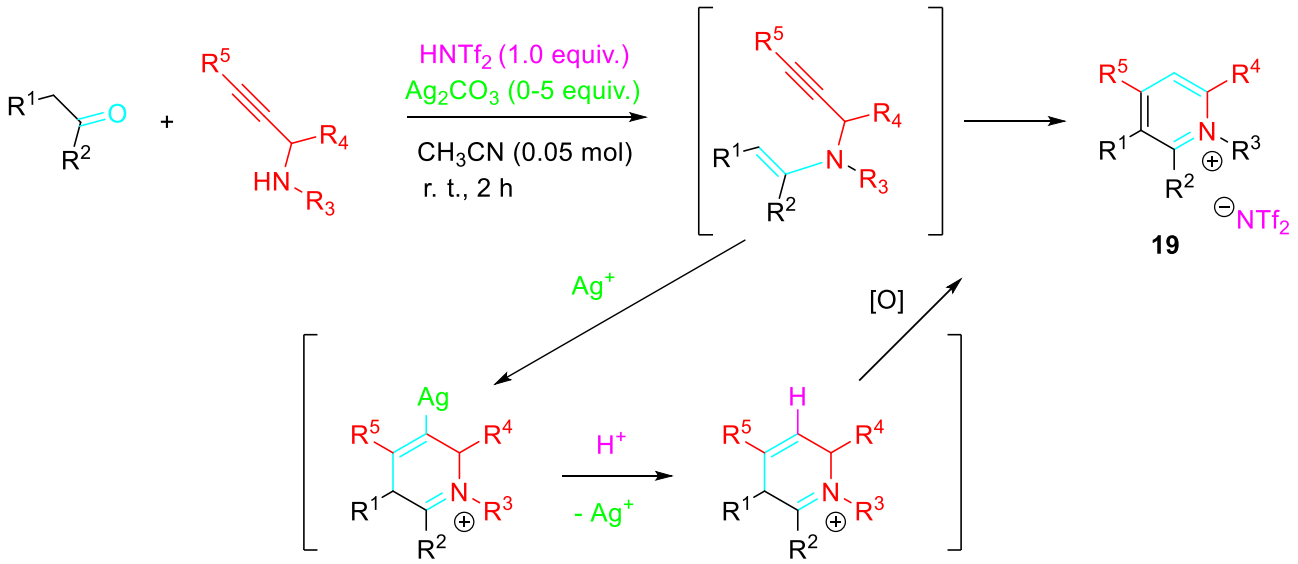


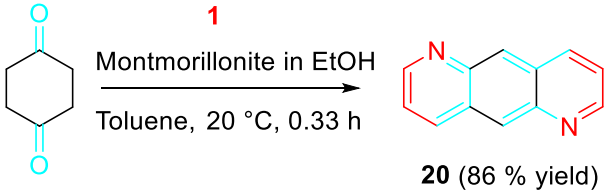
Scheme 18. Gold-catalyzed synthesis of 2,5-dihydropyridines **18**.

Substituted pyridinium salts **19** were obtained under mild conditions by a condensation reaction between carbonyls and propargylamine under the presence Ag_2CO_3/$HNTf_2$ synergistically acting catalyst system. The one-pot transformation should proceed via sequential 6-*endo-dig* cyclization of the in situ generated propargylenamine / protonolysis of the resulting vinyl-silver intermediate (Scheme 19). [37]



Scheme 19. Synthesis of pyridinium salts.

Interestingly, hetero-anthracene derivatives as **20**, used in the preparation of organic light emitting devices, were practically obtained under metal-free conditions (Scheme 20). [38]



Scheme 20. Metal-free synthesis of the hetero-anthracene derivative **20**.

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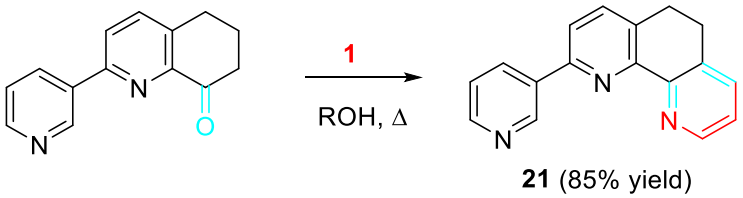
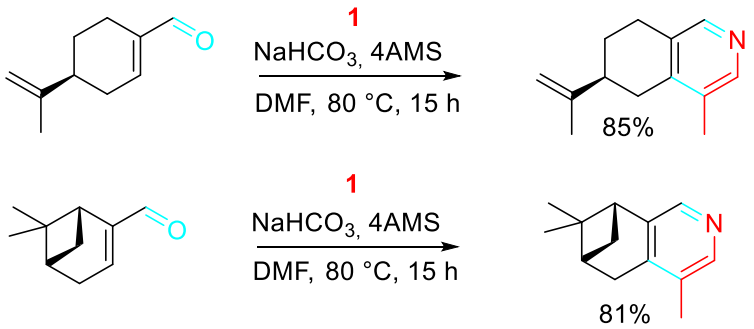
Moreover, substituted dihydrophenanthrolines **21** were easily obtained from 2-substituted 6,7-dihydroquinoline-8(5H)-ketones and propargylamine in alcohol at 70-130 °C. This metal-free method has the advantages of safety, cleanness and wide substrate applicability. The product can be efficiently isolated by adjusting the temperature or prolonging the reaction time (Scheme 21). [39]



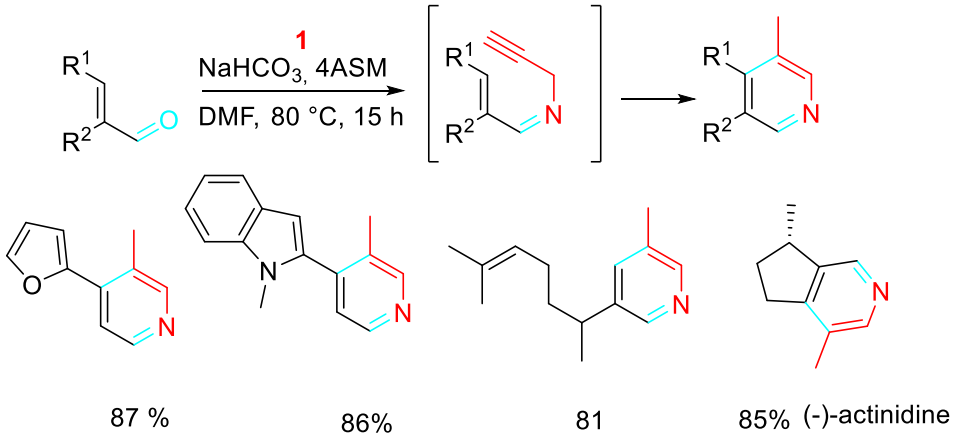
Scheme 21. Synthesis of the dihydrophenanthroline **21**.

The reaction of readily available α,ß-unsaturated carbonyl compounds with propargylamine provided a high atom- and pot-economy strategy for the synthesis of polyfunctionalised pyridines under metal-free conditions with relevant functional group tolerance. (Scheme 22). [40]



Scheme 22. Synthesis of polyfunctionalised pyridines from the reaction of α,ß-unsaturated carbonyl compounds with propargylic amines.

The extension to the synthesis of a variety of natural product was also reported (Scheme 23). [41]



Scheme 23. One-step synthesis of natural products.

The method was applied to the synthesis of pyridines from the cosmetic, flavor and fragrance agent (S)-(-)-perillaldehyde and the flavoring agent found in cardamom, (1R)-myrtenal (Scheme 24).

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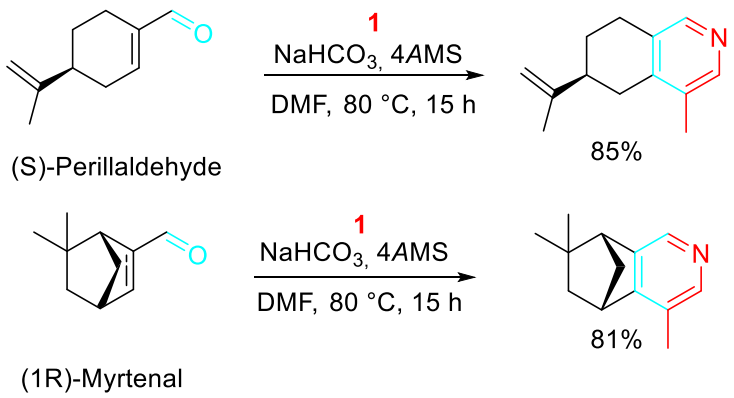
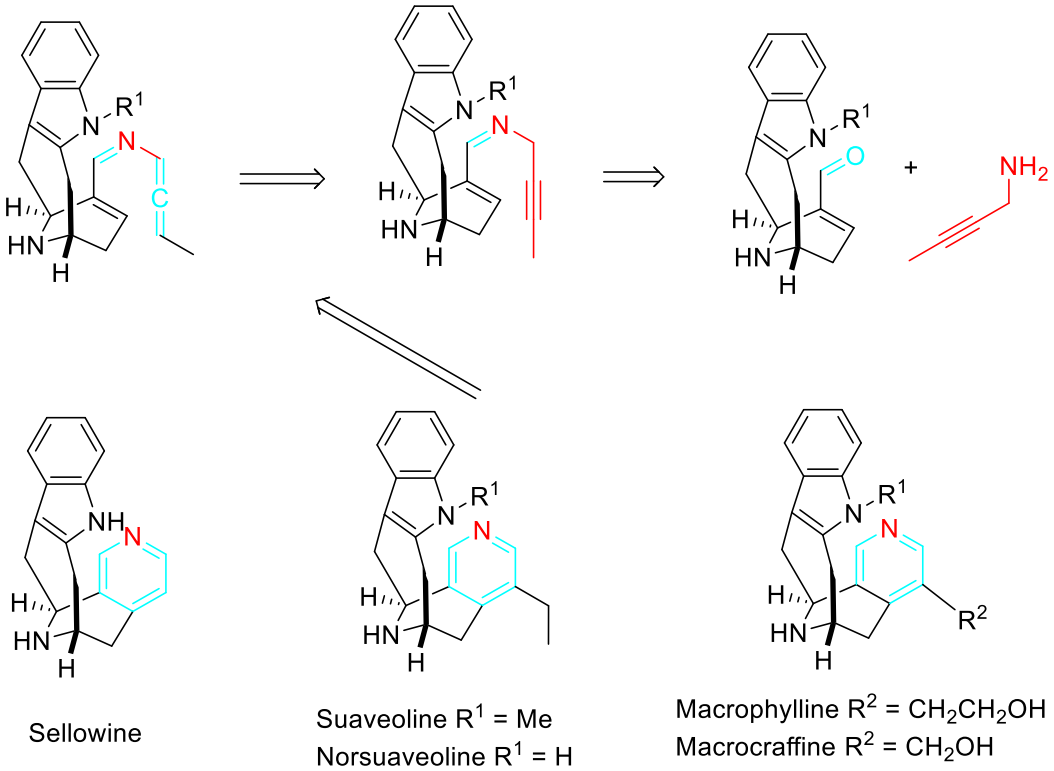


Scheme 24. Construction of pyridines starting from (S)-(-)-perillaldehyde and(1R)-myrtenal.

The process also achieved the total syntheses of Suaveoline alkaloids (Scheme 25). [42]



Scheme 25. Retrosynthetic pathway of Suaveoline alkaloids.

The practicality of the protocol for the sustainable synthesis of these kinds of molecules through a tandem condensation/alkyne isomerization/6π-3-azatriene electrocyclization sequence was highlighted (scheme 26). [43]

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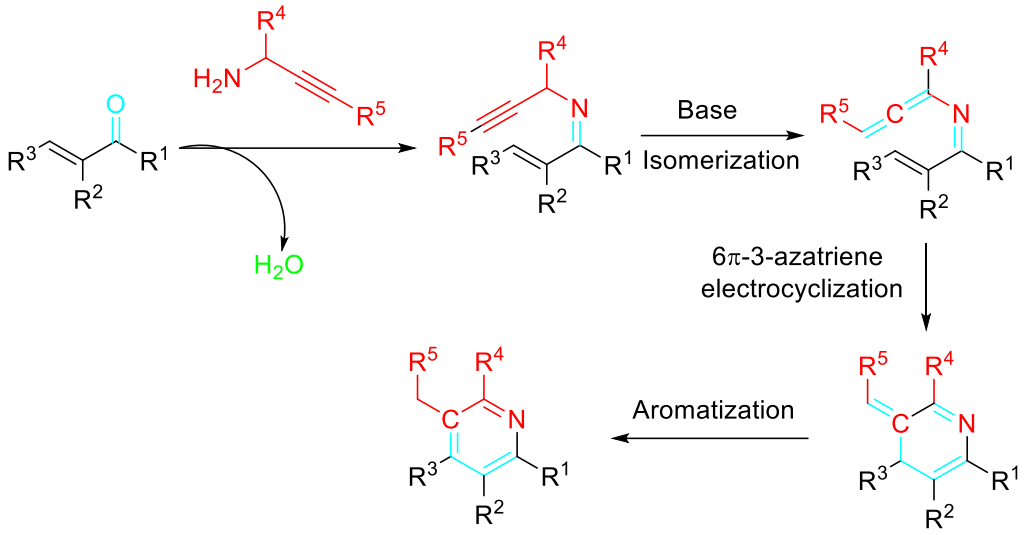
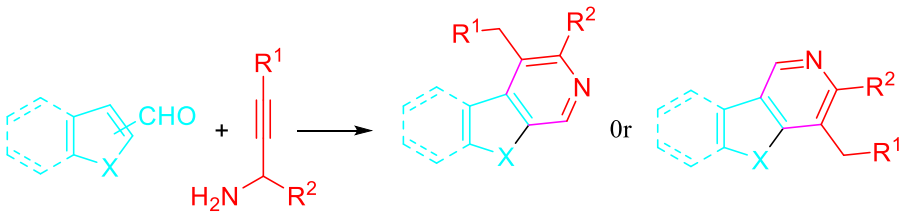


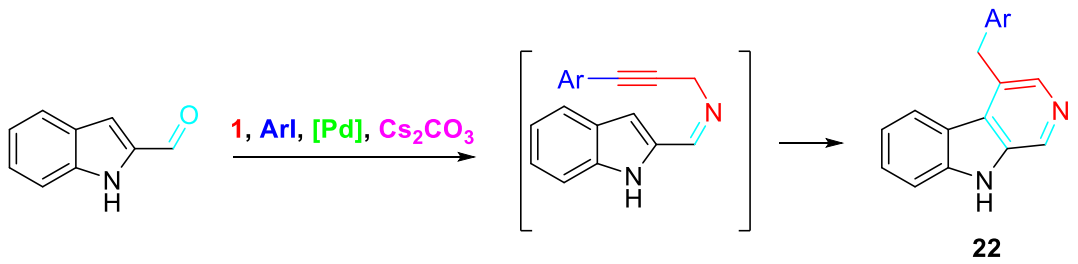
Scheme 26. Pyridine synthesis by a 6π-3-azatriene electrocyclization.

The reaction of propargylamines with (hetero)aromatic aldehydes efficiently afforded β-carbolines, γ-carbolines and other fused azaheteroaromatics under metal-free conditions (Scheme 27). [44]



Scheme 27. Synthesis of β- and γ-carbolines from indole aldehydes and substituted propargylic amines.

A one-pot, three-component method allowed the preparation of 3-substituted pyridines and carbolines **22** via copper-free, palladium-catalyzed Sonogashira cross-coupling with aryl iodides, followed by 6π-aza cyclization. This method provided selectively the fused pyridines in good yields (67–92%) (Scheme 28). [45]



Scheme 28. Synthesis of 4-benzylated carbolines **22**.

Alternatively, a further preparation method for the polysubstituted pyridine derivatives comprised the employment of an α,β-unsaturated carbonyl compound and propargylamine hydrochloride as raw materials in chlorobenzene (PhCl) with the sequential addition of 1,8-diaza-bicycloundecylenic-7-alkene (DBU) and magnesium sulfate ($MgSO_4$) (Scheme 29). The advantage of this alternative procedure is a relatively strong industrial application prospect. [46]

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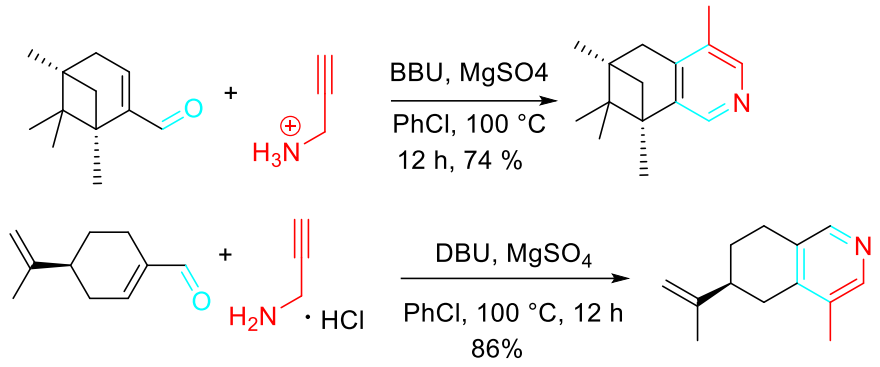
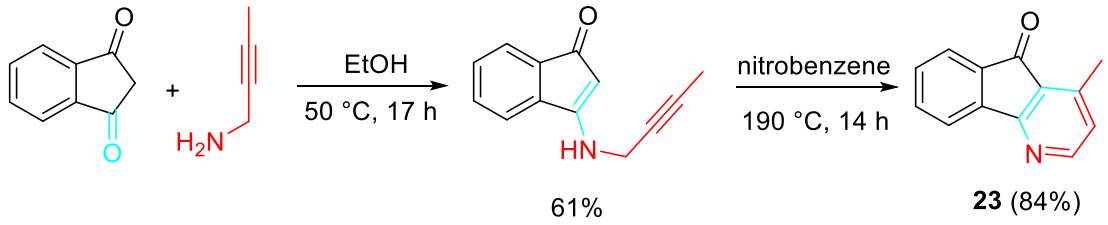


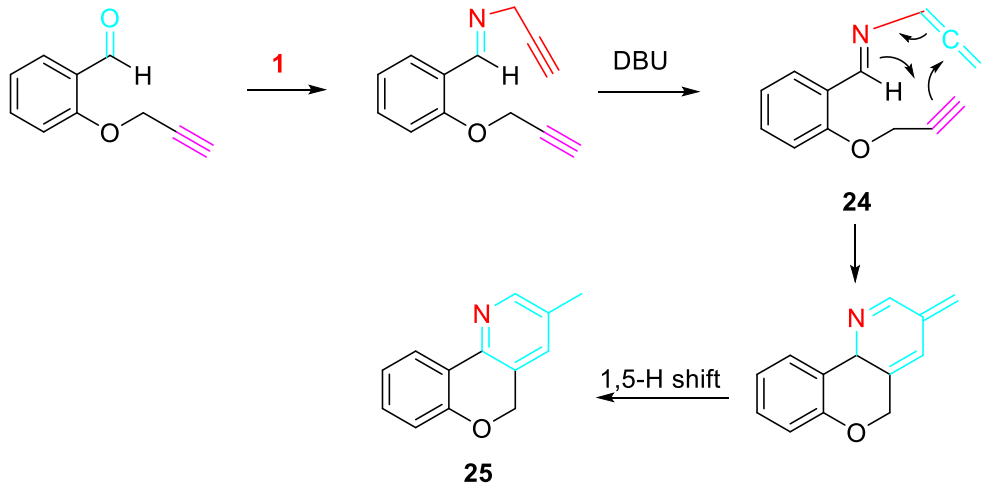
Scheme 29. Alternative synthesis of polysubstituted pyridine derivatives from α,β-unsaturated carbonyl compound and propargylamine hydrochloride.

Accordingly, an easy synthesis of Onychine **24,** an azafluorenone alkaloid isolated from a plant of the *Annonaceae* family, was reported to occur through Aza-Claisen rearrangement, tautomerization, 1,5-sigmatropic hydrogen shift, 6π electron cyclization, and oxidation of the *N*-propargyl enamine, obtained in a yield of 61% by dehydration condensation of but-2-yn-1-amine with 1,3-indanedione (Scheme 30). [47]



Scheme 30. Total synthesis of onychine **23**.

The sequential *O*-propargylation of aromatic hydroxyaldehydes/ condensation reaction with propargylamine allowed a simple approach the synthesis of chromenopyridine of and chromenopyridinone derivatives. The intramolecular cycloaddition reaction between the alkyne and azadiene of **24**, which is formed as an intermediate, furnished the desired skeleton of chromenopyridine **25** (Scheme 31). [48]



Scheme 31. Mechanism for the formation of chromenopyridines **25**.

Moreover, the *N*-propargylation of aromatic aminobenzaldehydes, followed by reaction with propargylamine in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)

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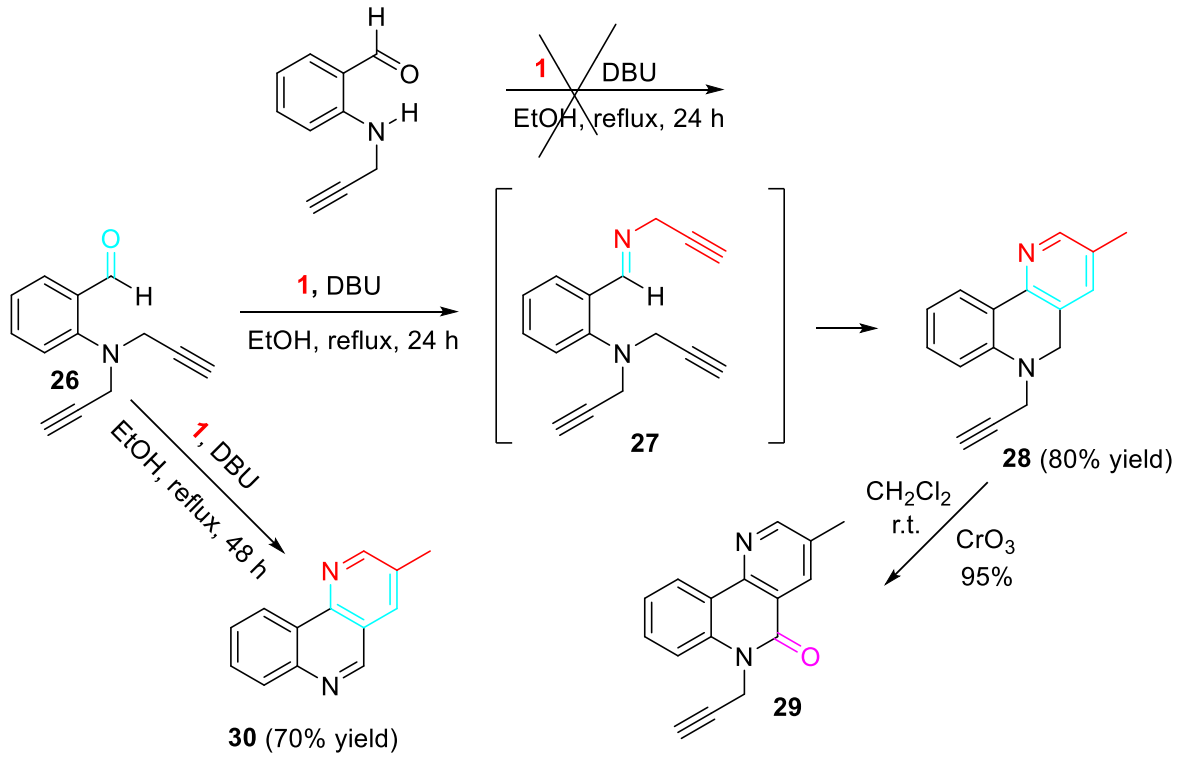
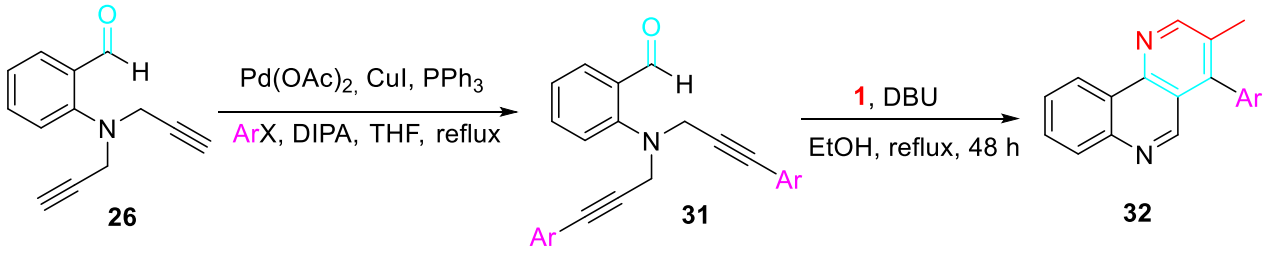
gave the corresponding benzo[*h*][1,6]-naphthyridines **30** (Scheme 32). [49] The lack of reactivity of the 2-(prop-2-yn-1-ylamino)benzaldehyde was surmounted by double propargylation of the aniline derivative leading to the intermediate **27** which cyclized in refluxing ethanol to afford the *N*-propargyl derivative **28** in 78 % yield. The 3-methylbenzo[*h*][1,6]-naphthyridine **30** was isolated by increasing the reaction time to 48 h. Oxidation of **28** with CrO_3 in pyridine in dichloromethane at room temperature gave the desired product **29** in 95 % yield.



Scheme 32. Sequential reaction of 2-(diprop-2-ynylamino)benzaldehyde **26** with the propargylamine amine.

Moreover, a variety of starting materials synthesized by Sonogashira coupling reactions **31** afforded the corresponding naphthyridine derivatives **32** by reacting with propargylamine in refluxing EtOH in the presence of DBU (Scheme 33).



Scheme 33. Synthesis of naphthyridines 32.

The approach was extended to the synthesis of the chromenopyrazinone derivatives **33** (Scheme 34).

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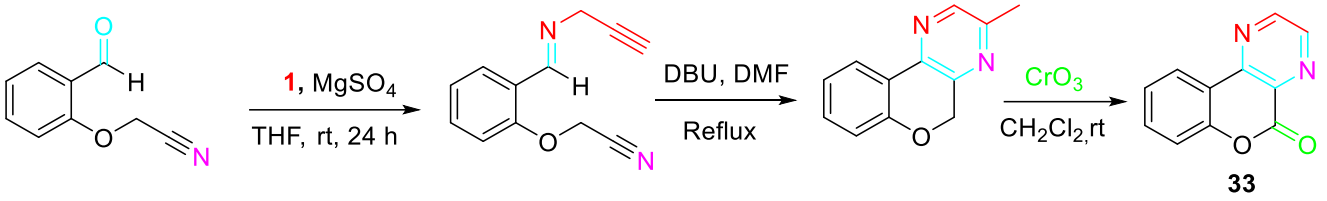
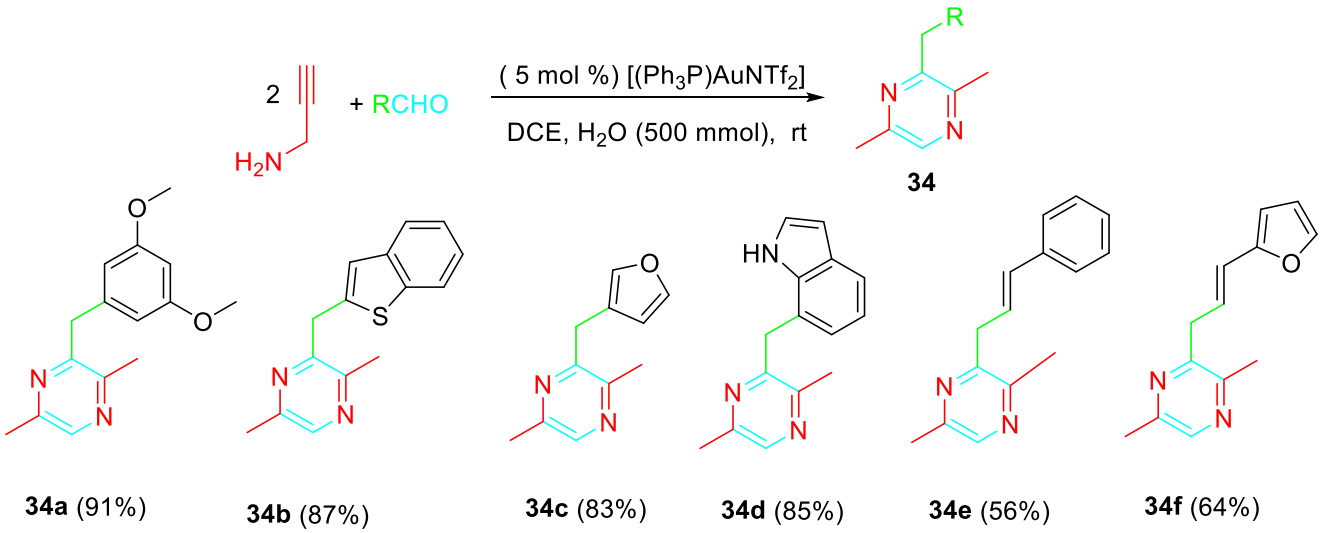


Scheme 34. Synthesis of the chromenopyrazinones 33.

Pyrazines **34** were also synthesized through the gold-catalysed coupling reaction of aldehydes with propargylamine by means of a different sequential process (Scheme 35). [50]



Scheme 35. Gold-catalyzed synthesis of pyrazines 34 from the reaction of propargylamine with aldehydes.

The following reaction mechanism was suggested. (Scheme 36).

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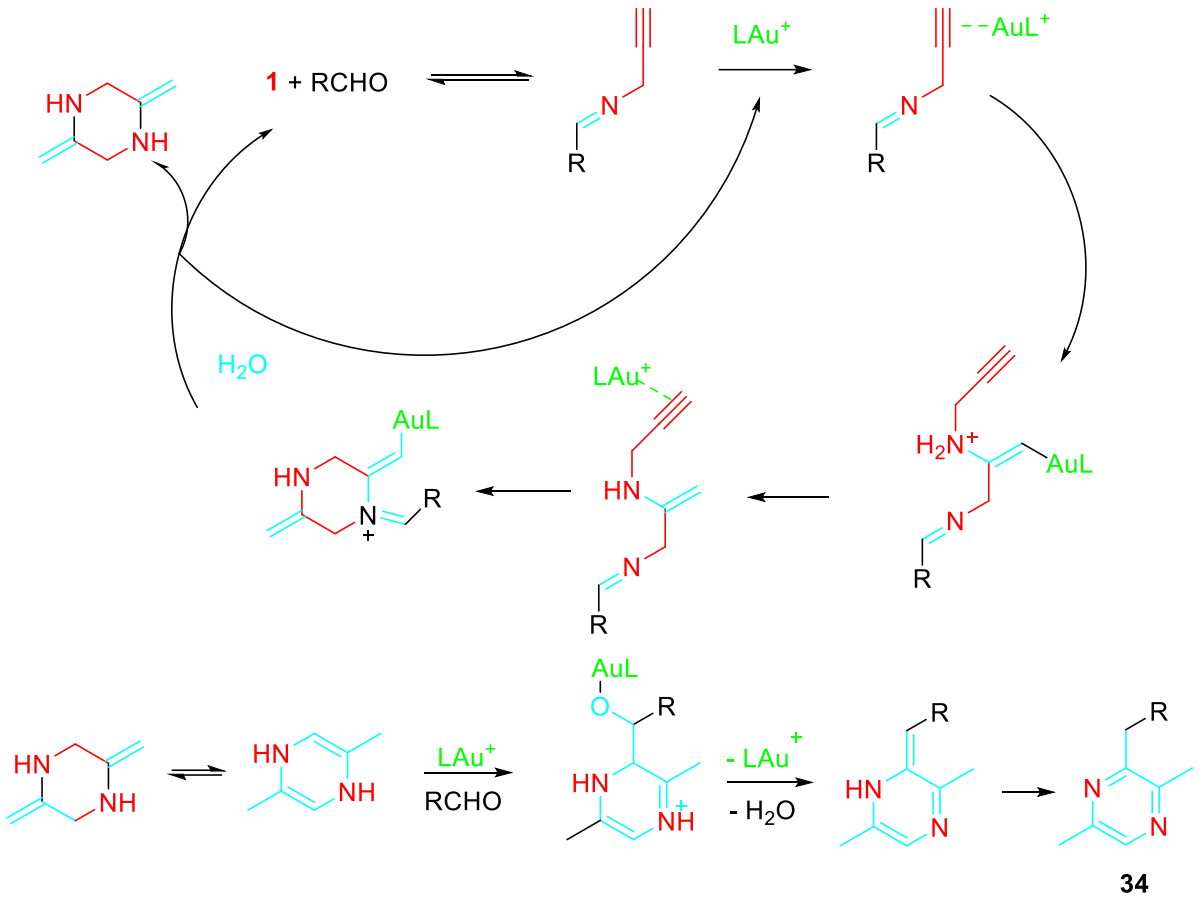
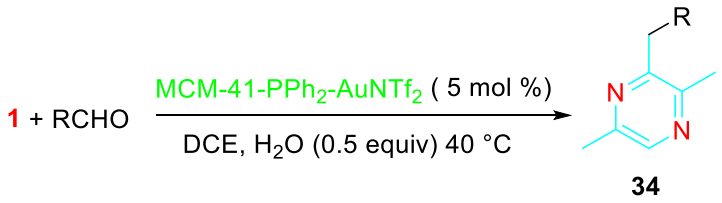


Scheme 36. Proposed mechanism for the Au-catalyzed formation of pyrazines **34**.

The heterogeneous gold(I)-catalyzed version of the cascade reaction of aldehydes with propargylamine occurred in 1,2-dichloroethane at 40 °C under the presence of the readily available MCM-41-immobilized phosphine gold(I) complex [MCM-41-PPh$_3$-AuNTf$_2$]. The easily preparable heterogeneous gold(I) catalyst could be recovered by filtration and recycled (Scheme 37). [51]



Scheme 37. Sequential reaction of propargylamine with aldehydes catalyzed by MCM-41-immobilized phosphine gold(I) complex [MCM-41-PPh$_3$-AuNTf$_2$].

A variant of sequential multicomponent assembly processes (MCAPs)-cyclization approach in accord with the plan outlined in Scheme 38 was explored for preparing a variety of 1,2,3-triazolo-1,4-benzodiazepines **35** of possible medical relevance by a sequential reductive amination of 2-azidobenzaldeyde derivatives with propargylamine / intramolecular Huisgen cycloaddition. [52]

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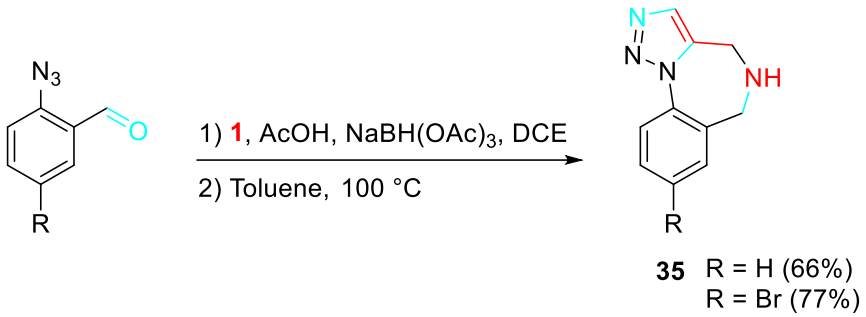
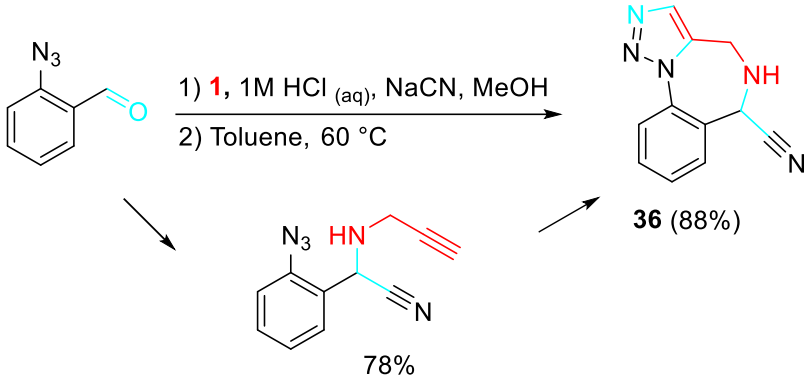


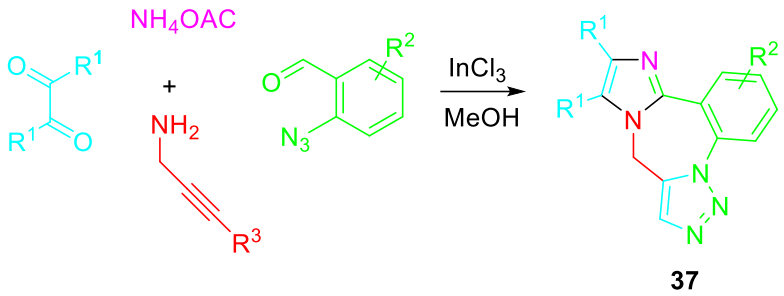
Scheme 38. Synthesis of 1,2,3-triazolo-1,4-benzodiazepines **35**.

A wide library was obtained through N-functionalizations, palladium-catalyzed cross-coupling reactions, and applications of α-aminonitrile chemistry (Scheme 39). [53]



Scheme 39. Diversely substituted 1,2,3-triazolo 1,4-benzodiazepines **36**.

An atom-economical multicomponent sequential $InCl_3$-catalyzed cyclocondensation / azide-alkyne 1,3-dipolar cycloaddition of 2-azidobenzaldehydes with propargylamines under the presence of α-diketone and ammonium acetate efficiently afforded the corresponding 9H-benzo[f]imidazo[1,2-d][1,2,3]triazolo[1,5-a][1,4]diazepines **37** (Scheme 40). [54]



Scheme 40. Indium-catalyzed multicomponent synthesis of 9H-benzo[f]imidazo[1,2-d][1,2,3]triazolo[1,5-a][1,4]diazepines **37**.

3. Sequential Reactions of β-Aminoalkynes with Carbonyls

Versatile β-aminoalkynes building blocks for the synthesis of nitrogen containing heterocyclic compounds are represented by 2-alkynylanilines **38** [55-57]. Their sequential reaction with carbonyl derivatives was directed towards the formation of different scaffolds by changing the reaction conditions. The reaction of **38** with simple ketones or β-ketoesters selectively afforded the corresponding *N-(Z)-* alkenyl indoles **40** under the presence of $InBr_3$ catalyst. The sequential reaction was considered to proceed through

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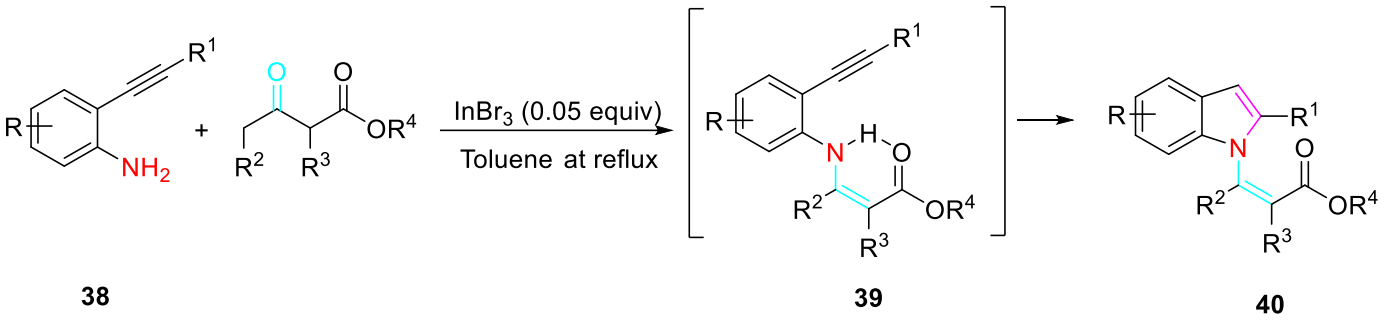
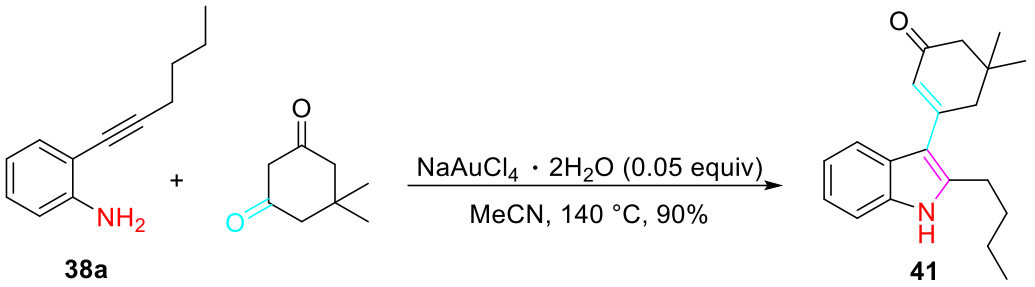
the activation of the β-keto esters / formation of β-enamino esters **39** / intramolecular *5-endo-dig* cyclization promoted by activation of the acetylene (Scheme 41). [58]



38 **39** **40**

Scheme 41. Indium-catalyzed synthesis of β-(*N*-indolyl)-α,β-unsaturated esters **40**.

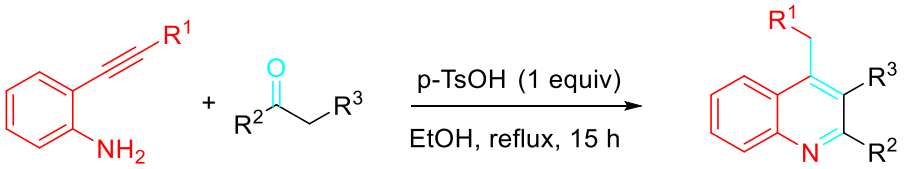
Conversely, the divergent cyclization/alkenylation sequence to give the indole derivative **41** occurred by reacting the 2-alkynylanilines **38a** with 1,3-dicarbonyls under presence of $NaAuCl_4 \cdot 2H_2O$ as the catalyst (Scheme 42). [59]



38a **41**

Scheme 42. Divergent sequential gold-catalyzed cyclisation/alkenylation reaction of 2-alkynylanilines with 1,3-dicarbonyl compounds.

Moreover, reactions between readily available 2-alkynylanilines and activated ketones promoted by *p*-toluenesulfonic acid (*p*-TsOH) afforded 4-alkyl-2,3-disubstituted quinolines **42**. The features of substituents at the other end of the triple bond of 2-alkynylanilines achieved to access to diversified 4-alkylquinolines, achievable with difficulty by classical Friedländer reaction (Scheme 43). [60]



38 **42**

Scheme 43. *p*-TsOH promoted synthesis of 4-alkyl-2,3-disubstituted quinolines **42**.

The procedure also achieved the preparation of quinoline dimers **43** with alkyl or aryl linkers at C-4 (Scheme 44).

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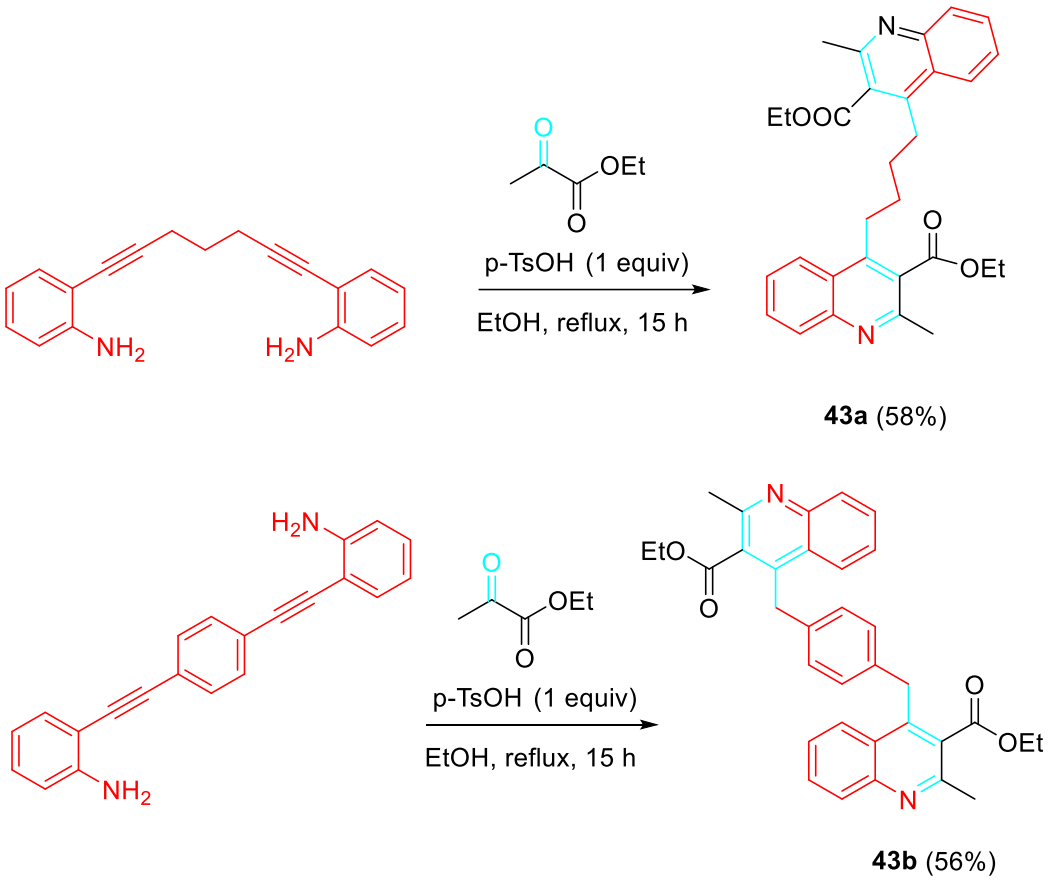
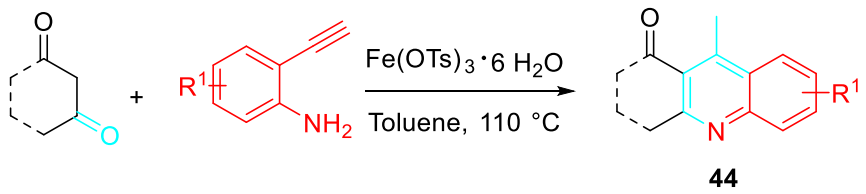


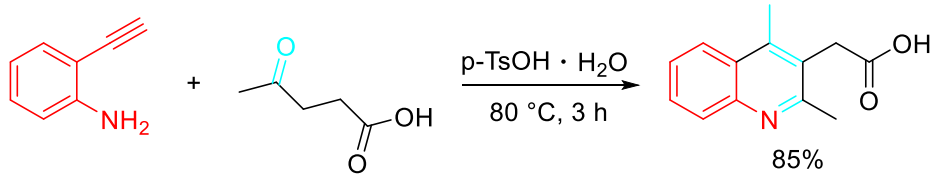
Scheme 44. Synthesis of dimeric quinolines **43**.

Alternatively, the one-pot synthesis of 4-methyl-2,3-disubstituted quinolines **44** was achieved by means of the inexpensive iron(III)catalyzed sequential condensation, cyclization and aromatization of 1,3-diketones with 2-ethynylaniline derivatives (Scheme 45). [61]



Scheme 45. Iron(III)-catalyzed sequential condensation, cyclization and aromatization of 1,3-diketones with 2-ethynylaniline to afford 4-methyl-2,3-disubstituted quinolines **44**.

Furthermore, a cost-effective p-TsOH promoted synthetic strategy for the synthesis of substituted quinolines was achieved by the reaction between levulinic acid with different 2-alkynylanilines under mild metal-free solventless conditions (Scheme 46). [62]



Scheme 46. Sequential reaction of levulinic acid with 2-ethynylaniline under solventless conditions.

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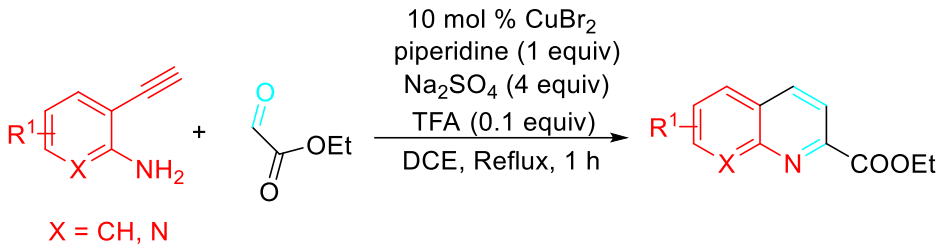
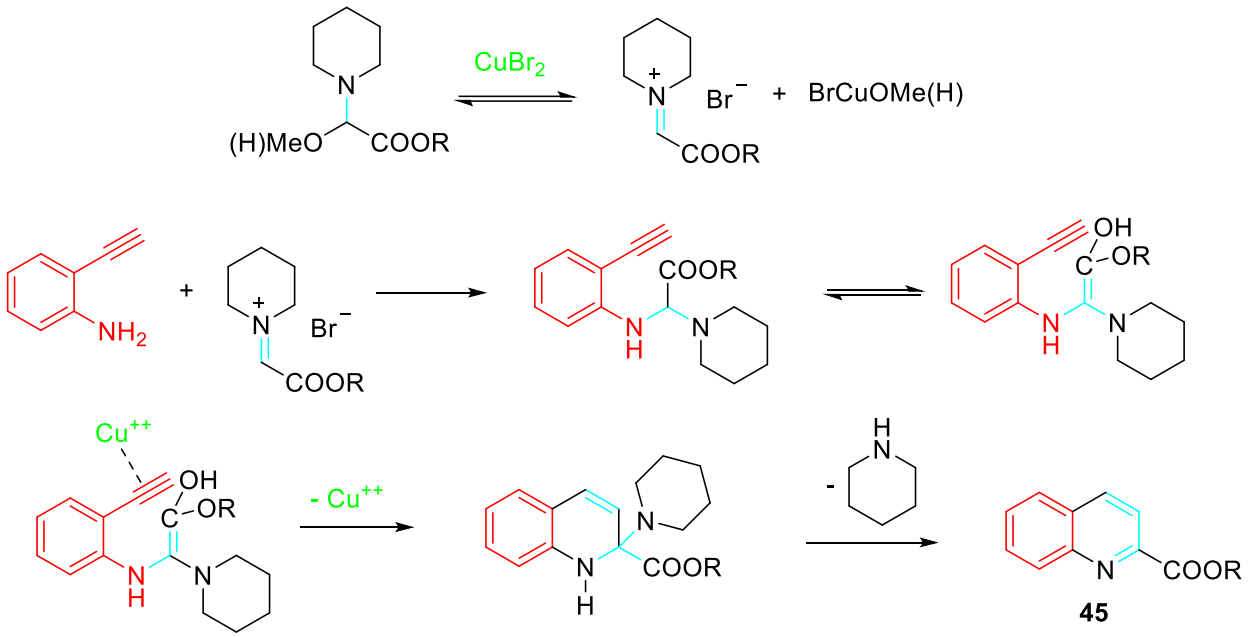
The combination of $CuBr_2$ and trifluoroacetic acid (TFA) directly afforded the corresponding quinolines/naphthyridines by reacting the 2-ethynylaniline with ethyl glyoxylate (Scheme 47). [63]



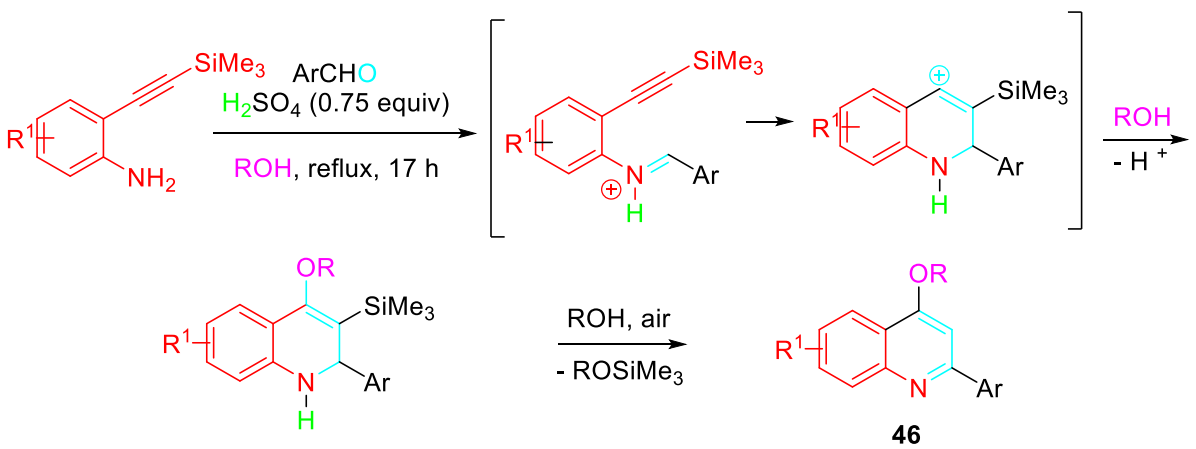
Scheme 47. Copper(I)-catalyzed synthesis of 2-acylquinolines.

N, O- acetals also functioned as a C1 part leading to the preparation of quinoline derivatives **45** according to the following path (Scheme 48). [64]



Scheme 48. Copper-catalyzed synthesis of quinolines **45** from ethynylaniline and ethyl glyoxylate.

A three-component, one-pot sulfuric acid mediated reaction of 2-(2-(trimethylsilyl) ethynyl)anilines with arylaldehydes in alcohol efficiently provided 4-alkoxy-2-arylquinolines **46** (Scheme 49). [65]



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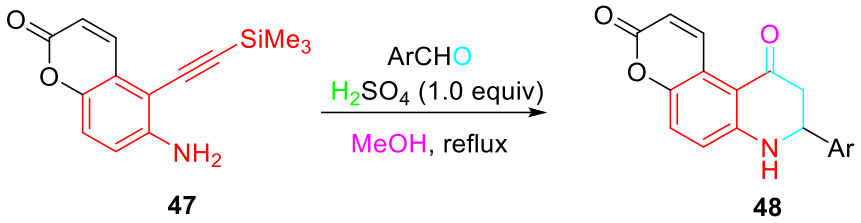
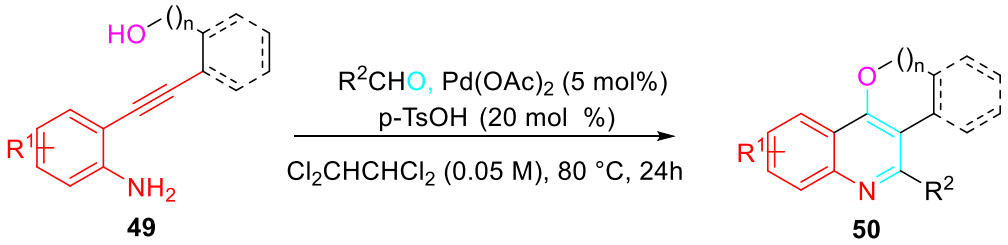
Scheme 49. Synthesis of 4-alkoxy-2-arylquinolines **46**.

This strategy was extended to efficiently afford the unusual formation of 8-aryl-8,9-dihydro-3*H*-pyrano[3,2-*f*]quinoline-3,10(7*H*)-dione derivatives **48** by condensative cyclization of 6-amino-5-[(trimethylsilyl)ethynyl]-2*H*-chromen-2-one **47** with aromatic aldehydes (Scheme 50). [66]



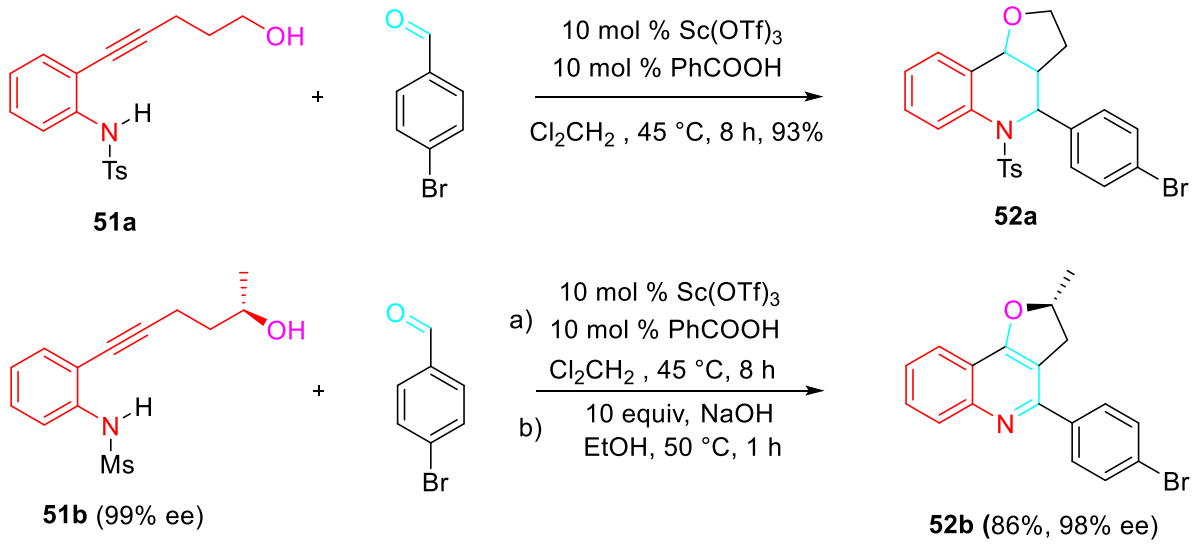
Scheme 50. Condensative cyclization of 6-amino-5-[(trimethylsilyl)ethynyl]-2*H*-chromen-2-one **47**.

It was envisioned that the *in situ* generated *N*-(2-alkynylphenyl)imine might be cyclized to give ring-fused quinoline derivatives. Indeed, a tandem reaction of 2-alkynylanilines **49** with aldehydes catalyzed by the combination of $Pd(OAc)_2$ and *p*-TsOH allowed the regioselective synthesis of ring-fused quinolines **50** (Scheme 51). [67]



Scheme 51. Synergistic effect of Pd(II) and acid catalysts on the synthesis of ring-fused quinolines.

Moreover, a $Sc(OTf)_3$-catalyzed tandem aza-Prins cyclization reaction of 2-alkynylaniline derivatives **51** with aldehydes afforded under mild reaction conditions fused tricyclic derivatives **52**. Interestingly, when the enantiopure optically active 2-alkynylaniline (R)-**51b**, having a central chirality (99% ee), was subjected to the optimized reaction conditions followed by subsequent treatment with NaOH, the quinoline derivative (R)-**52b** was obtained directly (86% yield, 98% ee) (Scheme 52). Six- and seven-membered oxacyclo-fused products were also easily synthesized. [68]



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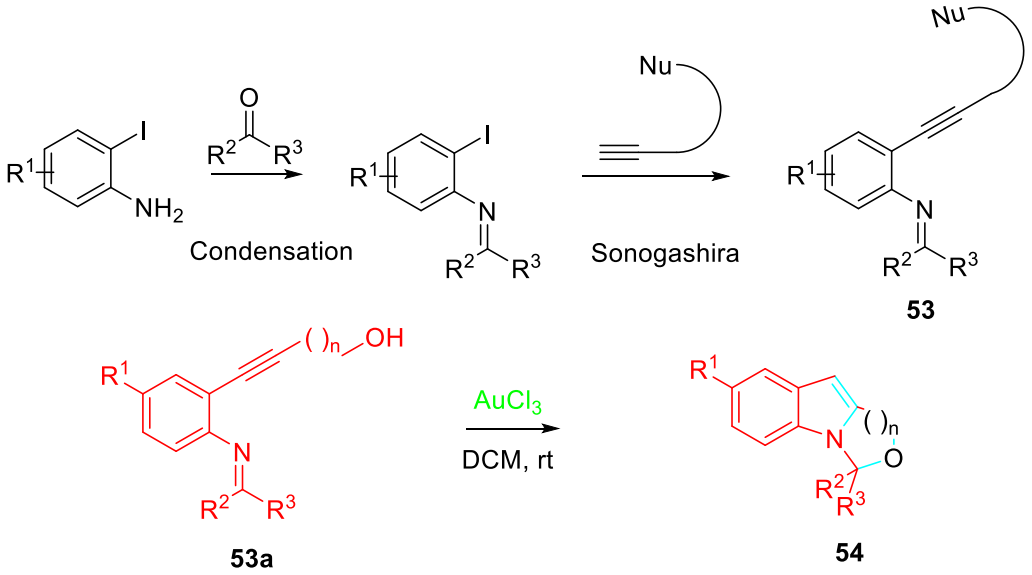
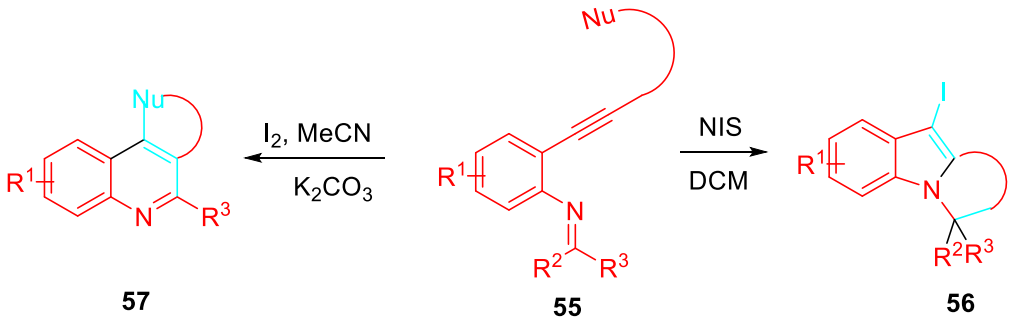
Scheme 52. Sc(OTf)$_3$-catalyzed bicyclization of 2-alkynylanilines with aldehydes.

It is worth noting that the *N*-(2-alkynylphenyl) imines **53** readily available by means of condensation of 2-iodoanilines with ketones or aldehydes followed by Sonogashira coupling with acetylenes were prone to undergo different sequential processes. Ring-fused indoles **54** were obtained from *N*-(2-alkynylphenyl) imines **53a** in high yields under mild conditions under the presence of a gold (III) as a catalyst (Scheme 53). [69]



Scheme 53. Gold-catalyzed synthesis of polycyclic frameworks **54**.

Furthermore, the *N*-(2-alkynylphenyl) imines intermediates **55** treated with NIS in DCM induced novel iodonium mediated domino reaction cascades, which provided ring-fused indole compounds **56** or simply by changing the reaction conditions ring fused quinoline compounds **57** (Scheme 54). [70]



Scheme 54. Iodonium induced tandem cyclization of *N*-(2-alkynylphenyl) imines **55**.

The application of the methodology to the synthesis of iodoquinolones from suitable *N*-(2-alkynylphenyl)imine [71] as well as to the construction of polycyclic indole derivatives through the [3 +2] cycloaddition of metal-containing azomethine ylides generated from *N*-(*o*-alkynylphenyl)imine derivatives and W(CO)$_5$(L) [72] were also reported. A Different sequential cycloisomerization/C3-functionalization of the in situ generated 2-alkynylanilines via Sonogashira coupling of 2-iodoanilines achieved a one-pot synthesis of 2,2′-disubstituted diindolylmethanes (Scheme 55). [73]

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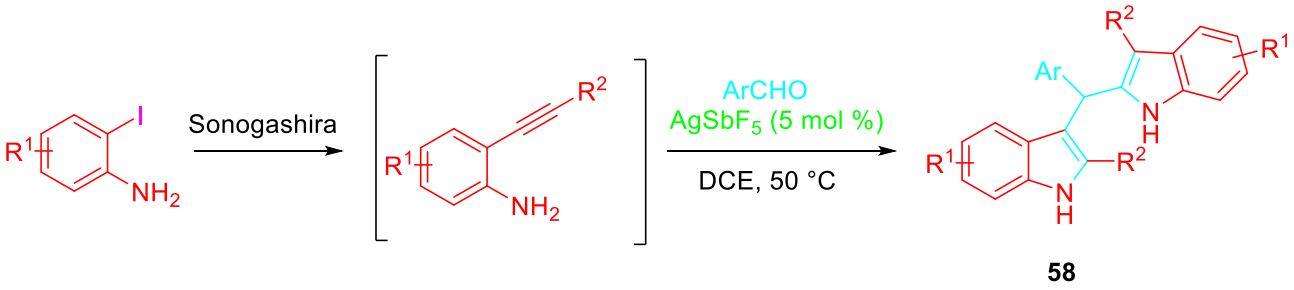
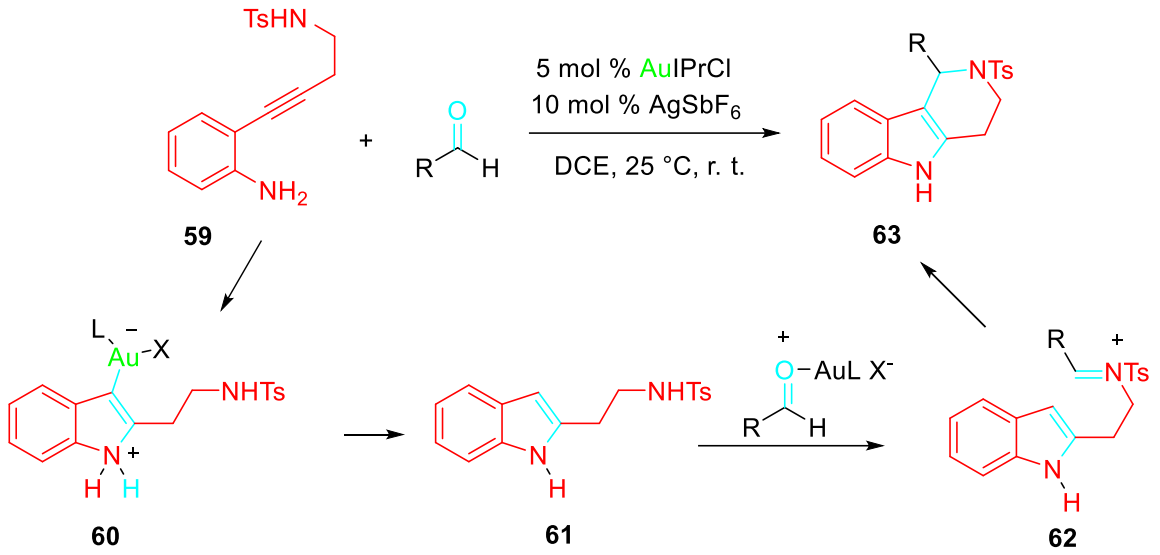


Scheme 55. One-pot synthesis of 2,2′-disubstituted diindolylmethanes **58**.

A one-pot strategy for the synthesis of 1-substituted 2-tosyl-2,3,4,5-tetrahydropyrido[4,3-b]indole scaffolds **63** through a sequential gold-catalyzed hydroamination/Pictet-Spengler cyclization of 2-(4-aminobut-1-yn-1-yl)aniline with aldehydes was demonstrated (Scheme 56). [74] The initial π-coordination of cationic Au(I) species with the alkyne moiety of 2-(4-aminobut-1-yn-1-yl)aniline **59** forms a π-complex which gave the cyclic intermediate **60.** The following protodemetalation affords the isotryptamine **61**. Subsequently, activation of aldehyde by Au(I) species followed by an intramolecular nucleophilic addition of indole moiety of **61** to a highly reactive *N*-sulfonyliminium intermediate **62** provides the tetrahydropyridoindole **63** with regeneration of the catalyst. Ag(I) also promotes the Pictet-Spengler reaction.



Scheme 56. Gold-catalyzed synthesis of 1-substituted 2-tosyl-2,3,4,5-tetrahydropyrido[4,3-b]indoles **63**.

A $Cu(OTf)_2$-catalyzed intramolecular radical cascade reactions efficiently enabled the synthesis of quinoline-annulated compounds **65**. [75] The method represents an effective route to natural products and a variety drug like libraries (Scheme 57).

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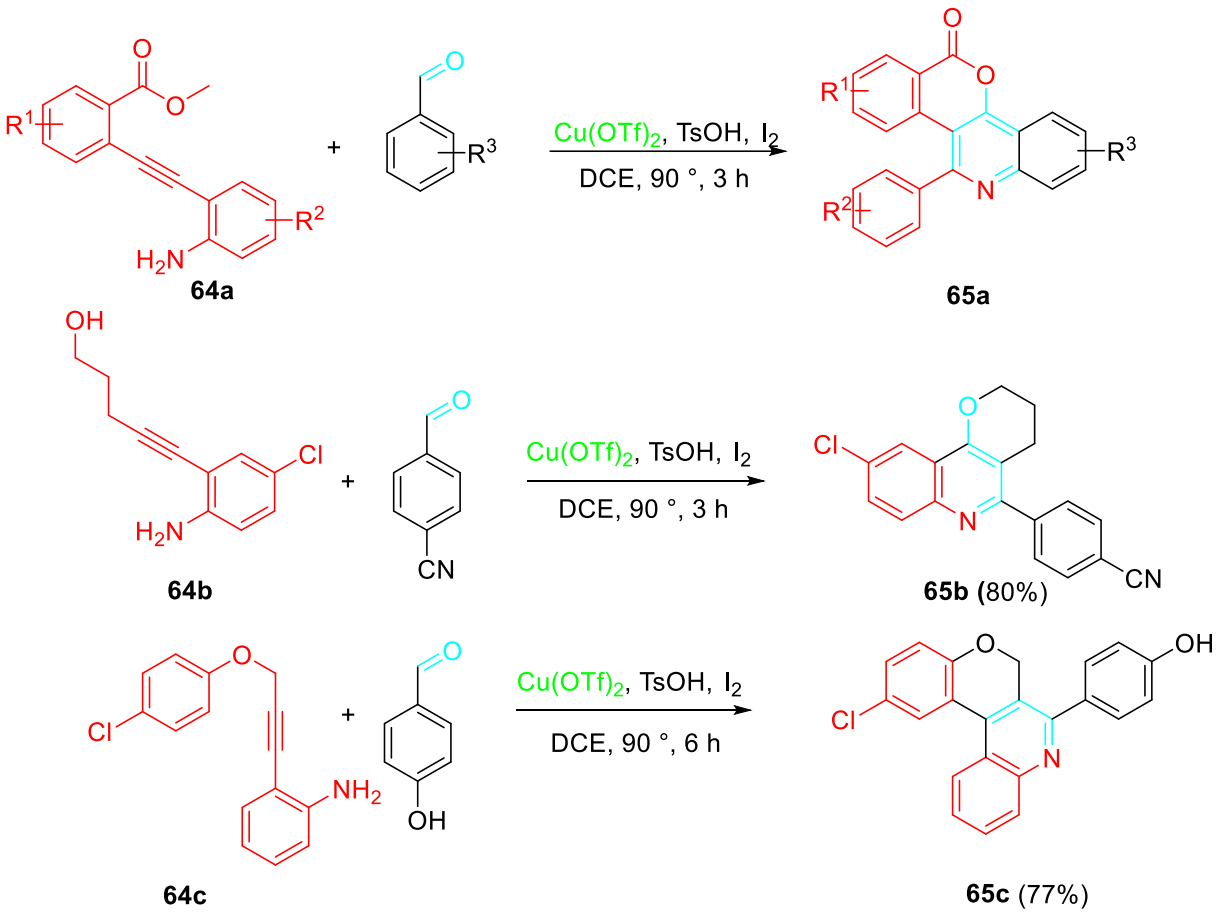

Scheme 57. Cu(OTf)$_2$-catalyzed synthesis of quinoline-annulated polyheterocyclic frameworks **66**.

The proposed mechanism for the synthesis of the polyheterocyclic scaffolds is shown in the following Scheme 58. The intermediate **66** undergoes a copper salt promoted one-electron oxidation to generate the radical cation **67**. Subsequent radical addition into the C-C bond of **68** affords the radical **69**, which cyclizes to give the radical **70**. Finally, trapping of the nitrogen radical by iodine radical generated from the oxidation of iodide affords the complex **71** which after iodide elimination furnishes the product **65**.

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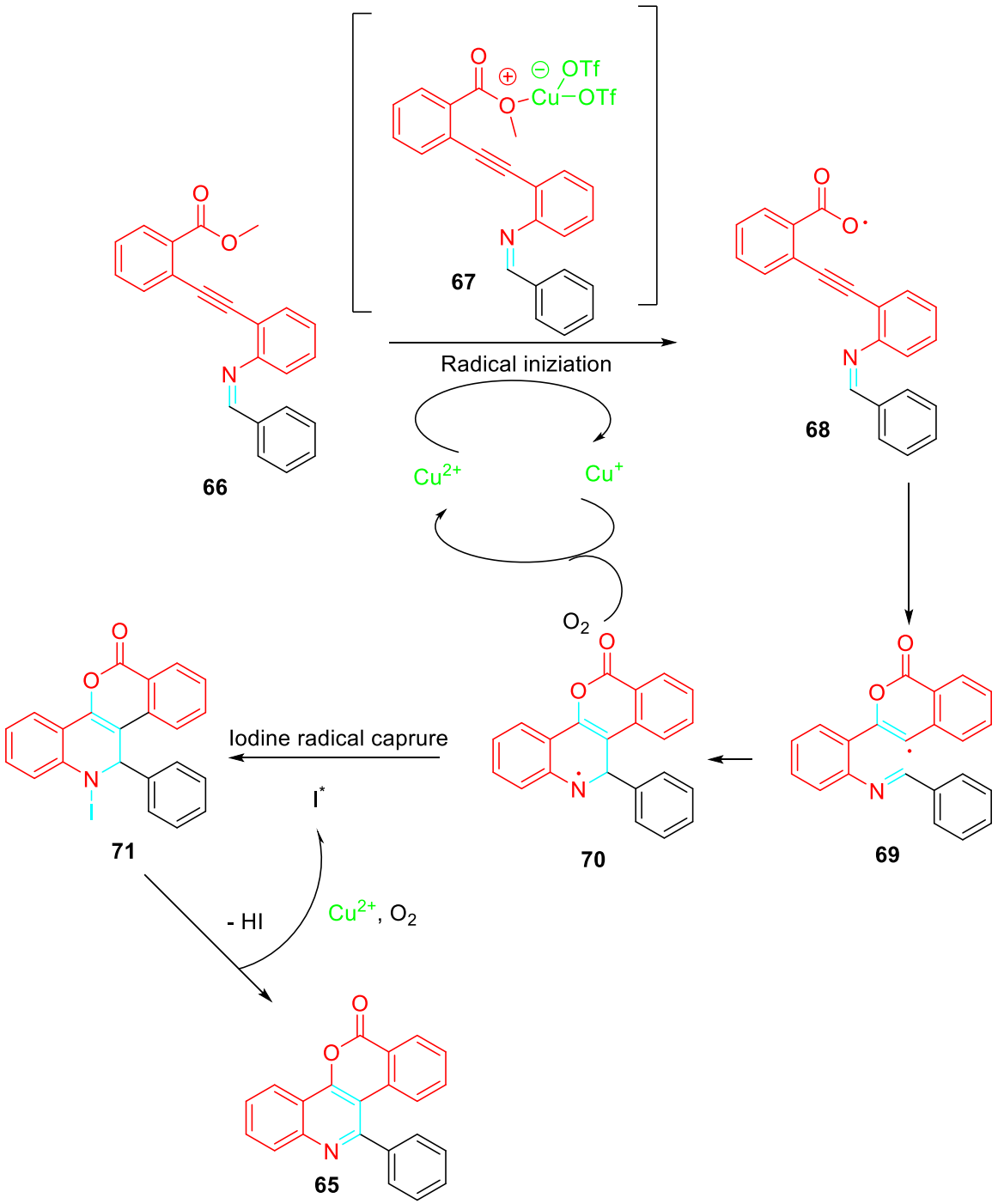

Scheme 58. Plausible reaction mechanism.

A regio- and stereoselective three-component, one-pot cascade reaction involving an imination/annulation/cyanation sequence was achieved by combining palladium(II) trifluoroacetate and copper(II) acetate with the readily available 2-alkynylanilines, cyclic ketones and trimethylsilyl cyanide in dimethyl sulfoxide to efficiently afford the corresponding 1-benzoazepine carbonitrile derivatives **72** (Scheme 59). [76]

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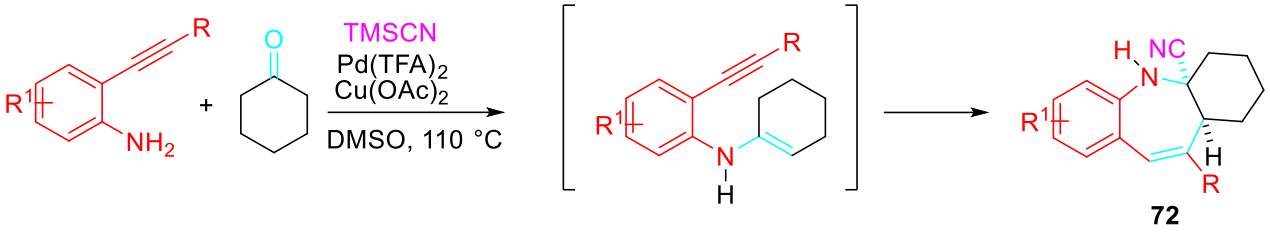
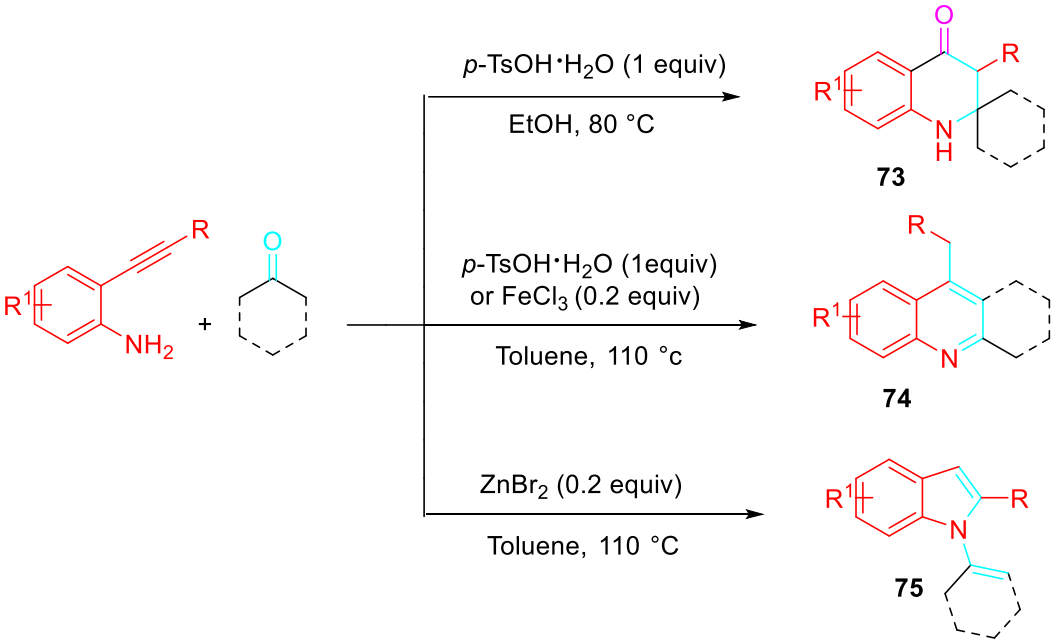


Scheme 59. Palladium-catalyzed synthesis of 1-benzoazepine carbonitriles **72**.

The construction of spirocyclic quinolones **73** which are difficult to synthesize through traditional methodologies was explored by selectively directing the reaction of 2-alkynylanilines with ketones under suitable reaction conditions. Interestingly, the same starting reagents selectively afforded the quinolines **74** or the *N*-alkenyl indoles **75** under different reaction conditions (Scheme 60). [77]



Scheme 60. Product selectivity control of the sequential reaction of 2-alkynylaniline with ketones.

Very likely, the condensation reaction under the Brønsted acid mediated conditions in EtOH led to the iminium ion intermediate **[A]** which undergoes *aza*-Prins to afford the intermediate which after quenching by ethanol, hydrolysis and tautomerization reactions gave the quinolinone **73** (Scheme 61).

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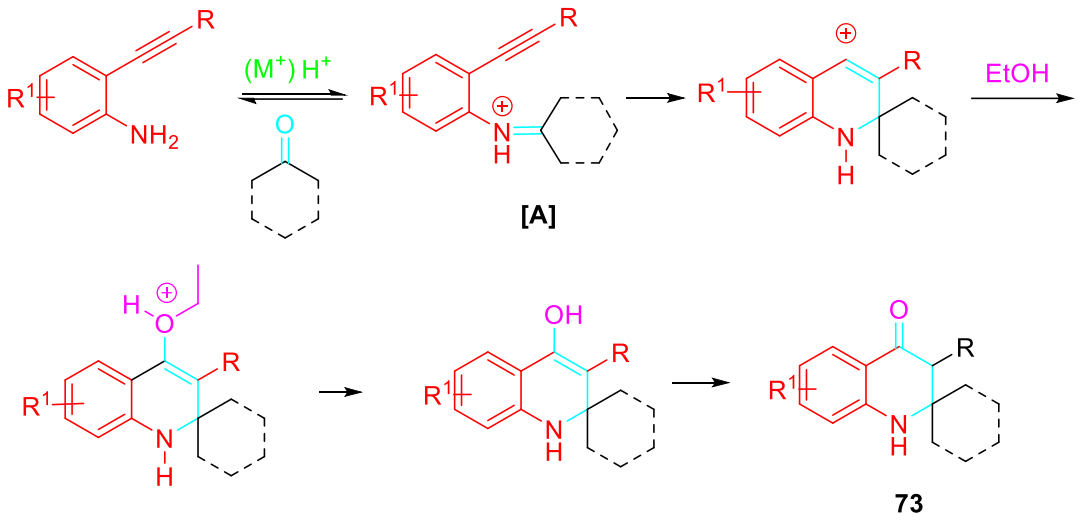
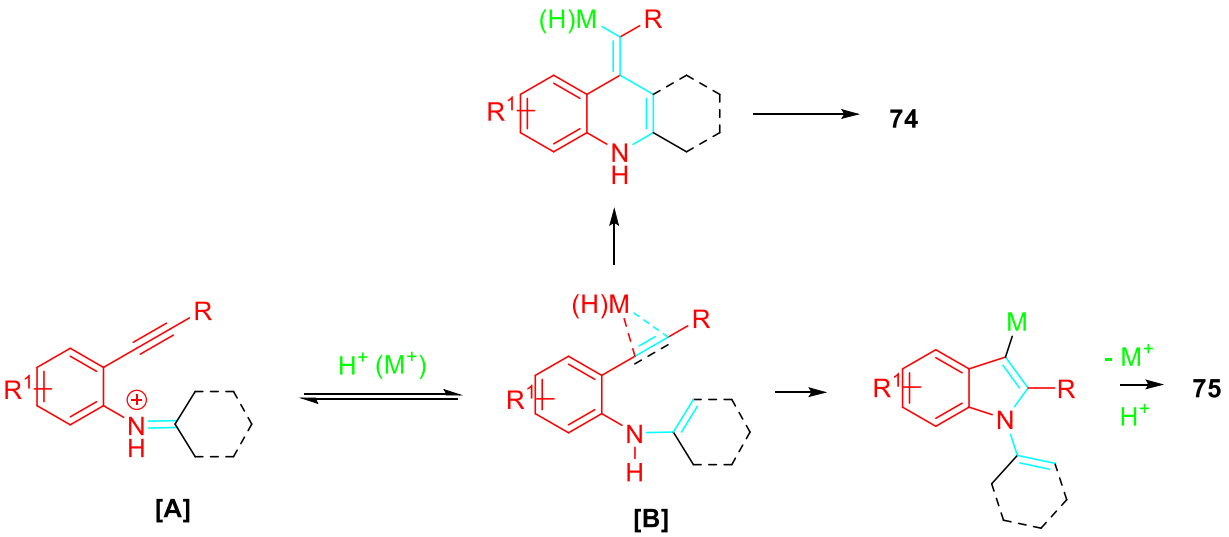


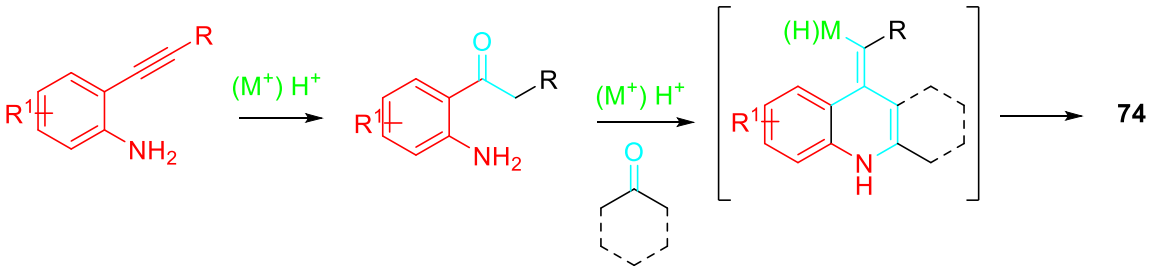
Scheme 61. Proposed mechanism for the synthesis of quinolinones **73**.

Conversely, isomerization of the iminium ion intermediate **[A]** to the intermediate **[B]** should led selectively to the indoles **75** via a *5-endo-dig* cyclization or to the quinoline **74** via a regio-divergent *6-exo-dig* cyclization (Scheme 62).



Scheme 62. Proposed mechanism for the synthesis of quinolines **74** and *N*-alkenylindoles **75**.

Alternatively, the quinolines **74** could be generated from the 2-aminoaryl ketone obtained by the fast hydration reaction of the 2-alkynylaniline both in the presence of a stoichiometric amount of *p*-TsOH·H_2O or 0.2 equiv. $FeCl_3$ in Toluene at 110 °C (Scheme 63).



Scheme 63. Alternative mechanism for the synthesis of quinolines **74.**

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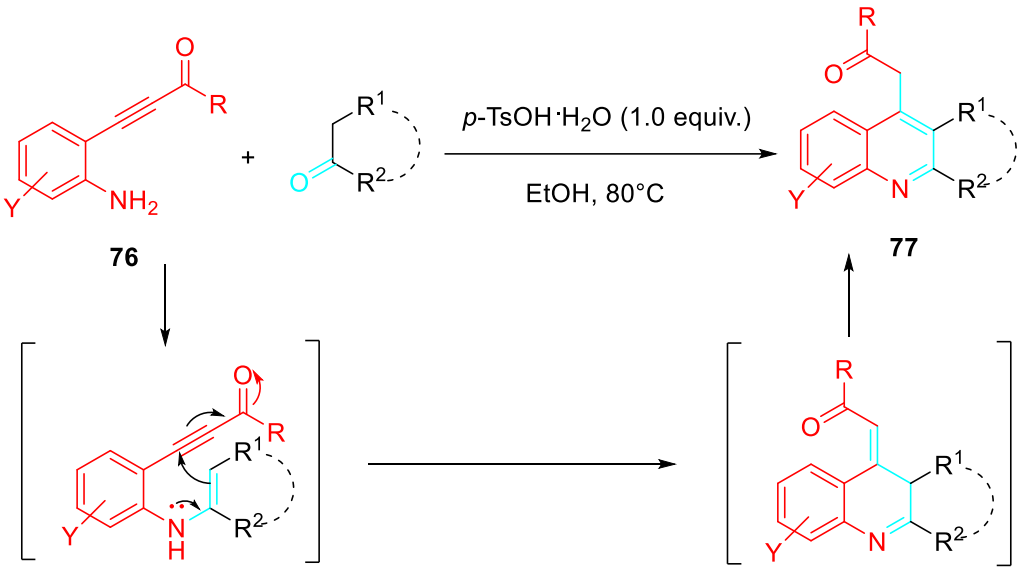
Interestingly, the features of the substituent bonded at the terminal position of the triple bond of the 2-alkynylaniline and of the reaction medium determined the reaction path. Internal alkynes allowed the *p*-TsOH·H_2O mediated preparation of quinolones **73** in EtOH at reflux or the formation of the quinolines **74** in Toluene at 110°C both in the presence of a stoichiometric amount of *p*-TsOH·H_2O or $FeCl_3$ as the catalyst. Conversely, the $ZnBr_2$-catalyzed reaction in Toluene at 110 °C of the same internal alkyne derivatives gave only the *N*-alkenylindoles **75**. The presence of a trimethylsilyl group or no substituent at the terminal position of the starting aminoalkyne resulted in the formation of the corresponding quinolines. Moreover, the sequential Brønsted acid mediated reaction with enolisable ketones in EtOH of the starting aminoalkynes β-(2-aminophenyl)-α,β-ynones **76** resulted in an efficient approach to only polycyclic quinolines **77** (Scheme 64). [78]



Scheme 64. Sequential amination/annulation/aromatization reactions of β-(2-aminophenyl)-α,β-ynones **76** with enolisable ketones.

Steroids bearing a simple ketone group at position 3, such as 5α-cholestan-3-one, produced only the corresponding linear cholestanoquinoline derivative in moderate yield. On the contrary, the optimised methodology allowed the divergent generation of the angular quinoline derivative, whose synthesis is generally considered more challenging and demanding, from 3-keto-Δ^4-polycyclic steroidal derivatives. Interestingly, with steroidal dicarbonyl derivatives, the condensation reaction took place selectively only on the conjugated carbonyl group at position 3, leaving the ketone group at position 17 unreacted (Scheme 65). A- and D-ring fused steroidal quinoline analogues represent potential antibacterial agents. [79]

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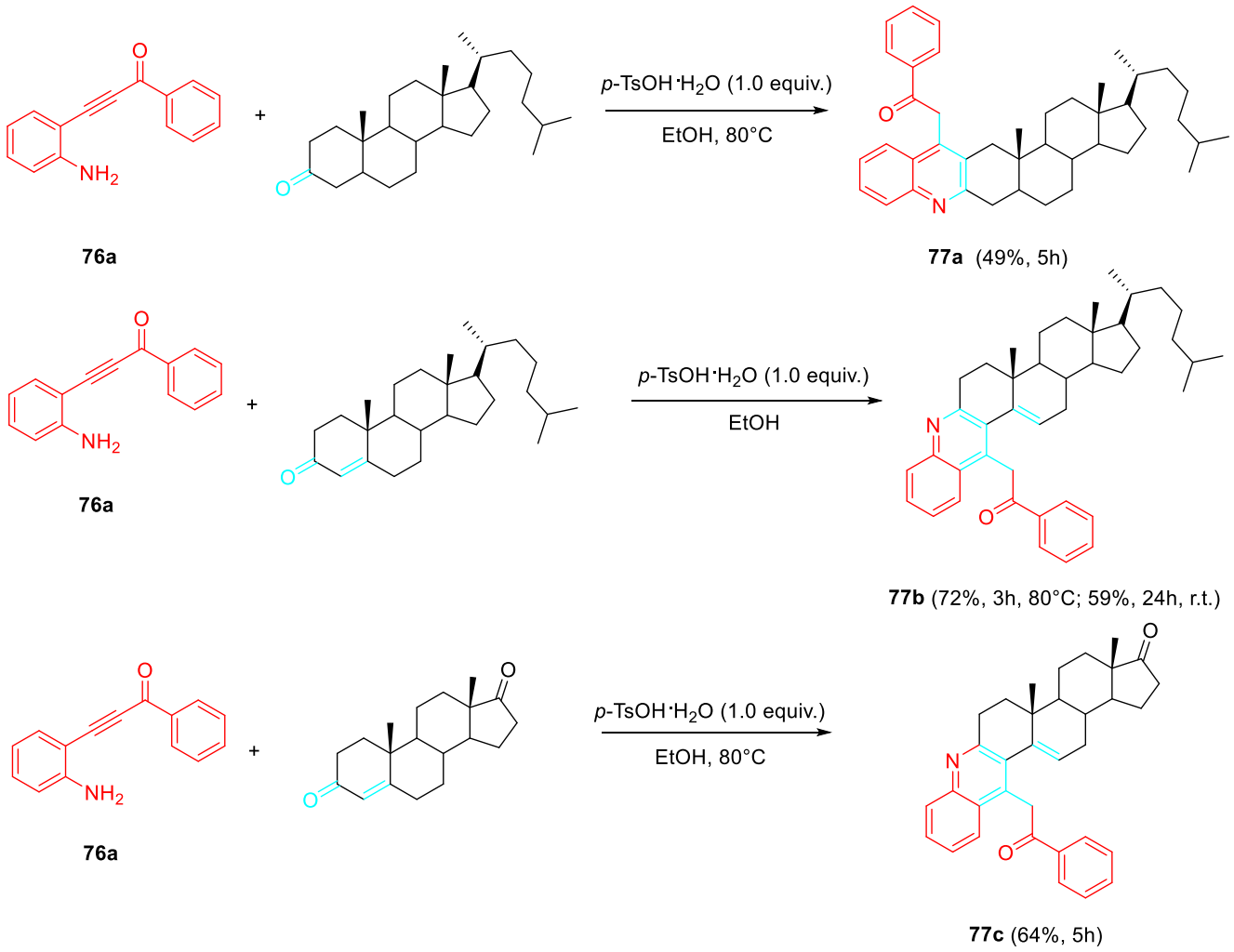

Scheme 65. Product selectivity control in the synthesis of polycyclic steroidal quinolines **77**.

The Brønsted acid-promoted reaction of β-(2-aminophenyl)-α,β-ynones with ketones was expanded to activated carbonyl compounds such as β-ketoesters and β-diketones. The carbonyl group at position 3 of the quinoline nucleus could further react with the other keto functionality in the alkyl-substituent at position 4, generating an additional [3,4]-fused 6-membered ring whose structure depends on the type of β-dicarbonyl compound used. Indeed, for β-ketoesters, a thorough screening of reaction conditions revealed that catalytic amounts of *p*-TsOH·H2O were sufficient to efficiently promote a cascade double-cyclisation leading to 4*H*-pyrano[3,4-c]quinoline-4-one derivatives **78**. On the contrary, with β-diketones, a stoichiometric amount of *p*-TsOH·H2O triggered a three-component reaction, involving a molecule of the alcoholic solvent to afford **79**. Both procedures appear to be simple and versatile and are expected to be of great impact since the multiple potential applications of the obtained organic compounds (Scheme 66). [80]

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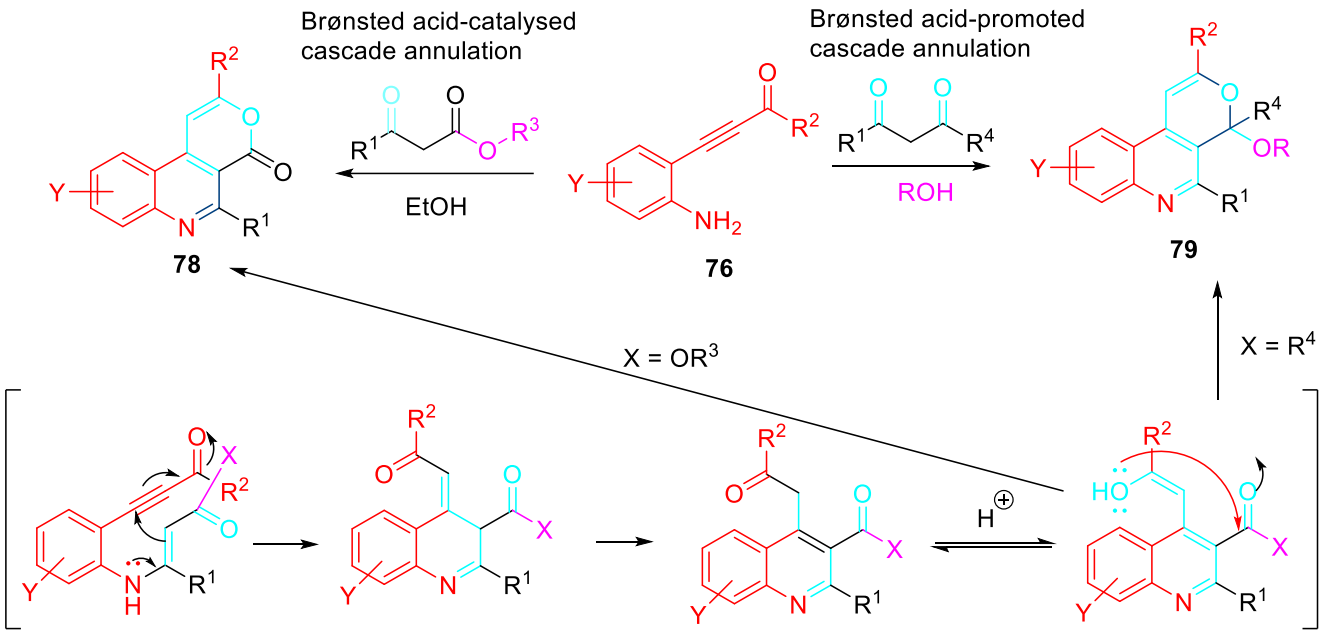
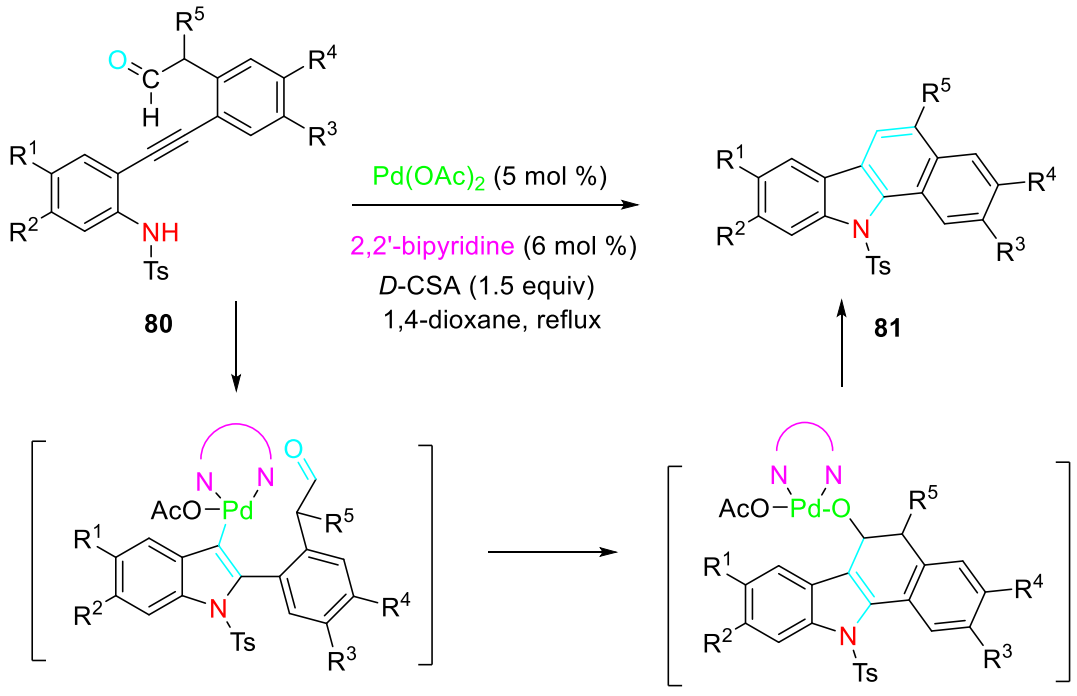


Scheme 66. Domino reactions of β-(2-aminophenyl) α,β-ynones with 1,3-dicarbonyls.

A sequential aminopalladation of β-amino alkyne derivatives **80**, followed by intramolecular nucleophilic addition of the generated carbon-palladium bond to a tethered aldehyde group achieved the synthesis of a variety of benzo[a]carbazoles **81** with remarkable diversification (Scheme 67). [81]



Scheme 67. Sequential aminopalladation of β-amino alkynes **80.**

The ongoing research activity devoted to the synthesis of indole derivatives encouraged to explore a high flexible approach to 11H-indolo[3,2-*c*]quinolines **83** according to the retrosynthetic Scheme 68.

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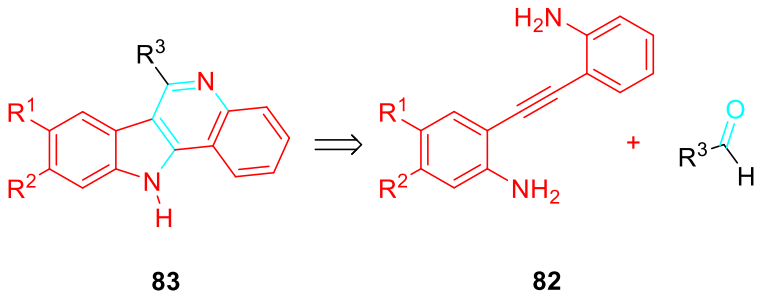
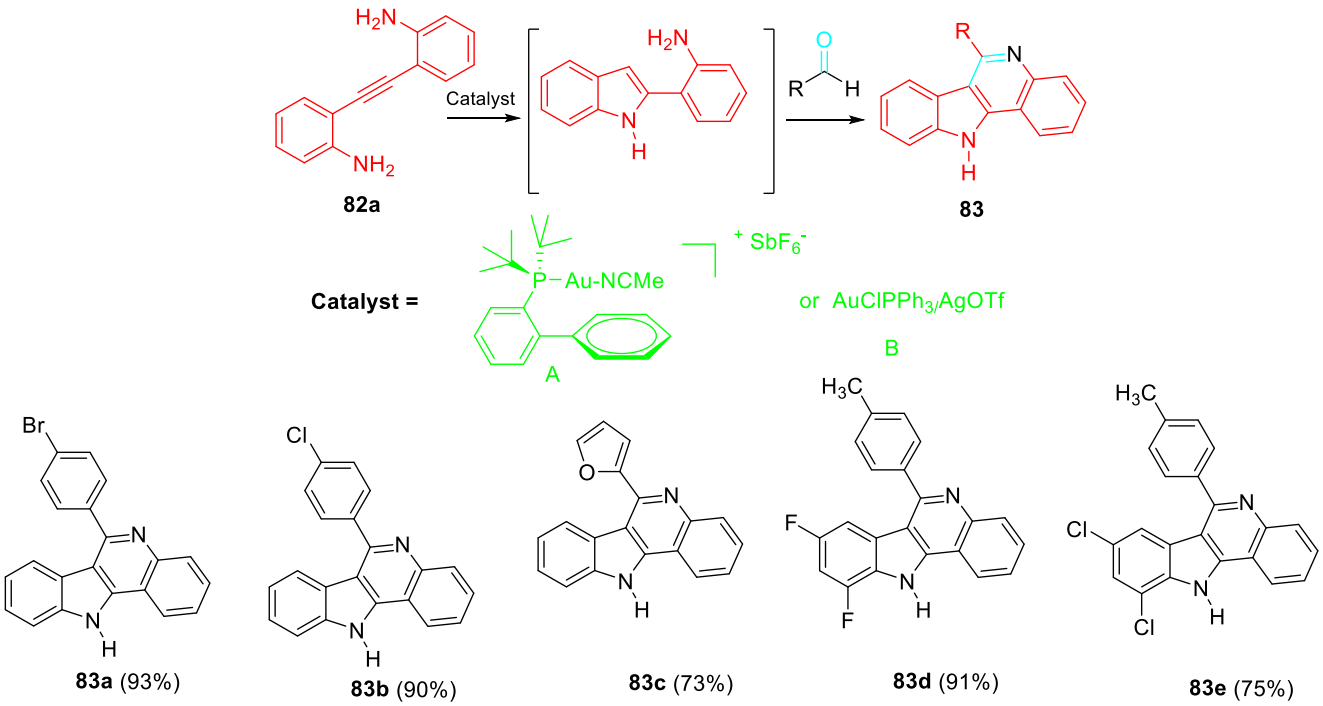


83 **82**

Scheme 68. Retrosyntetic assembly of 11H-indolo[3,2-*c*]quinolines.

Subsequently, the selective build-up of the 11H-indolo[3,2-c]quinoline **83** was carried out through a two-step one-pot gold-catalyzed reaction in CH_3CN at room temperature of aldehydes with the 2,2′-(ethyne-1,2-diyl)dianiline derivative **82a** as the starting β-aminoalkynes which was cyclised under the presence of Au catalyst (5 mol %). Then, the aldehyde (2 equiv.) was added and the reaction mixture was stirred till completion. This alternative high regioselective protocol is of wide applicability in mild neutral reaction conditions (Scheme 69). [82]



83a (93%) **83b** (90%) **83c** (73%) **83d** (91%) **83e** (75%)

Scheme 69. Gold-catalyzed synthesis of 11H-Indolo[3,2-*c*]quinoline **83**.

Surprisingly, the reaction of inexpensive aryl(heteroaryl)aldehydes with the same starting 2,2′-(ethyne-1,2-diyl)dianiline derivatives in the presence of a catalytic amount of HCl achieved the synthesis of 2,2'-disubstituted-1H,1'H-3,3'-biindoles **84** (Scheme 70). [83]

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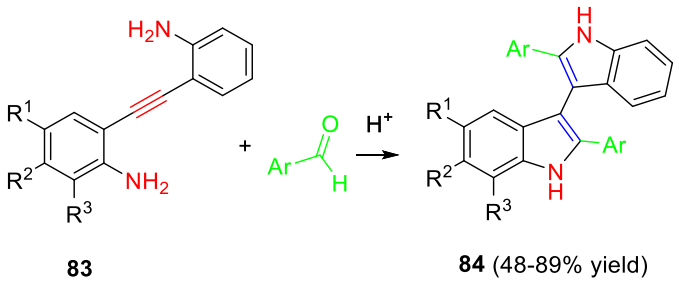
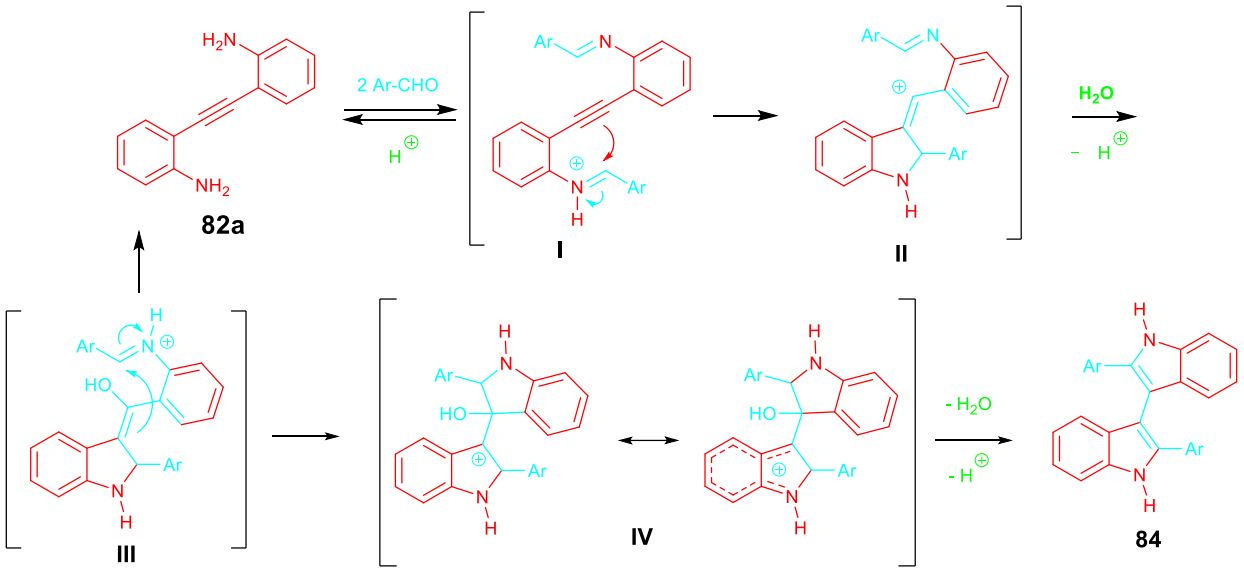


Scheme 70. Brønsted acid catalyzed synthesis of 2,2′-disubstituted 1H,1′H-3,3′-biindoles **84**.

Accordingly, a class of double D–p–A branched organic dyes based on 2,2′-disubstituted-1H,10H-3,3′-biindole moiety have been synthesised as photosensitizers for dye-sensitized solar cells. [84] Alternatively, the 2,2′-disubstituted 3,3′-biindoleswere were obtained by using an acidic DES able to exploit a double activity, i.e. solvent and BA catalyst under microwave heating at 70 °C. [85] Very likely, the Brønsted acid promotes the formation of the iminium ion **I** by reaction of **83** with two equiv. of the aldehyde. The iminium ion **I** undergo an aza-Prins type 5-*exo-dig* cyclization to the intermediate (**II**) quenched by the nucleophilic addition of water to give intermediate **III**. The subsequent cyclization generates the stabilized benzylic carbocation intermediate **IV** which provides the desired biindoles **85** by the loss of a molecule of water and the proton regeneration (Scheme 71).



Scheme 71. Proposed mechanism.

Analogously, the tandem gold-catalyzed 5-*endo-dig* / spirocyclization of 2-[(2-aminophenyl)ethynyl]phenylamines with isatins regioselectively afforded the corresponding 5′,11′-dihydrospiro-[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one derivatives **85** in good yields at room temperature. The reaction with ketones gave the 6,6-disubstituted-6,11-dihydro-5*H*-indolo[3,2-*c*]-quinolones **86** (Scheme 72). [86]

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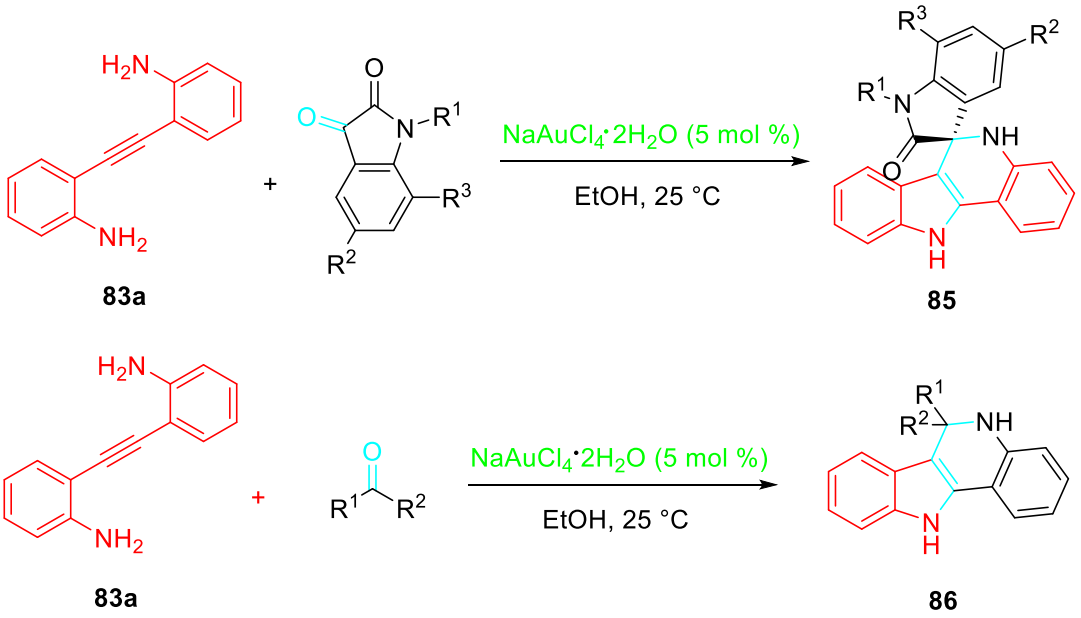
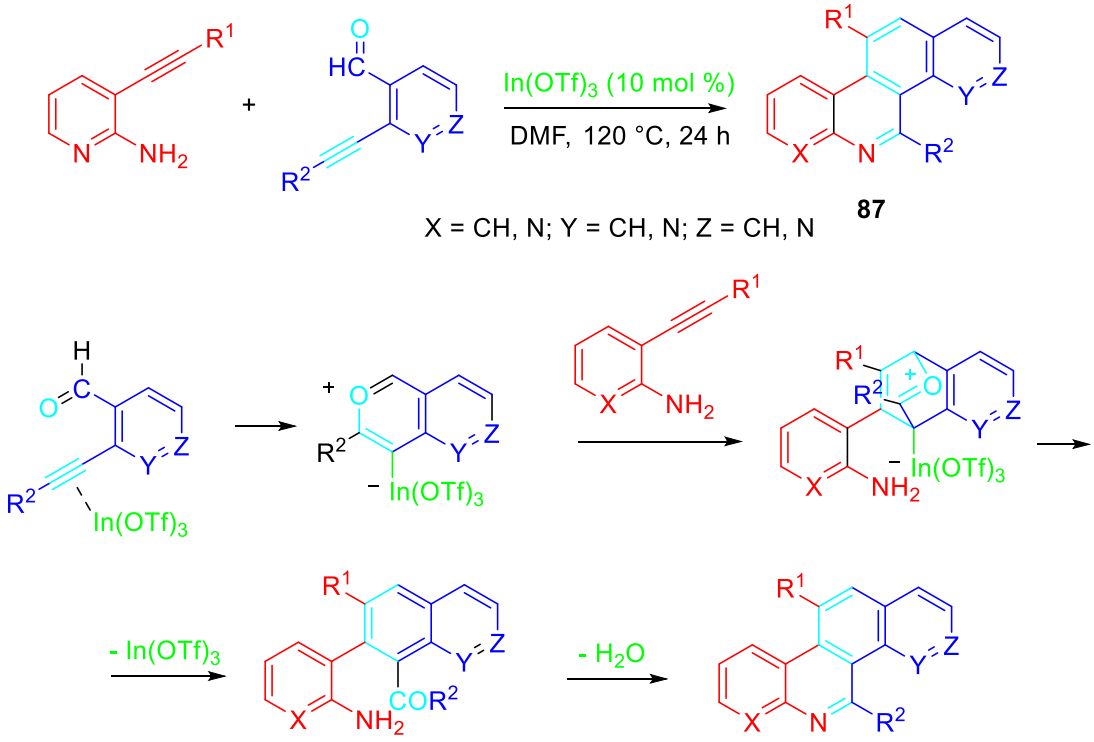


Scheme 72. Gold-catalyzed reaction of 2-[(2-aminophenyl)ethynyl]phenylamines **83** with isatins and ketones.

A sequential intramolecular nucleophilic attack/intermolecular cycloaddition/ dehydration reaction accomplished the synthesis of ring-condensed heteroaromatic compounds **87** starting from 2-alkynylbenzaldehydes and 2-alkynylanilines under the presence $In(OTf)_3$ catalyst (Scheme73). [87]



Scheme 73. Indium(III)-catalyzed sequential reaction of 2-alkynylanilines with 2-alkynylbenzaldehydes.

An intriguing three-component reaction of 2-alkynylanilines, aldehydes and α-(4-nitrophenyl)-α-isocyanoacetates in methanol at room temperature, followed by addition

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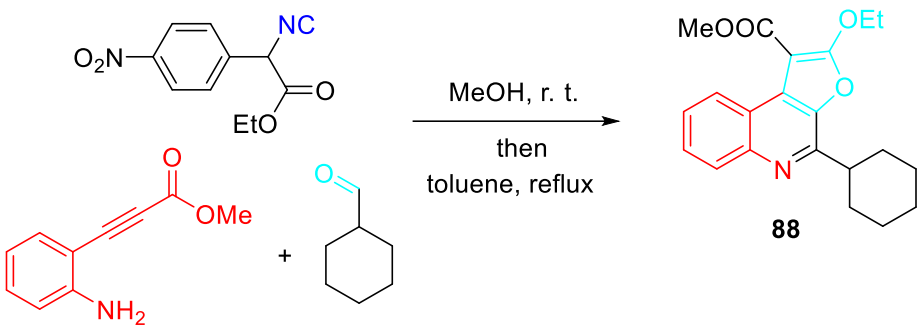
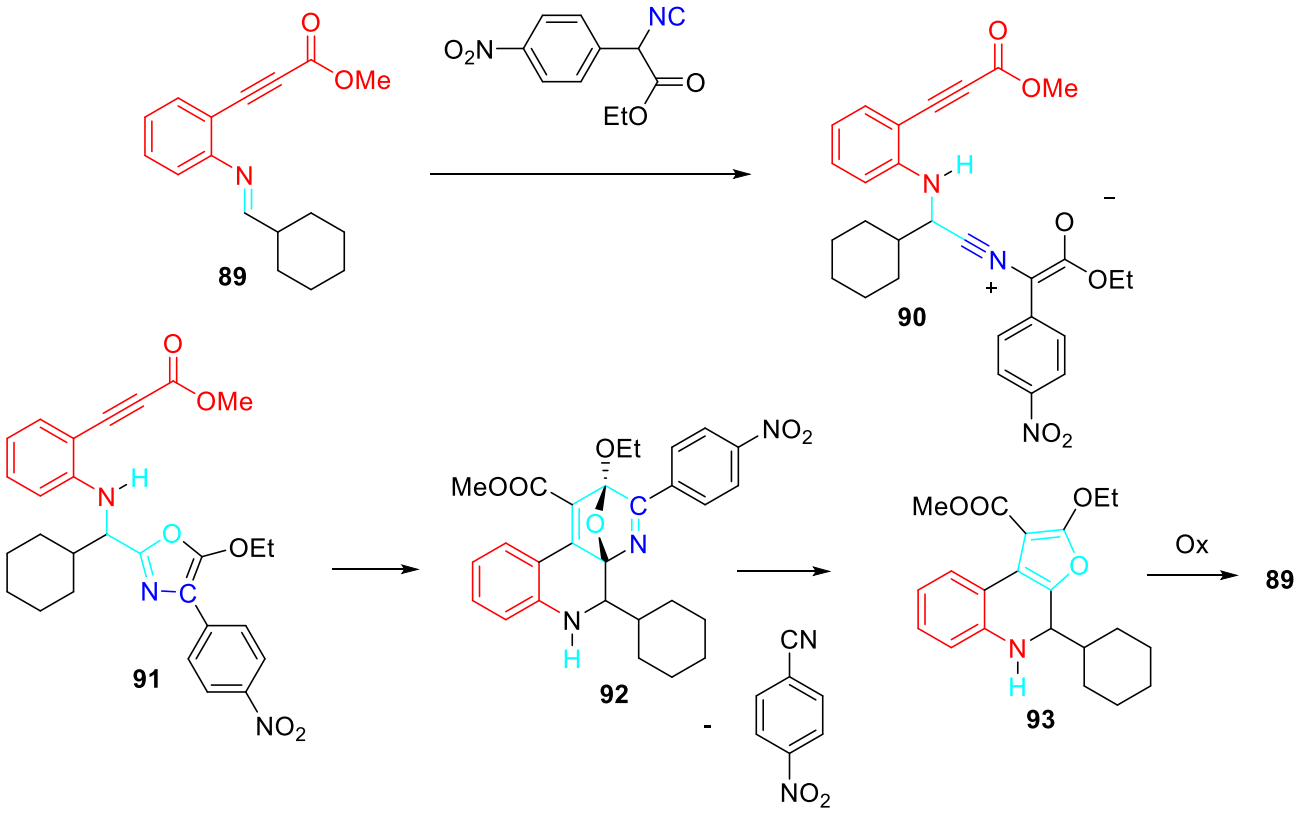
of toluene and heating to reflux, provided the polysubstituted furo[2,3-*c*]quinolines **88** in satisfactory yields (Scheme 74). [88]



Scheme 74. Synthesis of 2-alkoxyfuro[2,3-c]quinolones **88**.

The reaction of in the situ formed imine intermediate **89** with *α*-isocyanoacetates produces the 5-alkoxyoxazoles **91** which through an intramolecular Diels-Alder cycloaddition between the oxazole and the tethered triple bond would furnish oxa-bridged heterocycles **92**. Their subsequent fragmentation by a retro Diels-Alder process furnishes derivatives **93** and benzonitrile. Finally, oxidation mediated by atmospheric oxygen could generates the target aromatic 2-alkoxyfuro[2,3-*c*]- quinolones **88** (Scheme 75).



Scheme 75. Proposed mechanism.

A base-promoted post-Ugi 5-exo-dig ''Conia-ene''-type cyclization efficiently afforded a variety of 2,2-disubstituted 3-methyleneindoline derivatives **94** (Scheme 76). [89]

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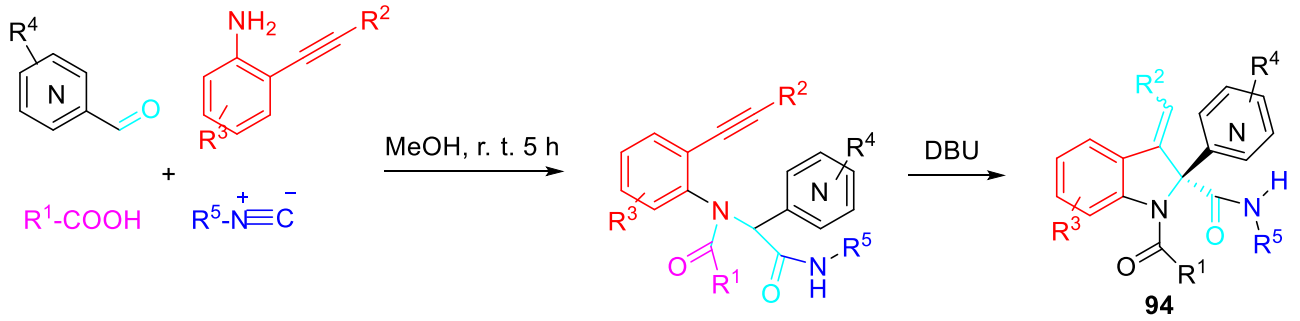
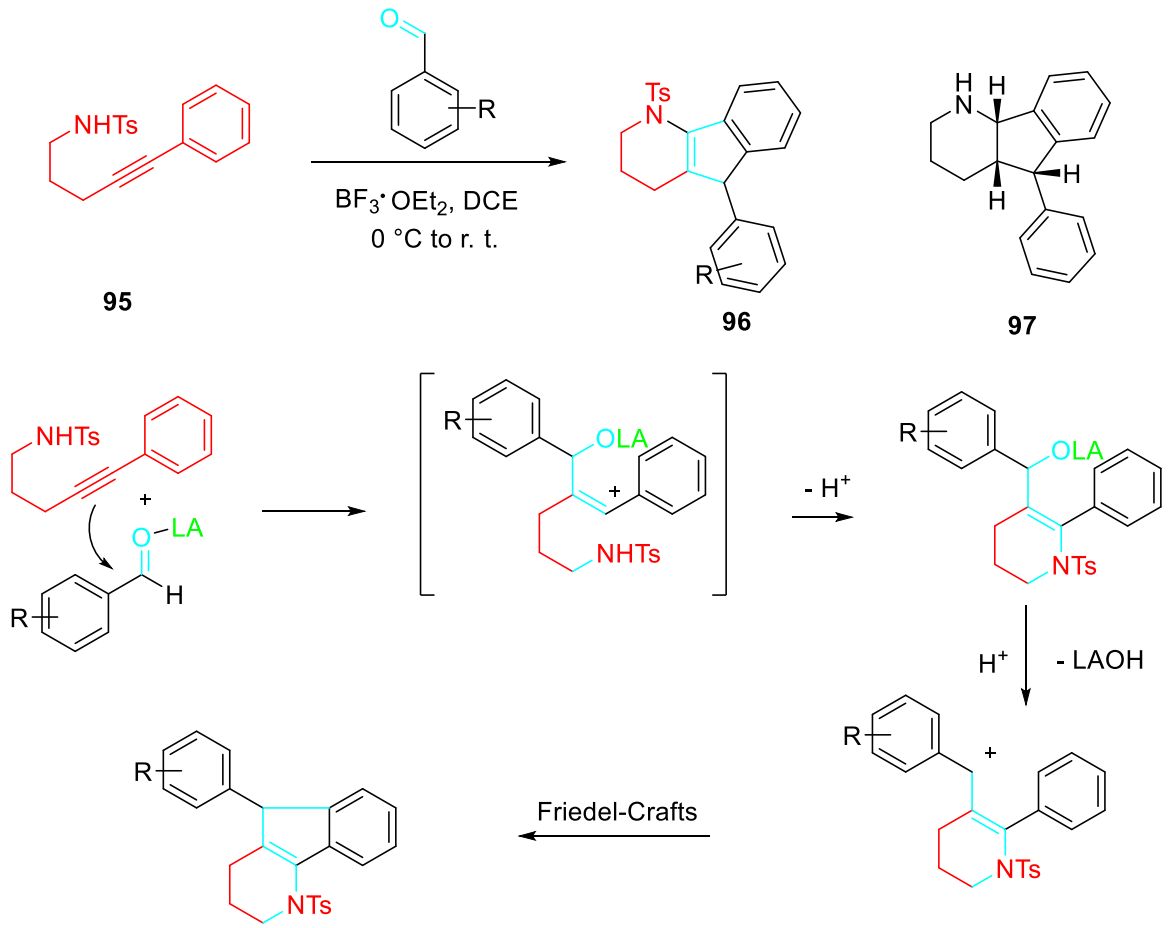


Scheme 76. Sequential multicomponent approach to 2,2-disubstituted 3-methyleneindolines **94**.

4. Sequential Reactions of γ- and δ-Aminoalkynes with Carbonyls

Sequential reactions of of γ- and δ-aminoalkynes with carbonyls were less investigated. A library of 1-tosyl-2,3,4,5-tetrahydro-1H-indeno[1,2-b]-pyridines **96** has been established by cascade cyclization / Friedel-Crafts reaction of 4-methyl-N-(pent-4-yn-1-yl)benzenesulfonamides **95** and aldehydes in good yields. The methodology was applied to the total synthesis of the antidepressant agent (±)-5-phenyl-2,3,4,4a,5,9b-hexahydro-1H-indeno[1,2-b]pyridine **97** (Scheme 77). [90]



Scheme 77. Synthesis of 1-tosyl-2,3,4,5-tetrahydro-1H-indeno[1,2-b]-pyridines **96**.

The sequential rhodium(III)-catalyzed intramolecular annulation of *o*-alkynyl amino aromatic ketones **98** / aromatization achieved the one pot building-up the pyrrolo[1,2-*a*]quinolines **99**. The protocol could be scaled-up and allowed the synthesis of challenging products suitable for further elaboration (Scheme 78). [91]

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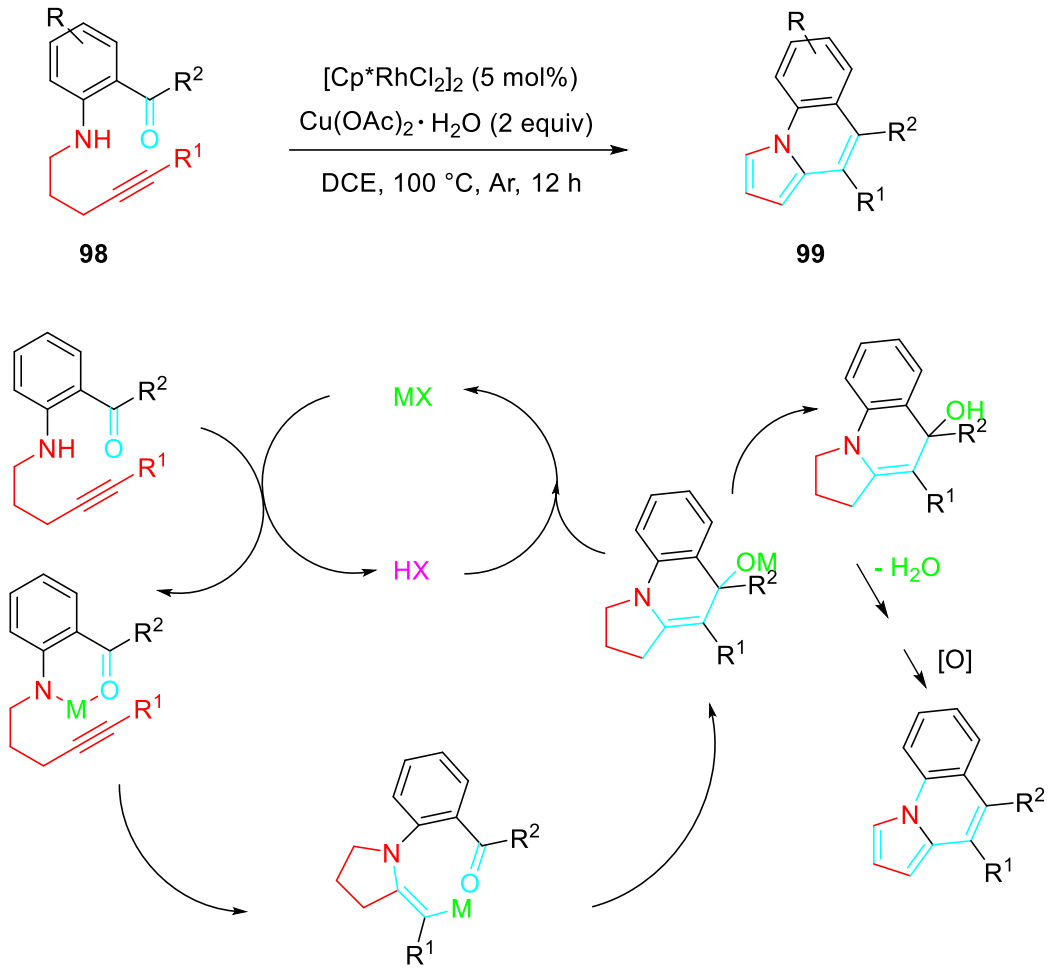

Scheme 78. Synthesis of pyrrolo[1,2-*a*]quinolines **99**.

Although the metal-catalyzed reaction of γ-aminoalkynes **100** with 1,3-diketones is expected to afford a wide variety of products, unexpectedly the reaction accomplished the isolation of only indolines **101** in up to 99% yield (Scheme 79). [92]

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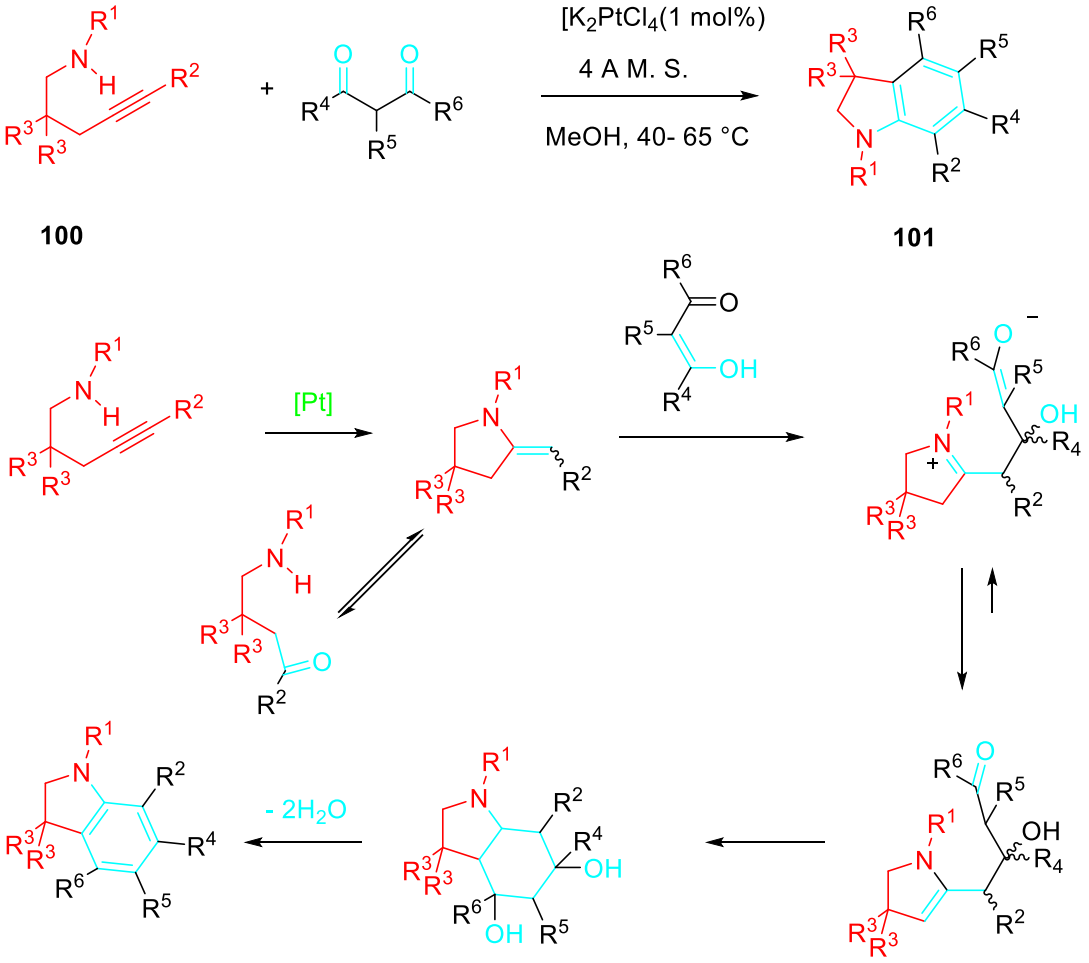
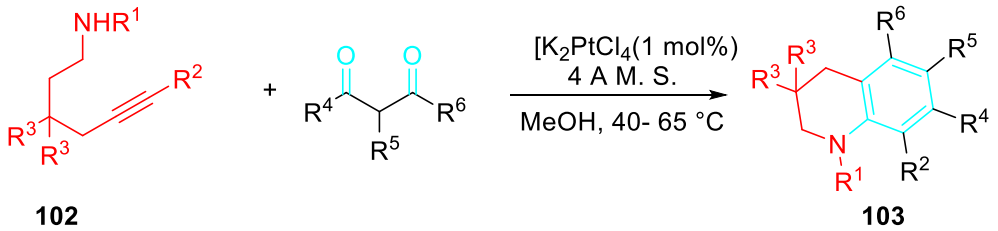


Scheme 79. Platinum(II)-catalyzed synthesis of indolines **101**.

The extension of the reaction to δ-aminoalkynes **102** gave in high yields the 1,2,3,4-tetrahydroquinolines **103** of importance in medicinal chemistry.



Scheme 80. Platinum(II)-catalyzed synthesis of tetrahydroquinolines **103**.

5. Conclusions and Outlook

A variety of aminoalkynes can trigger sequential reactions with carbonyls to generate valuable heterocyclic scaffolds. The increasing number of aminoalkynes as starting building blocks have greatly widened the scope of sequential approaches to large libraries of valuable nitrogen containing heterocyclic compounds which can be obtained from easily available reagents. Coinage metals dominated the field and in particular gold complexes demonstrated superior performance as catalysts for these transformations. Inexpensive and less toxic iron and zinc salts are growing in importance as efficient catalysts. As for reaction media, greener alternatives such water, ionic liquids and solventless reactions have been reported. Advantages of microwave irradiation over the convention-

al heating have also been highlighted. Extensive mechanistic studies allowed the identification of several intermediates and aid to explain the key role of the catalyst and the additives employed. Often, he activation of the alkyne moiety by metal catalysis is essential to boost the sequential process. We foresee that further advancements will achieve straightforward alternative easy access to a wide array of polyheterocyclic scaffolds with potential remarkable biological activity.

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Conflicts of Interest: The authors declare no conflict of interest.

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