catalysts

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Review

Metal-Catalyzed Cascade Reactions between Alkynoic Acids and Dinucleophiles: A Review

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Abstract: Cascade reactions provide a straightforward access to many valuable compounds and reduce considerably the number of steps of a synthetic sequence. Among the domino and multicomponent processes that involve alkynes, the cascade reaction between alkynoic acids and C-, N-, O- and S-aminonucleophiles stands out as a particularly powerful tool for the one-pot construction of libraries of nitrogen-containing heterocyclic compounds with scaffold diversity and molecular complexity. This reaction, based on an initial metal-catalyzed cycloisomerization that generates an alkylidene lactone intermediate, was originally catalyzed by gold(I) catalysts, along with silver salts or Brönsted acid additives, but other alternative metal catalysts have emerged in the last decade as well as different reaction media. This review examines the existing literature on the topic of metal-catalyzed cascade reactions of acetylenic acids and dinucleophiles and discusses aspects concerning substrate/catalyst ratio for every catalyst system, nature of the aminonucleophile involved and substrate scope. In addition, alternative solvents are also considered, and an insight into the pathway of the reaction and possible intermediates is also provided.

Keywords: cascade reactions; domino processes; metal catalysts; cycloisomerization

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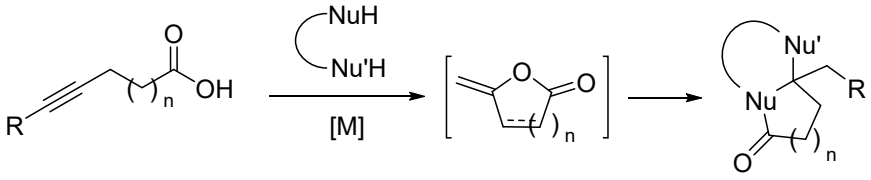
1. Introduction

In contrast with classical stepwise synthesis of organic compounds, cascade-based strategies provide a much faster, and in many cases, more efficient approach to an increasingly larger number of complex structures [1–4]. In fact, terms such as atom-economy and green chemistry are often associated with metal-catalyzed cascade reactions [5,6]. The last decades have witnessed significant advances in the fields of metal-catalyzed hydrofunctionalization of alkynes [7–13], and, more specifically, of cascade reactions involving alkyne hydrofunctionalization steps [14–19]. The intramolecular version of such cascade reactions, often based on the presence of suitably located carbo- and heteronucleophiles in the starting materials, has been also described [16,18,19]. In this regard, π-coordination of the C-C triple bond to a carbophilic transition metal catalyst can promote an initial cycloisomerization process that becomes the key step for a cascade approach to relatively complex frameworks. Among a number of substrates bearing alkyne and nucleophilic moieties (*o*-, γ-, or δ-alkynyl *N*-arylnitrones, amines, carboxamides, alkenes, arenes and heteroarenes, inter alia) [20–25], alkynoic acids stand out for their synthetic potential, since cycloisomerization of these acetylenic derivatives generates alkylidene lactones, which are prone to undergo nucleophilic attack (Scheme 1) [26–30].

In many cases, as a result of the above cascade reactions starting from alkynoic acids, analogs and isosteres of a number of pharmacologically relevant compounds have been straightforwardly prepared. Among others, tetrahydro-γ-carbolines (e.g., *Gevotroline*, *Tubastatin A* and *Dimebon*), identified as potent immunosuppressants and neuroprotective agents [31–38]; actinophenanthrolines [39] and quinazoline alkaloids such as

Vasicine (*peganine*), *Mackinazolinone*, *Batracyclin* and *Tryptanthrin* that exhibit anticancer, anti-inflammatory, antiprotozoal, antiallergic, antioxidant and antimicrobial activities [40–47] (Figure 1).



Scheme 1. An overall picture of metal-catalyzed cascade reaction of acetylenic acids and dinucleophiles.

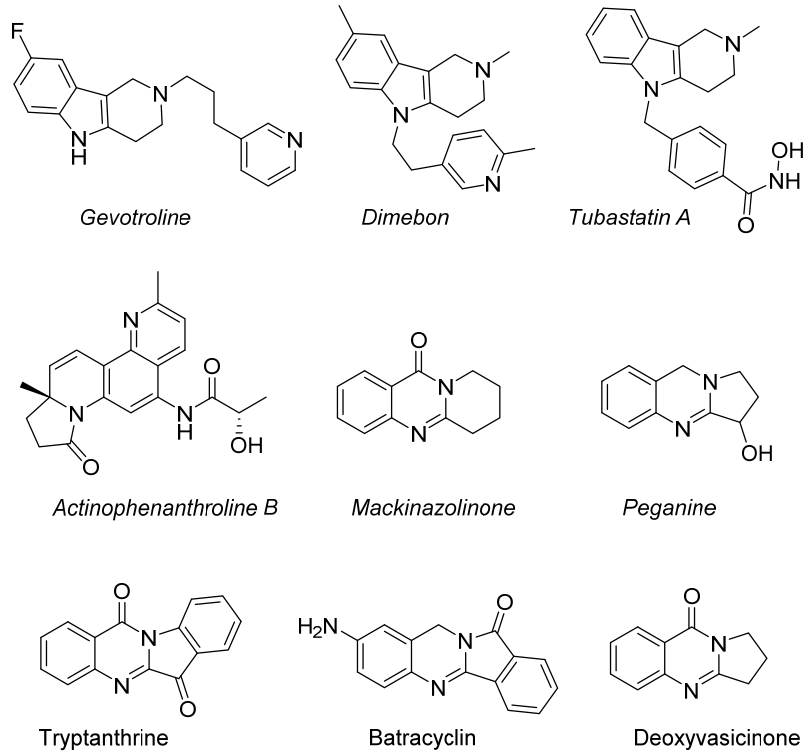
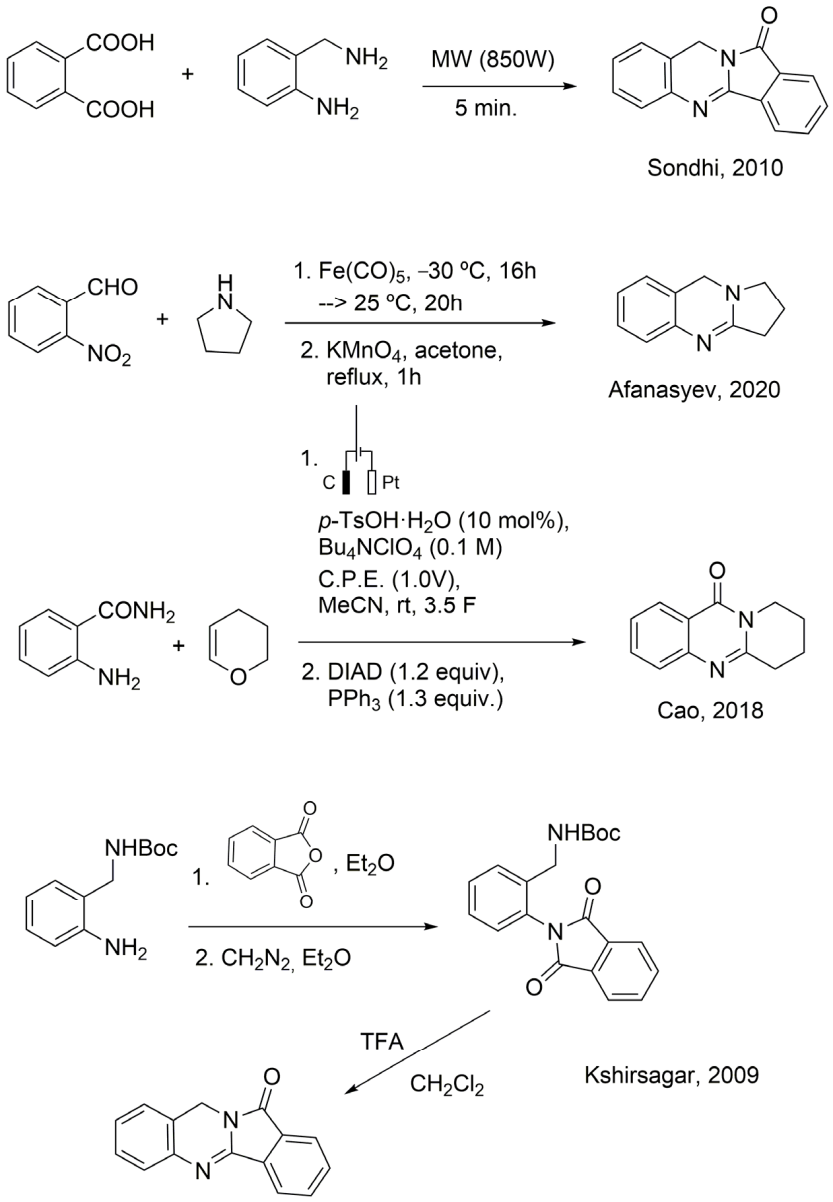


Figure 1. Structure of several tetrahydro-γ-carbolines, actinophenanthrolines and quinazoline alkaloids.

The synthesis of the latter structures has been limited to sequences involving two or more steps, although, recently, more efficient strategies often based on multiple condensations have been reported [45]. In this respect, the work of Sondhi and Rani on the solventless condensation of dicarboxylic acids with diamines under microwave irradiation [48], the one-pot oxidative condensation of anthranilamides with 3,3-dihydro-2*H*-pyrone followed by intramolecular Mitsunobu coupling, as reported by Kim and Cheon [49], the annulation/anodic oxidation of 2-aminobenzamides and aldehydes described by Cao et al. [50], the reductive condensation of *o*-nitrobenzaldehydes with amines using iron pentacarbonyl as reductant followed by oxidation, recently disclosed by the group of Chusov [51], and the reaction of *tert*-butyl 2-aminobenzylcarbamate and acid anhydrides to generate the corresponding imides, which are subsequently cyclized under acidic conditions [52] should be mentioned (Scheme 2).

In order to cover the literature on cascade reactions between alkynoic acids and dinucleophiles, this review is organized according to the metal catalyst used to promote the aforementioned cycloisomerization and further reaction with the dinucleophile species. In addition to the reaction scope, special emphasis will be given to the substrate: catalyst ratio and reaction media, and in some cases, the mechanistic proposals for such transformations will be described, along with several experiments performed to shed light of the role of the metal catalyst and other additives employed.



Scheme 2. Alternative strategies for the synthesis of tri- and tetracyclic quinazoline and quinazolinone derivatives. Sondhi, 2010: [48]; Afanasyev, 2020: [51]; Cao, 2018: [50]; Kshirsagar, 2009: [52].

2. Au Catalysts

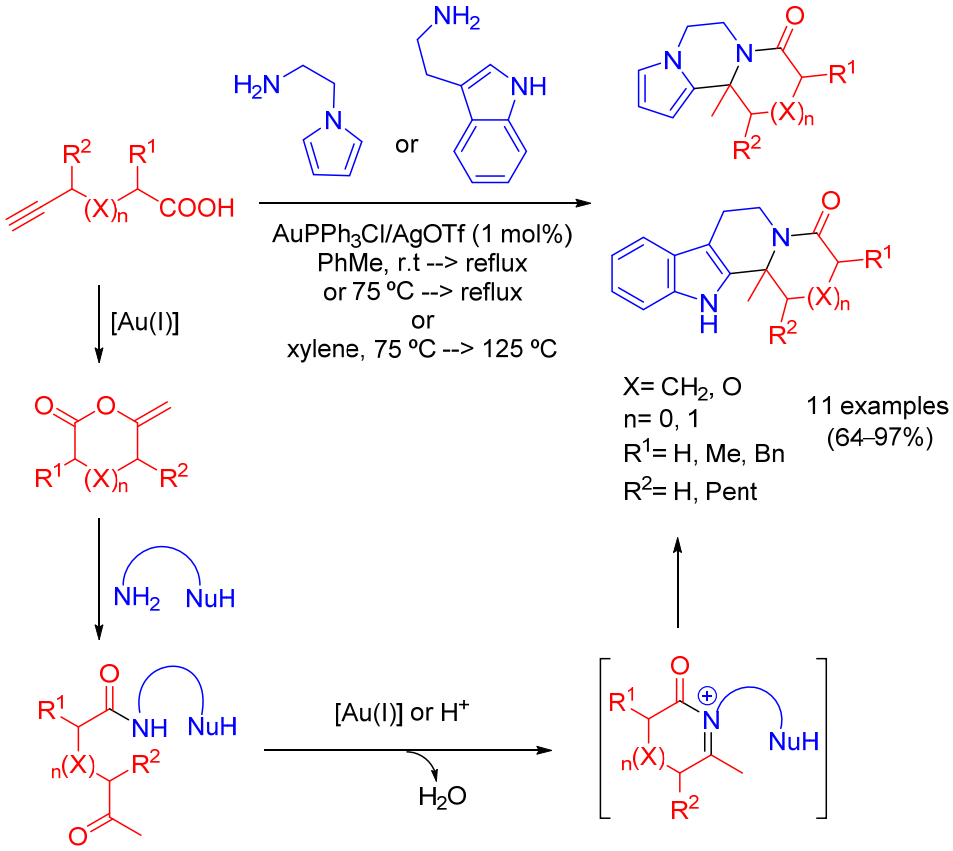
2.1. Introduction

Although some rivalling candidates have appeared along the way, gold-based catalysts have dominated the field from the very beginning. In addition to a relatively low catalyst amount, gold catalysts allow for the use of most aminonucleophiles explored so far. Indeed, this ample scope combined with a high efficiency have made gold the metal of choice for such transformations for a long time. In most cases, gold(I) catalysts were enough to promote the reactions, although occasionally combination with silver salts or Brönsted acids have led to optimized conditions.

2.2. Initial Reports

In 2007, Dixon and col. presented a pioneering work on the Au(I)-catalyzed cascade reaction of alkynoic and 2-propargyloxyethanoic acids with 1-(2-aminoethyl)pyrrole and 3-(2-aminoethyl)indole (tryptamine) in toluene or xylene [53]. Good to excellent yields were achieved in this $AuPPh_3Cl/AgOTf$-catalyzed reaction, and the authors proved not only the

participation of the alkynyl group as a masked ketone moiety released after nucleophilic attack at the initially formed exocyclic alkylidene lactone but also that a Lewis acid-assisted Brønsted acid catalysis is responsible for the formation of the *N*-acyliminium intermediate, which is the third stage of the cyclization cascade (Scheme 3).



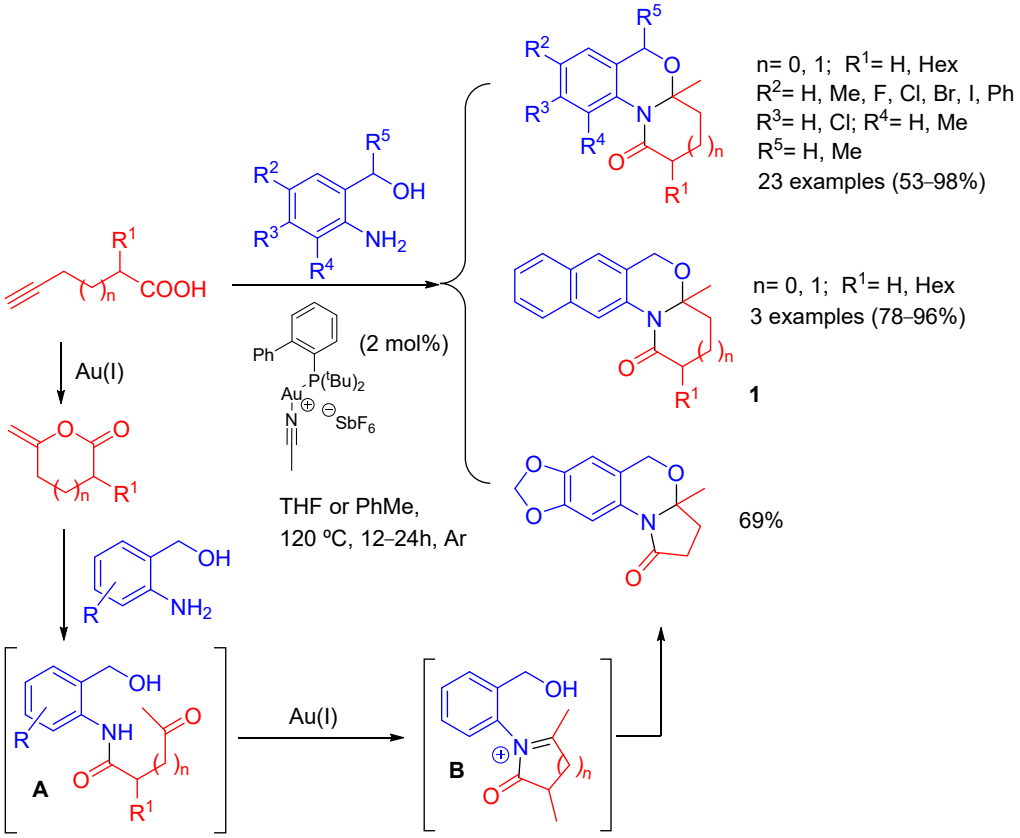
Scheme 3. Scope of the Au(I)-Catalyzed Cascade and mechanistic proposal.

In this regard, *N*-(2-(1*H*-pyrrol-1-yl)ethyl)-4-oxopentanamide, proposed as the ketoamide intermediate after the ring-opening of the initial alkylidene lactone with 1-(2-aminoethyl)pyrrole, was synthesized and subjected to several reaction conditions. Although boiling in toluene for 4 days resulted in no conversion, when a catalytic amount of triflic acid was added, the reaction provided target 10*b*-methyl-1,5,6,10*b*-tetrahydrodipyrrolo[1,2-*a*:2′,1′-*c*]pyrazin-3 (2*H*)-one. The results from these and other experiments with the same substrate in the presence of the 2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) base and the above gold catalyst led the authors to postulate that a Lewis acid-assisted Brønsted acid catalysis provides the activation required for the second stage of the cascade. 4-Hexynoic acid was also reacted with tryptamine and provided the corresponding heterocycle, although as a mixture of regioisomers. The same group published an enantioselective approach to the products derived from tryptamine by using preformed enol lactones and (*R*)-BINOL phosphoric acid derivatives as chiral Brönsted acid catalysts. A number of 5-monosubstituted and 4,5-disubstituted furan-2(3*H*)-ones and 6-methyl-3,4-dihydro-2*H*-pyran-2-one were reacted with several tryptamine derivatives in the presence of 3,3′-bis(triphenylsilyl)-(*R*)-BINOL phosphoric acid to provide the corresponding indolizino[8,7-*b*]indol-3-ones [54].

2.3. Au-Catalyzed Reaction between Alkynoic Acids and C-, O- and N-Aminonucleophiles; Further Advances in the Field

A large variety of pyrrolo- and pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones **1** were synthesized by Liu and col. from *o*-aminobenzyl alcohols and 4-pentynoic- and 5-hexynoic acids in the presence of a 2 mol% of [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}{CH_3CN}]SbF_6. Tetrahydrofuran

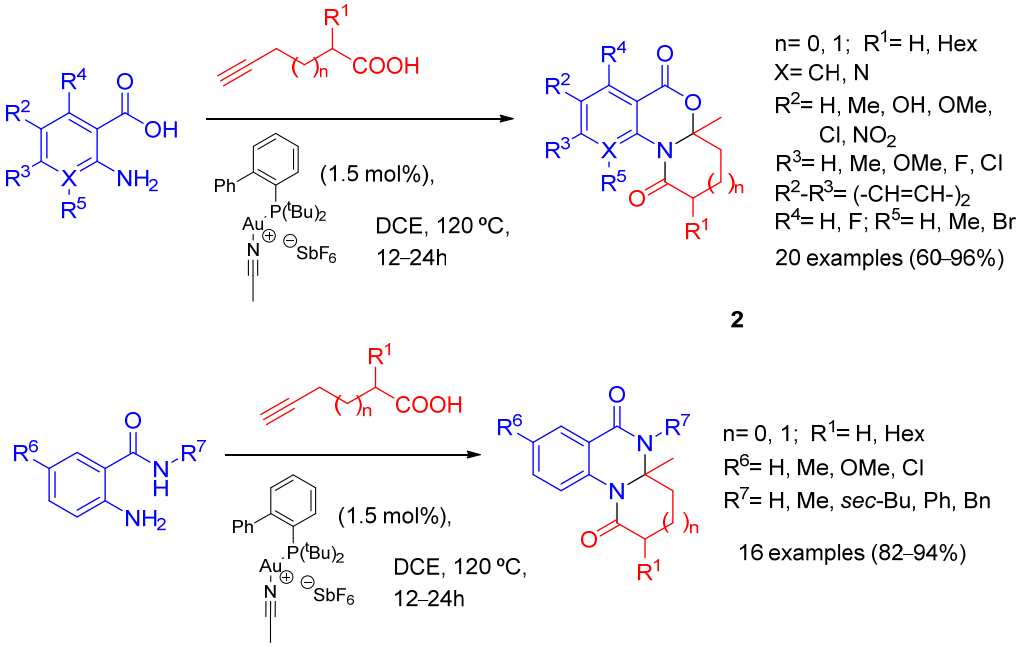
(THF) was the solvent of choice when dealing with most of the 4-pentynoic acid derivatives, while toluene was employed for reactions with 5-hexynoic acid. Regarding the reaction mechanism, the authors proposed that, after the initial cycloisomerization step, nucleophilic attack by the amino group generates a ketoamide intermediate **A** that, upon intramolecular condensation and the formation of the corresponding *N*-acyliminium ion **B**, undergoes nucleophilic attack by the carbinol moiety, thus providing tri- and tetracycles **1** with good yields [55] (Scheme 4).



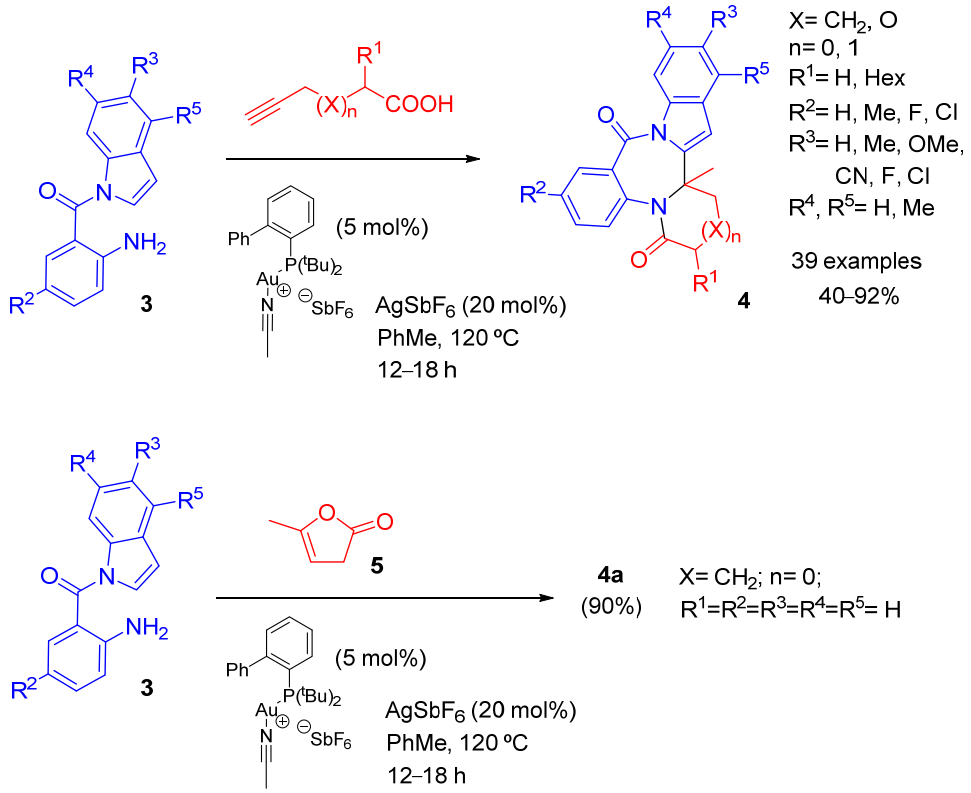
Scheme 4. Direct approach to benzo[*e*]indolo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine-3,9-diones and benzo[e]indolo[1,2-*a*]pyrido[2,1-*c*][1,4]diazepine-3,9-diones.

Almost simultaneously, this group reported the use of *o*-aminobenzoic acids and *o*-aminobenzamides as dinucleophiles to generate pyrrolo/pyrido[2,1-*a*][1,3]benzoxazinones and pyrrolo/pyrido [2,1-*a*]quinazolinones **2**. After a screening of different Au(III) and Au(I) sources, the same catalyst system was employed, although, this time, in 1,2-dichloroethane (DCE) was the solvent. It was confirmed not only that the reaction system was not sensitive to air and moisture at low catalyst loadings (1.5 mol%) but also that no silver salt or Brönsted acid ($AgSbF_6$ or CF_3COOH, respectively) was required to obtain optimal results or shorter reaction times. A similar mechanism was proposed for this transformation that took place at the same temperature (120 °C, Scheme 5) [56].

In 2011, another type of dinucleophiles, (2-aminophenyl)(1*H*-indol-1-yl)methanone derivatives **3**, was reacted with pentynoic, hexynoic and 2-propargyloxyethanoic acids. In this case, [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}{CH_3CN}]SbF_6 was combined with $AgSbF_6$ for optimal results in toluene as a solvent, thus obtaining benzo[*e*]indolo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine-3,9-diones and benzo[e]indolo[1,2-*a*]pyrido[2,1-*c*][1,4]diazepine-3,9-diones **4** with good yields. In order to prove the proposed mechanism, the authors reacted alfa-angelica lactone **5** (5-methyl-2(3*H*)-furanone) with dinucleophile **3** under the optimized reaction conditions, and the corresponding benzo[*e*]indolo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine-3,9-dione **4a** was obtained in 90% yield [57] (Scheme 6).



Scheme 5. Anthranilic acids and *o*-aminobenzamides as dinucleophiles for the gold-catalyzed cascade reaction with alkynoic acids.



Scheme 6. Cascade reaction with aminophenyl)(1*H*-indol-1-yl)methanone derivatives.

Contemporaneously, Patil and col. reported the cascade reaction of alkynoic acids with phenylenediamines or *o*-aminobenzylamines in the presence of 1 mol% of $Ph_3PAuOTf$ catalyst. Considering the substitution at the aromatic ring of these nucleophiles, the excellent regioselectivity observed for the 37 tri- and tetracycles obtained was attributed to the difference in nucleophilicity between amino groups. When α- or α,α′-substituted pentynoic acids were employed, the corresponding dihydrobenzimidazoles **6** and tetrahy-

droquinazolines **7** were obtained with good to excellent diastereomeric ratios (Figure 2), which was confirmed by NOE studies. In addition, the authors provided an alternative procedure based on microwave irradiation in the same solvent (1,2-dichloroethane), thus enhancing the reaction rate in comparison with conventional heating (30 min vs. 24 h). Finally, several mechanistic studies were conducted in order to shed light not only on the role of the Au(I) catalyst and the possible participation of Brönsted acid TfOH but also on the reason for the diastereoselectivity observed [58].

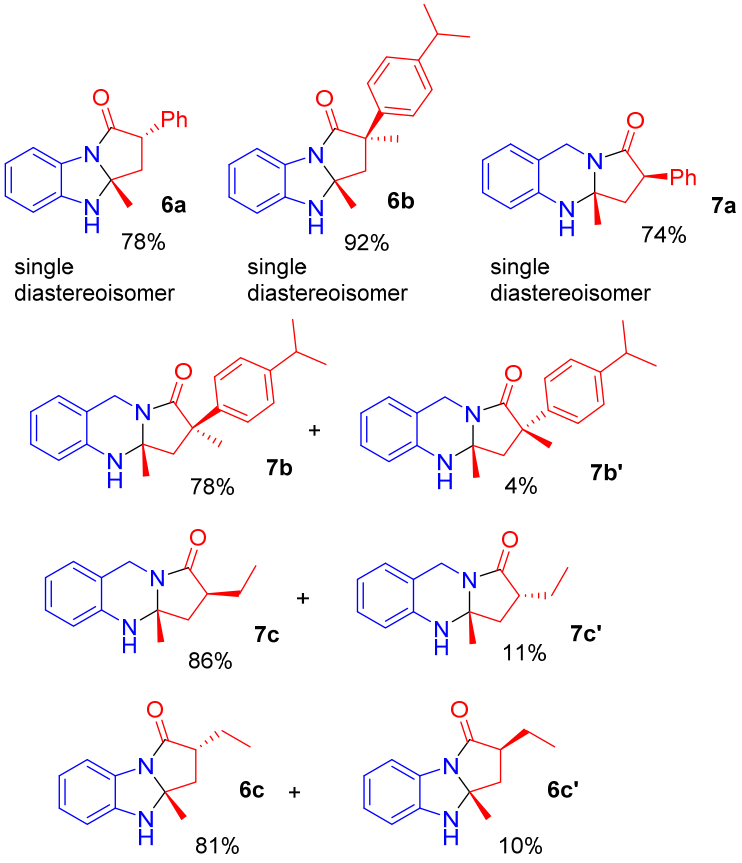


Figure 2. Diastereoselectivity observed in the cascade reactions with phenylenediamines or *o*-aminobenzylamines reported by Patil and col.

In 2013, the same group expanded dramatically the scope and synthetic potential of this cascade reaction by reacting equimolecular amounts of 30 different dinucleophiles (scaffold-building agents) and 8 alkynoic acids in dichloroethane at 100 °C for 24–36 h in the presence of the same Au(I) catalyst ($Ph_3PAuOTf$, 5 mol%). As a result of this combination, a library of 61 polycyclic structures (Figure 3) were readily prepared. Indeed, this reaction was used as a basis for a catalytic branching cascade that generates a large scaffold diversity, and therefore implemented as a powerful strategy for diversity-oriented synthesis. It should be also pointed out that most reactions took place with good yields and complete chemo- and regioselectivity [59].

In 2012, Liu's group reported a more sustainable reaction media for the cascade between 4-pentynoic acid and 2-(1*H*-indol-1-yl)ethan-1-amine derivatives. The reaction was carried out in water using 10 mol% of chloro[(1,1′-bi-phenyl-2-yl)di*tert*-butylphosphine]gold(I) catalyst at 150 °C under microwave irradiation, providing several tetrahydropyrrolopyrazino[1,2-a]indolones with good yields (88–97%). However, when α-substituted pentynoic acids or 5-hexynoic acid or 3-(1*H*-indol-1-yl)propan-1-amine were employed as substrates or when electron-withdrawing groups were present in the 2-(1*H*-indol-1-yl)ethan-1-amine dinucleophile, a one-pot two-step procedure was required to prepare target tetracycles in

good yields. Thus, after reacting in the presence of the above Au(I) catalyst, trifluoroacetic acid (1 equiv.) was added and microwave heating continued for a further 30 min [60].

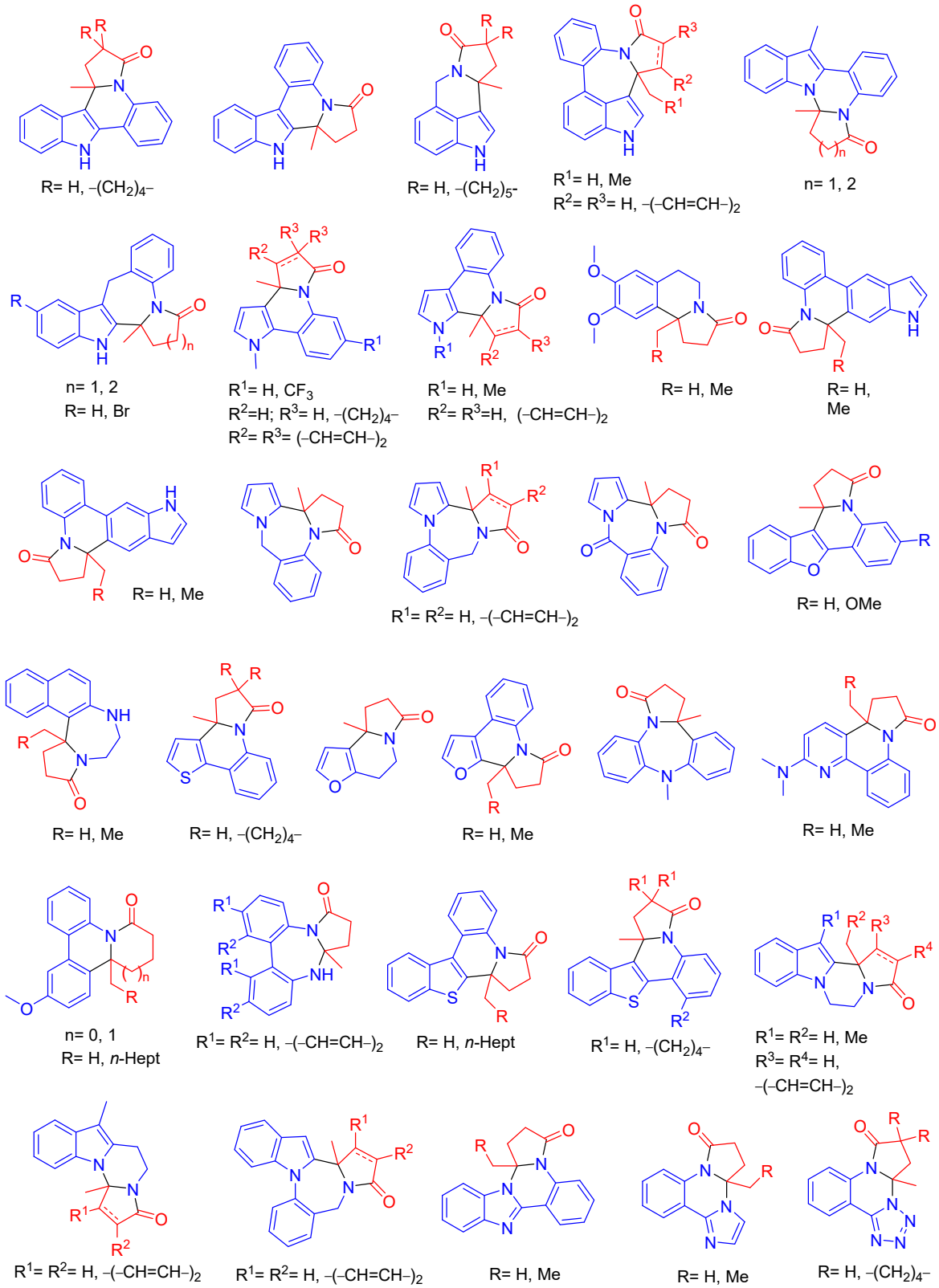
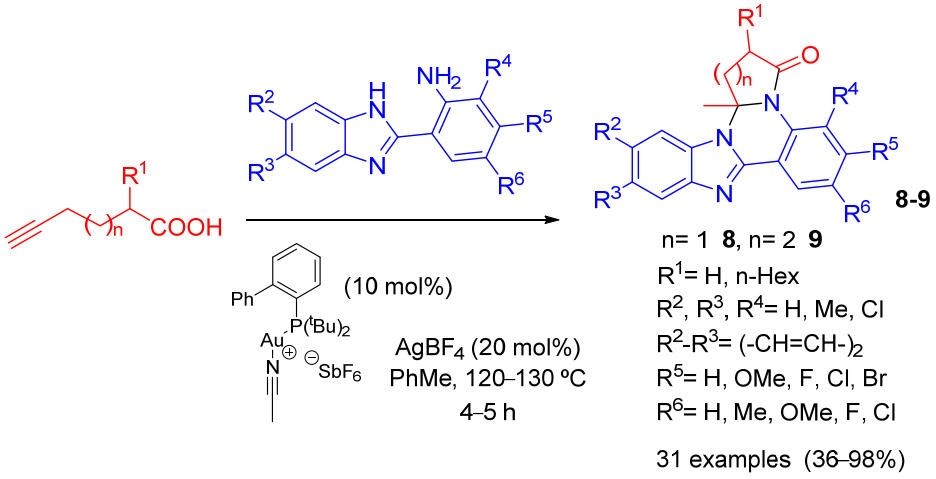


Figure 3. Library of compounds prepared by a relay catalytic branching cascade from alkynoic acids and dinucleophiles. Note: The moieties derived from alkynoic acids and dinucleophiles are depicted respectively in red and blue in the final products.

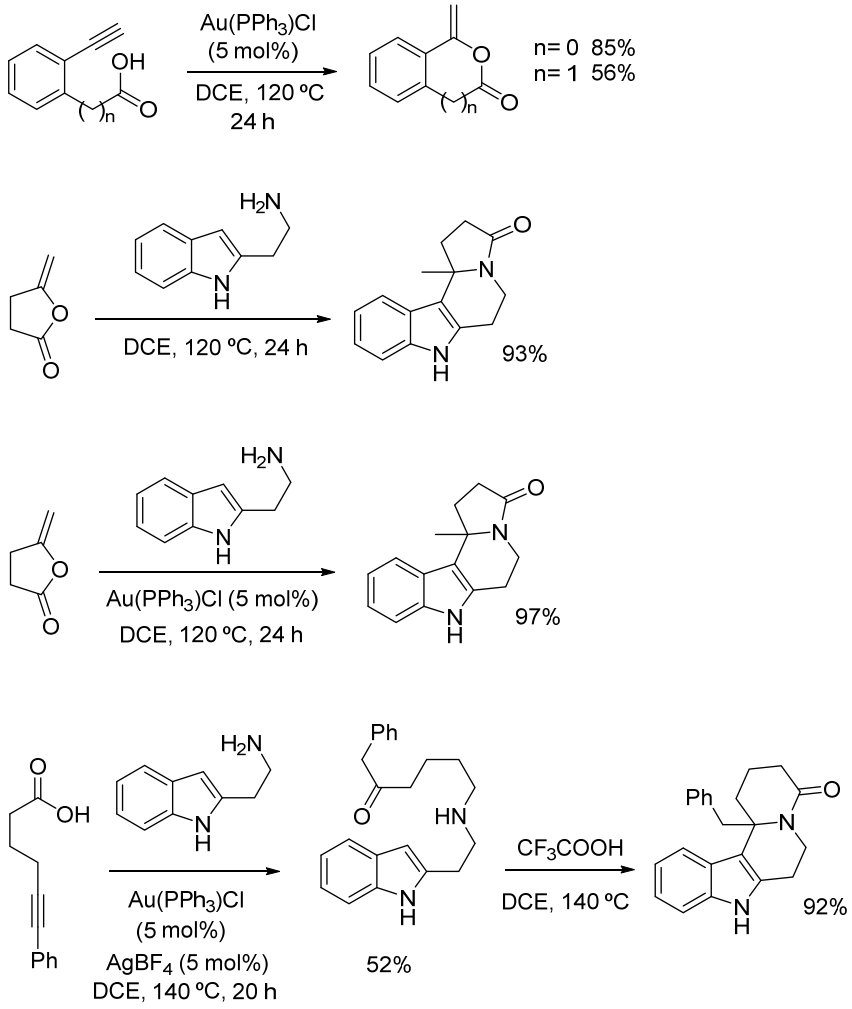
The same group reported the preparation of 31 benzo[4,5]imidazo[1,2-*c*]pyrrolo[1,2-*a*]quinazolinones **8** by reacting 2-(1*H*-benzo[*d*]imidazol-2-yl)anilines with 4-pentynoic acids in the presence of 10 mol% of [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}{CH_3CN}]SbF_6 and 20 mol% of $AgBF_4$ in toluene at 120–130 °C. These optimized conditions were determined by testing a number of Au(I) and Ag catalysts, including $AuCl(PPh_3)$, $AgSbF_6$, and $AgBF_4$, among others. Possible additive effects from the combination of cocatalysts ($AgSbF_6$, $AgBF_4$, AgO_2CCF_3, AgOTf, and trifluoroacetic acid) were also examined. The authors studied the influence of the substituents at both the benzoimidazole and aniline moieties in the reaction outcome. In this regard, they observed that the presence of electron-donating substituents such as methyl or methoxy at the aniline moiety, and specially at the *ortho*-position (R^4 substituent, Scheme 7) caused a substantial decrease in the reaction yield. A similar effect related to the presence of methyl or chloro groups at the benzimidazole moiety of the 2-(1*H*-benzo[*d*]imidazol-2-yl)aniline reagent was also observed (R^2 and R^3 substituents). A decreased yield could be attributed to a possible steric hindrance when using α-substituted 3-ethynylnonanoic acid was also accounted for. When the optimized protocol was applied to 5-hexynoic acid, the corresponding benzo[4,5]imidazo[1,2-*c*]pyrido[1,2-*a*]quinazolin-6-ones **9** were obtained, albeit in lower yields than those from 4-pentynoic acid, even at slightly higher temperatures (130 °C). The same decreasing effects related to the presence of R^2-R^3 substituents at the benzimidazole moiety, and R^4-R^6 at the aniline fragment of the 2-(1*H*-benzo[*d*]imidazol-2-yl)aniline *N*-aminonucleophile were noticed, with 5-hexynoic acid as the counterpart [61] (Scheme 7).



Scheme 7. Cascade reaction with 2-(1*H*-benzo[*d*]imidazol-2-yl)aniline derivatives.

Some years later, in 2019, this group described the first use of 1,3-unsubstituted 2-(1*H*-indol-2-yl)ethanamines as aminonucleophiles. Taking $Au(PPh_3)Cl$ as catalyst and an extensive number of dinucleophiles, they carried out the construction of a library of indole/pyrrole/thiophene/benzene/naphthalene/pyridine-based nitrogen-containing heterocyclic compounds with scaffold diversity (more than 78 examples were prepared). However, in many cases, it was necessary to perform a one-or two-step procedure which involved the addition of trifluroacetic acid and heating in the second step (1. $Au(PPh_3)Cl$ (5 mol%), DCE, 120–140 °C, 20–24 h; 2. CF_3COOH (1 equiv.), 120–140 °C, 20–24 h). Several additional experiments (Scheme 8) showed not only the participation enol lactone intermediates but also that the gold catalyst is responsible for the formation of enol lactone intermediate and for the iminium ion formation. In addition, a 90% yield was obtained from the reaction between 2-(1*H*-indol-2-yl)ethanamine and 4-pentynoic acid on a gram scale. A simple carbonyl group reduction with $LiAlH_4$-$AlCl_3$ of some the compounds of the above library provided several α_{1A}-adrenoceptor antagonists. In addition, after a pharmacological screening of the compounds directly accessed through the cascade reaction, the authors reported the antiproliferative activities against human cancer cell lines of two compounds,

a tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione and a tetrahydroindolo[3′,2′:3,4]pyrido[2,1-*a*]isoquinolin-6(5*H*)-one [62].



Scheme 8. Mechanistic studies performed by Liu, Zhao and col.

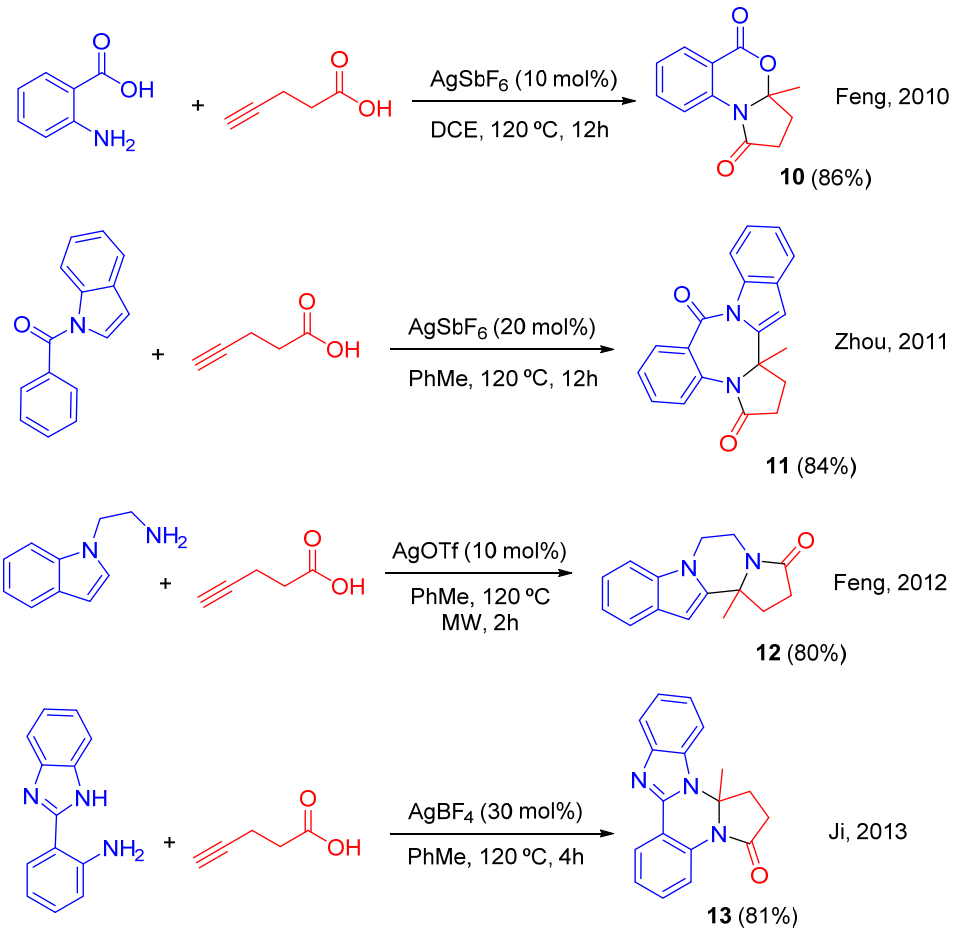
Following their research on such cascade reactions in water [60], Liu and Zhao's group also disclosed a more efficient method based on the same Au(I) catalyst (1 mol%) and Brønsted acid for reactions performed in water as the only solvent. More than 70 compounds were prepared under these conditions, with yields ranging 18–96%. As in previous cases, depending on the substrates involved, an Au(I)-catalyzed genuine cascade or a one-pot two-step tandem reaction was required to access target compounds. The authors also conducted deuteration and ^{18}O labeling experiments for mechanistic purposes, and some of the obtained tetra- and pentacycles were derivatized by reducing the amide carbonyl group with $LiAlH_4/AlCl_3$ [63].

3. Ag Catalysts

3.1. Introduction

During the screening of metal catalysts, it was observed that several silver(I) salts could promote the reaction between alkynoic acids and aminonucleophiles. However, due to the slightly lower yields and considerably higher catalyst amounts required, silver catalysts were discarded and replaced with more efficient gold catalysts, although in some cases a combination of both metal catalysts showed a synergistic effect, as outlined in Sections 2.2 and 2.3 [53,57,61] (Schemes 3, 6 and 9). Anyway, even with the limitation of a narrow substrate scope, the synthesis of several polycyclic compounds by reacting

alkynoic acids and aminonucleophiles in the presence of silver salts as the sole catalysts has been described.



Scheme 9. Cascade reaction between 4-pentynoic acid and different aminonucleophiles in the presence of silver catalysts. Feng, 2010: [56]; Zhou, 2011: [57]; Feng, 2012: [60]; Ji, 2013: [61].

3.2. Ag-Catalyzed Reaction between Alkynoic Acids and Aminonuclephiles

Among different coinage and precious metal catalysts, AgOTf (1 mol%) was tested to promote reaction between phenylene diamine and 4-pentynoic acid in 1,2-dichloroethane (DCE) at 100 °C, and the corresponding tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one was obtained by Patil and col. with a moderate 40% yield [58]. Increasing the amount of $AgSbF_6$ catalyst to a 10 mol% allowed Liu and col. to prepare benzo[d]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione **10** with an 80% yield from anthranilic and 4-pentynoic acids (Scheme 9) [56]. The same group also tested several Ag(I) salts to synthesize benzopyrrolo[2′,1′:3,4][1,4]diazepino[1,2-*a*]indole-3,9(2*H*)-dione **11** by reacting 4-pentynoic acid and (2-aminophenyl)(4-methyl-1H-indol-1-yl)methanone. Although a 5 mol% of AgOTf, $AgBF_4$ and $AgSbF_6$ in toluene provided target compound with moderate results (45–50%), the yield rose to 84 when a 20 mol% of $AgSbF_6$ was employed (Scheme 9) [57]. Another C-aminonucleophile, 2-(1*H*-indol-1-yl)ethan-1-amine, was reacted with 4-pentynoic acid to provide tetrahydropyrrolopyrazino[1,2-*a*]indolone **12** in the presence of AgOTf or $AgSbF_6$ (Scheme 9) [60]. Structurally related 2-(1*H*-indol-2-yl)ethanamine, which could act as both C-amino- and N-aminonucleophile, was also reacted using AgOTf and $AgSbF_6$ catalysts [62]. Finally, dihydrobenzo[4,5]imidazo[1,2-*c*]pyrrolo[1,2-*a*]quinazolin-3(2*H*)-one **13** was obtained with a good yield (81%) when 2-(1*H*-benzo[d]imidazol-2-yl)aniline was employed as N-aminonucleophile, although catalyst loading was increased to a 30 mol% (Scheme 9) [61].

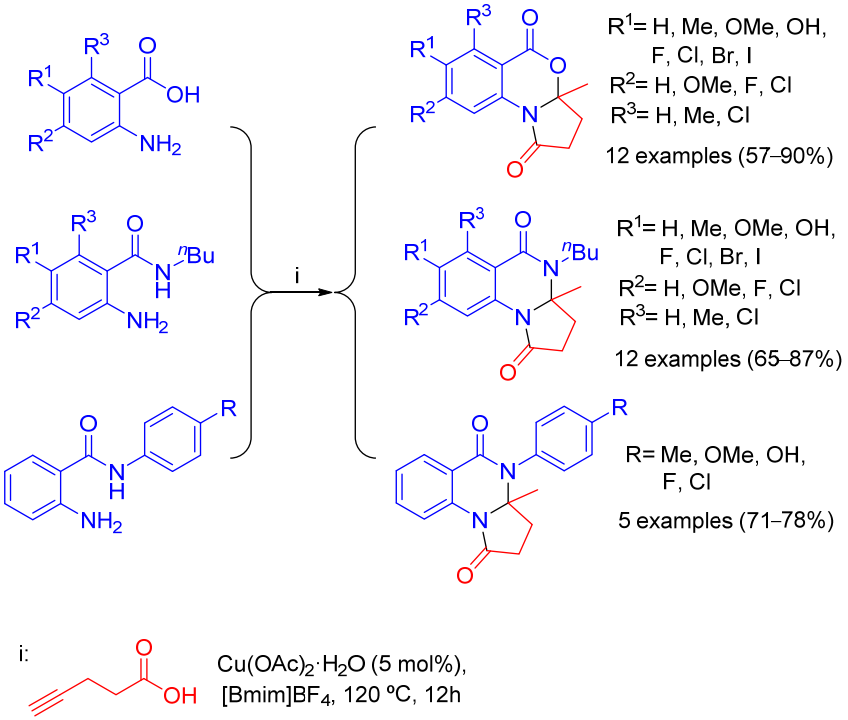
4. Cu Catalysts

4.1. Introduction

The incorporation of alternative metals to more established gold and silver catalysts started with copper. Although copper salts were tested as catalysts in some of the aforementioned initial screenings (e.g., $Cu(OTf)_2$ in [58] and $Cu(OAc)_2$ in [62]), notably, inferior yields had been obtained in comparison to Au or Ag catalysts. However, the combination of a copper salt and a ionic liquid changed this trend, although the reaction scope is still limited to N- and O-aminonucleophiles.

4.2. Cu-Catalyzed Cascade of 4-Pentynoic Acid and Aminonucleophiles

After a screening of different copper sources and reaction media, Reddy and col. discovered that the cascade reaction between 4-pentynoic acid and 2-aminobenzyl alcohol could be carried out using a 5 mol% of a cheap and available copper(II) salt, $Cu(OAc)_2 \cdot H_2O$ in [bmim]OTf ionic liquid, at 100 °C. Several 2-aminobenzyl alcohols were then reacted with 4-pentynoic and 5-hexynoic acids to provide the corresponding benzo[d]pyrrolo- and benzo[d]pyridooxazin-1-ones with good yields (63–95%). They proved that this catalyst-solvent system was responsible for the initial cycloisomerization process as well as for the subsequent condensation reactions with the resulting alkylidene lactone [64]. In 2017, the same group described a similar regioselective process conducted with anthranilic acid and 2-aminobenzamide derivatives as aminonucleophiles. Good to excellent yields were obtained in all cases (Scheme 10), and the authors successfully recycled and reused the catalytic system (copper salt and ionic liquid) for five times without significant loss of the catalytic activity. Regarding the reaction mechanism, the authors described a similar pathway to that proposed in their initial paper [65].



Scheme 10. Copper-catalyzed cascade reaction in ionic liquid.

5. Ru Catalysts

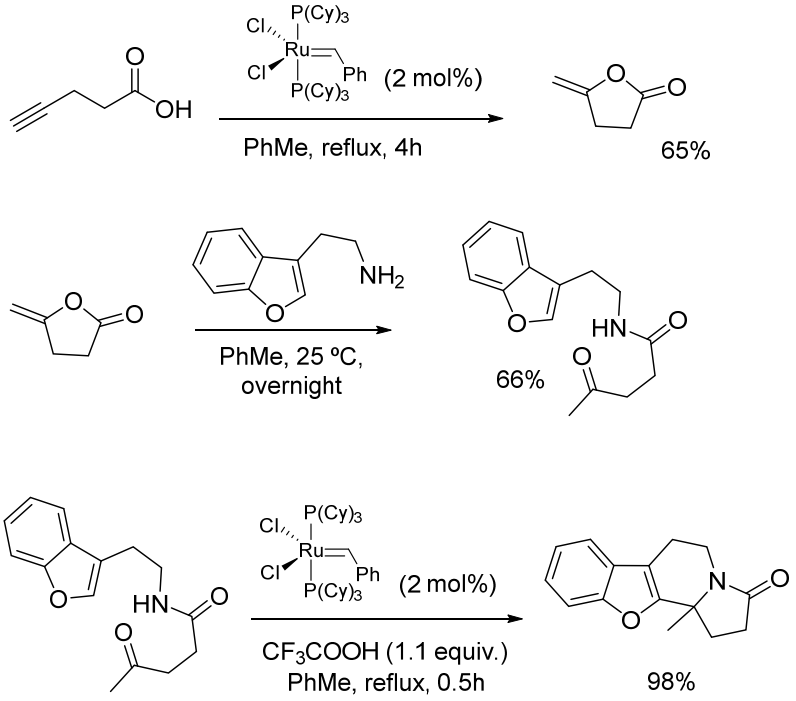
5.1. Introduction

Ruthenium is another carbophilic metal employed in alkyne hydrofunctionalization reactions but was unexplored in the field of the interaction of acetylenic acids and aminonucleophiles until as recently as 2020. Quite interestingly, in contrast with simple ruthenium

salts or complexes, ruthenium carbenes turned out to be effective catalysts that allowed the use of a wide number of dinucleophiles.

5.2. Cascade Reaction of Alkynoic Acids and Aminonucleophiles in the Presence of Ruthenium Carbenes

As a meaningful example of a new non-metathetic application of ruthenium carbenes [66–70], in 2020, Lei and col. described the preparation of arene-fused heterocycles by the cascade reaction between 4-pentynoic acid and 2-(hetero)aryletanamine nucleophiles in the presence of 2 mol% of Grubbs' first generation catalyst and 1 equiv. of trifluoroacetic acid in toluene. On the basis of the reports by Verpoort, Öztürk and Verpoort that ruthenium carbenes enabled hydrocarboxylation of terminal alkynes [71–73], the authors screened the performance of four different Grubbs' ruthenium carbenes and one ruthenium complex and observed that the target cascade process took place in the presence of a 2 mol% of all the ruthenium carbenes when trifluroacetic acid (1.1 equiv.) was added, although AgOTf could be also used as additive. The scope of this method (Grubbs' first generation catalyst 2 mol%, CF_3COOH 1.1 equiv., toluene, reflux.) was subsequently extended to other alkynoic acids, including hexynoic acid, 2-propargyloxyacetic acid and 2-ethynylbenzoic acid, and later to other N- and O-aminonucleophiles. However, in contrast with 2-propargyloxyacetic acid, only traces of target products were observed when *N*-benzyl-*N*-(prop-2-yn-1-yl)glycine or *N*-(prop-2-yn-1-yl)-*N*-tosylglycine were employed as partners of the reaction regardless of the nature of the employed dinucleophile. This unexpected behavior was attributed to the possible formation of inactive species or stable chelate complex of these acids with Grubbs' catalyst. Anyway, on account of the excellent results obtained (even with challenging 5-hexynoic acid), the profile of catalyst system presented clearly rivaled that of the aforementioned Au catalysts. By a series of control experiments (Scheme 11), the authors proved that the ruthenium catalyst was essential for the cycloisomerization step, while trifluoroacetic acid was required for the *N*-acyliminium ion formation and final cyclization steps through electrophilic aromatic substitution (2-(hetero)aryletanamines) or N/O nucleophilic attack (N-/O-aminonucleophiles). This synergistic effect led to the construction of more than 30 compounds [74].



Scheme 11. Control experiments performed to get more insight into the reaction mechanism of the ruthenium-catalyzed cascade reported by Lei and col.

6. Pd and Fe Catalysts

6.1. Introduction

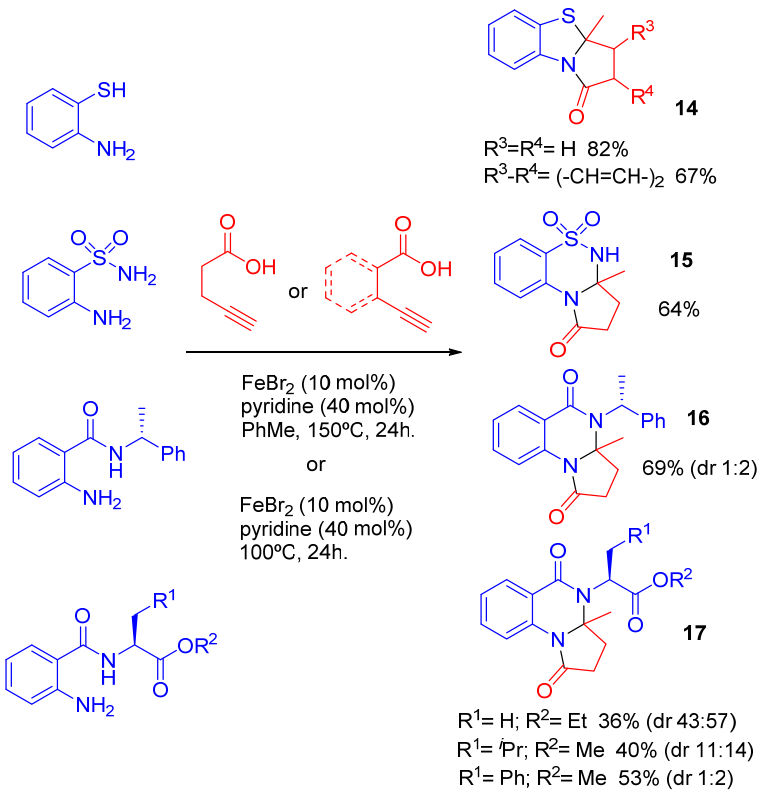
In spite of the ubiquitous use of palladium catalysts in a plethora of organic transformations (cross coupling reactions, C-H activation, redox processes, carbonylation and asymmetric reaction, inter alia), only in one report dealing with the reaction of alkynoic acids and aminonucleophiles there had been an initial screening that include a palladium catalyst [62], and the results described were not encouraging. With regard to iron, an abundant and less toxic first-row transition metal, it remained unexplored in this context until recently.

6.2. Fe-Catalyzed Cascade Reaction between Alkynoic Acids and Aminonucleophiles

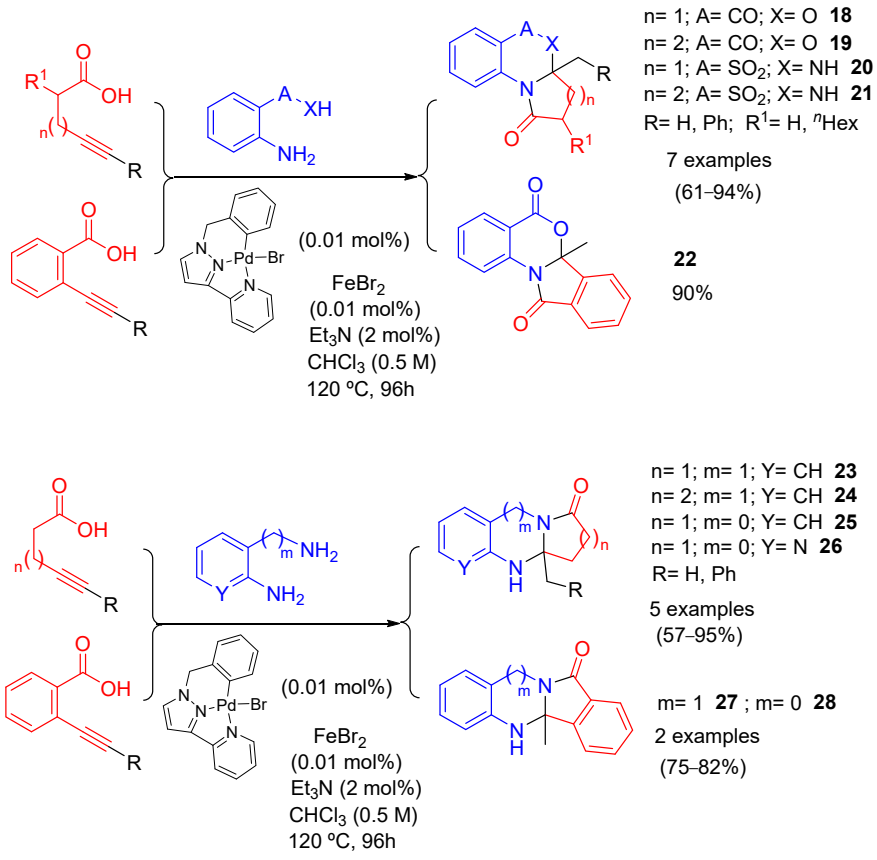
Following their research on iron-catalyzed hydrofunctionalization reactions [75], and more specifically, on iron-catalyzed cascade reactions involving alkynoic acids [76], Diaz de Sarralde et al. recently described the formation of 20 pyrrolo and isoindolo-fused heterocycles **14**–**17** by reacting different N-, O- and S-aminonucleophiles with 4-pentynoic acid, 5-hexynoic acid, 5-phenylpentynoic acid and 2-ethynylbenzoic acid in the presence of a catalytic amount (10 mol%) of iron(II) bromide and pyridine (40 mol%). The catalytic performance of this iron(II) salt was significantly superior to other iron catalysts or Lewis acids. Other inorganic and organic bases such as Na_2CO_3, Cs_2CO_3 and DMAP were also tested. Although the optimized reaction conditions required toluene as solvent at 150 °C, an alternative solvent-free method that allowed the use of lower temperatures (100 °C) was also disclosed. Ethanol could be also used as solvent, at least with the model substrates (4-pentynoic acid and *o*-aminobenzylamine). The authors pointed out the abundance and low toxicity of iron salts, as well as the fact that this cheap and convenient catalyst system had provided better yields for some of the above heterocycles than the previously reported methodologies. However, the scope of this iron-catalyzed procedure was limited to N-, O- and S-aminonucleophiles, and no C-aminonucleophiles could be used [77]. Among the N-aminonucleophiles tested, *o*-aminosulfonamide was for the first time employed to prepare the corresponding sultam **15**, and a benzo[*d*]pyrrolo[2,1-*b*]thiazol-1(2*H*)-one (**14**) was synthesized by reaction between 4-pentynoic acid and 2-aminobenzenethiol, the first successful S-aminonucleophile so far in this field. After preparing optically active *o*-aminobenzamides by amidation of anthranilic acid derivatives with chiral amines, these benzamides were reacted under the optimized conditions with pentynoic acid. Unfortunately, low diastereoselectivity was observed for the corresponding tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-diones **16**–**17** (Scheme 12).

6.3. Cascade Reaction of N- and O-Aminonucleophiles with Alkynoic Acids in the Presence of a Palladium Pincer Complex

Almost simultaneously, the same group reported a remarkably efficient catalyst system that enabled the access to pyrrolo and isoindolo-fused heterocycles **18**–**28**, including benzopyrrolothiadiazinone and benzopyridothiadiazinone dioxides **20**–**21** derived from 2-aminobenzenesulfonamide. After their report on the highly efficient intramolecular hydrocarboxylation of acetylenic acids in chloroform catalyzed by a palladium(II) pincer complex [78], the authors envisaged that this complex could also promote the reaction with different nucleophiles under similar conditions. Indeed, just a 10^{-2} mol% of the above palladium compound was enough to promote the reaction in some cases. However, the optimized reaction conditions involved combining this NNC pincer complex (10^{-2} mol%) with $FeBr_2$ (10^{-2} mol%) and triethylamine (2 mol%) in $CHCl_3$ at 120 °C [79] (Scheme 13). A comparison of the catalytic profile of the said complex and other palladium catalysts was also carried out.



Scheme 12. A selection of the products obtained by the FeBr2-catalyzed cascade reaction reported by Diaz de Sarralde et al.



Scheme 13. Substrate scope of the cascade reaction in the presence of a palladium pincer complex.

In order to determine the role of the catalysts in this cascade reaction, the authors carried out a series of experiments. 5-Methylenedihydrofuran-2(3*H*)-one was easily prepared by reacting 4-pentynoic acid with the above NNC complex (10^{-2} mol%) and triethylamine (2 mol%) in dichloromethane at room temperature and then treated with anthranilic acid under the optimized reaction conditions to provide target benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione **18** in 90% yield. The kinetic plot of the conversion of anthranilic acid vs. time showed neither sigmoidal shape nor induction time, and when the reaction was performed in the presence of several poisoning agents (mercury drop test, carbon disulfide and polyvinylpyridine, among others), no inhibition was observed, thus suggesting the participation of truly homogeneous catalytic species in the reaction. The absence of palladium nanoparticles, as determined by TEM-EDX analysis of the reaction mixture, provided additional proof to confirm the hypothesis of homogeneous catalysis. Moreover, some key intermediates were detected by UPLC-MS of the reaction mixture. Accordingly, a more nuanced mechanism describing the role of the metal species and transient intermediates detected by UPLC-ESI was also proposed [79] (Figure 4). These results are in accordance with several examples of bimetallic co-catalysis, including the aforementioned reports on the gold-silver co-catalyzed cascade reactions (Sections 2.2 and 2.3, Schemes 3, 6 and 7) [53,57,61] and other accounts on metal-metal synergistic effects and metal–ligand cooperation [80–82].

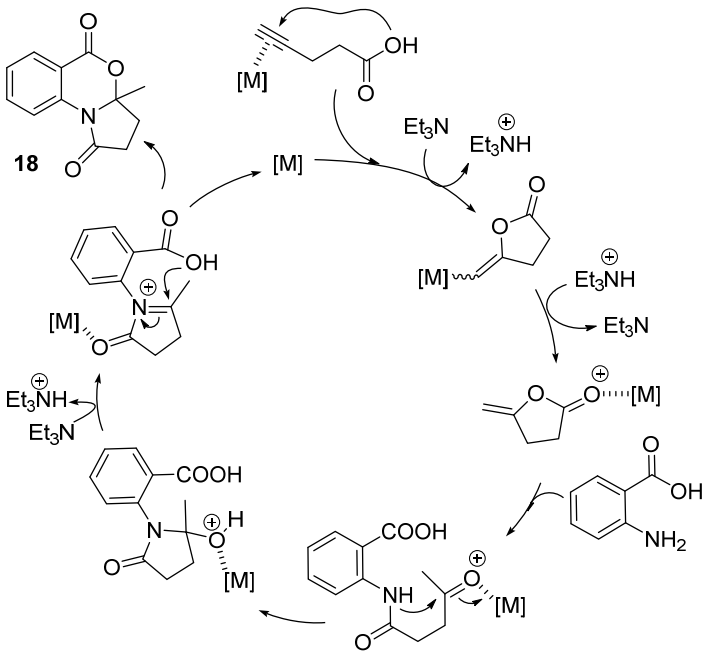


Figure 4. Proposed catalytic pathway for the cascade reaction performed in the presence of a palladium pincer complex and iron(II) bromide.

7. Conclusions and Outlook

In the presence of several dinucleophiles, a carbophilic metal-catalyzed intramolecular hydrocarboxylation of alkynoic acids triggers a cascade reaction that generates relatively complex polycyclic structures. The increasing number of acetylenic acids and dinucleophiles (C-, N-, O- and S-aminonucleophiles) that can serve as substrates have greatly extended the scope of this multi-step process so that a large library of valuable nitrogen-containing heterocyclic compounds can be easily prepared from commercially or readily available substrates or reagents. Regarding the catalyst required for these transformations, although gold(I) complexes either alone or along with Ag(I) salts or Brönsted acid (trifluroacetic acid) have dominated the field and demonstrated a superior performance and substrate scope, other competitors based on copper(II) salts in ionic liquids, ruthenium carbenes, palladium(II) complexes and iron salts have appeared in recent years. These alter-

native candidates show an excellent catalyst profile, but, with the exception of ruthenium carbenes, they appear to be unable to promote the reaction with C-aminonucleophiles, thus limiting the reaction scope to N-, O- or S-aminonucleophiles. It is certainly difficult to compare all these catalytic profiles if, in addition to the substrate scope, efficiency and economic value are also considered. Indeed, typical catalyst loading ranges from 1 to 20 mol% for Au, Ag, Cu, Ru and Fe catalysts, although the use of a PCN palladium complex along with $FeBr_2$ allowed a much higher substrate/catalyst ratio (10,000:1). Iron, an abundant and less toxic first row transition metal, can also catalyze the reaction although with the substrate limitations noted above. The high economic value of Au, Ag, Ru and Pd precious metal catalysts cannot be underestimated, although this issue should be examined in view of the amount of catalyst required (e.g., the economic cost of 20 mol% of a silver catalyst is much higher than that of a 10^{-2} mol% of a palladium complex). As for reaction media, toluene is by far the solvent of choice in many of the transformations described, even if greener alternatives such as water, ionic liquids and solventless reactions have been described. Conventional heating is almost ubiquitous in all the reports, although microwave irradiation has been also reported. Exhaustive mechanistic studies carried out for many of the catalyst systems reported have led to the identification of several intermediates of the reaction (the alkylidene lactone generated from the initial cycloisomerization step, the ketoamide produced as a result of the subsequent aminolysis and the *N*-acyliminium ion prior to the attack by the second nucleophilic group of the aminonucleophile). In addition, such experiments have aided to define the role of the catalyst and the additives employed. In most cases, metal catalyst is essential for the initial intramolecular alkyne hydrocarboxylation (sometimes helped by substoichiometric amounts of a base-like triethylamine or pyridine) and provides, alone or with the help of certain silver or Brönsted acid additives, the activation required for the second stage of the cascade.

We foresee the development of new catalyst systems for this synthetically powerful reaction in the coming years. Such future catalysts will probably overcome the described limitations and will provide more sustainable protocols for a cascade reaction that offers straightforward access to a whole array of polyheterocyclic compounds, some of them showing remarkable biological activity.

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