processes

MDPI

Review

Recent Access to Polycycles via Post-Ugi Reactions

Xiao Tang [1] and Liangliang Song [2,*]

[1] College of Science, Nanjing Forestry University, Nanjing 210037, China
[2] Jiangsu Provincial Key Lab for the Chemistry and Utilization of Agro-Forest Biomass, Jiangsu Co-Innovation Center of Efficient Processing and Utilization of Forest Resources, Jiangsu Key Lab of Biomass-Based Green Fuels and Chemicals, International Innovation Center for Forest Chemicals and Materials, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China
* Correspondence: liangliangsong@njfu.edu.cn

Abstract: Ugi reactions have been widely studied due to their mild reaction conditions, high structural variability, and wide applications. Ugi adducts have proved to be highly efficient for different kinds of post-transformations by carefully choosing the starting four components. Considering the importance of polycycles, diverse post-Ugi transformations have been employed for the construction of structurally novel polycyclic N-heterocycles. This minireview summarizes the recent developments of post-Ugi reactions for the synthesis of polycycles after the year 2019. Through transition metal catalysis from gold, rhodium, silver, copper, and palladium, as well as transition metal-free approaches, versatile polycycles are constructed in a highly efficient and step-economical manner.

Keywords: polycycle; Ugi reaction; post-Ugi cyclization

Citation: Tang, X.; Song, L. Recent Access to Polycycles via Post-Ugi Reactions. *Processes* **2023**, *11*, 699. https://doi.org/10.3390/pr11030699

Academic Editor: Alexander Novikov

Received: 8 February 2023
Revised: 23 February 2023
Accepted: 24 February 2023
Published: 26 February 2023

1. Introduction

The Ugi reaction was discovered in 1959, starting from carbonyl compound (aldehyde or ketone), primary amine, carboxylic acid, and isonitrile [1], affording peptidomimetics with high biological activity and structural diversity [2]. Moreover, the Ugi reaction bearing economic and environmentally friendly characteristics is tolerated with water as the solvent [3]. Considering the mild reaction conditions, high structural variability, and wide applications, Ugi reactions have been treated as one of the highly explored reactions for the formation of multifunctional adducts [4]. By carefully choosing the starting four components, Ugi-adducts could be manipulated to provide an opportunity for a number of post-transformations [5]. Due to the high structural flexibility of Ugi-adducts, post-Ugi transformation has become an increasingly efficient tool in the synthesis of versatile heterocycles, natural products, and macrocyclic molecules with a wide range of biological activities (Figure 1) [6–8], such as ecteinascidin 743 and (+)-furanomycin [9,10]. Additionally, post-Ugi cyclization has proved to be an important strategy in the synthesis of many drugs for treating various diseases [6], such as HIV protease inhibitor MK 639 and praziquantel for the treatment of the parasitical disease schistosomiasis [11,12].

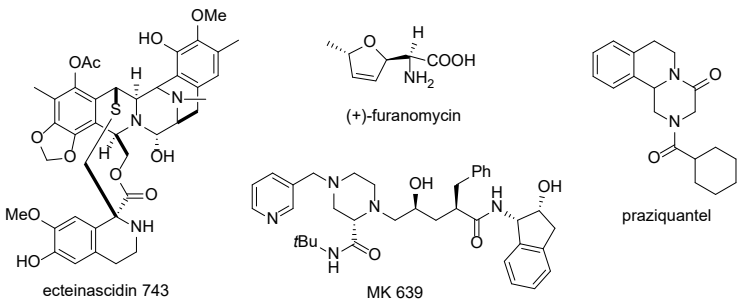
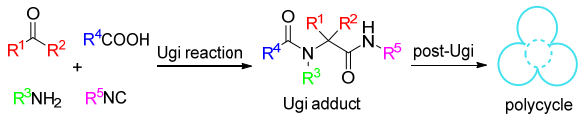


Figure 1. Important compounds from post-Ugi reactions.

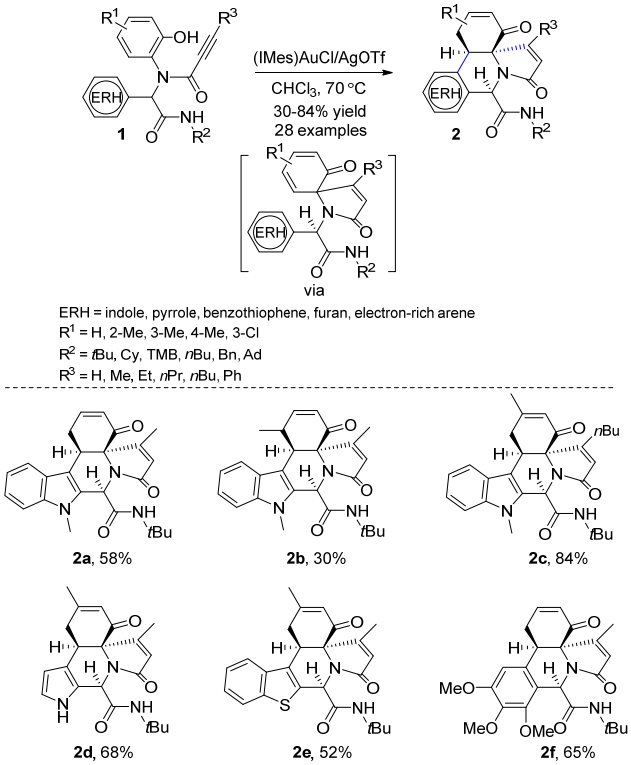
A number of post-Ugi reactions are reported to construct diverse heterocycles and have been covered in several elegant reviews [5,13–16]. In 2018, Van der Eycken summarized the transformations of the Ugi-adducts for the construction of diverse heterocyclic compounds from the year 2014 [15]. After that, great success on the post-Ugi cyclizations has been achieved to generate a myriad of unusual heterocycles, especially important polycycles. In this minireview, we wish to highlight the recent advances of post-Ugi reactions for the synthesis of versatile polycycles after the year 2019 (Scheme 1). For the sake of clarity, we have divided this minireview into the following sections: (a) gold catalysis, (b) other transition metal catalysis, and (c) transition metal-free catalysis.



Scheme 1. Synthesis of polycycles via post-Ugi transformations.

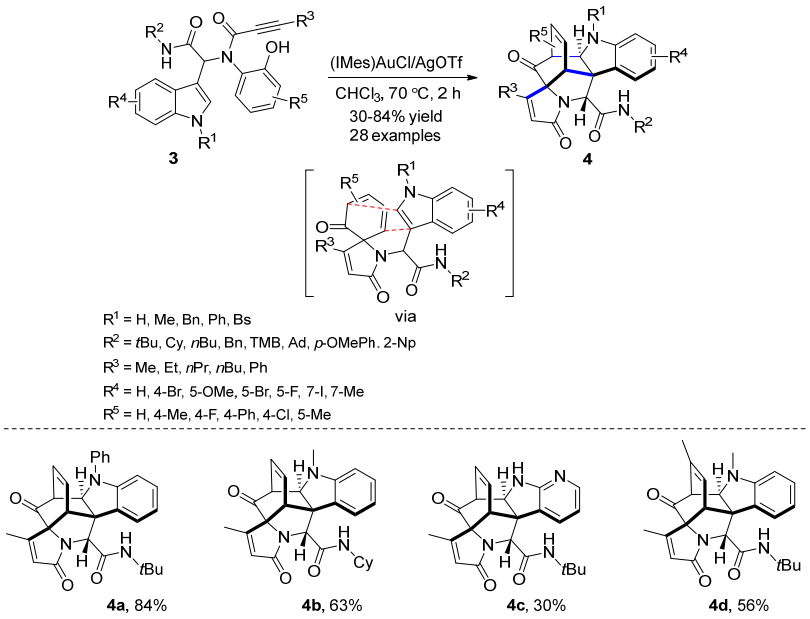
2. Gold Catalysis

In 2019, Van der Eycken and co-workers combined gold-catalyzed post-Ugi dearomative spirocyclization and 1,6-addition for the preparation of various fused polyheterocyclic scaffolds [17]. This reaction featured high chemo- and diastereoselectivity, and broad substrate scope involving indole, pyrrole, benzothiophene, furan, or electron-rich arene moieties (Scheme 2). For Ugi-adducts derived from indole-2-carboxaldehydes, a hydrogen or a benzyl group at the indole nitrogen atom was tolerated to give the corresponding products in moderate to good yields, while the acetyl group was not compatible with the reaction conditions. A methyl or a chloro group on different positions of the newly formed cyclohexanone was well-tolerated, while the methyl group on the α-position failed to afford the desired product. Moreover, hydrogen and alkyl groups such as methyl, ethyl, *n*-propyl, and *n*-butyl, or a phenyl group on the propiolamide fragment, could deliver the corresponding products in moderate to good yields.



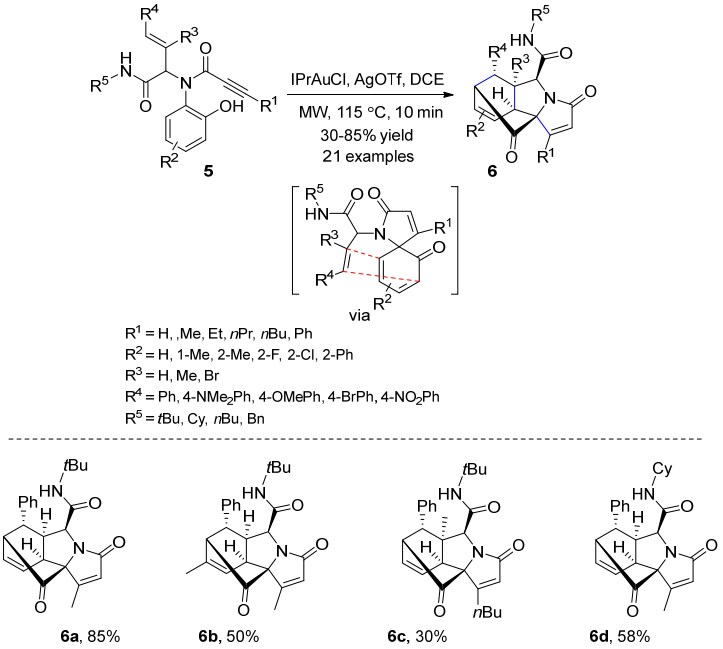
Scheme 2. Gold-catalyzed post-Ugi dearomative spirocyclization and 1,6-addition.

Subsequently, the same group developed a modular and streamlined approach to the bridged indole alkaloid-like heterocycles [18]. Through gold-catalyzed chemo- and diastereoselective dearomative spirocarbocyclization/concerted [4+2] cyclization, architecturally complex heterocyclic scaffolds were constructed in good yield and diastereoselectivity (Scheme 3). This reaction performed well with a methyl, a hydrogen, a benzyl, and a phenyl group at the indole nitrogen atom. The electron-withdrawing benzenesulfonyl group generated the bridged heterocycle in much lower yield, and the acetyl group failed to afford the desired product. These results indicated that the C3 nucleophilicity of the indole moiety plays a crucial role in the cascade process. For propiolamide fragments, hydrogen was incompatible, and alkyl groups such as methyl, ethyl, *n*-propyl, and *n*-butyl were well tolerated to give the desired products in good yields. However, Ugi-adduct bearing a bulky phenyl-substituted propiolamide moiety delivered the corresponding product in much lower yield. Moreover, the electron-donating groups such as methyl and methoxy, or electron-withdrawing groups such as fluoro, bromo, and iodo on the phenyl ring of the indole moiety were well-tolerated. The Ugi-adduct with a pyrrolo [2,3-*b*]pyridine moiety was also compatible with the reaction conditions. However, a methyl substituent on the C2 of the indole moiety failed to give the desired product probably due to the steric effect.



Scheme 3. Gold-catalyzed dearomative spirocarbocyclization/concerted [4+2] cyclization.

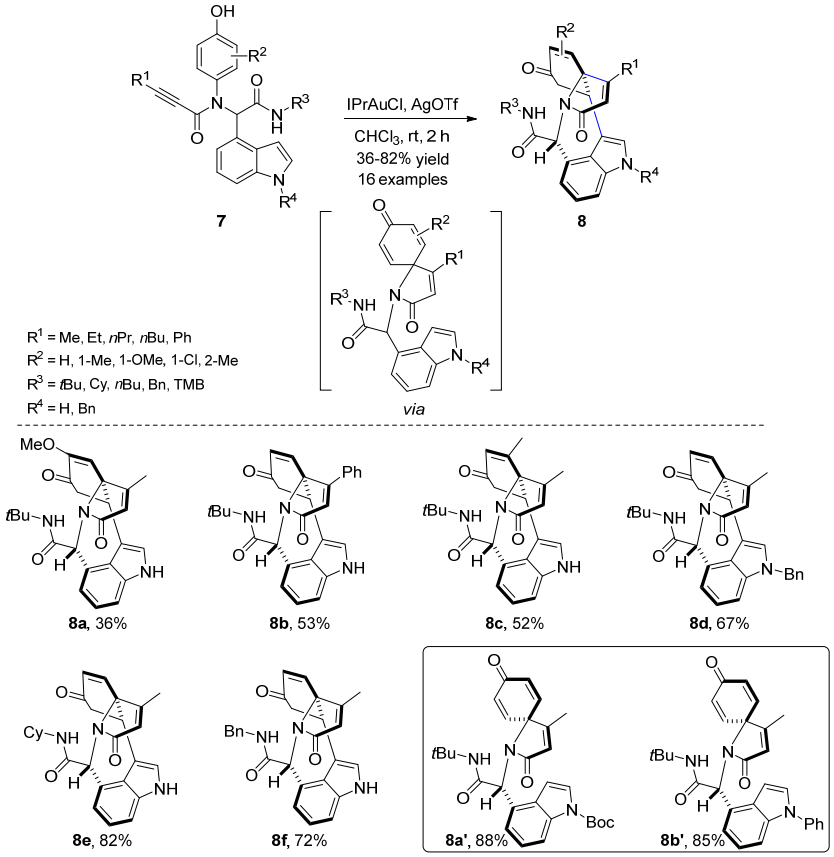
Different from the above work using indole-3-carboxaldehydes in an Ugi reaction [18], the combination of the Ugi reaction employing trans-cinnamaldehydes and gold catalysis could provide distinct complex polycycles [19]. With the aid of microwave irradiation, diverse bridged polycyclic N-heterocycles were synthesized in 10 min via a gold-catalyzed dearomative spirocarbocyclization/Diels–Alder reaction sequence (Scheme 4). The efficiency of microwave was also shown in the improved diastereoselectivity. Both hydrogen and various alkyl groups such as methyl, ethyl, *n*-propyl, and *n*-butyl, or the phenyl group on the propiolamide moiety, afforded the corresponding products in moderate to good yields. Methyl groups in different positions of phenol moiety proceeded smoothly. Fluoro or chloro installed in the *meta*-position of phenol moiety were also tolerated. Interestingly, Ugi-adducts bearing a *meta*-phenyl-substituted phenol moiety reacted sufficiently well, suggesting that a steric effect does not influence the cascade process. *Para*-substituted electron donating (NMe_2 and OMe) and electron withdrawing (Br and NO_2) groups at the phenyl ring of alkene fragment were compatible with these reaction conditions. Notably, α,β-disubstituted alkene moieties were well tolerated to give good yields, but poor diastereoselectivities.



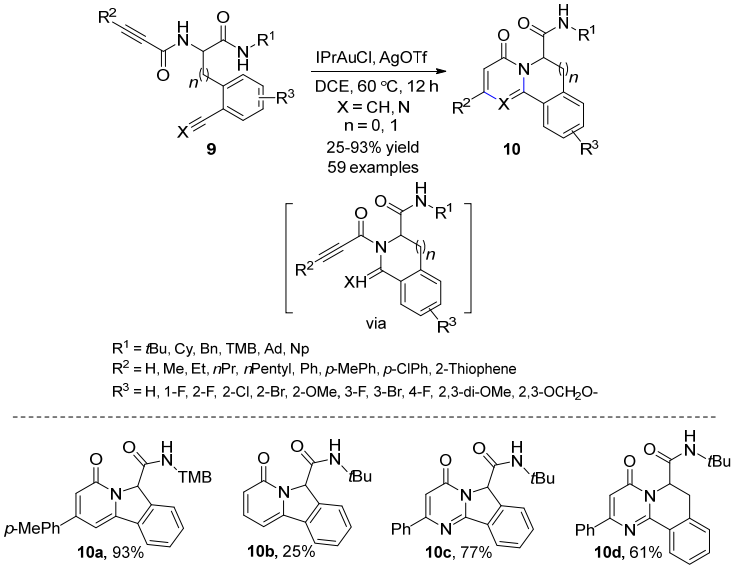
Scheme 4. Gold-catalyzed dearomative spirocarbocyclization/Diels-Alder reaction.

Based on their previous work [20], Van der Eycken and co-workers used indole-4-carboxaldehydes to produce Ugi-adducts, which then underwent a gold-catalyzed post-Ugi dearomatization/Michael addition sequence [21]. By this modular and straightforward process, the highly functionalized azepino[5,4,3-*cd*]indole scaffolds were prepared in high yield and excellent chemo-, regio-, and diastereoselectivity (Scheme 5). Notably, the functional group on the nitrogen of the indole moiety had an important influence on the results. The Bn group could give the corresponding polycyclic product, while the Boc group only delivered the spiro-fused indole intermediate. Increasing the reaction temperature to 80 °C for 5 h could generate the polycyclic product without the Boc group. The Ph group only afforded the spiro-fused intermediate even employing an elevated temperature and extended reaction time. This is probably because of the electron-withdrawing characteristic of the Boc and Ph groups, reducing the nucleophilicity of the C3-position in the indole. The internal alkyne moieties with methyl, ethyl, *n*-propyl, and *n*-butyl groups performed well, delivering the corresponding products in good yields. However, the terminal alkyne-tethered Ugi-adduct failed to form the desired product, possibly due to the δ-activated model of gold catalyst on the terminal triple bond, resulting in the formation of thermodynamically unstable spirocyclohexadienonyl-β-lactam. Notably, Ugi-adducts bearing a phenyl-substituted alkyne moiety went on smoothly, affording the desired product in moderate yield, showing that a sterically hindered group is also tolerated with this reaction.

Later on, the same group employed gold-catalyzed hydroamination/cycloisomerization cascade in the concise and flexible construction of polycyclic N-heterocycles [22]. By using alkyne- and nitrile-tethered aldehydes in the Ugi reaction, highly functionalized 1,6-annulated 2-pyridones and 2,3-annulated 4-pyrimidinones could be elaborated in excellent yield (Scheme 6). Bulky groups on the secondary amide moiety derived from the isonitriles, such as adamantyl and 1,1,3,3-tetramethylbutyl, performed smoothly to generate the 1,6-annulated 2-pyridones in good yields. While lower yields were obtained in the case of less bulky groups such as *t*-butyl, cyclohexyl, naphthyl, and benzyl. Changing a small hydrogen into larger alkyl groups such as methyl, ethyl, *n*-propyl, and *n*-pentyl, or aryl groups such as phenyl or thiophene on the 2-ynamide moiety, led to increasing yields of 1,6-annulated 2-pyridones. This reaction showed wide scope and good functional group tolerance and could be used as the key ring-forming step for the total synthesis of (±)-seco-antofine and (±)-septicine.



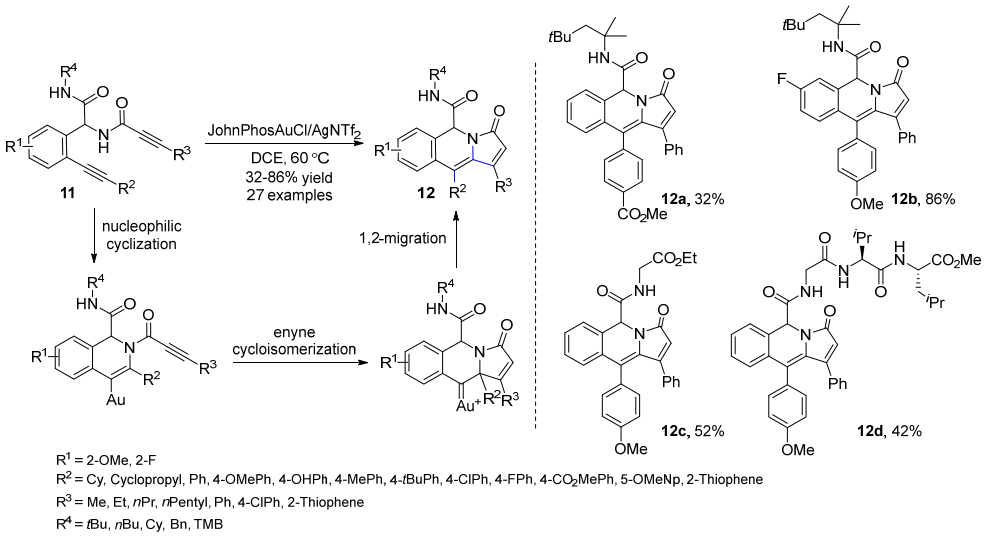
Scheme 5. Gold-catalyzed post-Ugi dearomatization/Michael addition.



Scheme 6. Gold-catalyzed hydroamination/cycloisomerization.

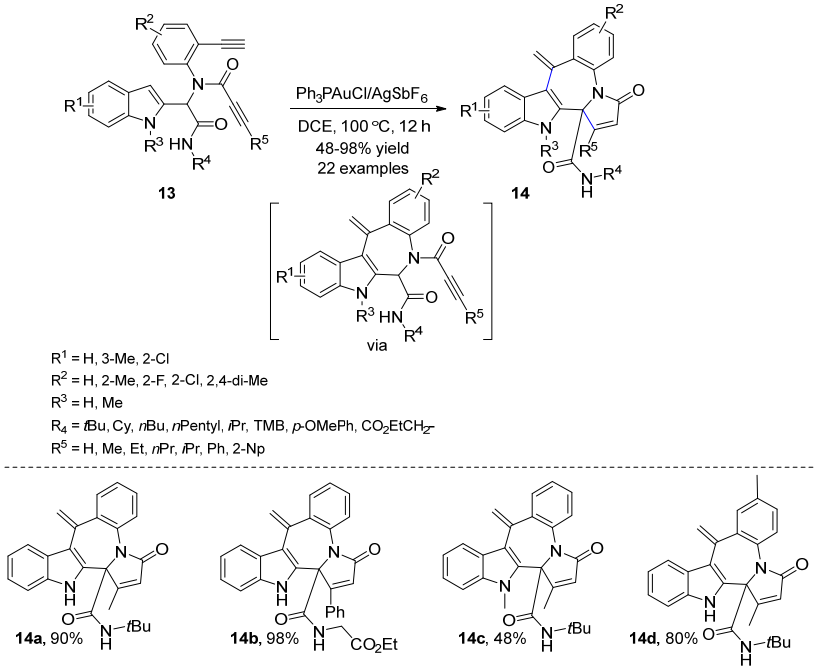
In 2022, Van der Eycken and co-workers reported a gold-catalyzed tandem 6-*endo-dig* cyclization/enyne cycloisomerization/1,2-migration process of Ugi-adducts for the construction of diverse highly functionalized pyrrolo[1,2-*b*]isoquinolines [23]. This reaction featured mild reaction conditions, high chemo- and regioselectivity, and various migrating groups such as aryl, heteroaryl and alkyl (Scheme 7). Alkyl groups such as methyl, ethyl, *n*-propyl, and *n*-pentyl, or aryl groups such as phenyl or thiophene on the 2-ynamide moiety, reacted smoothly and delivered the desired products in good yields. Bulky groups on the secondary amide moiety derived from the isonitriles, such as 1,1,3,3-tetramethylbutyl and

t-butyl, produced higher yields than those bearing a less bulky group such as cyclohexyl, benzyl, and *n*-butyl. This approach could be extended to the late-stage diversification of oligopeptides in a rapid and step-economical manner.



Scheme 7. Gold-catalyzed 6-*endo-dig* cyclization/enyne cycloisomerization/1,2-migration process.

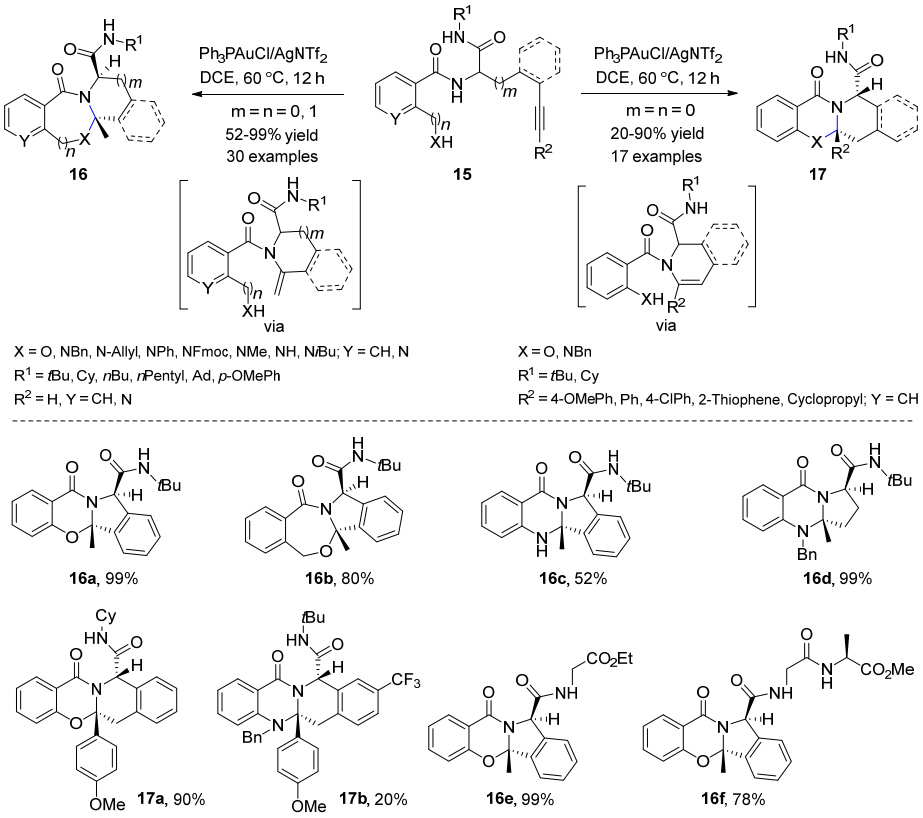
Afterwards, the same group integrated gold-catalyzed hydroarylation with Michael addition for the production of diverse benzazepinoindole polycyclic scaffolds in a highly efficient manner [24]. This method showed a broad substrate scope, excellent functional group tolerance, and high yield (Scheme 8). Hydrogen and alkyl groups such as methyl, ethyl, *n*-propyl, and *i*-propyl, or aryl groups such as phenyl or 2-naphthyl on the propiolamide fragment, could deliver the desired products in high yields.



Scheme 8. Gold-catalyzed hydroarylation and Michael addition.

Very recently, Van der Eycken and co-workers disclosed a novel strategy towards polycycles [25]. Through gold-catalyzed intramolecular bicyclization of Ugi-adducts, the divergent synthesis of quinazolinone and ampakine analogues was achieved in high

efficiency and step-economy (Scheme 9). When terminal alkyne-tethered aldehydes were used in the Ugi reaction, *exo-dig* cyclization was observed. Ugi-adducts derived from the 2-ethynylbenzaldehydes bearing an electron-donating dimethyl group or an electron-withdrawing chloro group reacted smoothly to give the ampakine analogues in high yields. Additionally, Ugi-adducts derived from pent-4-ynal or hex-5-ynal were well tolerated. Ugi-adducts derived from 2-(hydroxymethyl)benzoic acids were also applicable to this reaction, delivering the seven-member ring fused ampakine analogues in good yields. Ugi-adducts derived from various 2-aminobenzoic acids worked well, delivering the desired quinazolinones. While Ugi-adducts derived from internal alkyne-tethered aldehydes preferred to undergo *endo-dig* cyclization. Various substituents on the triple bond, such as methoxyphenyl, chlorophenyl, phenyl, thiophenyl, and cyclopropyl, were well tolerated. Notably, Ugi-adducts derived from diverse substituted salicylic acids or 2-aminobenzoic acids proceeded smoothly to yield the corresponding products. The practicality of this method was further demonstrated by a scale-up reaction and oligopeptide modification.

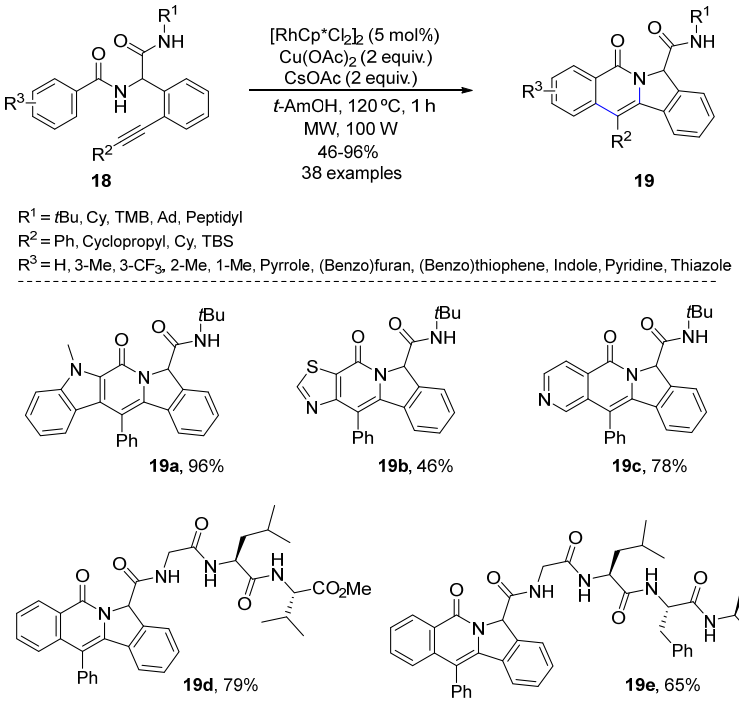


Scheme 9. Gold-catalyzed intramolecular bicyclization.

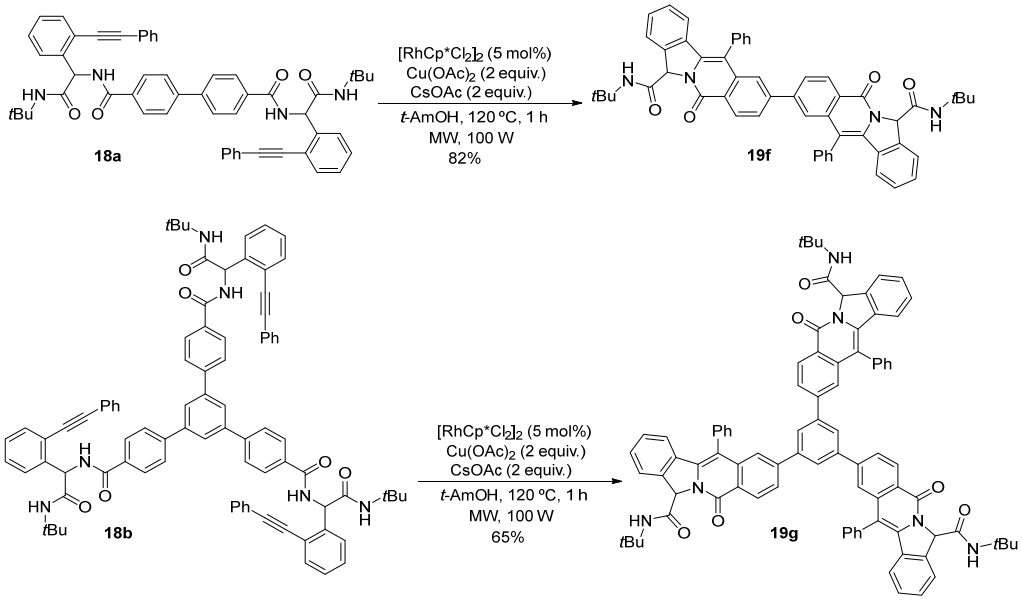
3. Other Transition Metal Catalysis

In 2019, Van der Eycken and co-workers employed rhodium(III)-catalyzed C-H activation in the post-Ugi transformations [26]. Through microwave-assisted C-H activation/annulation, different kinds of indolizinone and quinolizinone scaffolds were constructed in a rapid, step-economical, and chemoselective manner (Scheme 10). Substituents on the secondary amide moiety derived from the isocyanides, such as cyclohexyl, *t*-butyl, 1,1,3,3-tetramethylbutyl, and adamantyl, produced the corresponding indolizinones in high yields. However, Ugi-adduct derived from *p*-tolylsulfonymethyl isocyanide did not give the desired product. The phenyl group on the alkyne moiety could be superseded by cyclopropyl, cyclohexyl, or TBS. While the terminal alkyne-tethered substrate was not compatible with the reaction conditions. Substrates bearing a longer carbon chain between the benzamide and the phenylacetylene worked well, resulting in the corresponding quinolizinones. Ugi-adducts derived from carboxylic acids bearing diverse heteroaryl groups,

such as furan, thiophene, pyrrole, benzofuran, benzothiophene, indole, pyridine, and thiazole, proceeded smoothly. α-Substituted acrylamide substrates were also applicable to this reaction, while β-substituted and α, β-disubstituted acrylamide substrates failed to give the desired products, probably due to the unsuccessful formation of cyclometallation. This approach was well tolerated with peptide substrates, affording the decorated oligopeptides in good yields. Notably, twofold and threefold C-H activation/annulation cascade proved to be productive, yielding complex fused ring systems in high efficiency (Scheme 11).



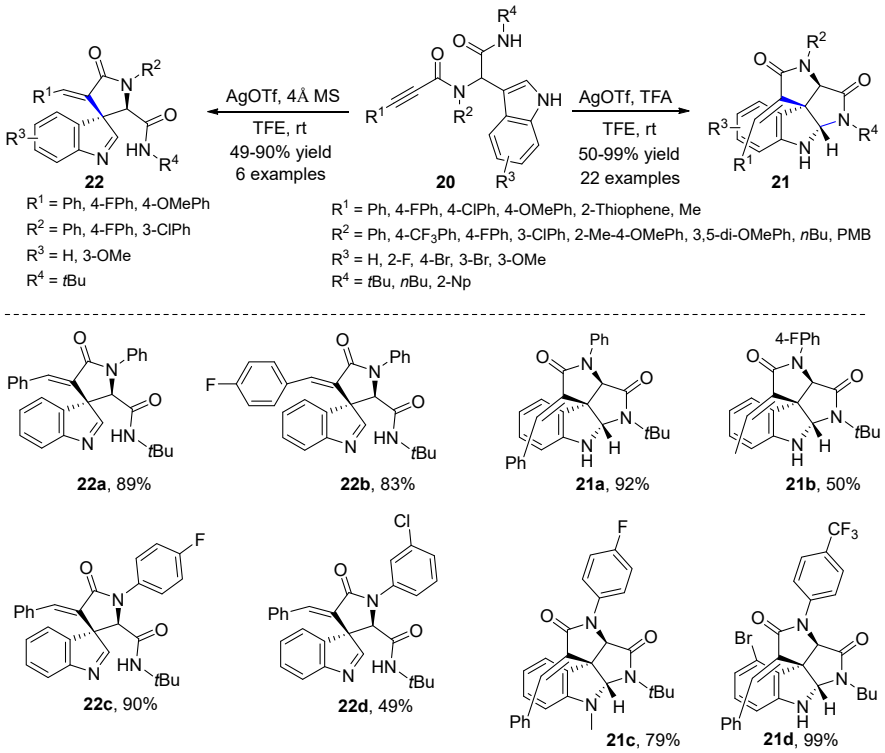
Scheme 10. Rhodium(III)-catalyzed C-H activation/annulation.



Scheme 11. Twofold and threefold C-H activation/annulation.

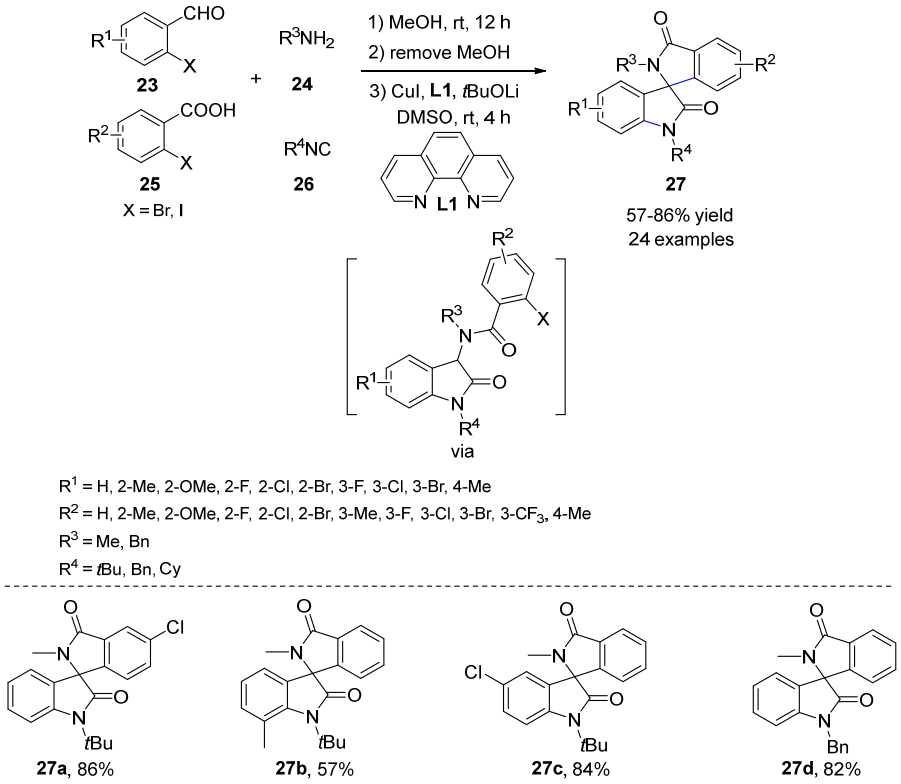
In 2020, silver(I) triflate-catalyzed post-Ugi synthesis of polycycles was performed by Pereshivko and Peshkov. The Domino Friedel–Crafts *ipso* cyclization/imine trapping process enabled the formation of versatile tetracyclic spiroindolines in high yield [27].

Compared to reported gold-catalyzed version using Ugi-adducts derived from aliphatic amines and 3-alkyl propiolic acids [28], this silver-catalyzed process worked best for indole-3-carbaldehyde-derived Ugi adducts derived from anilines and 3-aryl propiolic acids, which was a good complementarity (Scheme 12). Diverse aryl groups on the triple bond were tolerated to produce high yields. The Ugi-adducts derived from thiophen-2-yl propiolic acid and tetrolic acid delivered lower yields. Ugi-adducts derived from aromatic and aliphatic amines were tested, showing that those from aromatic amines gave better results. In addition, the combination of the Ugi reaction and silver-catalyzed tetracyclic indoline formation could be performed in a two-step one-pot process. However, more catalyst loading was needed to generate a full conversion, probably due to the negative influence of water generated from the Ugi reaction. Therefore, molecular sieves were also added to effectively avoid the decomposition of the catalyst via the interactions with water. Notably, without adding Brønsted acid, only tricyclic spiroindolines were obtained due to the suppressed imine trapping.

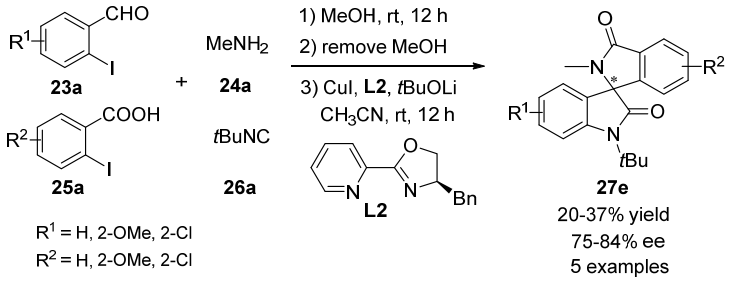


Scheme 12. Silver(I)-catalyzed post-Ugi synthesis of polycycles.

In 2021, Zhou and Cai presented a new method for the synthesis of spiroindolinone-isoindolinone skeletons [29]. Through the Ugi reaction and sequential copper-catalyzed intramolecular tandem C-N/C-C coupling process, diverse spirooxindole structures were constructed in highly efficiency under mild reaction conditions (Scheme 13). Various substituents on the phenyl moiety derived from 2-iodobenzoic acid or 2-iodobenzaldehydes were well tolerated, while substrates derived from *ortho*-substituted 3-methyl-2-iodobenzaldehyde required higher reaction temperature to obtain moderate yield. Substrates derived from 2-iodophenylacetic acid failed to give an isoquinolinone ring. Moreover, the substrate scope could be extended to 2-bromobenzaldehydes and 2-bromobenzoic acids by using higher reaction temperature, leading to spiroindolinone-isoindolinone skeletons. Control experiments indicated that the formation of the C-C bond is enabled by copper catalysis, rather than previously proposed base promoted nucleophilic aromatic substitution process [30]. By using the chiral oxazoline ligand, the asymmetric version could be achieved in good enantioselectivity, but low yield (Scheme 14).

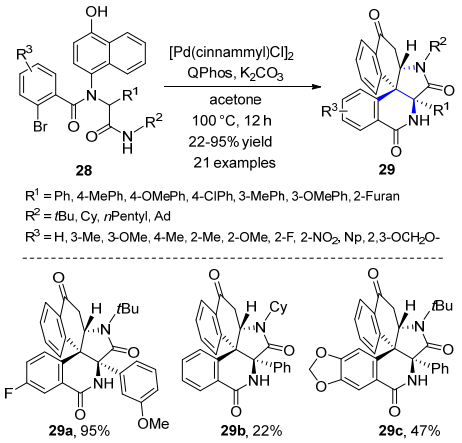


Scheme 13. Copper-catalyzed intramolecular tandem C-N/C-C coupling.

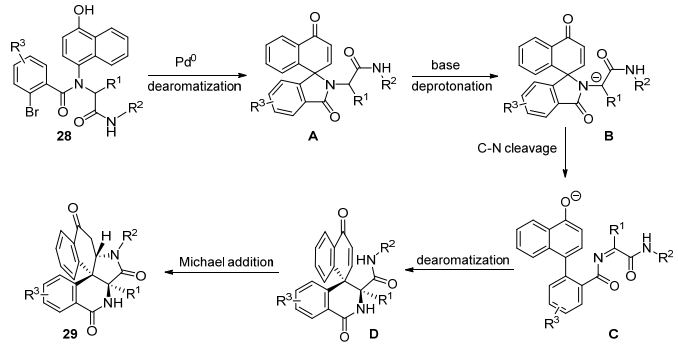


Scheme 14. Copper-catalyzed asymmetric synthesis of spiroindolinone-isoindolinone skeletons.

In the same year, Van der Eycken and co-workers disclosed a novel palladium-catalyzed arylative dearomatization and subsequent aromatization/dearomatization/aza-Michael addition process of Ugi-adducts [31]. By this sequence, diverse Zephycarinatine and Zephygranditine scaffolds containing two adjacent quaternary carbon stereocenters were constructed in good yield, with excellent chemo- and diastereoselectivity (Scheme 15). Bulky groups on the secondary amide moiety derived from the isonitriles, such as *t*-butyl and adamantyl, delivered high yields than less bulky groups such as cyclohexyl and *n*-pentyl. These results indicated that the steric hindrance on the nitrogen atom of the secondary amide moiety is beneficial for this reaction. Diverse Ugi-adducts derived from substituted benzaldehydes and heterocyclic furan-3-aldehyde were well tolerated. Notably, control experiments showed that this intramolecular arylative dearomatization of 1-naphthol is enhanced by palladium catalysis, and K_2CO_3 plays a critical role for the subsequent aromatization/dearomatization/aza-Michael addition process. According to the mechanism (Scheme 16), Ugi-adduct firstly undergoes palladium(0)-catalyzed intramolecular arylative dearomatization to give the key spirocyclic intermediate **A**, followed by deprotonation and subsequent aromatization-driven C-N bond cleavage to generate ketimine intermediate **C**. The dearomatization of **C** and sequential intramolecular aza-Michael addition would afford the final product.

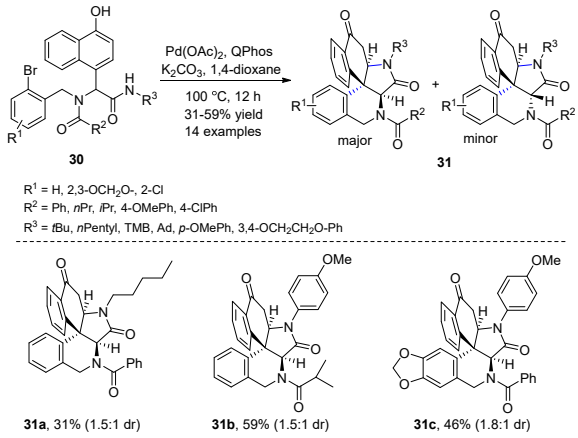


Scheme 15. Palladium-catalyzed post-Ugi reactions for the synthesis of Zephycarinatine and Zephygranditine scaffolds.



Scheme 16. Proposed mechanism for the palladium-catalyzed post-Ugi reactions.

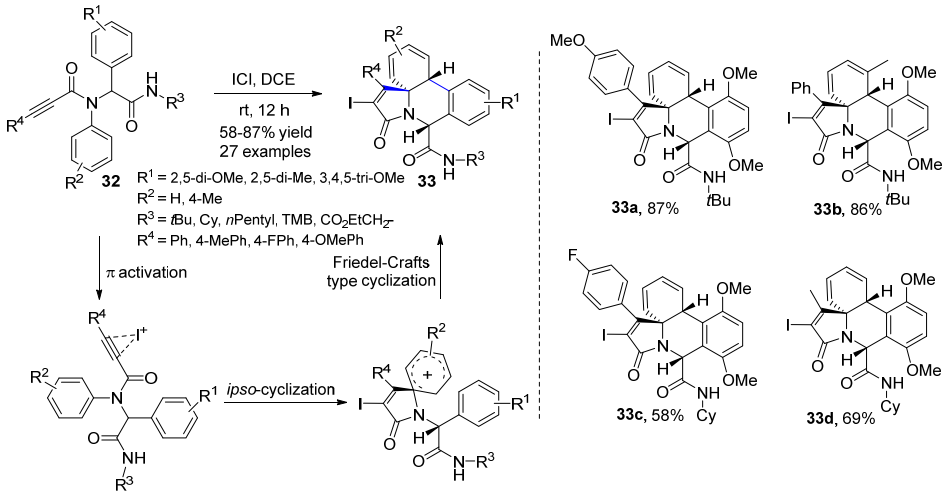
Based on the above work, the same group applied 4-hydroxy-1-naphthaldehyde and 2-bromobenzylamine in the Ugi reaction [32]. The following palladium-catalyzed intramolecular cyclization of Ugi-adducts delivered various plicamine analogues via a cascade dearomatization/aza-Michael addition process (Scheme 17). Diverse aliphatic or aromatic groups on the secondary amide moiety derived from the isocyanides, were compatible with the reaction conditions, giving the plicamine derivatives in moderate yields. Substrates with an electron donating dioxol or an electron withdrawing chloro group on the benzylamine moiety derived from the corresponding amines reacted smoothly to deliver the desired products. Substrates bearing aliphatic or aromatic substituents on the tertiary amide moiety derived from the corresponding acids were well tolerated.



Scheme 17. Palladium-catalyzed dearomatization/aza-Michael addition.

4. Transition Metal-Free Catalysis

In 2019, Sharma and co-workers employed ICl-mediated cyclization in post-Ugi reactions [33]. The highly constrained tetrahydroquinoline-fused tetracyclic heterocycles were prepared in good yield via a metal-free diastereo-/regio-selective fashion (Scheme 18). Electron-donating substituents derived from substituted phenyl propiolic acids gave better results than those bearing fluorine substituents. As proposed, Ugi-adduct firstly undergoes iodonium ion-induced π activation, followed by *ipso* nucleophilic cyclization to give spirocyclic carbocation intermediate. Final Friedel–Crafts-type cyclization via trapping of the carbocation generates the desired product. Notably, the obtained polycyclic compounds displayed promising anticancer activity against human cancer cell lines.

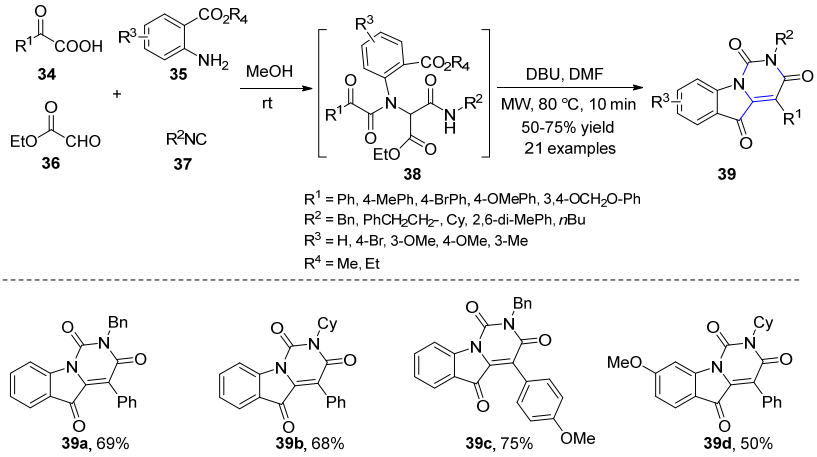


Scheme 18. ICl-Mediated post-Ugi cyclizations.

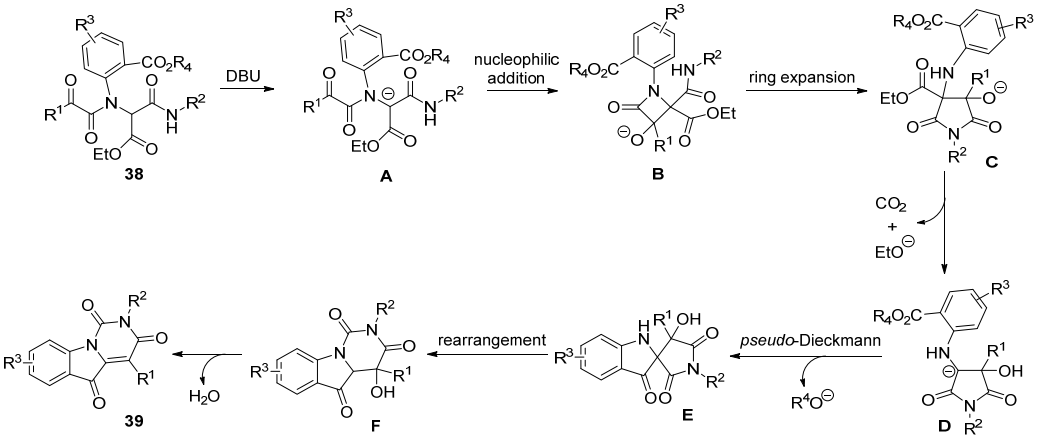
In 2020, Li, Chen and Xu discovered an Ugi reaction, ring expansion, *pseudo*-Dieckmann condensation, and rearrangement cascade for the preparation of indoline-piperidinones [34]. This reaction showed a good yield, mild reaction, and simple operation procedure (Scheme 19). The utilization of microwave irradiation largely shortened the reaction time to 10 min. After the removal of the reaction solvent under a gentle stream of nitrogen, the initial obtained Ugi-adducts were then employed directly in the next step without purification to give the desired indoline-piperidinones. Electron withdrawing and donating phenyl substituents derived from carboxylic acids were well tolerated. Ugi-adducts bearing electron-withdrawing bromo derived from 2-aminobenzoates afforded better yields compared to those bearing electron donating methoxy or methyl. However, Ugi-adduct derived from 2-aminobenzoate bearing a 4-NO_2 functional group was not formed. Ugi-adducts derived from aromatic and aliphatic isocyanides were well tolerated. Mechanically (Scheme 20), deprotonated intermediate **A** attacks the α-carbonyl to form 4-membered ring intermediate **B**, which undergoes ring expansion to generate intermediate **C**. The removal of ethoxyl group and CO_2 delivers the carbanion intermediate **D**, followed by *pseudo*-Dieckmann condensation, to afford intermediate **E**. Sequential rearrangement and dehydration would produce the final product.

Later on, Al-Harrasi and co-workers developed a route for the synthesis of fused polycyclic scaffolds through post-Ugi reactions [35]. Sequential nucleophilic aromatic substitution and second-order nucleophilic substitution of Ugi-adducts under basic conditions delivered structurally new spiro-β-lactam-pyrroloquinolines in high yield (Scheme 21). The presence of electron-donating groups on the quinoline moiety resulted in lower yields. 5-Methoxy substituted quinolines failed to give the desired products. Electron-withdrawing groups on the quinoline moiety had no significant influence on the yields. Notably, Ugi-adduct derived from 2-bromobenzaldehyde only afforded piperazine-2,5-dione, indicating the necessity of 2-chloro-quinoline moiety for the formation of spiro-

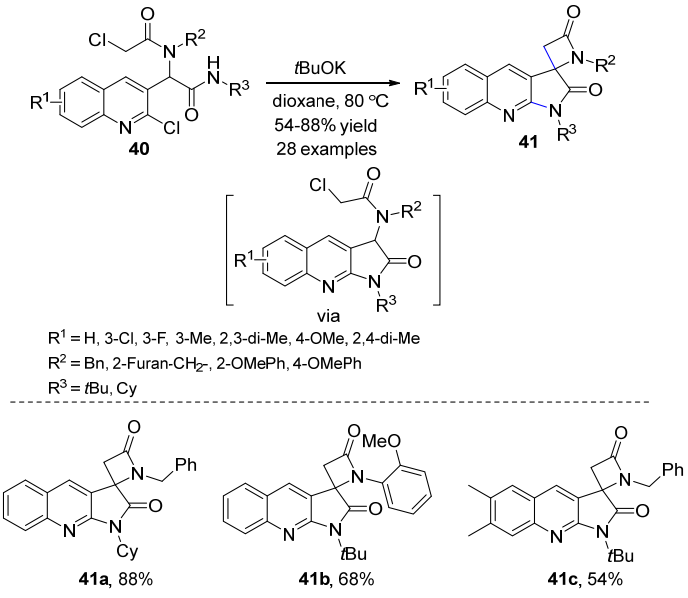
β-lactam-pyrroloquinolines (Scheme 22). This is due to the higher electrophilicity of the 2-position at the quinoline moiety bearing the nitrogen atom in the structure, enhancing the electrophilicity compared to the simple phenyl ring in 2-bromobenzaldehyde.



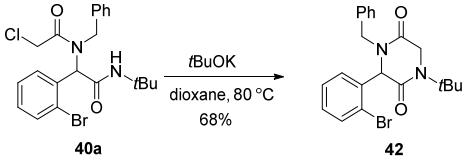
Scheme 19. Post-Ugi cyclizations for the preparation of indoline-piperidinones.



Scheme 20. Proposed mechanism for the preparation of indoline-piperidinones.

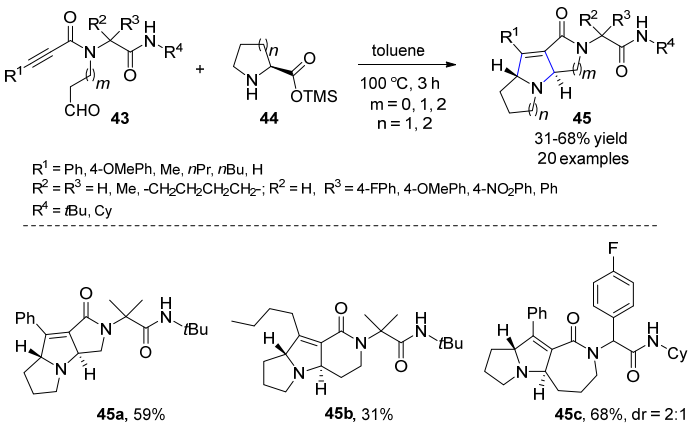


Scheme 21. Post-Ugi cyclizations for the preparation of spiro-β-lactam-pyrroloquinolines.

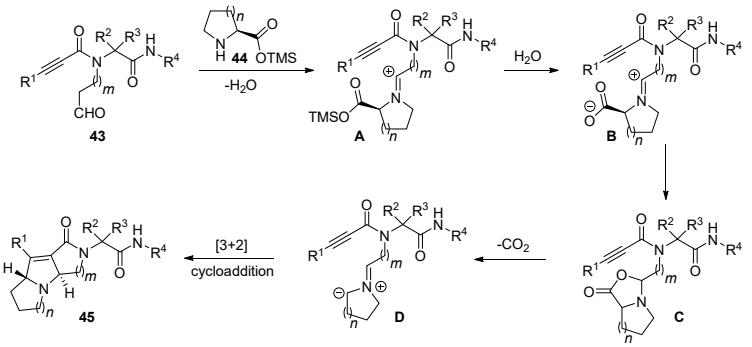


Scheme 22. Synthesis of piperazine-2,5-dione.

Interestingly, [3+2]-dipolar cycloaddition was successfully employed in post-Ugi reactions by Srivastava and co-workers [36]. The aldehyde-tethered Ugi-adducts were obtained from Ugi reaction using ethanolamine and subsequent Dess–Martin periodinane oxidation (Scheme 23). Through the [3+2]-dipolar cycloaddition of aldehyde-tethered Ugi-adducts with trimethylsilyl amino esters, uniquely functionalized pyrrolo-pyrrolizinones, pyrido-pyrrolizinones, and azepino-pyrrolizinones were prepared in good yield. Different with trimethylsilyl proline ester affording pyrrolo-pyrrolizinones, trimethylsilyl piperidine-2-carboxylate reacted with oxidized Ugi-adduct to give the completely oxidized pyrroloindolizinone. This is probably due to the ring strain in pyrrolo-pyrrolizinones that reduces the oxidation. According to the mechanism (Scheme 24), firstly, the condensation of Ugi-adduct and trimethylsilyl amino ester gives iminium intermediate **A**, which reacts with water and releases trimethylsilyl moiety to form intermediate **B**. This is followed by the attack of carboxylate anion and removal of CO_2 to afford intermediate **D**. Final intramolecular [3+2]-dipolar cycloaddition delivers the desired product.



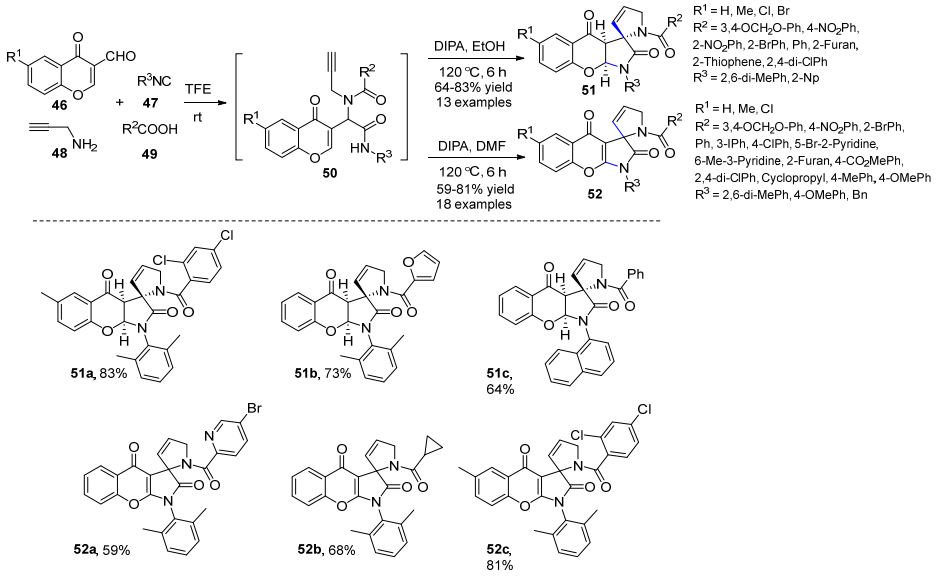
Scheme 23. Post-Ugi reaction via [3+2]-dipolar cycloaddition.



Scheme 24. Proposed mechanism for the [3+2]-dipolar cycloaddition.

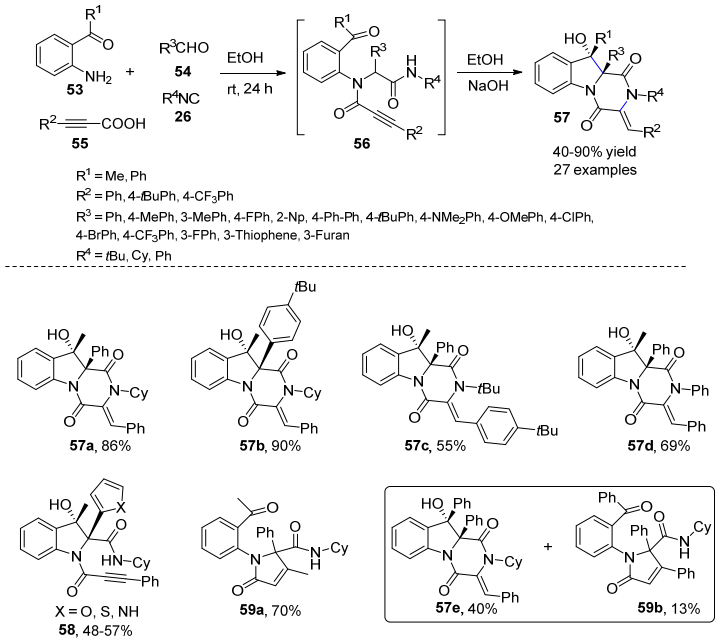
In 2021, Li, Chen, and Xu reported a metal-free approach to spiro-γ-lactams from chromone-tethered Ugi-adducts [37]. Through Michael addition and subsequent nucleophilic cyclization to form C-N/C-C bonds, diverse functionalized chromanones were synthesized in good yield under basic conditions (Scheme 25). Ugi-adducts bearing electron-withdrawing or -donating groups derived from chromone-3-carboxaldehydes successfully

afforded the desired chromanones in good yields. Diverse phenyl and heteroaryl groups derived from carboxylic acids were also well tolerated. When altering solvent from EtOH to DMF, a series of oxidized chromones were generated. Ugi-adducts derived from alkyl carboxylic acids and acids bearing electron-withdrawing or electron-donating groups on the phenyl ring were compatible with the reaction conditions to give the corresponding chromones in good yields. Electron-withdrawing or -donating groups derived from chromone-3-carboxaldehydes were also tolerated to afford the desired chromones. Notably, the obtained Ugi-adducts did not need purification by column chromatography, and the crude Ugi-adducts had no important influence on the overall yield of final products. Notably, obtained spiro-γ-lactams showed comparable anticancer activities with legendary anticancer drug paclitaxel in the PANC and U87 cell lines.



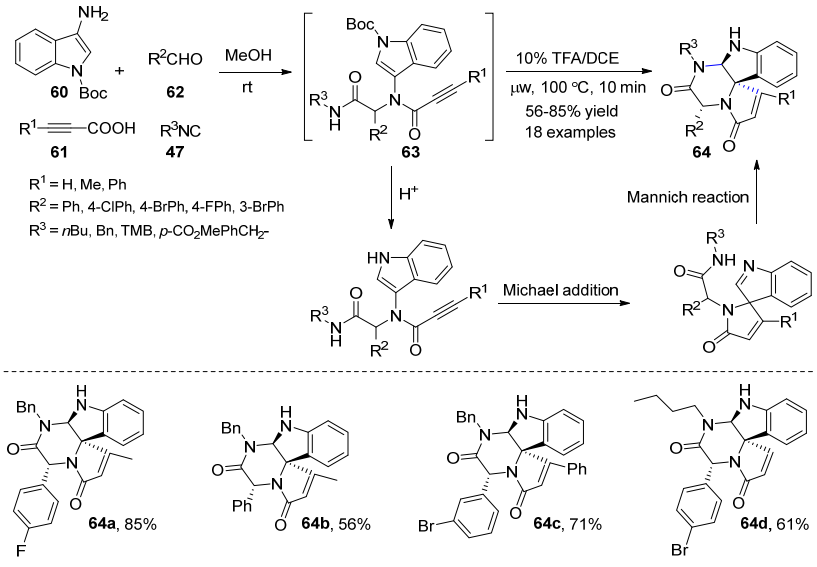
Scheme 25. Synthesis of spiro-γ-lactams via Michael addition and nucleophilic cyclization.

Subsequently, Chang and Chen developed a novel post-Ugi transformation for the preparation of indoline-fused 2,5-diketopiperazine scaffolds in a one-pot process [38]. Through 5-*exo-trig* Aldol type addition and sequential 6-*exo-dig* cyclization, tricyclic products were generated in high yield and excellent diastereo- and regioselectivity under basic conditions (Scheme 26). Electron-donating groups at the *para* position derived from aromaticaldehydes such as methyl, *t*-butyl, dimethylamino, and methoxy, afforded the products in higher yields than those bearing electron-withdrawing groups, such as Cl, Br, CF_3, and *meta*-F. Ugi-adducts derived from *p*-hydroxybenzaldehyde and aliphatic aldehydes did not favor the formation of the desired products, although excess sodium hydroxide was used. Ugi-adducts derived from 3-substituted heteroaromatic aldehydes were tolerated, such as 3-thiophenecarboxaldehyde and 3-furancarboxaldehyde. However, Ugi-adducts derived from heteroaromatic aldehydes substituted at the 2-position mainly afforded 5-*exo-trig* five-membered indolines, such as 2-furancarboxaldehyde, thiophene-2, and pyrrole-2-carboxaldehyde. This is probably due to the strong hydrogen bond between the heteroatom derived from heteroaromatic aldehydes and the NH group derived from isocyanides. Ugi-adduct derived from pyridine-2-carboxaldehyde generated pyrrolidine-2,5-dione derivative via the formation of a β-lactam intermediate, followed by ring expansion. Electron-donating and -withdrawing groups derived from phenylpropiolic acids did not evidently influence the yields; they only affected the reactivity. Electron-withdrawing groups could accelerate the reaction and reduce the reaction time. Ugi-adducts derived from aliphatic propiolic acids only gave 5-*endo-dig* Michael addition products, while Ugi-adducts derived from 2′-aminobenzophenone delivered the mixture of tricyclic products and 5-*endo-dig* products due to the steric hindrance of phenyl group in benzophenone.



Scheme 26. Synthesis of indoline-fused 2,5-diketopiperazine scaffolds.

Recently, Li, Chen, and Xu presented a metal-free one-pot protocol through the combination of Ugi reaction and TFA-mediated cyclization [39]. By using microwave irradiation, natural-product inspired spiroindolines were efficiently synthesized in high yield under 10 min (Scheme 27). The sequential deprotection, Michael addition from C3 of indole, and Mannich reaction process provided polycyclic products in excellent chemo- and diastereoselectivity. For all cases, the crude Ugi-adducts after the removal of the solvent under a gentle stream of nitrogen, were used directly in the next step without purification. A hydrogen, methyl, or phenyl group on the propiolamide fragment was well tolerated to deliver the corresponding products in good yields. Ugi-adducts derived from diverse aromatic aldehydes reacted smoothly. Various substituents on the secondary amide moiety derived from the isonitriles, such as benzyl, 4-CO_2MePhCH_2-, *n*-butyl, and 1,1,3,3-tetramethylbutyl, performed well to afford the corresponding products in good yields. Notably, the naturally existing spiroindolines displayed potential application as anti-cancer agents in diverse human cancer cell lines.



Scheme 27. Synthesis of spiroindolines via TFA-mediated cyclization.

5. Conclusions

Polycycles, as a class of important compounds, are widely existed in lots of bioactive molecules, natural products, advanced chemicals, and functional materials. Therefore, many efforts have been made to synthesize structurally diverse polycycles for a wide range of useful applications. Among different strategies, post-Ugi transformation has become one of the highly explored reactions for the construction of diverse polycycles due to the mild reaction conditions, wide scope, and high variability of Ugi reactions. Under gold catalysis, dearomatization, hydroamination, and hydroarylation have been employed in the preparation of versatile polycyclic N-heterocycles through the combination of other processes, such as Michael addition, 1,6-addition, [4+2] cyclization, and cycloisomerization. Other transition metals have also been investigated in the construction of novel polycycles, such as rhodium(III)-catalyzed C-H activation, silver(I)-catalyzed Friedel-Crafts cyclization, copper-catalyzed cross-coupling, and palladium-catalyzed dearomatization. Additionally, transition metal-free strategies also show powerful potential in the synthesis of structurally complex polycycles, such as cascade cyclization mediated by ICl, acid, and base. We hope that this minireview, which focuses on the synthesis of polycycles via post-Ugi transformations, would help researchers to better understand the chemistry behind post-Ugi reactions and stimulate future developments in the construction of polycycles.

Author Contributions: Conceptualization, L.S.; writing—original draft preparation, X.T.; writing—review and editing, L.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Natural Science Foundation of Jiangsu Province (BK20220409) and the Natural Science Research of Jiangsu Higher Education Institutions of China (22KJB150008).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Abbreviations

TMB, 1,1,3,3-tetramethylbutyl; Ad, adamantyl; Cy, cyclohexyl; Bn, benzyl; Np, naphthyl; Bs, benzenesulfonyl; IMes, 1,3-bis(mesityl)imidazole-2-ylidene; OTf, trifluoromethanesulfonate; IPr, 1,3-bis[2,6-di-i-propylphenyl]-4,5-dihydroimidazol-2-ylidene; DCE, 1,2-dichloroethane; MW, microwave; rt, room temperature; JohnPhos, [1,1′-biphenyl]-2-yldicyclohexylphosphine; NTf_2, bis(trifluoromethane sulfonimide); Fmoc, 9-fluorenylmethyloxycarbonyl; Cp*, pentamethylcyclopentadiene; *t*-AmOH, tertiary amyl alcohol; TBS, tert-butyl dimethyl silyl; TFA, trifluoroacetic acid; TFE, trifluoroethanol; DMSO, dimethyl sulfoxide; DMF, N,N-dimethylformamide; OAc, acetate; QPhos, 1,2,3,4,5-pentaphenyl-1′-(di-tert-butylphosphino)ferrocene; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF, N,N-dimethylformamide.

References

1. Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. Versuche mit isonitrilen. *Angew. Chem.* **1959**, *71*, 386.
2. Ruijter, E.; Scheffelaar, R.; Orru, R.V. Multicomponent reaction design in the quest for molecular complexity and diversity. *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246. [CrossRef] [PubMed]
3. Dömling, A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem. Rev.* **2006**, *106*, 17–89. [CrossRef] [PubMed]
4. Song, L.; Cai, L.; Van der Eycken, E.V. Microwave-assisted post-Ugi reactions for the synthesis of polycycles. *Molecules* **2022**, *27*, 3105. [CrossRef]
5. Sharma, U.K.; Sharma, N.; Vachhani, D.D.; Van der Eycken, E.V. Metal-mediated post-Ugi transformations for the construction of diverse heterocyclic scaffolds. *Chem. Soc. Rev.* **2015**, *44*, 1836–1860. [CrossRef]
6. Fouad, M.A.; Abdel-Hamid, H.; Ayoup, M.S. Two decades of recent advances of Ugi reactions: Synthetic and pharmaceutical applications. *RSC Adv.* **2020**, *10*, 42644–42681. [CrossRef]
7. Toure, B.B.; Hall, D.G. Natural product synthesis using multicomponent reaction strategies. *Chem. Rev.* **2009**, *109*, 4439–4486. [CrossRef]

8. Reguera, L.; Mendez, Y.; Humpierre, A.R.; Valdes, O.; Rivera, D.G. Multicomponent reactions in ligation and bioconjugation chemistry. *Acc. Chem. Res.* **2018**, *51*, 1475–1486. [CrossRef]
9. Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. Total synthesis of ecteinascidin 743. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554. [CrossRef]
10. Semple, J.E.; Wang, P.C.; Lysenko, Z.; Joullie, M.M. Total synthesis of (+)-furanomycin and stereoisomers. *J. Am. Chem. Soc.* **1980**, *102*, 7505–7510. [CrossRef]
11. Rossen, K.; Pye, P.; DiMichele, L.; Volante, R.; Reider, P.J. An efficient asymmetric hydrogenation approach to the synthesis of the Crixivan® piperazine intermediate. *Tetrahedron Lett.* **1998**, *39*, 6823–6826. [CrossRef]
12. Cao, H.; Liu, H.; Dömling, A. Efficient multicomponent reaction synthesis of the schistosomiasis drug praziquantel. *Chem. Eur. J.* **2010**, *16*, 12296–12298. [CrossRef]
13. Hulme, C.; Dietrich, J. Emerging molecular diversity from the intra-molecular Ugi reaction: Iterative efficiency in medicinal chemistry. *Mol. Divers.* **2009**, *13*, 195–207. [CrossRef]
14. Koopmanschap, G.; Ruijter, E.; Orru, R.V. Isocyanide-based multicomponent reactions towards cyclic constrained peptidomimetics. *Beilstein J. Org. Chem.* **2014**, *10*, 544–598. [CrossRef]
15. Bariwal, J.; Kaur, R.; Voskressensky, L.G.; Van der Eycken, E.V. Post-Ugi cyclization for the construction of diverse heterocyclic compounds: Recent updates. *Front. Chem.* **2018**, *6*, 557. [CrossRef]
16. Xiuming, L.; Xueshun, J.; Liang, Y. Recent progress on post-Ugi reaction. *Chin. J. Org. Chem.* **2017**, *37*, 2237.
17. He, Y.; Wu, D.; Li, Z.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E.V. Facile construction of diverse polyheterocyclic scaffolds via gold-catalysed dearomative spirocyclization/1, 6-addition cascade. *Org. Biomol. Chem.* **2019**, *17*, 6284–6292. [CrossRef]
18. He, Y.; Liu, Z.; Wu, D.; Li, Z.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E.V. Modular access to diverse bridged indole alkaloid mimics via a gold-triggered cascade dearomative spirocarbocyclization/[4+2] cycloaddition sequence. *Org. Lett.* **2019**, *21*, 4469–4474. [CrossRef]
19. He, Y.; Narmon, T.; Wu, D.; Li, Z.; Van Meervelt, L.; Van der Eycken, E.V. A gold-triggered dearomative spirocarbocyclization/Diels–Alder reaction cascade towards diverse bridged N-heterocycles. *Org. Biomol. Chem.* **2019**, *17*, 9529–9536. [CrossRef]
20. He, Y.; Li, Z.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E.V. A gold-catalyzed domino cyclization enabling rapid construction of diverse polyheterocyclic frameworks. *Angew. Chem. Int. Ed.* **2018**, *57*, 272–276. [CrossRef]
21. He, Y.; Song, L.; Liu, C.; Wu, D.; Li, Z.; Van Meervelt, L.; Van der Eycken, E.V. Access to polycyclic azepino [5, 4, 3-cd] indoles via a gold-catalyzed post-Ugi dearomatization cascade. *J. Org. Chem.* **2020**, *85*, 15092–15103. [CrossRef] [PubMed]
22. Tian, G.; Song, L.; Li, Z.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E.V. A gold (I)-catalyzed hydroamination/cycloisomerization cascade: Concise synthesis of (±)-seco-antofine and (±)-septicine. *Org. Lett.* **2020**, *22*, 8441–8445. [CrossRef] [PubMed]
23. Song, L.; Liu, C.; Tian, G.; Van Meervelt, L.; Van der Eycken, J.; Van der Eycken, E.V. Late-stage diversification of peptidomimetics and oligopeptides via gold-catalyzed post-Ugi cyclization. *Mol. Catal.* **2022**, *522*, 112240. [CrossRef]
24. Liu, C.; Van Meervelt, L.; Peshkov, V.A.; Van der Eycken, E.V. The synthesis of diverse benzazepinoindoles via gold-catalyzed post-Ugi alkyne hydroarylation/Michael addition sequence. *Org. Chem. Front.* **2022**, *9*, 4619–4624. [CrossRef]
25. Liu, C.; Bolognani, A.; Song, L.; Van Meervelt, L.; Peshkov, V.A.; Van der Eycken, E.V. Gold (I)-catalyzed intramolecular bicyclization: Divergent construction of quinazolinone and ampakine analogues. *Org. Lett.* **2022**, *24*, 8536–8541. [CrossRef]
26. Song, L.; Tian, G.; Blanpain, A.; Van Meervelt, L.; Van der Eycken, E.V. Diversification of peptidomimetics and oligopeptides through microwave-assisted rhodium (III)-catalyzed intramolecular annulation. *Adv. Synth. Catal.* **2019**, *361*, 4442–4447. [CrossRef]
27. Zaman, M.; Hasan, M.; Peshkov, A.A.; Van Hecke, K.; Van der Eycken, E.V.; Pereshivko, O.P.; Peshkov, V.A. Silver (I) triflate-catalyzed protocol for the post-Ugi synthesis of spiroindolines. *Adv. Synth. Catal.* **2020**, *362*, 261–268. [CrossRef]
28. Modha, S.G.; Kumar, A.; Vachhani, D.D.; Jacobs, J.; Sharma, S.K.; Parmar, V.S.; Van Meervelt, L.; Van der Eycken, E.V. A diversity-oriented approach to spiroindolines: Post-Ugi gold-catalyzed diastereoselective domino cyclization. *Angew. Chem. Int. Ed.* **2012**, *51*, 9572–9575. [CrossRef]
29. Zhong, X.; Luo, J.; Zhou, W.; Cai, Q. A Synthesis of spirooxindole-isoindolinones through Ugi reaction followed by copper-catalyzed tandem C−N/C−C coupling process. *Adv. Synth. Catal.* **2021**, *363*, 4969–4973. [CrossRef]
30. Butani, H.H.; Vachhani, D.D.; Bhoya, U.C.; Shah, A.K.; Van der Eycken, E.V. Regio-and chemoselective formation of spiroindolinone–isoindolinone by a palladium-catalyzed Buchwald–Hartwig addition–elimination sequence. *Eur. J. Org. Chem.* **2014**, *2014*, 6634–6638. [CrossRef]
31. Liu, C.; Song, L.; Van Meervelt, L.; Peshkov, V.A.; Li, Z.; Van der Eycken, E.V. Palladium-catalyzed arylative dearomatization and subsequent aromatization/dearomatization/aza-Michael addition: Access to Zephycarinatine and Zephygranditine skeletons. *Org. Lett.* **2021**, *23*, 5065–5070. [CrossRef]
32. Liu, C.; Zhao, R.; Song, L.; Li, Z.; Tian, G.; He, Y.; Van Meervelt, L.; Peshkov, V.A.; Van der Eycken, E.V. Palladium-catalyzed post-Ugi arylative dearomatization/Michael addition cascade towards plicamine analogues. *Org. Biomol. Chem.* **2021**, *19*, 9752–9757. [CrossRef]
33. Singh, K.; Malviya, B.K.; Jaiswal, P.K.; Verma, V.P.; Chimni, S.S.; Sharma, S. Phenanthridine-fused tetracyclic ring system: Metal-free diastereoselective modular construction of highly constrained polyheterocycles via post-ugi tandem modifications. *Org. Lett.* **2019**, *21*, 6726–6730. [CrossRef]
34. Lei, J.; Song, G.-T.; Luo, Y.-F.; Tang, D.-Y.; Yan, W.; Li, H.-y.; Chen, Z.-Z.; Xu, Z.-G. Synthesis of indoline-piperidinones via a novel Ugi, ring expansion, pseudo-Dieckmann condensation and rearrangement cascade reaction. *Org. Chem. Front.* **2020**, *7*, 737–741. [CrossRef]

35. Golmohammadi, F.; Balalaie, S.; Fathi Vavsari, V.; Anwar, M.U.; Al-Harrasi, A. Synthesis of Spiro-β-lactam-pyrroloquinolines as Fused Heterocyclic Scaffolds through Post-transformation Reactions. *J. Org. Chem.* **2020**, *85*, 13141–13152. [CrossRef]
36. Ghoshal, A.; Yadav, A.; Srivastava, A.K. [3+2]-Dipolar cycloaddition of aldehyde-tethered alkynamides and trimethylsilyl amino esters: A gateway to uniquely functionalized polycyclic N-heterocycles via post-Ugi functionalization. *J. Org. Chem.* **2020**, *85*, 14890–14904. [CrossRef]
37. Lei, J.; He, L.J.; Tang, D.Y.; Wen, J.; Yan, W.; Li, H.y.; Chen, Z.Z.; Xu, Z.G. Solvent-dependent chemoselective and stereoselective approach to synthesis of spiro-γ-lactams with potent anticancer activity. *Adv. Synth. Catal.* **2021**, *363*, 2996–3000. [CrossRef]
38. Wu, C.Y.; Murugan, S.P.; Wang, Y.W.; Pan, H.W.; Sun, B.J.; Lin, Y.T.; Fatimah, S.; Chang, A.H.; Chen, C.; Lee, G.H. Synthesis of indoline-fused 2, 5-diketopiperazine scaffolds via Ugi-4CR in the basic mediated tandem consecutive cyclization. *Adv. Synth. Catal.* **2021**, *363*, 4960–4968. [CrossRef]
39. Li, S.-Q.; Yan, W.; He, L.-J.; Zhang, M.; Tang, D.-Y.; Li, H.-y.; Chen, Z.-Z.; Xu, Z.-G. One-pot synthesis of natural-product inspired spiroindolines with anti-cancer activities. *Org. Chem. Front.* **2022**, *9*, 682–686. [CrossRef]