

**POST-UGI TRANSFORMATION OF *N*-SUBSTITUTED-2-ALKYNEAMIDES
FOR THE CONSTRUCTION OF DIVERSE HETEROCYCLIC SCAFFOLDS**

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Abstract. *Post-Ugi transformation reactions are well known to form molecular complexity, fused heterocyclic backbones. Existence of alkyne moiety in the structure of Ugi-4CR products allows post condensation cyclizations establishing carbon-carbon bonds by means of metal-catalyzed reactions or metal-free reactions. Synthesis of different heterocyclic backbones such as 2-oxindoles and spiroindolines can be constructed based on alkyne cyclization of post-Ugi reaction.*

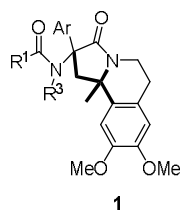
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1. Introduction

The alkyne moiety is one of the most important functional groups in organic chemistry, and could be involved in a variety of cascade cyclization reactions.¹ The selection of a functionalized alkyne is an efficient approach for the synthesis of heterocycles and also multifunctional compounds. Cyclization of alkynes could be done through π -activation with metal salts or formation of the desired metal acetylide.²

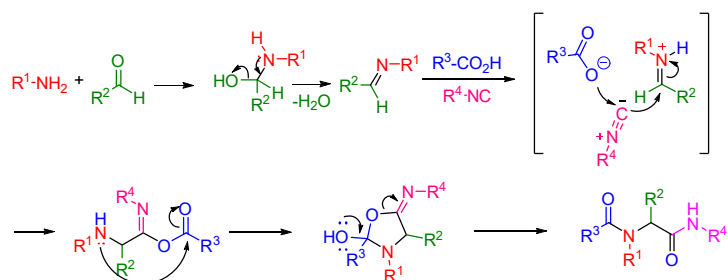
The Ugi four-component reaction (Ugi-4CR) has been widely explored because of its high bond-forming efficiency, simple and mild reaction conditions.³ The combination of established Ugi-4CR with post-transformational reactions has become a useful tool for generating complex and diverse molecular libraries with novel properties. Thus a logical extension is to use post-transformational reactions through the deployment of secondary functional groups in the initial starting materials.⁴ To have an ideally proceeding one-pot sequential transformation, existence of other active functional groups is necessary.⁵ Post-Ugi transformations showed high potential in the synthesis of complex molecules such as functionalized β -lactams^{6a} and benzoindolizidine alkaloids,^{6b} such as compound **1** in Figure 1. In this personal account our endeavors in the area of post-Ugi transformation reactions of *N*-substituted-2-alkyneamides to access diverse heterocyclic skeletons are summarized.



1
Figure 1

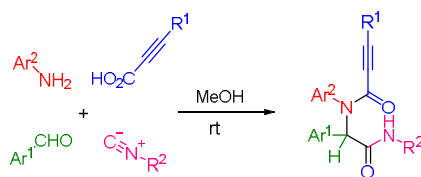
2. Synthesis of functionalized *N*-substituted-2-alkyneamides through Ugi-4CR

The Ugi-4CR reaction is one of the most versatile and robust multicomponent reaction. The typical Ugi reaction utilizes an aldehyde, a primary amine, a carboxylic acid, and an isocyanide affording a pseudopeptide (Scheme 1).⁷



Scheme 1. The Ugi-4CR to access pseudopeptides.

N-Substituted-2-alkyneamides have proved to be valuable building blocks in organic synthesis. *N*-Substituted-2-alkyneamides could be synthesized through the amidation reaction of primary amines and propiolic acid derivatives.⁸ To increase the molecular diversity and molecular complexity of the product and also carrying out the post-Ugi transformation, the strategy of single reactant replacement was selected. To access the functionalized Ugi-4CR product, Ugi-4CR was done using the functionalized starting materials (Scheme 2).



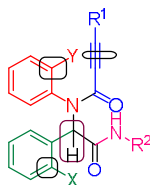
Scheme 2. Synthesis of functionalized *N*-substituted-2-alkyneamides.

Nucleophilic addition to activated alkynes has naturally attracted the attention of synthetic chemists and has led to the synthesis of medicinally relevant intermediates. Due to existence of alkyne moiety in the structure of *N*-substituted-2-alkyneamides, carrying out the sequential one-pot Ugi/nucleophilic addition reactions based on 5-component condensation (5-CC) and 6-component condensation (6-CC) for the synthesis of highly functionalized enaminones and dithiocarbamates. Addition of secondary amines,⁹ primary alcohols, phenols,¹⁰ dithiocarbamates,¹¹ and hydrazides¹² to the Ugi-4CR products of *N*-substituted-2-alkyneamides were investigated.

3. Post-Ugi transformation reaction based on *N*-substituted-2-alkyneamides

The change of the partners in Ugi-4CR is an attractive strategy for the discovery of new reactions and reactivity with interesting molecular scaffolds. Therefore, some carboxylic acids and the functionalized amines, isocyanides and benzaldehyde derivatives could be selected as reactants for the one-pot reaction. Further possibilities emerge when the various substituents of the primary Ugi-product are involved in additional reactions, e.g. Knoevenagel condensations or Diels-Alder cycloadditions with activated double or triple bonds.¹³

Based on these changes, the functionalized *N*-substituted-2-alkyneamides have some different active sites such as: a) an alkyne moiety for nucleophilic addition and carbopalladation; b) an active sp³ C-H for cyclization; c) a halide in position 2 of the aromatic amines and aromatic aldehyde backbones; d) a secondary amide moiety to be exploited in cyclization reaction (Scheme 3).



Scheme 3. Active sites of *N*-substituted-2-alkyneamides for post-Ugi-transformation reactions.

4. Metal-catalyzed post-Ugi transformation of *N*-substituted-2-alkyneamides

Metal-catalyzed reactions were used as an efficient approach to access the heterocyclic backbones in the recent years. Different catalysts were used for the cyclization reactions. For example Pd and Au catalysts have a brilliant position in metal-catalyzed post-Ugi transformations. Van der Eycken published a review about metal-catalyzed post-Ugi transformation reactions.¹⁴ We concentrate in this section some examples of Pd and Au catalyzed post-Ugi transformations.

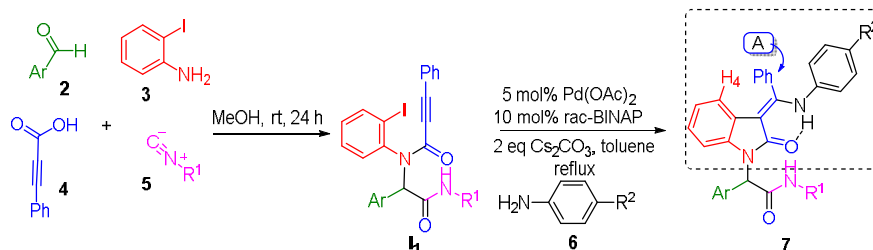
4.1. Pd-catalyzed post-Ugi transformation of functionalized *N*-substituted-2-alkyneamides

Oxindoles occupy a key place among the various classes of heterocyclic organic compounds that possess a common basic framework in natural products and pharmaceutically active compounds. 3-(Aminomethylene)-2-oxindoles have recently captured attention due to the utility of such structure in the development of biologically active compounds and new drugs as well. The small molecule hesperadin, is one notable 3-(anilinoaryl)methylene)-2-oxindole that has been identified as an Aurora B kinase inhibitor, a family of mitotic serine/threonine kinases. To access these molecules, a post-Ugi transformation reaction was used and the functionalized 2-oxindoles were formed.¹⁵

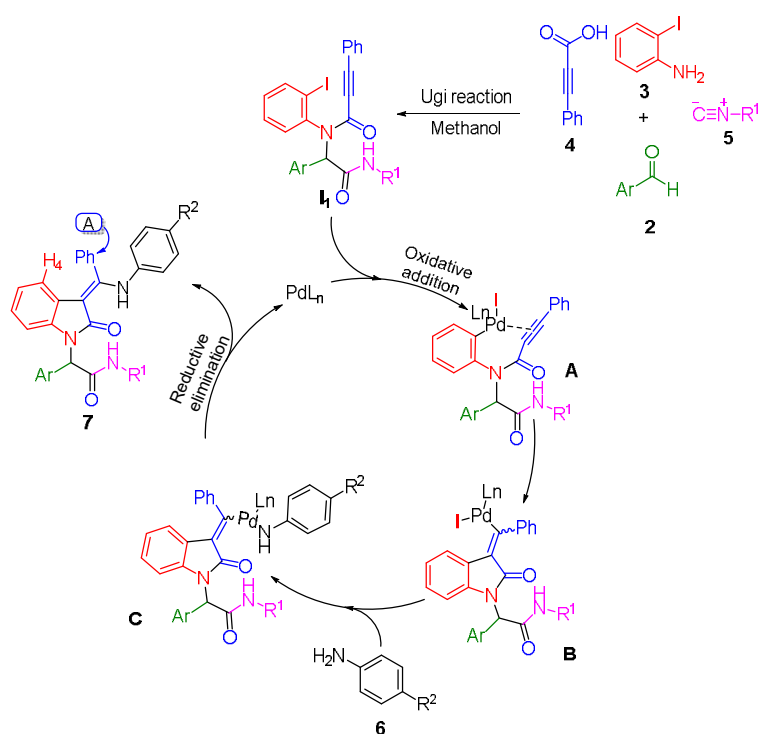
The Ugi-4CR product from the reaction of arylaldehyde **2**, 2-iodoaniline **3**, phenylpropionic acid **4**, and isocyanides **5** in MeOH, which led to *N*-substituted-2-alkynamides was chosen as an intermediate for the second step (domino Heck/Buchwald coupling reaction). In this approach, the reaction conditions were optimized using Pd(OAc)₂ as the catalyst, cesium carbonate as base and rac-BINAP as phosphine ligand. The *Z*-configuration of the products was established by analysis of the ¹H NMR spectrum of compounds **7**, in particular by the signal at δ 5.98-6.08 ppm for the H-4 oxindole proton. This unusual chemical shift is related to anisotropy of phenyl ring. Also, the -NH protons are deshielded and the chemical shifts were observed at 11.86-12.13 ppm. These results were not surprising due to the intramolecular hydrogen bond that can exist between the amino group and the carbonyl group in *Z*-stereoisomer (Scheme 4).

The proposed mechanism is shown in Scheme 5. After the formation of Ugi-adduct, the domino reaction occurs through Heck carbocyclization/Buchwald coupling of intermediates **I**₁ with aniline derivatives **6** as a domino insertion, a coupling sequence to form the 3-(anilinoaryl)methylene)-2-oxindoles **7**. According to the known Pd chemistry, the second step of the proposed mechanism is a known domino Heck/Buchwald reaction process, and the reaction procedure could be categorized respectively as follows: 1) occurrence of oxidative addition of haloarene **I**₁ to Pd⁰ to generate a Pd^{II} species **A**; 2) insertion reaction to alkyne moiety and formation of intermediate **B** (carbopalladation); 3) use of aniline derivatives **6** as

nucleophiles would result in the generation of a Pd-N bond through ligand substitution, leading to the formation of a C-N linkage (intermediate C); 4) reductive elimination of C would afford the products 7 with concurrent regeneration of Pd⁰ species. Based on the obtained results, besides *syn*-carbopalladation, *anti*-carbopalladation process also occurred. It seems that, after a *syn*-carbopalladation reaction, a *cis-trans*-isomerization takes place in the coordination sphere of the metal. Meanwhile, the *Z*-configuration of the products was confirmed using ¹H NMR spectroscopy with a diagnostic signal for the *Z*-isomer observed at δ 5.56-5.64 (H-4 of the oxindole). This unusual high-field shift is related to the aromatic ring current of the phenyl group (Phenyl A, compound 7). NOE experiments further confirmed the structure as the *Z*-isomer.



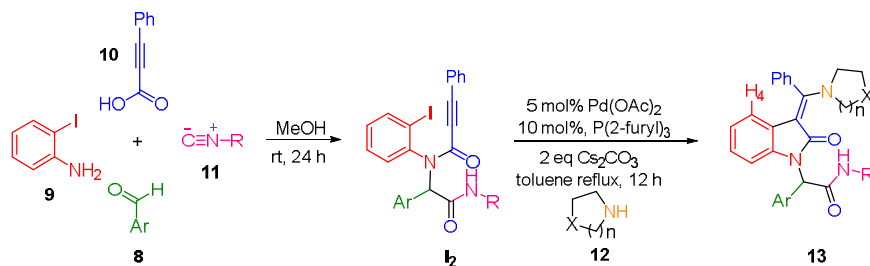
Scheme 4. Stereoselective synthesis of 3-(anilinoaryl)methylene-2-oxindoles 7.



Scheme 5. Possible mechanism for the synthesis of 3-(anilinoaryl)methylene-2-oxindoles 7.

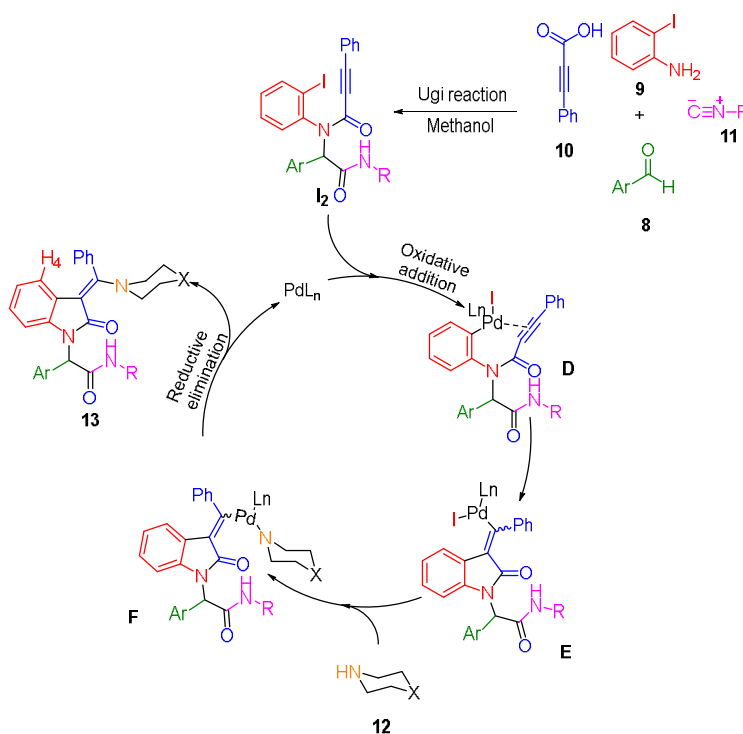
Another example of post-Ugi transformation reactions is Pd-catalyzed cyclization of *N*-substituted-2-alkynamide **I**₂ with secondary amines which produces 3-(aminoaryl)methylene-2-oxindoles *via* sequential Ugi/Heck/Buchwald reactions.¹⁶ The formation of **I**₂ was demonstrated in a control

experiment, where the intermediate was isolated and characterized. Then, Heck carbocyclization/Buchwald coupling of intermediates **I**₂ with secondary amines **12** as a domino insertion, coupling sequence to form the 3-(aminoarylmethylene)-2-oxindoles **13** occurred (Scheme 6).



Scheme 6. Stereoselective synthesis of *Z*-isomer 3-(aminoarylmethylene)-2-oxindoles **13** through sequential reactions.

The proposed reaction mechanism is shown in Scheme 7.



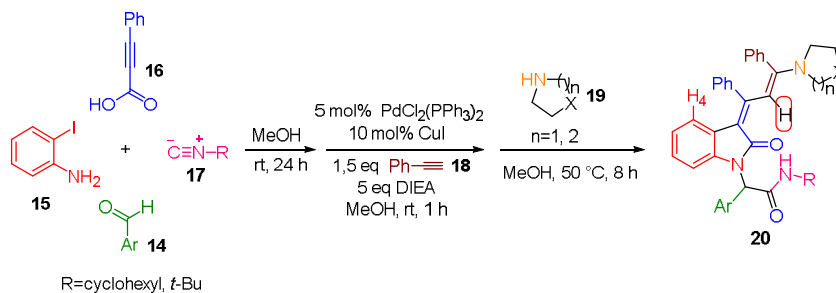
Scheme 7. Possible mechanism for the synthesis of 3-(aminoarylmethylene)-2-oxindoles **13** via 5-component sequential Ugi/Heck-carbocyclization/Buchwald reaction.

According to the known Pd chemistry, the second step of the proposed mechanism is a known domino Heck/Buchwald reaction process, and the reaction procedure could be categorized, respectively, as follows: 1) occurrence of oxidative addition of haloarene **I**₂ to Pd⁰ to generate a Pd^{II} species **D**; 2) insertion reaction to alkyne moiety and formation of intermediate **E** (carbopalladation); 3) use of secondary amines **12** as

nucleophiles would result in the generation of a Pd-N bond through ligand substitution, leading to the formation of a C-N linkage (intermediate **F**); 4) reductive elimination of **F** would afford the 3-(aminoarylmethylene)-2-oxindoles **13** with concurrent regeneration of Pd⁰ species.

4.2. Six-component reaction for the stereoselective synthesis of 3-arylidene-2-oxindoles *via* sequential one-pot Ugi/Heck carbocyclization/Sonogashira/nucleophilic addition

A six-component reaction of arylaldehyde **14**, 2-iodoaniline **15**, phenylpropionic acid **16**, isocyanides **17**, phenylacetylene **18**, and secondary amines **19** was used for the synthesis of 3-arylidene-2-oxindoles **20** in MeOH in the presence of Pd catalyst in an one-pot sequence (Scheme 8). The reaction could be carried out in the presence of 5% PdCl₂(PPh₃)₂, 10% CuI, and *N*-ethyl-diisopropylamine (DIEA) as the base in MeOH. Control experiments indicate that this sequential reaction could proceed in three steps, namely: 1) Ugi-4CR to access *N*-substituted-2-alkyneamides **I**₃; 2) Heck carbocyclization/Sonogashira cross-coupling of *N*-(2-iodophenyl) alkyneamides with phenylacetylene as a domino insertion, coupling sequence; 3) the formation of the intermediates **21** (*E*-isomer) and **22** (*Z*-isomer) and nucleophilic addition of secondary amines to activated triple bond in dihydroindolones **21** and **22** to form the 3-arylidene-2-oxindoles **20**.¹⁷

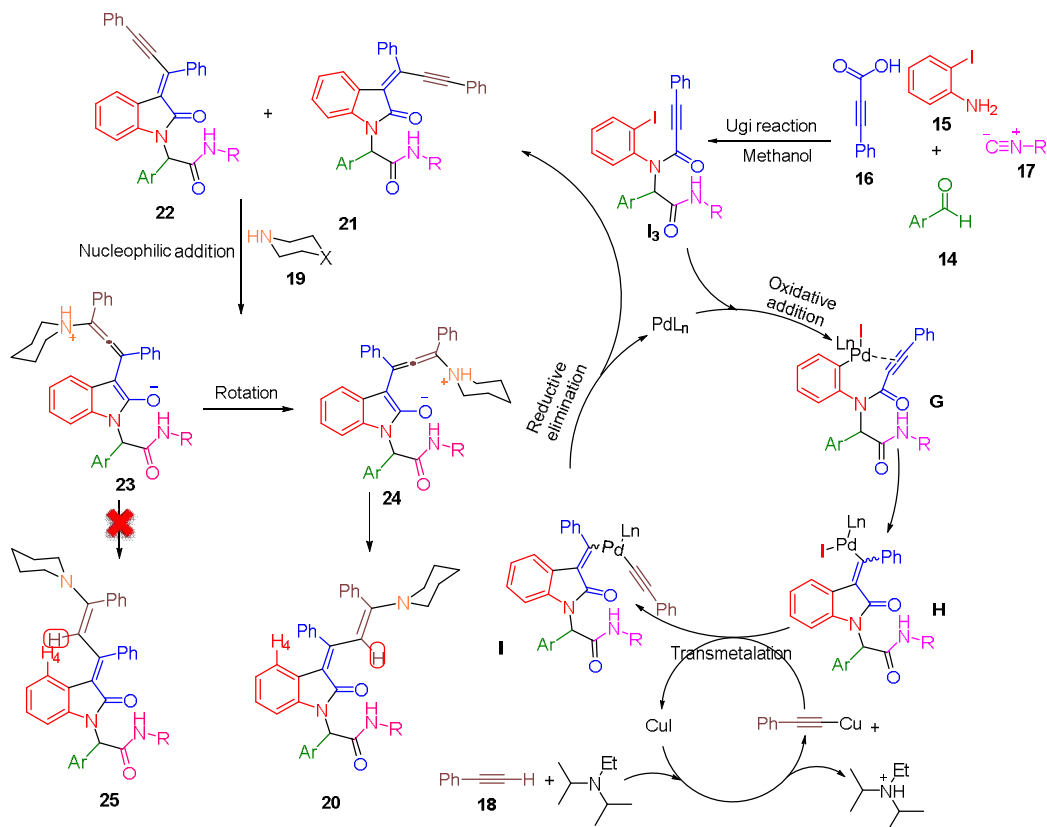


Scheme 8. Ugi/Heck carbocyclization/Sonogashira/nucleophilic addition reaction sequences for the synthesis of 3-arylidene-2-oxindoles **20**.

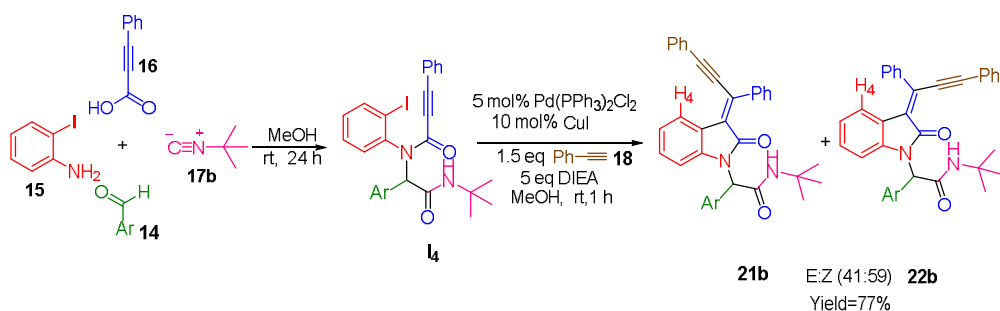
The proposed mechanism is shown in Scheme 9. The following steps show the role of Pd catalyst in the formation of 3-arylidene-2-oxindoles. The second step of the proposed mechanism is a known domino Heck/Sonogashira reaction process and the reaction procedure could be categorized, respectively: 1) oxidative addition of haloarene to Pd⁰ to afford intermediate **G**; 2) insertion reaction to alkyne moiety and formation of intermediate **H** (carbopalladation); 3) transmetalation with Cu and the addition of Cu phenylacetylide to intermediate **H** and formation of intermediate **I**₃; 4) final reductive elimination leads to the formation of the mixture of *E*- and *Z*- isomers of dihydroindolones **21** and **22**. Nucleophilic addition of the secondary amines to the electrophilic carbon center in the alkynyl moiety of the intermediate **21** or **22** would produce the zwitterionic intermediates **23** and **24**. The intermediate **23** leads to product **25** which has a strong steric hindrance. As it is shown, the intermediate **23** could be converted into the intermediate **24** due to steric hindrance in the structure of **25** compared to **20**. Rotation of the newly formed bond between the indole core and the allenyl moiety and subsequent tautomerization lead to stereoselective synthesis of **20**. In all cases, the *Z*-isomers of compounds **20** were obtained as the only product because of the phenyl group participation.

The ratio of *E*- and *Z*-isomers for compounds **21b** and **22b** depends on the polarity of the solvent. The ratio of **21b**:**22b** (*E*:*Z*) in THF was 65:35, whereas in MeOH it was 41:59. There is a distinguished peak in the ¹H NMR spectra of the products. As a model compound, in the structure of compound **20** (R=*t*-Bu, Ar=Ph, **19**=morpholine), proton H-4 resonates at δ 5.49 ppm as a doublet compared to that of H-4 in compound **21b** (δ 8.49 ppm). The shielding effect for this proton is related to the ring current of aryl group. In fact, this proton lies in the diamagnetic region of the ring which could be observed for all the products **20**. Meanwhile, the structure of compound **20** (R=*t*-Bu, Ar=Ph, **19**=morpholine) was unambiguously supported by NOE experiment. It should be mentioned that the decoupling of the H-4 proton at δ 5.49 ppm does not

cause any changes in the intensity of the singlet at δ 7.74 for the olefinic proton (=CH) in the structure of **20**, and in this way, the geometry of the double bond could be confirmed (Scheme 10).



Scheme 9. Proposed mechanism for the one-pot Ugi/Heck carbocyclization/Sonogashira/nucleophilic addition reaction sequences for the synthesis of 3-arylidene-2-oxidoles **20**.



Scheme 10. Reaction of benzaldehyde, 2-iodoaniline, phenylpropionic acid, and *t*-butyl isocyanide in MeOH, selected as a model. Synthesis of *E*- and *Z*-isomers **21b** and **22b**.

4.3. Sequential Ugi-4CR/C-H activation using (diacetoxyiodo)benzene for the synthesis of 3-(diphenylmethylidene)-2,3-dihydro-1*H*-indol-2-ones

A sequential Ugi-4CR/C-H activation reaction was used to access 3-(diphenylmethylidene)indolin-2-ones. The reaction was done using Pd catalyst in the presence of PhI as source of Ph group. However, the desired 3-(diphenylmethylidene)indolin-2-ones as sole products were formed by use of benzaldehydes bearing electron-donating groups ($R^1=EDG$), while with benzaldehydes which contained electron-withdrawing groups ($R^1=EWG$) the products were 3-(phenylmethylidene)indolin-2-ones instead (Figure 2).^{18a}

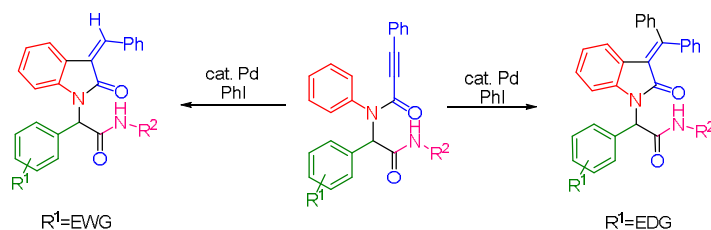
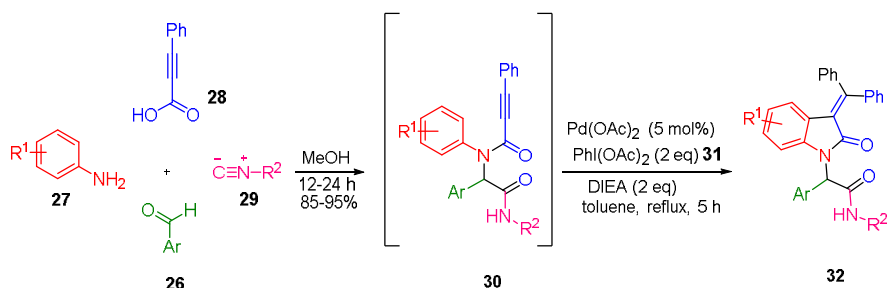


Figure 2. Synthesis of 3-(diphenylmethylidene)indolin-2-ones and 3-(phenylmethylidene)indolin-2-ones through C-H activation.

Diacetoxy-iodobenzene (DIB) **31** and DIEA as the base in toluene under reflux was used in a sequential Ugi/C-H activation reaction as a source of the phenyl group for the synthesis of 3-(diphenylmethylene)indolin-2-ones **32**, without obtaining 3-(phenylmethylidene)-2-oxindoles as byproduct, by reaction of arylaldehyde **26**, substituted anilines **27**, phenylpropionic acid **28**, and isocyanides **29** through formation of Ugi adduct **30** (Scheme 11).^{18b}

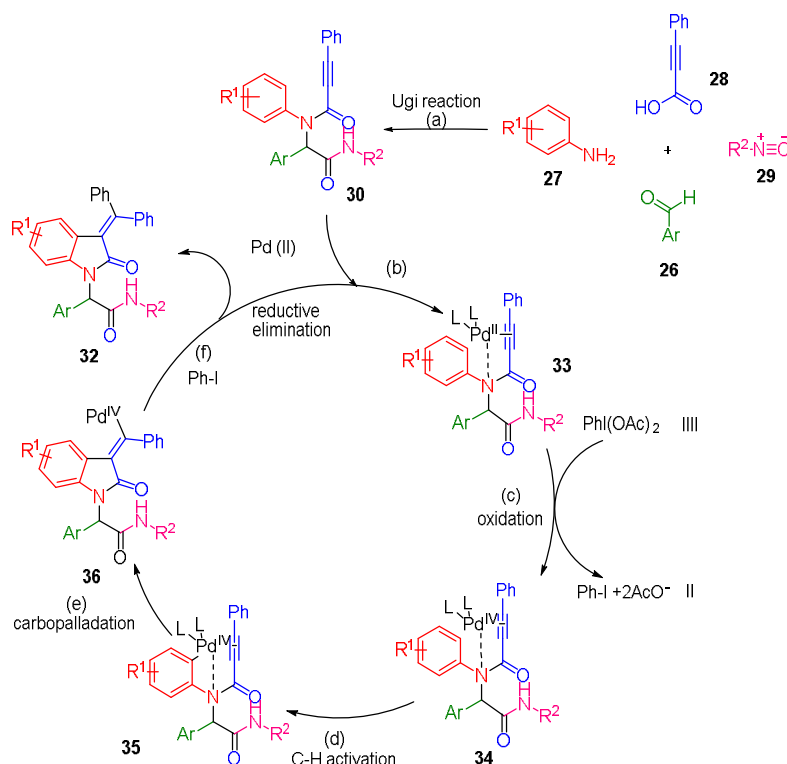


Scheme 11. Use of DIB **31** in sequential Ugi/C-H activation for the synthesis of 3-(diphenylmethylene)indolin-2-ones **32**.

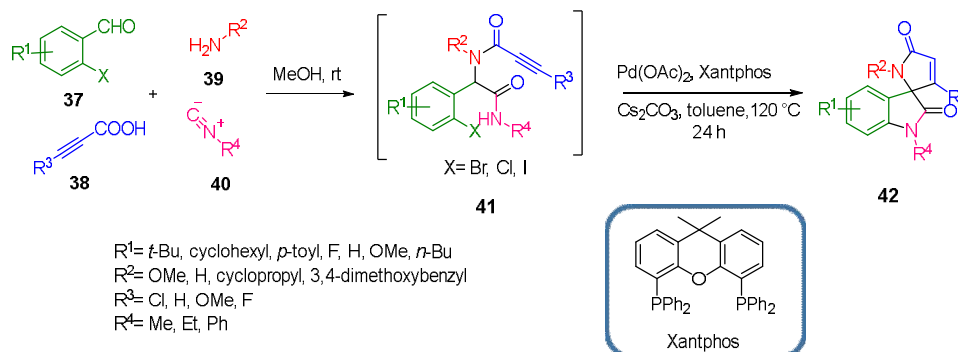
The reported reaction is a model of sequential Ugi/C-H activation reaction. The proposed reaction mechanism based on the sequential reaction is as follows: after formation of Ugi-4CR product **30** (path a, Scheme 12), insertion of Pd^{II} to **30** (path b) to give **33**, and oxidation of Pd^{II} to Pd^{IV} and complexation of Pd^{IV} with N of the aniline part leads to intermediate **34**. The key step for the formation of **34** is related to the conversion of DIB to PhI through reduction of I^{III} to I^I (path c). Then $C(sp^2)$ -H activation leads to the formation of C-Pd bond (path d). Carbopalladation of **35** results in the formation of intermediate **36** (path e). Insertion of PhI (path f) and, finally reductive elimination leads to the formation of the desired 3-(diphenylmethylidene)indolin-2-ones **32**.

Van der Eycken reported the synthesis of spiro[indoline-3,2-pyrrole]-2,5-diones **42** through Pd-catalyzed post-Ugi cascade reaction of arylaldehydes **37**, propionic acids **38**, substituted amines **39**, and isocyanides **40**.¹⁹ The Ugi adduct **41** contained alkyne moiety and then, after Buchwald-Hartwig/Michael addition reaction sequence, the desired spiro product was formed **42**. The type of phosphine ligand had an

essential role in the progress of the reaction. The best results were obtained using Xantphos as ligand (Scheme 13).



Scheme 12. Proposed mechanism for the formation of 3-(diphenylmethylidene)indolin-2-ones **32**.



Scheme 13. Using post-Ugi domino Buchwald-Hartwig/Michael reaction to afford functionalized spiro[indoline-3,2'-pyrrole]-2,5'-diones **42**.

5. Au-catalyzed post-Ugi transformation of functionalized *N*-substituted-2-alkyneamides

Au-catalyzed cyclizations of alkynes offer new pathways for the synthesis of different heterocyclic backbones. Meanwhile, the soft Lewis acidity of cationic Au^{I} species towards alkynes leads to diverse transformations and formation of new heterocycles and in some cases polycyclic compounds (Figure 3).^{20a}

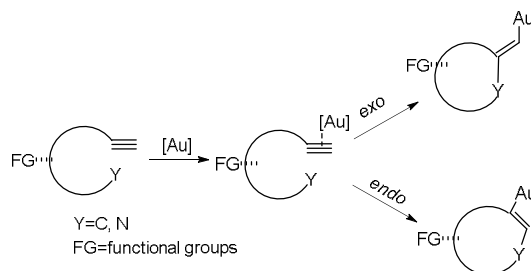


Figure 3. Reaction pathways for C-C and C-Y cyclization of alkyne.

Van der Eycken is a pioneer for the Au-catalyzed Ugi-4CR of functionalized *N*-substituted-2-alkyneamides and the results of his work was published in several papers and reviews.^{20b}

Compound **47** was formed through the Ugi-4CR of indole-3-carboxaldehyde **43**, propiolic acid **44**, primary amine derivatives **45** and isocyanides **46**. The reaction of Ugi-4CR product **47** with Au(PPh₃)SbF₆ (5%) afforded the fused polycyclic system with high diastereoselectivity. This is the first report of the synthesis of spiroindolines **48** (Figure 4).²¹

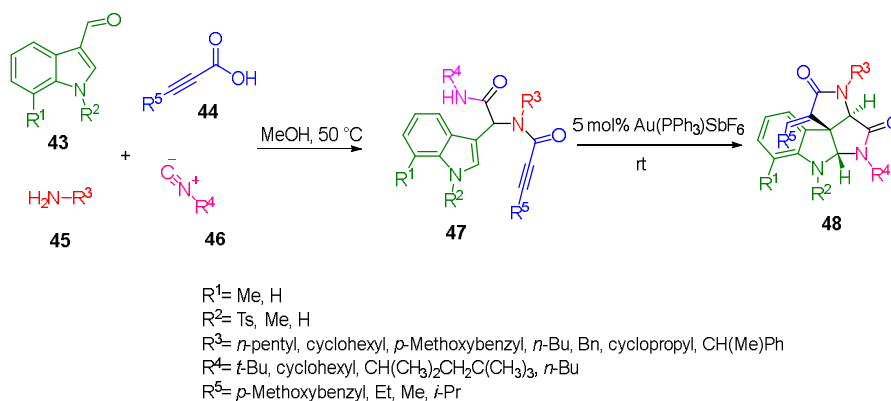


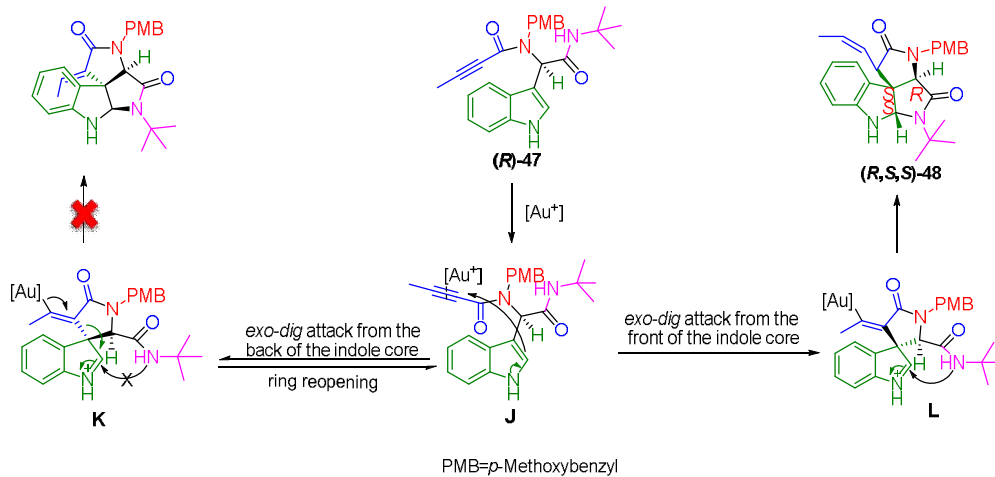
Figure 4. Synthesis of spiroindolines **48**.

In the proposed reaction mechanism, the observed diastereoselectivity of the reaction was explained. (Scheme 14). First the activation of the triple bond by cationic Au occurs to give **J**, then nucleophilic addition of activated alkyne from two sides takes place through *exo-dig* attack from the indole core at the 3-position to form intermediates **K** and **L**. Due to the direction of nucleophilic attack, the diastereoselective synthesis of spiroindoline **48** is possible.

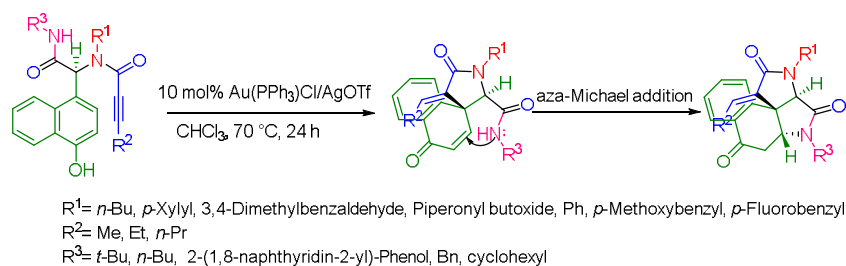
Van der Eycken reported a diversity-oriented diastereoselective synthesis of complex tetracyclic benzo[*e*]pyrrolo[2,3-*c*]indole-2,4,7(*5H*)-triones through a post-Ugi Au^I-catalyzed domino dearomatization/*ipso*-cyclization/*aza*-Michael sequence (Scheme 15).²²

In the proposed reaction mechanism, the alkyne moiety is activated by cationic Au^I, followed by nucleophilic attack at C-4 of naphthol in a *5-exo-dig* fashion. Then the nucleophilic addition of amide to activated double bond generates the tetracyclic scaffold (Scheme 16).

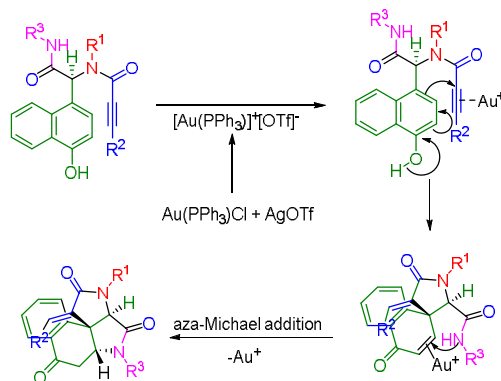
In another experiment, Van der Eycken carried out the Ugi-4CR of arylaldehyde **49** with propargyl amine **50**, 4,4-dimethylpentynoic acid **51** and isocyanides **52** in methanol at rt to give the corresponding *N*-propynylbutynamide **53**. Its reaction with 5 mol% of *i*-PrAuNTf₂ ([1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene] [bis(trifluoromethanesulfonyl)imide]gold(I)) in CDCl₃ at 80 °C for 24 h, led to the major product **54** via intramolecular nucleophilic attack of the β-carbon of the Au acetylide on the β-carbon of the butynamide, followed by a second cyclization²³ (Scheme 17).



Scheme 14. Proposed mechanism for the diastereoselective domino cyclization to spiroindolines **48**.



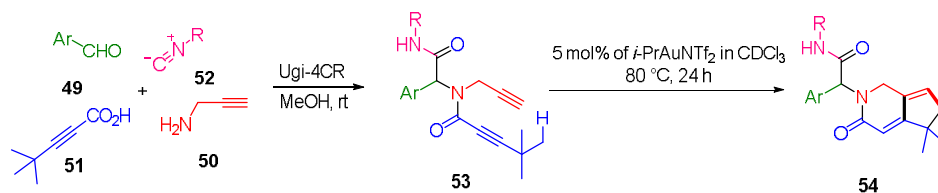
Scheme 15. Au-catalyzed cyclization for fused azaspiro tetracycles.



Scheme 16. Proposed mechanism for the Au-catalyzed diastereoselective domino cyclization.

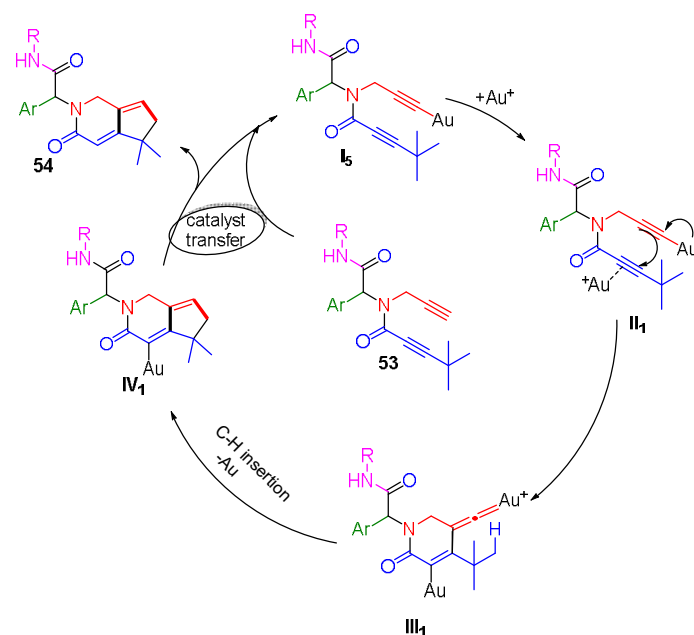
This is an example of *i*-PrAuCl (Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I))/AgOTf efficiently catalyzed regioselective cascade cyclization of *N*-propynylbutynamide via sp^3 C-H functionalization for the synthesis of (spiro)cyclopentapyridinones (Scheme 18). In the proposed reaction mechanism, the first step is the transformation of **53** into Au acetylide **I₅** which, upon π -activation of the butynamide **II₁**, directs the *6-endo-dig*-cyclization, resulting in the formation of the Au-vinylidene

intermediate **III₁**. This highly reactive species may undergo facile C-H insertion to give **IV₁**, which, upon protodeauration, forms the final product **54** (Scheme 18).



R= cyclohexyl, *t*-Bu, Bn, 3,3',5,5'-tetramethylbenzidine

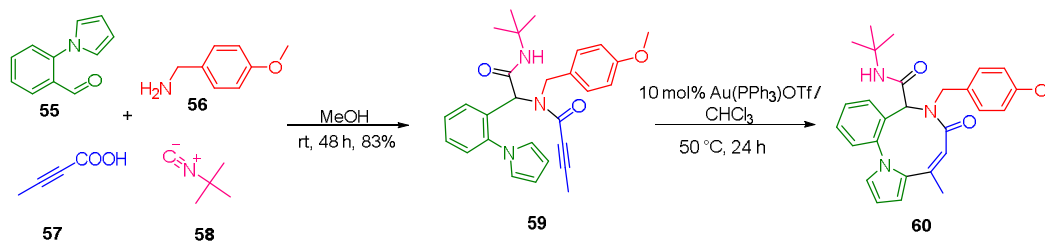
Scheme 17. The Au-catalyzed tandem cyclization *via* sp^3 C-H activation to give **54**.



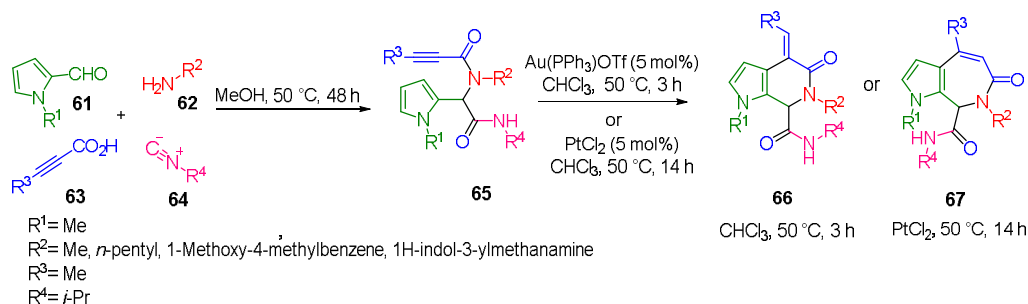
Scheme 18. Plausible mechanism for Au-catalyzed tandem cyclization.

Another post-Ugi reaction is combination of Ugi-4CR with hydroxyarylation reaction. Van der Eycken reported the Ugi-4CR of 2-(1*H*-pyrrol-1-yl)benzaldehyde **55**, *p*-methoxybenzylamine **56**, 2-butynoic acid **57**, and *t*-butyl isocyanide **58** in methanol at room temperature.²⁴ Then, the Ugi adduct **59** was reacted with 10 mol% Au(PPh₃)OTf to give the desired benzo[*b*]pyrrolo[2,1-*i*][1,5]diazonin-7(6*H*)-one **60** (Scheme 19). In the proposed mechanism, after alkyne activation by cationic Au, nucleophilic attack from the C-2 position of the pyrrole through *endo-dig* fashion occurred and finally the desired product was formed.

Recently, Van der Eycken has designed an Ugi-4CR using 2-aminophenole derivative and their post-Ugi transformation using Au catalyst to afford a diastereoselective synthesis of spirocyclic pyrrole-2-one-dienones through *ipso*-cyclization.²⁵ The use of 2-formylpyrrole in Ugi-4CR could provide its potentiality for further reaction. The Ugi-4CR of 2-formylpyrrole **61**, primary amine **62**, alkyne acid **63**, and isocyanide **64** in methanol at 50 °C gives Ugi adducts **65**. The reaction of Ugi adduct with Au(PPh₃)OTf in chloroform at 50 °C for three hours leads to the corresponding pyrrolopyridinones through *exo-dig* cyclization of the pyrrole on the internal alkyne **66**. The synthesis of isomer **67** through *endo-dig* cyclization as major product is possible changing the reaction conditions, as summarized in Scheme 20.²⁶



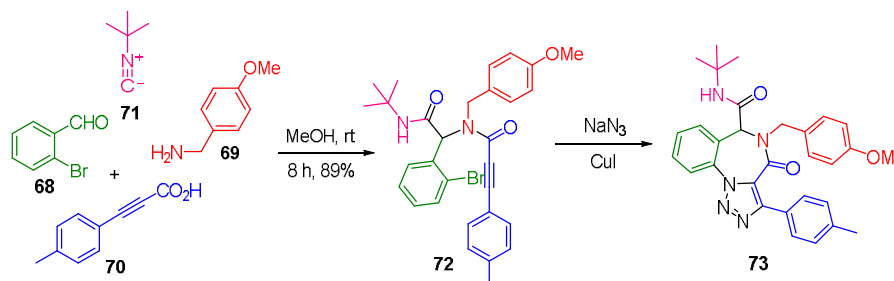
Scheme 19. Synthesis of **60** by intramolecular hydroarylation of *N*-substituted-2-alkyneamide using Au catalyst.



Scheme 20. Regioselective synthesis of pyrrolopyridinones **66** and pyrroloazepinones **67** via post-Ugi Au^I-catalyzed intramolecular hydroarylation.

The same reaction conditions were used with 2-formylindoles and the fused pyrroloazepinones were formed. This approach was used for other formyl heterocyclic skeletons such as 2-thiophene caraldehyde, 2-formylthiophene and *N*-alkyl-2-formylpyrrole. This allows a diversity-oriented synthesis of substituted pyrrolopyridinones, pyrroloazepinones, thiophenoazepinones, azepinoindoles, and azepinobenzothiophenes.²⁶

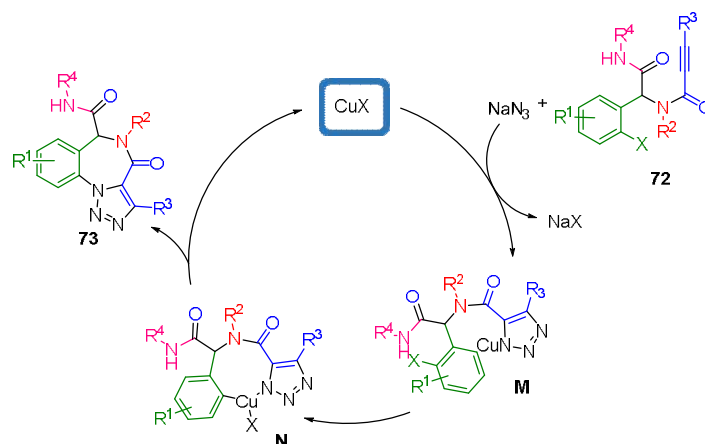
Van der Eycken designed a post-Ugi Cu-catalyzed tandem azide-alkyne cycloaddition (AAC)/Ullmann coupling strategy for the synthesis of triazolo[1,5-*a*][1,4]benzodiazepinones. To access this goal 2-bromo-benzaldehyde **68**, 4-methoxybenzylamine **69**, arylpropionic acids **70** and *t*-butyl isocyanide **71** were used as starting materials in Ugi-4CR **72**. Then, the intramolecular trapping of the *N*-Cu intermediate formed by the CuAAC and Ullmann coupling give rise to **73** with sodium azide (Scheme 21).²⁷



Scheme 21. The tandem AAC/Ullmann approach towards triazolo[1,5-*a*][1,4]benzodiazepinones **73**.

The plausible mechanism for the Cu-catalyzed tandem reaction is depicted in Scheme 22. The reaction of Ugi-4CR adduct **72** with sodium azide through [3+2]-cycloaddition forms intermediate **M** that contains a

N-Cu bond. Then, insertion of Cu into the aryl halide bond leads to intermediate N, and the final Cu elimination leads to the formation of triazolo[1,5-*a*][1,4]benzodiazepinone **73**.

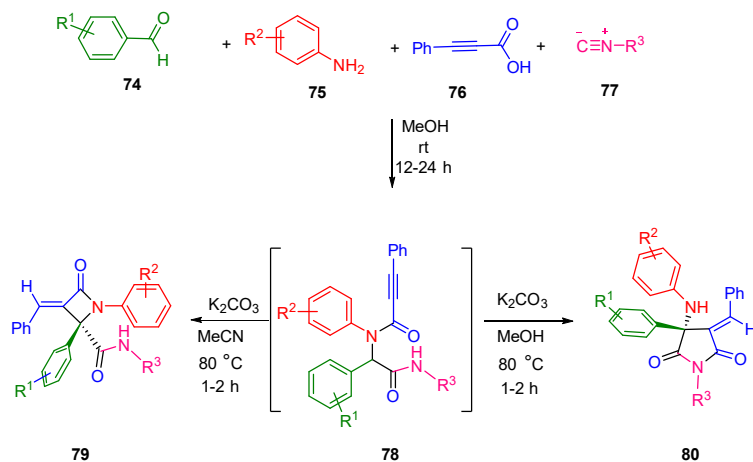


Scheme 22. A plausible mechanism for the Cu-catalyzed tandem formation of **72** and **73**.

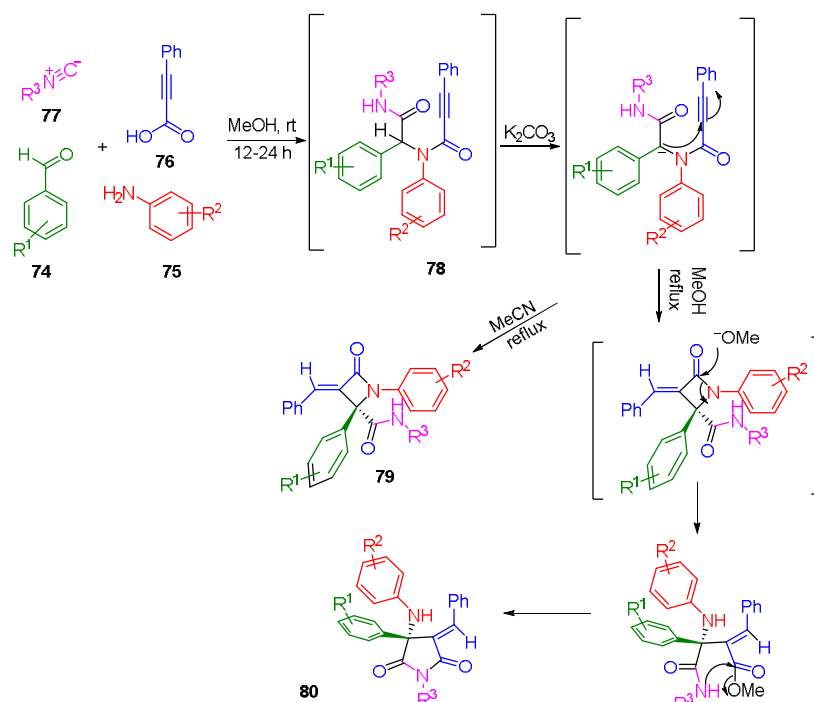
6. Metal-free post-Ugi transformation of functionalized *N*-substituted-2-alkynamides to access heterocycles

In recent years, some functionalized *N*-substituted-2-alkynamides were used for further post-transformation reactions such as nucleophilic addition or cyclization using suitable starting materials and Pd or Au catalysts. Meanwhile, Pd catalyst was used for the transition-metal catalyzed cycloisomerization of alkynyl *N*-acyl enamines to access lactams.²⁸ Zhang *et al.* reported a highly enantioselective cycloisomerization approach to access functionalized lactams using Rh-based catalysts.²⁹ Due to the biological activities of lactams,³⁰ finding new methods that allow the formation of C-N bond and the stereoselective generation of functionalized lactams is an interesting subject in organic synthesis.³¹ Ugi-4CR has been reported for the synthesis of β -lactams and the use of functionalized starting materials has an important role in cyclization reaction process.³² We developed a metal-free cyclization through sequential Ugi-4CR/cyclization reaction for the synthesis of functionalized β -lactams and pyrrolidine-2,5-diones (Scheme 23).³³ Ugi-4CR between benzaldehyde derivatives **74**, aniline derivatives **75**, phenyl propiolic acid **76** and isocyanides **77** was done and product **78** was formed. The *N*-substituted 2-alkynamides were precipitated and separated. Then they were treated with different bases and solvents. Potassium carbonate (K_2CO_3) was the most effective base to provide cyclization products compared to other bases. Carrying out the reaction in acetonitrile led to the synthesis of β -lactam **79**, while in methanol the only product was pyrrolidine-2,5-dione **80**. In all cases, the β -lactam skeleton with some functional groups was produced in good to high yields. A significant point in formation of β -lactams is the *E*-geometry for double bond in all cases. It seems that the secondary interaction (π - π stacking) could affect the geometry of formed β -lactams. In the structure of functionalized *N*-substituted 2-alkynamides **78**, there are two amide moieties, a triple bond and also a C-H bond has an acidic character. It can be deprotonated using a suitable base and form the carbanion which in turn could be added to the triple bond through intramolecular nucleophilic addition.

A plausible mechanism for these cyclization reactions is depicted in Scheme 24. The reactions proceed *via* the formation of intermediate **78** through Ugi-4CR. There are two feasible pathways from **78** in different solvents. Initially, the carbanion is formed by treatment with the base. It is reasonable to assume that the intramolecular nucleophilic addition of carbanion to triple bond in Ugi product **78**, forms the β -lactam **79** skeleton in both solvents. But, it can act as an intermediate in MeOH and the attack of methoxide to the carbonyl group in β -lactam skeleton takes place immediately to afford regioselectively pyrrolidine-2,5-dione **80**.



Scheme 23. Synthesis of β -lactams **79** and pyrrolidine-2,5-diones **80** through metal-free sequential Ugi-4CR/cyclization.



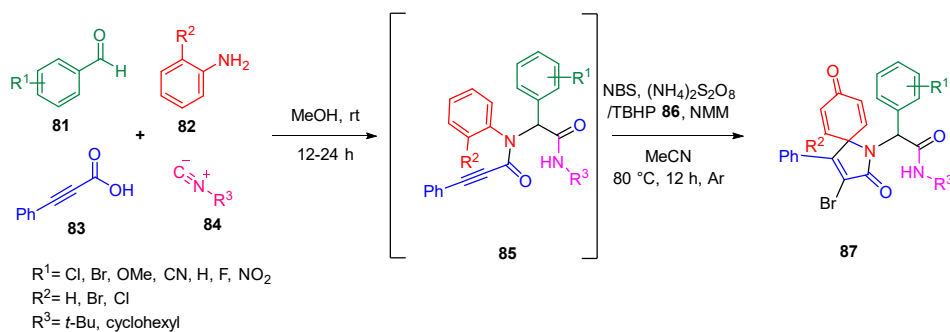
Scheme 24. Plausible mechanism for the formation of β -lactam **79** and pyrrolidine-2,5-dione **80** in methanol.

6.1. Post-Ugi transformation through radical formation

Among the recently synthesized azaspirocycle-containing compounds, azaspiro[4.5]trienones have attracted the attention due to their chemistry and their biological activities.³⁴

Recently, and in the light of the intense interest to develop constrained tamoxifen mimics, Srivastava *et al.* reported azaspiro[4.5]trienones as novel scaffolds for anticancer drug development.³⁵ Furthermore, these compounds also serve as valuable intermediates for the construction of azaspiro-fused tricyclic cores with promising anticancer activity by inducing DNA damage in cancer cells.

In light of these findings and as a result of our interest in combination of the Ugi-4CR with an efficient post-transformation for generating complex and diverse molecular libraries, Ugi-4CR/*ipso*-bromocyclization was used for the synthesis of fully functionalized 3-bromoazaspiro[4.5]trienones **87** through the radical cyclization and metal-free reaction of arylaldehydes **81**, aniline derivatives **82**, phenylpropionic acid **83**, and isocyanides **84** (Scheme 25).³⁶ The corresponding Ugi adduct **85** was formed in good to high yields. The use of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ /*t*-butyl hydroperoxide (TBHP) (3 eq/5 eq) **86** as the oxidant in the presence of *N*-methylmorpholine (NMM, 0.5 eq) in acetonitrile at 80 °C under argon atmosphere produced the desired spiro compounds. Between different radical initiators, TBHP was found to be the best, while switching to 2,6-di-*t*-butyl-4-pyridine, *t*-butyl-4-pyridine, and *m*-chloroperoxybenzoic acid failed to give satisfactory yields.



Scheme 25. Synthesis of 3-bromoazaspiro[4.5]trienones **87** via Ugi-4CR followed by *ipso*-bromocyclization.

The proposed reaction mechanism involves the formation of vinyl radical **I**₆ through the addition of bromo radical generated from *N*-bromosuccinimide (NBS) and $(\text{NH}_4)_2\text{S}_2\text{O}_8$ to the alkyne group of the Ugi product. Subsequent intramolecular radical cyclization yields the intermediate **II**₂. Trapping of the radical intermediate **III**₂ by the *t*-butylperoxy radical generated from TBHP, and the following of *t*-butyl alcohol provides the desired product (Scheme 26).

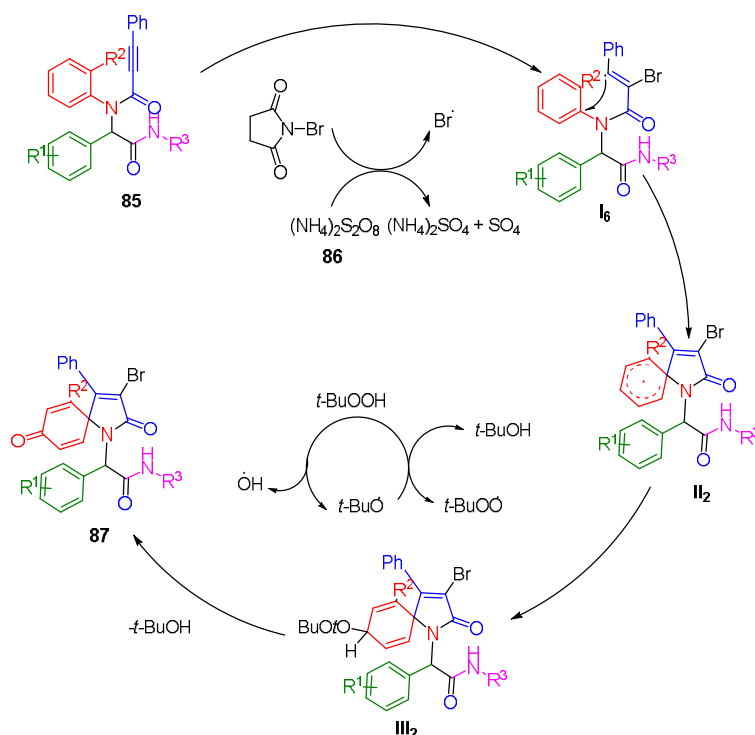
In this approach, a diverse array of fully functionalized 3-bromoazaspiro[4.5]trienones has been prepared through Ugi-4CR followed by *ipso*-bromocyclization.

6.2. Metal-free synthesis of fused triazolodiazepino[5,6-*b*]quinoline derivatives via a sequential Ugi-4CR/nucleophilic substitution/intramolecular click reaction

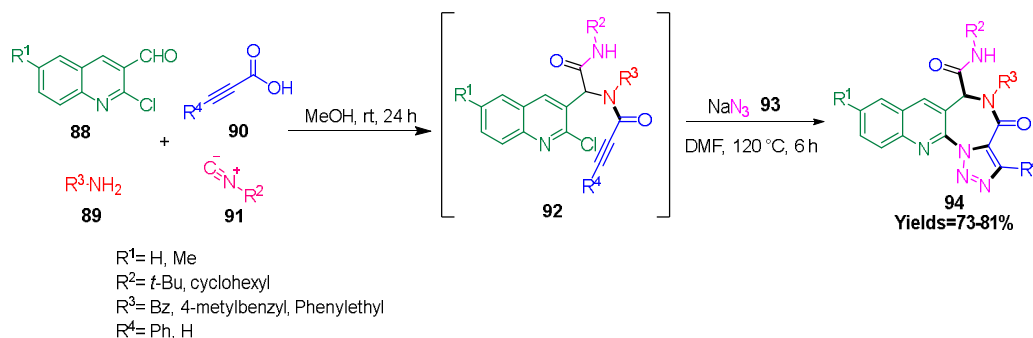
2-Chloro-3-formylquinoline was used as functionalized aldehyde to carry out Ugi-4CR and its reaction with propionic acids, primary amines and isocyanides led to desired *N*-substituted-2-alkyneamides. These compounds are suitable for post-Ugi transformation reactions. This approach was used in a one-pot catalyst-free strategy for the construction of quinoline/triazole/diazepinone-fused skeletons. The initial investigations were centered on the construction of quinoline fused diazepinones **94** via Ugi-4CR of 2-chloro-3-formylquinoline **88**, primary amine **89**, propionic acid derivative **90**, and isocyanide **91** in methanol at room temperature for 24 hours as the model reaction. Treatment of **92** with sodium azide **93**, afforded **94**, through a reaction that could be categorized as Ugi/1,3-dipolar cycloaddition/cyclization (Scheme 27).³⁷

The proposed mechanism for the production of compound **94** is shown in Scheme 28. At first, the Ugi adducts **92** were formed. Then, two possible mechanistic pathways can be considered for the synthesis of products **94**. Route A includes the nucleophilic addition of sodium azide to the Ugi adducts **92** and formation of intermediate **I**₇, which is in equilibrium with intermediate **II**₃.³⁸ Further intramolecular click reactions

between the azide group and the alkyne group of intermediate **I**₇ results in the production of the desired products. Route B involves the click reaction between alkyne moiety of Ugi adduct **92** with azide group and formation of triazole containing intermediate **III**₃. Subsequently, the intramolecular nucleophilic addition of the triazole ring will lead to the desired products **92**.



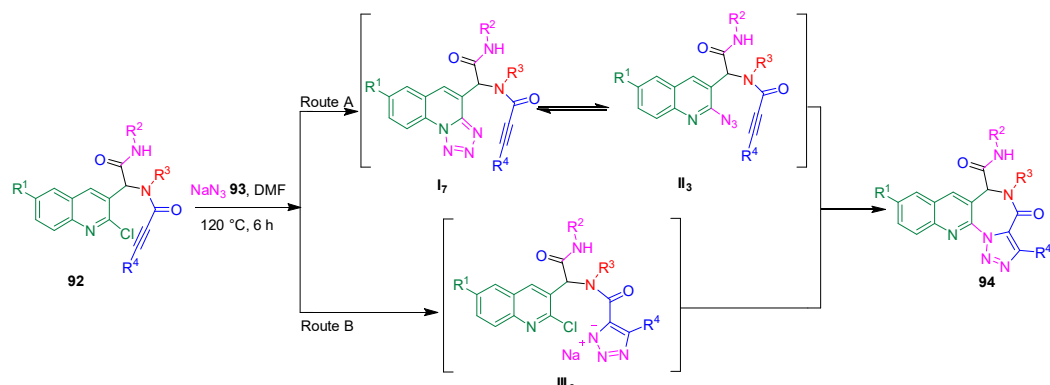
Scheme 26. The proposed reaction mechanism for the synthesis of 3-bromoazaspiro[4.5]trienones **87**.



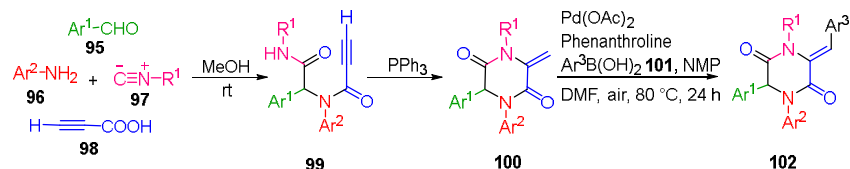
Scheme 27. Synthesis of quinoline fused diazepinons **94** through sequential Ugi/1,3-dipolar cycloaddition/cyclization reaction.

In continuation of our efforts to adapt post-transformation reactions to a high-throughput format, diastereoselective synthesis of diketopiperazines **102** through the post-Ugi transformation/cyclization/oxidative Heck reaction sequence was explored (Scheme 29).³⁹ In the first step, Ugi-4CR product was formed through the reaction of arylaldehydes **95**, aniline derivatives **96**, isocyanides

97, and propiolic acid derivatives **98**. The *N*-substituted-2-alkynamide **99** was precipitated and separated. The reaction of compounds **99** with a catalytic amount of triphenylphosphine in ethanol led to desired diketopiperazines **100** (Schemes 29 and 30). The 2,5-diketopiperazines **100** have a methyldiene group that has a very good potential for C-C bond formation. Transition metal-catalyzed cross-couplings such as Heck and Suzuki reactions have been used for the formation of C-C bond. Meanwhile, the regioselectivity of the Heck reaction is the main point which must be considered in planning synthetic routes.⁴⁰⁻⁴¹



Scheme 28. Proposed mechanism for the synthesis of triazolodiazepino[5,6-*b*]quinoline derivatives **94**.



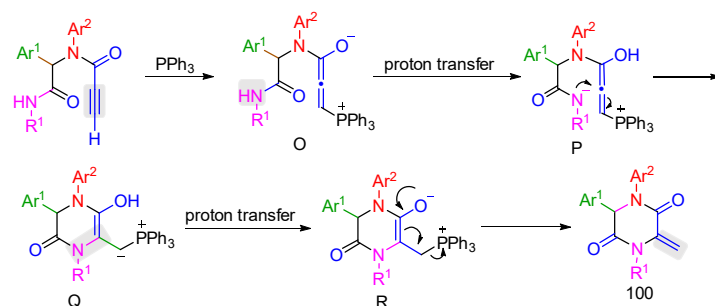
R¹= cyclohexyl, CH₂CO₂Et, *t*-Bu

Ar¹= 4-Bromophenyl, Ph, 4-Chlorophenyl, 4-Methoxyphenyl, 4-Cyanophenyl, Thiophene

Ar²= 4-Fluorophenyl, Ph, 2-Bromophenyl, 2-Iodophenyl

Ar³= Ph, 4-*t*-Butylphenyl

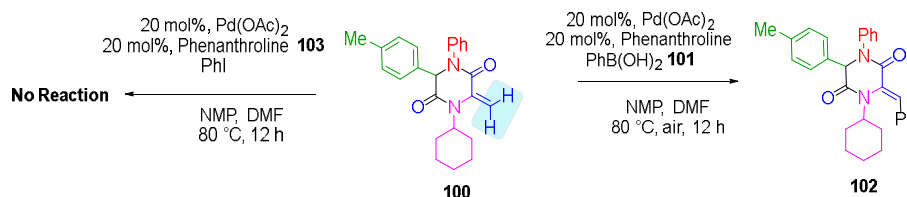
Scheme 29. Designed post-transformation approach for the synthesis of arylidene-2,5-diketopiperazines **102**.



Scheme 30. Proposed mechanism for the synthesis of 2,5-diketopiperazines **100** through triphenylphosphine catalyzed nucleophilic addition to alkynes.

Oxidative Heck reaction conditions were selected first. To access this goal, the reaction of diketopiperazines **100** (R¹=cyclohexyl, Ar¹=*p*-Me-C₆H₄, Ar²=Ph) with arylboronic acid **101** in the presence of Pd acetate (20%), phenanthroline (20%) **103** and air as oxidant was studied in DMF solvent at 80 °C.

Arylmethylidene Z-diketopiperazines **102** were formed diastereoselectively. By contrast the reaction, leading to the same product, but performed under Heck conditions did not work and we were unable to isolate **102** (Scheme 31).



Scheme 31. Difference between Mizoroki-Heck and oxidative Heck reactions.

7. Conclusion

In conclusion, post-Ugi transformation are known as an efficient approach in heterocycle synthesis. The synthesis of diverse functionalized heterocyclic backbones are possible through the selection of starting material that contained alkyne moiety. The alkyne cyclization could be done using metal-catalyzed such as Pd and Au catalysts, metal-free conditions using bases or conditions involving the formation of a radical. A study to find other active functional groups such as allenes to design novel post-Ugi transformation is in progress in our laboratory.

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