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Review

Ru-Catalyzed One-Pot Synthesis of Heterocyclic Backbones

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Abstract: Ruthenium complexes are remarkable catalysts for the C–H activation approaches and organic transformations. Combining a Ru-catalyst with oxidants and other additives in a one-pot process is considered a sustainable approach due to the reduction in reaction steps and the minimal usage of solvents during synthesis, work-up, isolation of chemicals, and purification of the products. This review highlights the ruthenium-catalyzed organic transformations in a one-pot manner to achieve heterocyclic backbones, including indoles, benzofurans, indazoles, pyrans, pyrimidines, quinolines, and isoquinolines.

Keywords: ruthenium; organic transformation; one-pot reaction; C–H activation; C–H functionalization; heterocyclic backbones

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1. Introduction

Metal-assisted C–H activation offers a great potential to form C–C bonds and is valuable in the construction of various carbo- and hetero-cyclic molecules used in a wide variety of scientific fields, such as drug discovery, natural product synthesis, and developing optical and electronic devices [1,2]. In the past two decades, following Oi and Inoue's report in 2001 [3,4], ruthenium catalysts have been extensively used to promote C–H functionalization, such as Ru-catalyzed alkylation, arylation, and heteroarylation, which were started by Ackermann, Bruneau, and Dixneuf [5–7]. In 2010, Ackermann reviewed a series of Ru(II)-catalyzed alkylation and introduced this method as an efficient alternative to Friedel–Crafts alkylation [8]. Later, Li and Dixneuf discussed Ru(II)-catalyzed C–H functionalization of (hetero)arenes using various reactants, such as aryl halides, tosylates, alcohols, and annulation with alkynes [9,10]. Grubb's catalysts are also Ru-complexes, which are broadly used in metathesis reactions [11].

A one-pot procedure includes multiple catalytic events, converting the reactants to the target product in a single work-up step, without separation of the intermediates. In 2004, Fogg and dos Santos clarified the differences between one-pot catalytic processes and tandem catalysis. They believe that the transformation of reactants to the corresponding product through two catalytic elaborations, i.e., introducing the second catalyst after the first one, is categorized as a one-pot reaction, not tandem catalysis. In contrast, tandem catalytic systems contain all catalytic species at once [12].

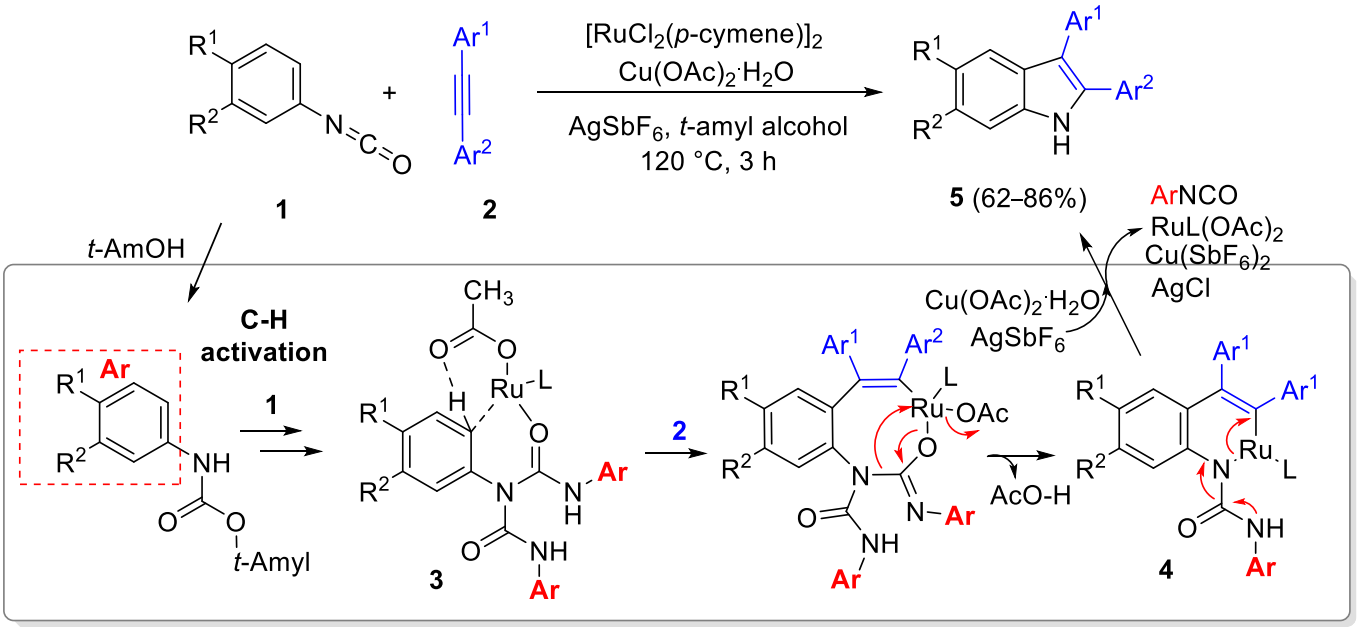
A literature survey shows many review articles focusing on the one-pot synthesis of heterocycles, especially multicomponent reactions [13–18]. In 2004, Lee et al. considered one-pot multi-catalysts for organic transformations [19]. In 2014, Ackermann reviewed the alkyne annulation through Ru(II)-catalyzed C–H activations [20]. In 2015, Lessing and Müller reviewed the role of Pd-mediated transformations in the one-pot cyclocondensation reaction [21]. Recently, Rajai-Daryasarei et al. discussed the approaches developed for the one-pot synthesis of heterocycles using aryl methyl ketone catalyzed by molecular iodine [22]. Moreover, Gramage-Doria and Bruneau highlighted different achievements involving Ru-catalyzed one-pot or tandem transformations within C–H bond functionalization [23]. Consequently, the focus of this review is specifically on the synthesis of

heterocycles through sequentially ruthenium-catalyzed one-pot processes. Special attention will be given to mechanisms of sequences that are intercepted by annulation events.

2. Ru-Catalyzed One-Pot Synthesis of Heterocycles

2.1. Indole Backbone Synthesis

Oxidative cyclization of phenyl isocyanates **1** with internal alkynes **2** led to the formation of substituted indole **5** in the presence of Ru(II) as a catalyst, Cu(II) as an oxidant, and $AgSbF_6$ as an additive. This reaction is promoted by the formation of Ru-complexed intermediate **3**, which in turn reacted with alkyne **2**. Upon the acetate anion's aid with acetic acid release, intermediate 4 is obtained. By the release of reduced Ru and oxidizing role of Cu(II), the final product is formed (Scheme 1). The presence of electron-donating groups, such as methoxy, on the isocyanate ring increased the efficiency of this reaction, while electron-withdrawing groups had no significant impact on the reaction yields [24]. It should be noted that combining two equivalents of alkyne with phenyl isocyanates **1** (Scheme 2) or pyrazolones **7** (Scheme 3) yields indolo[2,1-*a*]isoquinolines **6** [25,26].



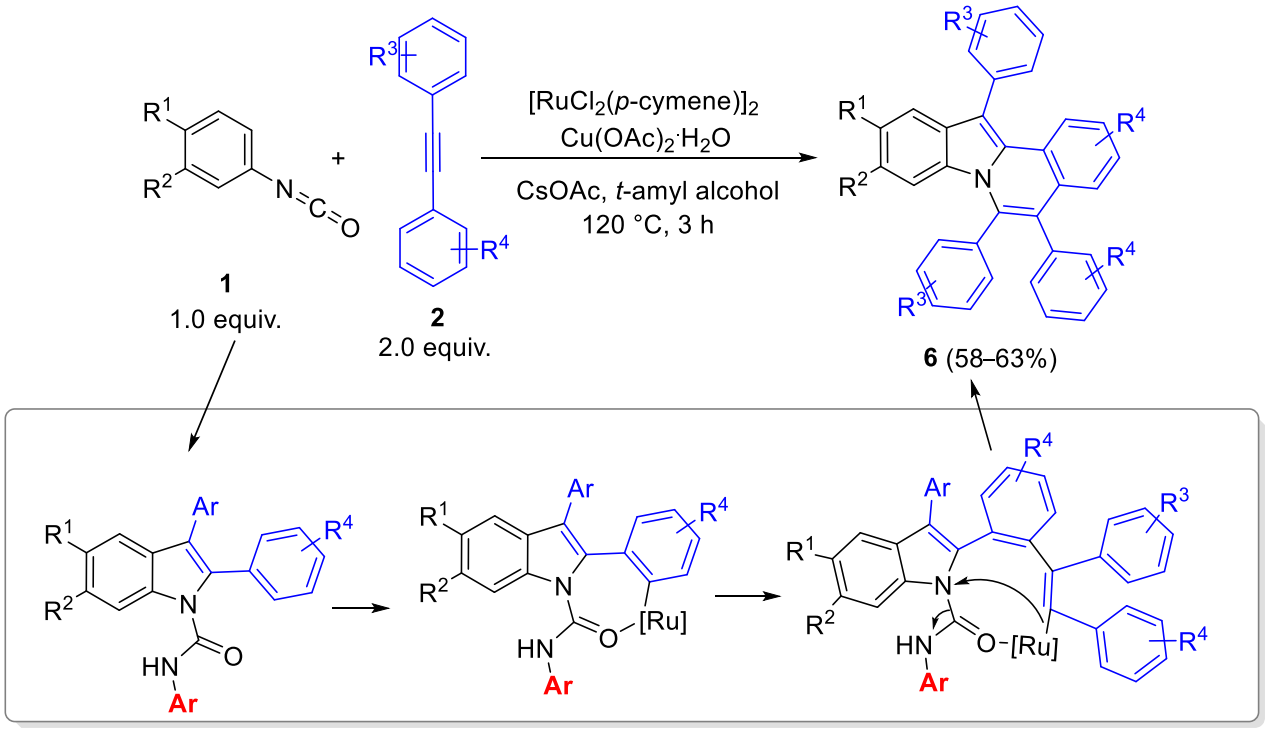
R^1 = H, Me, OMe, CF_3, OCF_3, Cl, Br

R^2 = H, Me, OMe, CF_3, Cl

Ar^1, Ar^2 = 3-benzithiophenyl, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-*t*-BuC_6H_4, 4-$MeOC_6H_4$

Scheme 1. Synthesis of indole using isocyanates and alkynes.

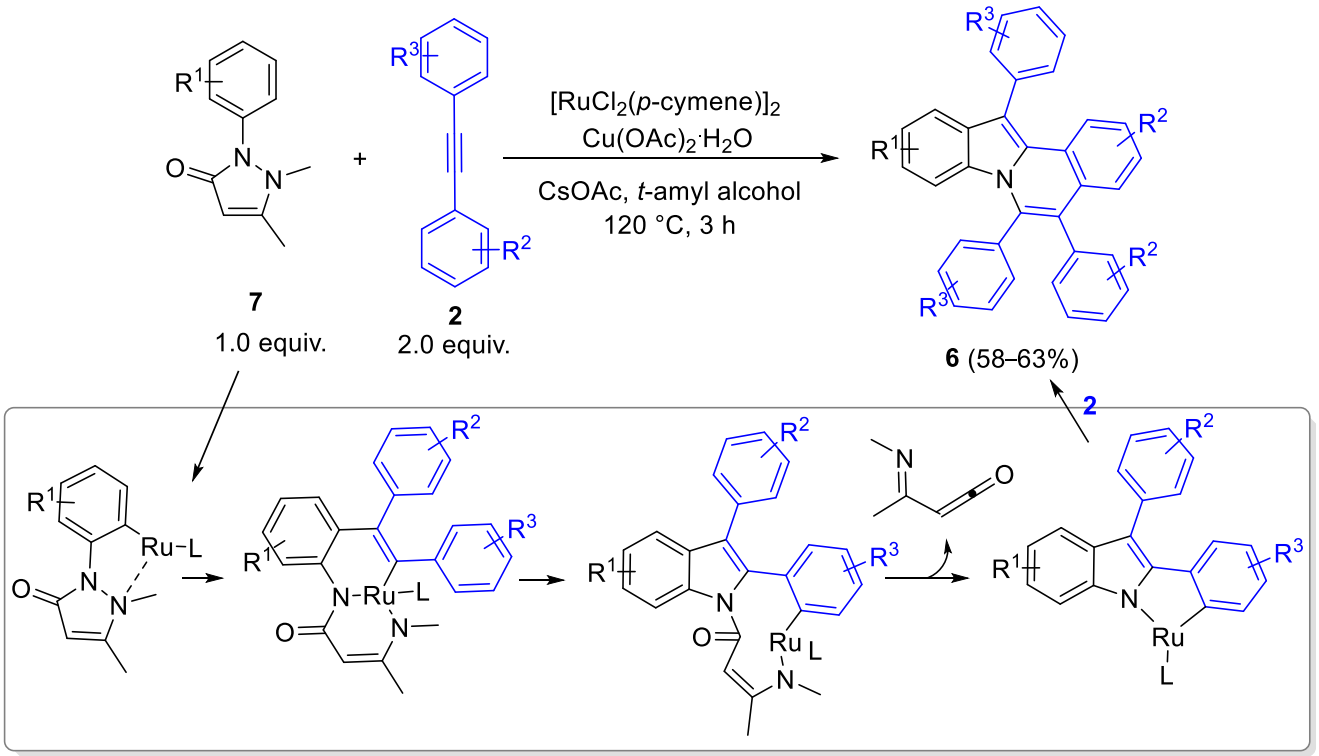
Functionalized indoles can be utilized for the synthesis of fused indoles. In this regard, Singh et al. architected pyrrolo[1,2-*a*]indoles **10** by reacting *N*-acylindoles **8** with acrylates **9** in the presence of a Ru(II)/Cu(II) catalytic system. This reaction was promoted by C–H activation of *N*-acylindoles **8**, followed by migratory insertion of acrylates **9**, reductive elimination of ruthenium, radical formation, and finally cyclization (Scheme 4). This reaction was regioselective, and the products were a mixture of diastereomers with *cis*:*trans* ratios ranging from 3:1 to 9:1 [27].



R^1 = H, Me, OMe, CF_3, OCF_3, Cl, Br R^2 = H, Me, OMe, CF_3, Cl

R^3, R^4 = H, 4-F, 4-Cl, 4-Me, 4-*t*-Bu, 4-*n*-Bu, 4-OMe

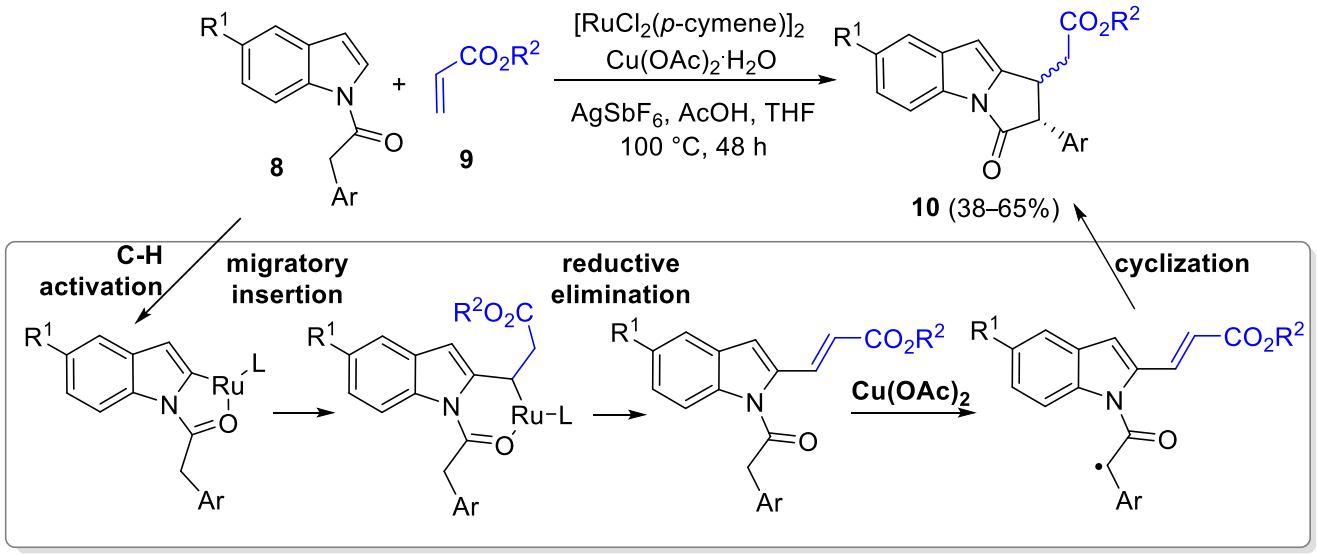
Scheme 2. Synthesis of indolo[2,1-*a*]isoquinolines.



R^1 = H, 4-Me, 3-Me, 4-*i*-Pr, 4-OMe, 4-CF_3, 3-F, 4-F, 4-Cl, 4-Br, 3,4-Me_2, 3,5-F_2, 3,4-Cl_2

R^2, R^3 = H, 4-F, 4-Cl, 4-Me, 4-OMe

Scheme 3. Synthesis of indolo[2,1-*a*]isoquinolines using pyrazolone **7**.



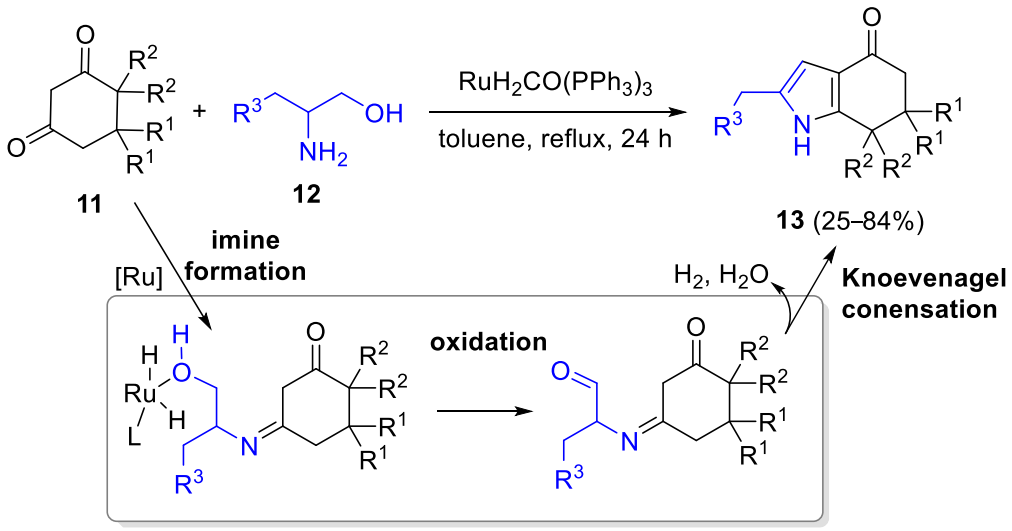
R^1 = H, Me, Br

R^2 = Me, Et, *n*-Bu (*t*-Bu gave no product)

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 4-FC_6H_4, 2-BrC_6H_4, 3-ClC_6H_4, 4-$O_2NC_6H_4$, 3,4-$Cl_2C_6H_3$

Scheme 4. Synthesis of pyrrolo[1,2-*a*]indoles.

The Ru(II)-catalyzed reaction of 1,3-dicarbonyls **11** and aminoalcohols **12** produced 6,7-dihydro-1*H*-indol-4(5*H*)-ones **13**. Initially, an imine was formed, followed by oxidation of the alcohol moiety, and a Knoevenagel condensation occurred to give the target product **13** plus hydrogen gas and water (Scheme 5). Moreover, the diversity of this reaction was tested with various 2-aminobenzyl alcohols and 2-hydroxybenzyl alcohols to obtain acridine and xanthene products, respectively [28]. The importance of this synthetic route is to construct a dihydroindol-4-one core that is found in the skeleton of some bioactive molecules, including molindone and piquindone as antipsychotic agents (Figure 1) [29–31].



R^1,R^1 = H,H; Me,Me; H,Me; H,4-$Me_2NC_6H_4$ R^3 = H, Ph, CH_2SMe

R^2,R^2 = H,H; Me,Me

Scheme 5. Synthesis of 6,7-dihydro-1*H*-indol-4(5*H*)-one.

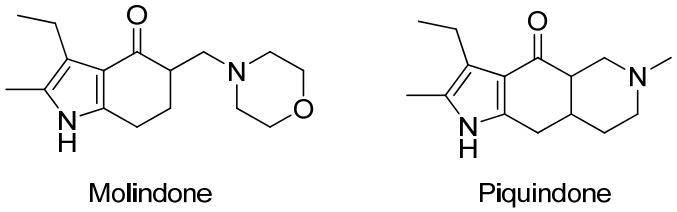
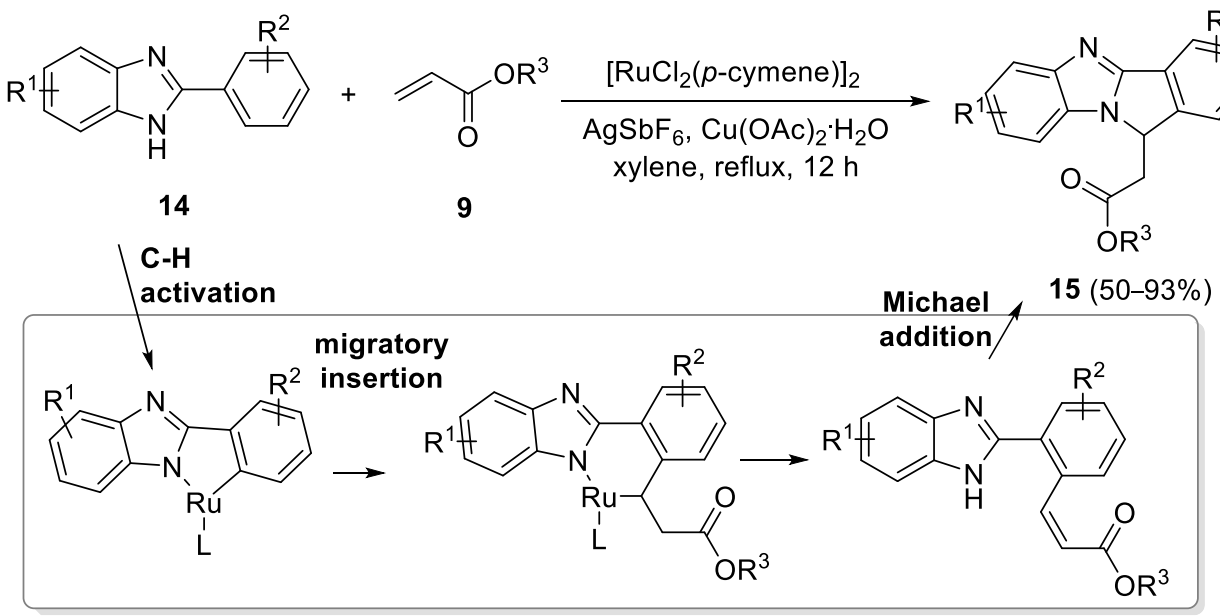


Figure 1. The structure of molindone and piquindone.

2.2. Isoindole Backbone Synthesis

The Ru(II)-catalyzed reaction between 2-arylbenzimidazoles **14** and acrylates **9** generated benzoimidazoisoindoles **15** in moderate to high yields. Running this reaction with 2-heteroarylbenzimidazoles failed the annulation, affording olefin-substituted products (Scheme 6). Moreover, the presence of halogen, as R^1, at the 5-position of benzimidazole ring **14** led to the formation of regioselective products, while 5-nitro, 5-carboxylate, or 5-methyl (R^1) functionalized benzimidazoles resulted in the formation of a mixture of products due to the extended resonance [32]. The use of alkynes will fuse a six-membered ring to the imidazole moiety. Zheng et al. could react phenanthroimidazoles with alkynes in the presence of a Rh catalyst to obtain a π-extended product [33].

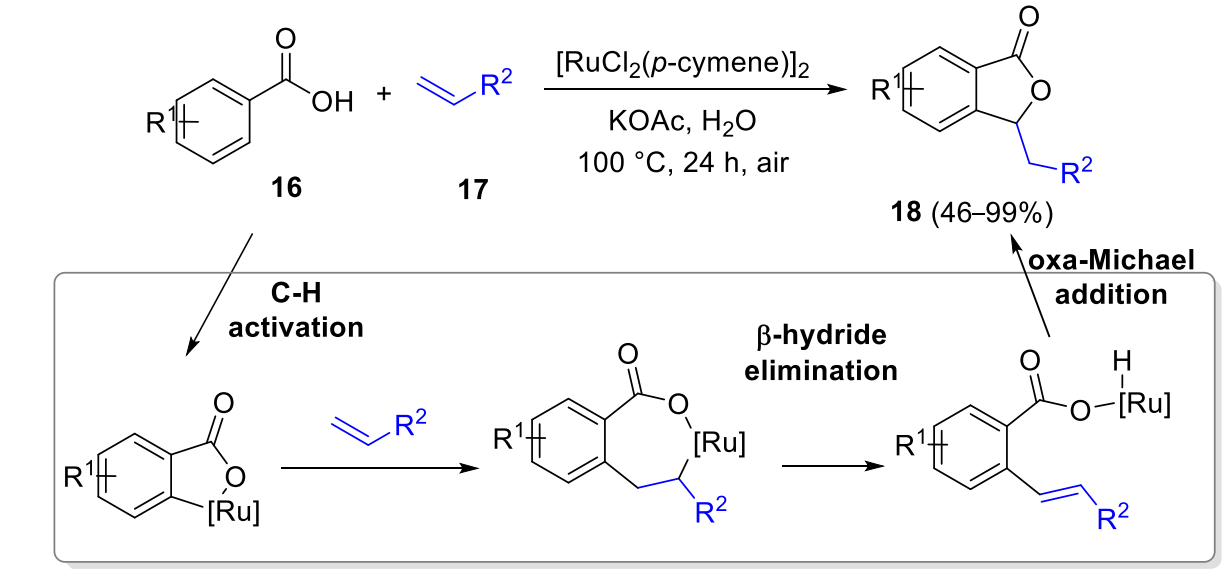


R^1 = H, 5-CO_2Me, 5-NO_2, 5-F, 5-Cl, 5-Br, 4-Me, 5-Me
R^2 = H, 3-Me, 4-Me, 4-Cl, 4-CF_3, 4-OMe
R^3 = Me, Et, *n*-Bu, *t*-Bu, Cyclohexyl, Bn

Scheme 6. Synthesis of benzoimidazoisoindoles.

2.3. Benzofuran Backbone Synthesis

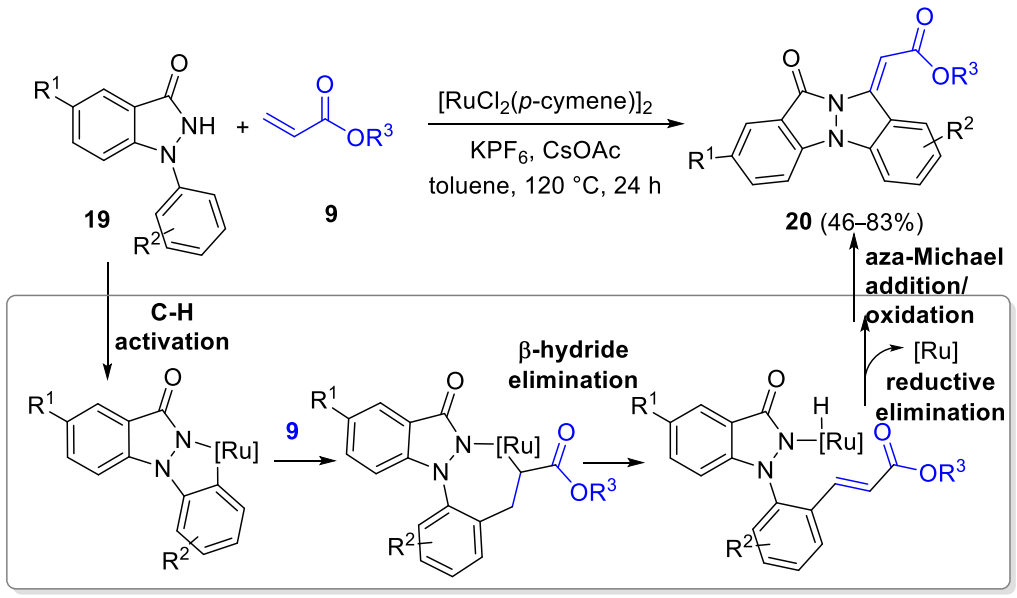
The Ru(II)-catalyzed reaction between benzoic acid derivatives **16** and olefins **17** was developed for the synthesis of phthalide derivatives **18**. The progress of this reaction depends on the C–H activation of benzoic acid, migratory insertion of olefin, β-hydride elimination, and finally oxa-Michael addition due to the presence of electron-withdrawing groups on the olefin moiety (Scheme 7). This kind of synthesis can be efficiently accomplished in water [34,35] or a mixture of water and polyethylene glycol (PEG) [36].



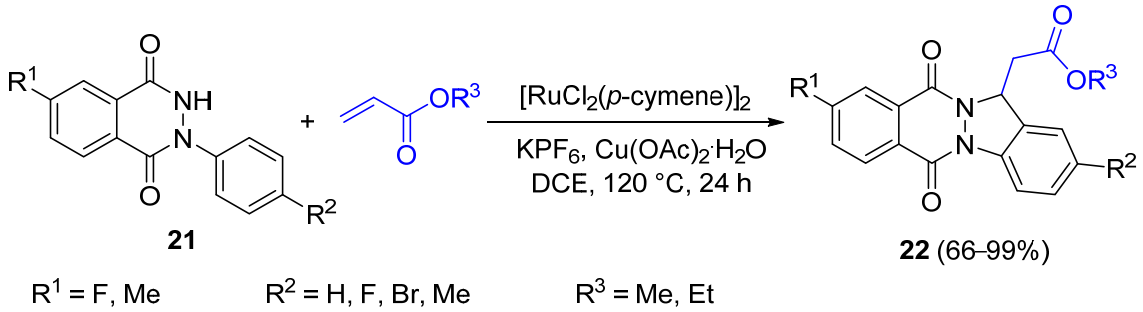
Scheme 7. Synthesis of phthalide derivatives.

2.4. Indazole Backbone Synthesis

Ru(II)-catalyzed C–H activation of indazolone **19**, followed by migratory insertion of alkyl acrylates **9**, passed from β-hydride elimination and aza-Michael addition/oxidation, resulting in the formation of indazolo[1,2-*a*]indazolone derivatives **20** in moderate to high yields (Scheme 8). The bulkier alkyl group of acrylates led to lower yields of the products [37]. Similarly, phthalazine-1,4-diones **21** were converted to indazolo[2,1-*b*]phthalazine-6,11-diones **22** (Scheme 9) [38]. It should be noted that the use of alkynes instead of alkenes will fuse the cinnoline ring to the used indazole or phthalazine reactants [39].

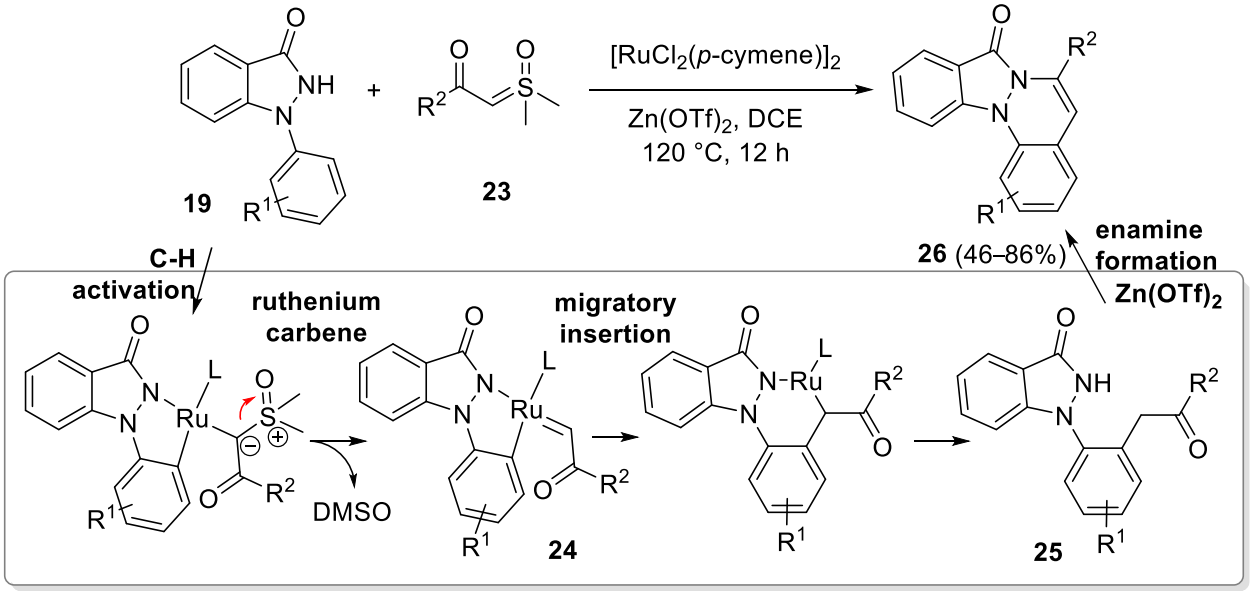


Scheme 8. Synthesis of indazolo[1,2-*a*]indazolone derivatives.



Scheme 9. Synthesis of indazolo[2,1-*b*]phthalazine-6,11-diones.

α-Carbonyl sulfoxonium ylides are suitable synthons to develop C–H acylmethylation and annulation reactions [40–42]. Annulation of 1-arylindazolones **19** with sulfoxonium ylides **23** passed from ruthenium carbene **24**. The migratory insertion and reductive elimination of Ru(II) generates intermediate **25** which was fused in the presence of Zn(II) to give the indazolo[1,2-*a*]cinnolinones **26** in moderate to high yields (Scheme 10). This reaction was also applicable to the synthesis of phthalazino[2,3-*a*]cinnolindiones [43].

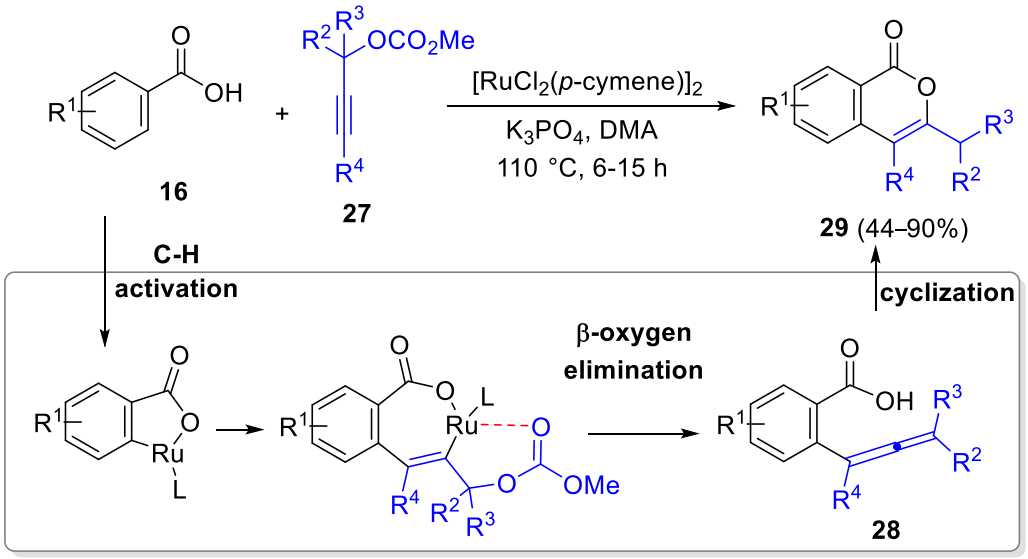


Scheme 10. Synthesis of indazolo[1,2-*a*]cinnolinones.

2.5. Pyran Backbone Synthesis

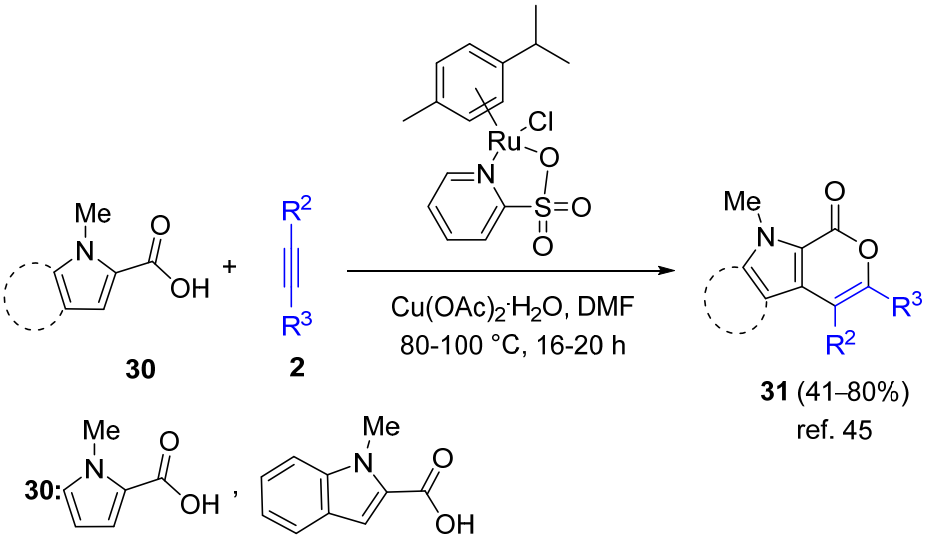
Previously, it was discussed that the reaction of benzoic acids with alkenes, containing electron-withdrawing substituents, gives phthalides. In another study, the reaction between benzoic acids **16** and the alkyne group of propargylic carbonates **27** yielded isocoumarins **29**. This is a result of β-oxygen elimination to form intermediate **28**, followed by cyclization to produce the six-membered heterocyclic ring of product **29** (Scheme 11) [44]. Benzoic acid can be replaced with *N*-methyl-pyrrole-2-carboxylic acid or *N*-methyl-indole-2-carboxylic acid **30** to react with symmetrical or unsymmetrical internal alkynes **2**, yielding pyrano[3,4-*b*]pyrrolones **31**. The reaction of *N*-methyl-indole-2-carboxylic acid with unsymmetrical alkynes was not regioselective, generating a mixture of substituted products (Scheme 12) [45]. Catalyzing this reaction by $[RuCl_2(p\text{-cymene})]_2$ instead of ($[RuCl(PySO_3)(p\text{-cym})]$ would improve the efficiency of this reaction. Moreover, changing the solvent from DMF to water will highly

control the regioselectivity of this reaction when unsymmetrical alkyne was subjected [46]. Yu et al. studied the molecular orbital model of the reaction shown in Scheme 11 via density functional theory (DFT) calculations. They computed Gibbs free energy changes of the formed intermediates in different solvents, suggesting the more polar the solvent, the more chemoselective the product. This study also recommends the use of terminal alkynes, in the case of using unsymmetrical alkynes, to control the regioselectivity of this reaction [47].



R^1 = H, 2-Me, 4-Me, 4-OMe, 4-OH, 2-F, 3-COH, 4-Cl, 4-Br, 4-NH_2, 4-SO_2Me, 4-vinyl
4-CN, 4-COMe, 4-SO_2NPr_2, NHCOMe, CONHMe, N-pyrazolyl, O(2-pyridyl)
(R^2,R^3) = (H, Et), (Me, Et), (Et, *n*-Pr), (cyclopentyl)
R^4 = Ph, 3-thiophenyl

Scheme 11. Synthesis of isocoumarin derivatives using benzoic acids and propargyl carbonates.

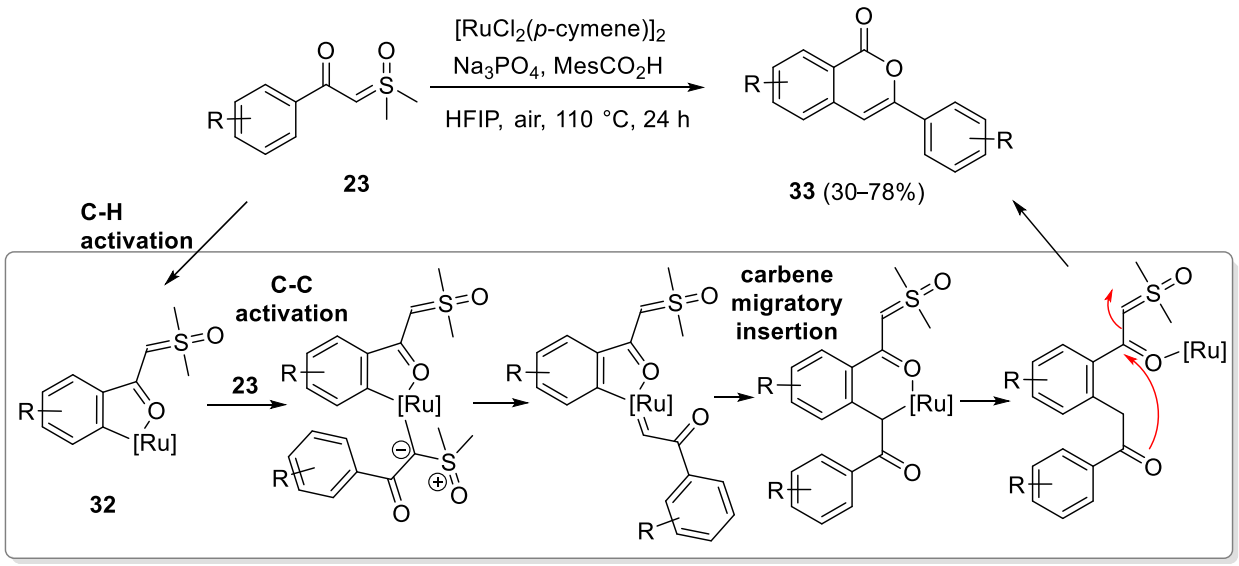


R^2,R^3 = (Ph,Ph), (Me,Ph), (Pr,Pr), (Et,Et), (Me,Me)

ref. 46 conditions: [$RuCl_2$(*p*-cymene)]$_2$, $Cu(OAc)_2{\cdot}H_2O$, DMF, 80-100 °C, 16-20 h, 25-91%
or [$RuCl_2$(*p*-cymene)]$_2$, $Cu(OAc)_2{\cdot}H_2O$, H_2O, 100 °C, N_2, 16-20 h, 30-90%

Scheme 12. Synthesis of pyrano[3,4-*b*]pyrrolones.

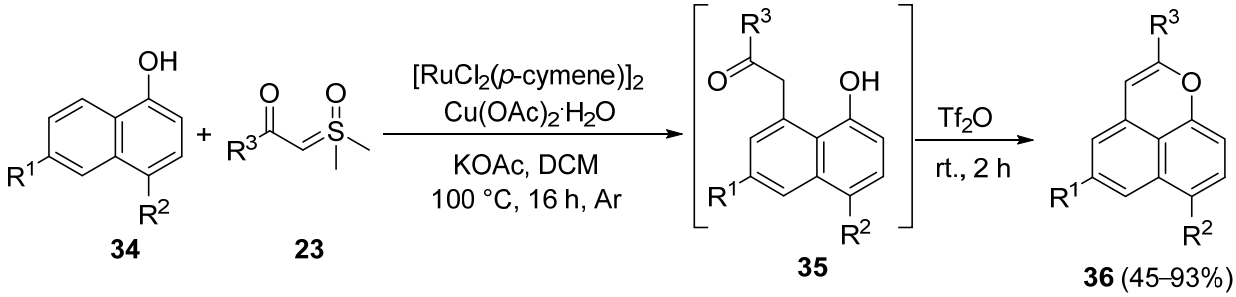
Treatment of sulfoxonium ylides **23** with Ru(II) gave rise to the C–H activation, furnishing intermediate **32**. Then, the next molecule of ylide **23** was added to the latter through C-C activation, followed by carbene migratory insertion, giving the target isocoumarins **33**. Electron-withdrawing substituted ylides **23**, such as nitro, nitrile, and carboxylates, gave no products, while halogen-substituted ylides resulted in the formation of the products with the lowest yields (Scheme 13) [48].



R = H, 4-Me, 4-*t*-Bu, 4-OMe, 3-OMe, 2-OMe, 4-OPh, 2-OPh, 2-F, 3-F, 3-Cl, 2-Cl, 3-CF_3, 4-CF_3

Scheme 13. Synthesis of isocoumarin derivatives using α-carbonyl sulfoxonium ylides.

In another experiment, α-naphthols **34** reacted with α-carbonyl sulfoxonium ylides **23** through Ru(II)-catalyzed acyl methylation, passing from intermediate **35**, to give naphtho[1,8-*bc*]pyrans **36** (Scheme 14). This reaction is highly chemo- and regioselective [49].



R^1, R^2 = H, Br

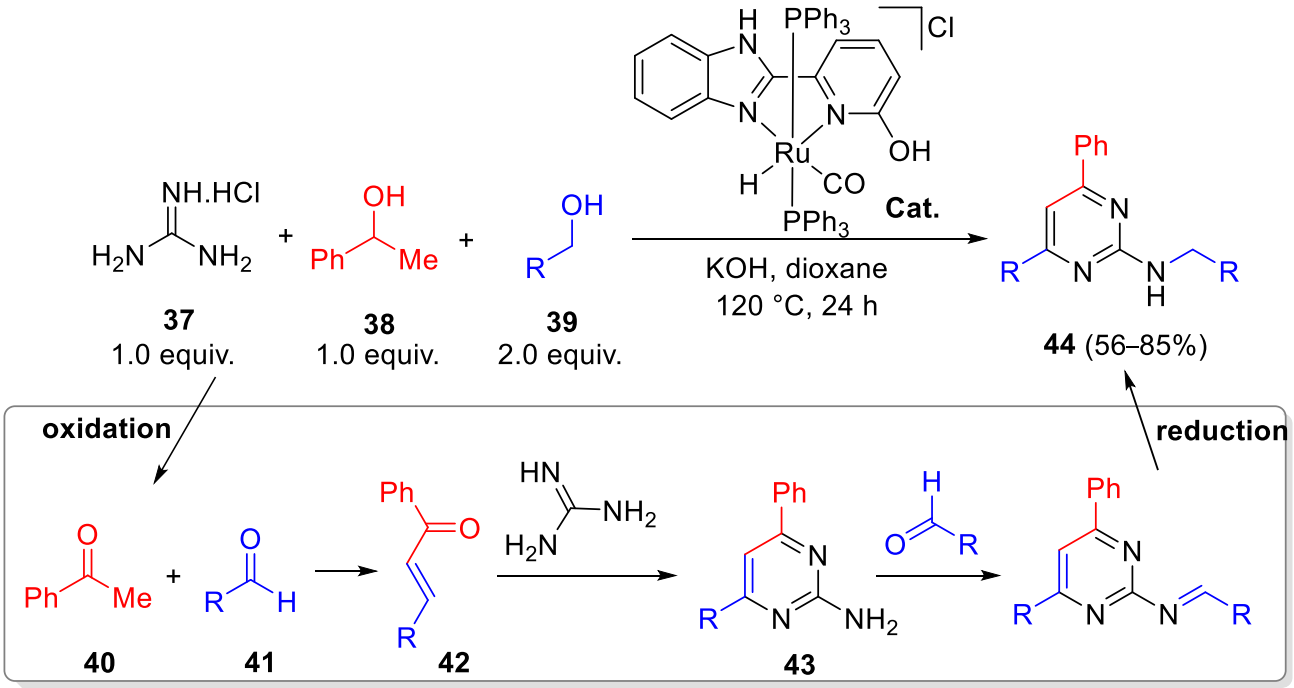
R = Adamantyl, 2-thienyl, 4-FC_6H_4, 4-ClC_6H_4, 4-IC_6H_4, 4-$F_3CC_6H_4$, 4-PhC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3-MeC_6H_4, 2-MeC_6H_4, 3-BrC_6H_4, 2-FC_6H_4, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 4-Br-3-$MeOC_6H_3$

Scheme 14. Synthesis of naphtho[1,8-*bc*]pyrans.

2.6. Pyrimidine Backbone Synthesis

A series of 2-(*N*-alkylamino)pyrimidines **44** was synthesized through Ru(II)-catalyzed reaction of guanidine hydrochloride **37** and a mixture of primary and secondary alcohols. The promotion of this reaction relied on the oxidation of the used alcohols **38** and **39** to form benzophenone **40** and aldehyde **41**, respectively. A crossed Aldol condensation occurred between the formed intermediates to give chalcone **42**. The latter was annulated with guanidine, and the free amine of adduct **43** reacted with the next equivalent of

aldehyde, followed by the reduction of the imine bond, generating the target product **44** (Scheme 15) [50].



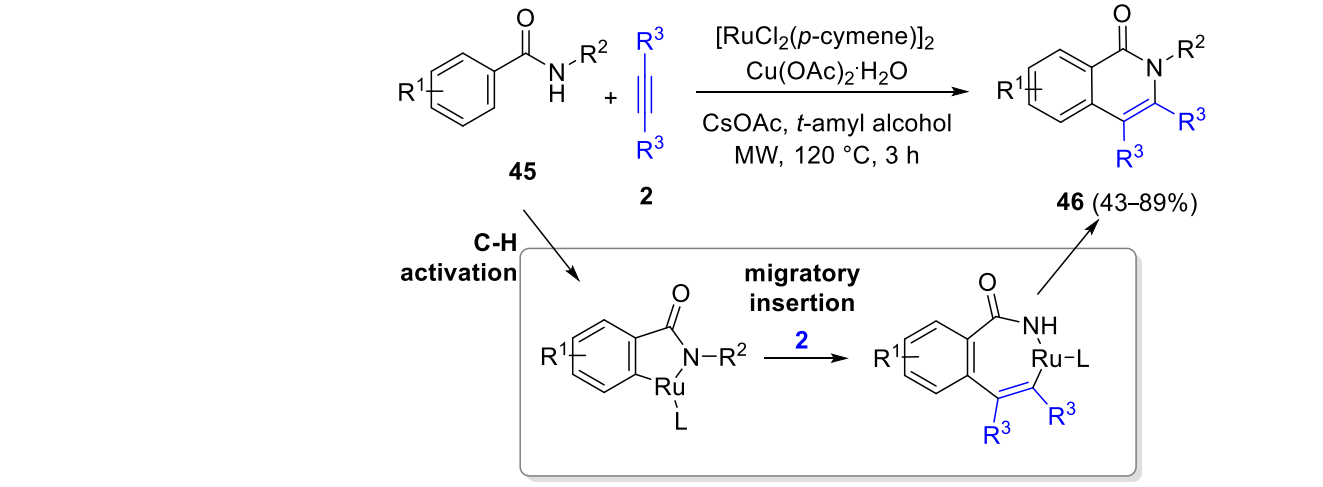
R = Cy, *n*-Pr, *n*-$C_{11}H_{23}$, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-pyridyl

Scheme 15. Synthesis of 2-(*N*-alkylamino)pyrimidines.

2.7. Quinoline and Isoquinoline Backbone Synthesis

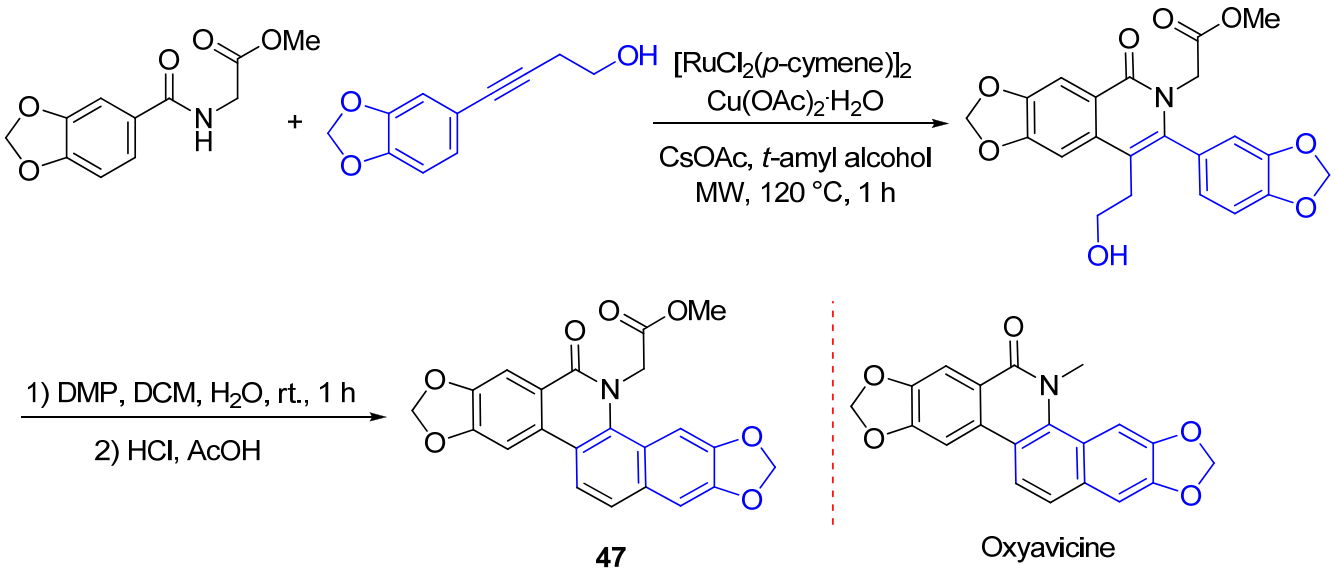
A microwave-assisted annulation of *N*-benzoyl glycine esters **45** with alkynes **2** resulted in the formation of substituted isoquinolones **46** through sequential C–H activation, migratory insertion, and oxidation reaction (Scheme 16). The use of unsymmetrical alkynes gave a mixture of substituted products. The ester group of the final product has the potential to be used for the production of isoquinoline-containing peptides. This synthetic method was then employed for the production of an oxyavicine derivative **47** (Scheme 17) [51]. Kumar et al. synthesized similar products **46** in a two-step reaction that included the Ru(II)-catalyzed reaction of benzamides and alkynes to form allene derivatives and K_2CO_3-promoted annulation of allene compounds [52]. Oxyavicine is a cytotoxic natural isoquinoline, isolated from *Broussonetia papyrifera* and *Zanthoxylum nitidum* [53–55]. Tulichala et al. synthesized a series of chromeno[3,4-*c*]pyridin-4-ones **48** using a similar method, starting from chromene-3-carboxamides **49** (Scheme 18) [56].

Ghosh et al. designed a one-pot double C–H functionalization by reacting α-carbonyl sulfoximine **50** with internal alkynes **2**. The first C–H activation occurred on the carbon atom of the aryl group between the sulfoximine and ether groups, creating the intermediate **51**. The intramolecular migratory insertion of an alkene group, followed by the rotational conformation of a Ru(II)-sulfoximine group, led to the formation of furan **52**. The second C–H activation of the latter, then, the migratory insertion of alkyne **2**, generated the dihydrofuran-fused isoquinolones **53** (Scheme 19) [57,58].

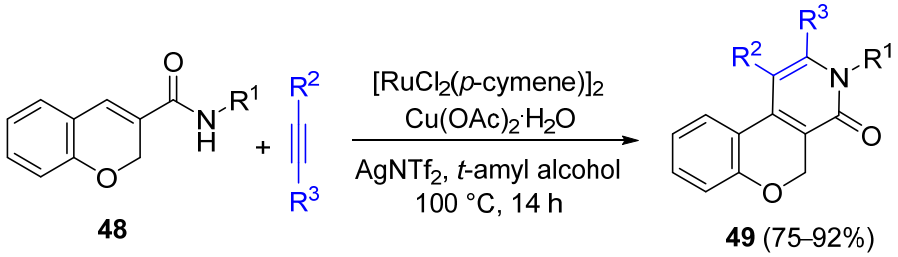


R^1 = H, 4-Me, 3-Me, 2-Me, 4-OMe, 4-OBn, 4-F, 4-Cl, 3-Cl, 3-F, 3-Br, 4-CF_3, 4-Ph, 4-NO_2
R^2 = CH_2CO_2Me, CH_2CO_2Et
R^3 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-BrC_6H_4, 4-$O_2NC_6H_4$, Et, *n*-Pr, 3-pyridyl, 2-thienyl

Scheme 16. Synthesis of isoquinolones.

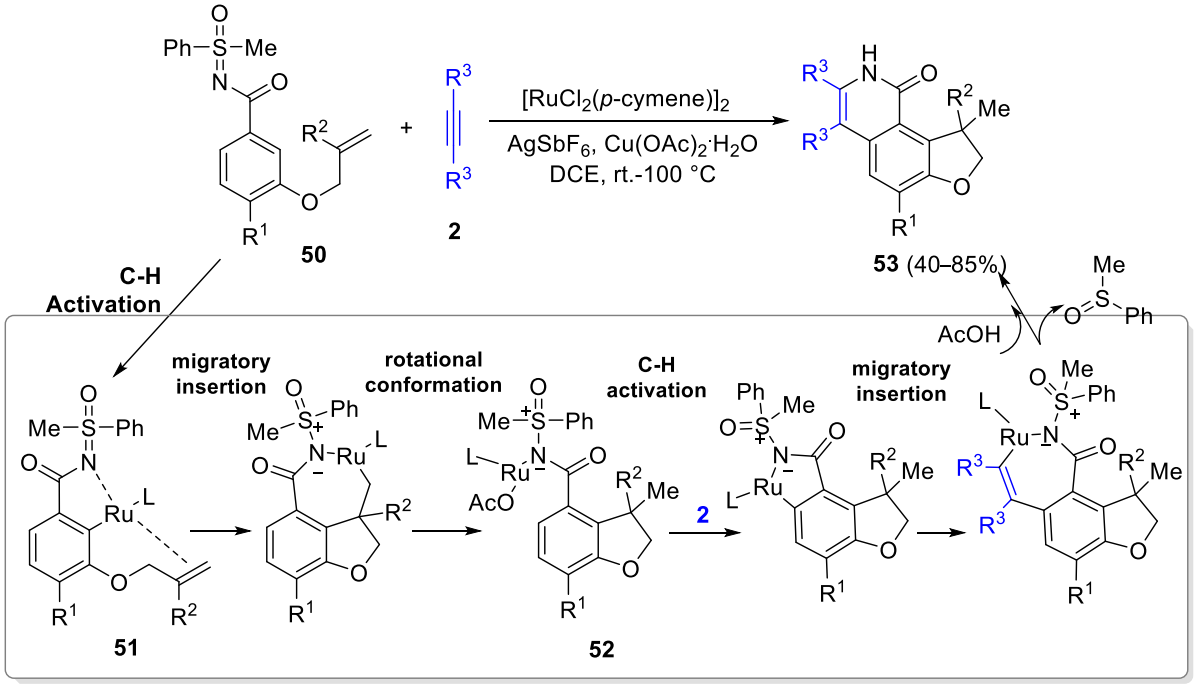


Scheme 17. Synthesis of oxyavicine derivative **47**.



R^1 = CH_2(4-$MeOC_6H_4$), 4-MeC_6H_4, 3-MeC_6H_4, *i*-Pr, *n*-Bu, cyclohexyl
R^2,R^3 = (both Et), (both Ph), (both 4-$MeOC_6H_4$), (both 4-ClC_6H_4), (both 4-FC_6H_4), (both 4-$F_3CC_6H_4$), (both 3,5-$Me_2C_6H_3$), (both thiophenyl), (both MOM), (Et, Ph), (Me, Ph), (Ph, 4-$MeOC_6H_4$)

Scheme 18. Synthesis of chromeno[3,4-*c*]pyridin-4-one derivatives.

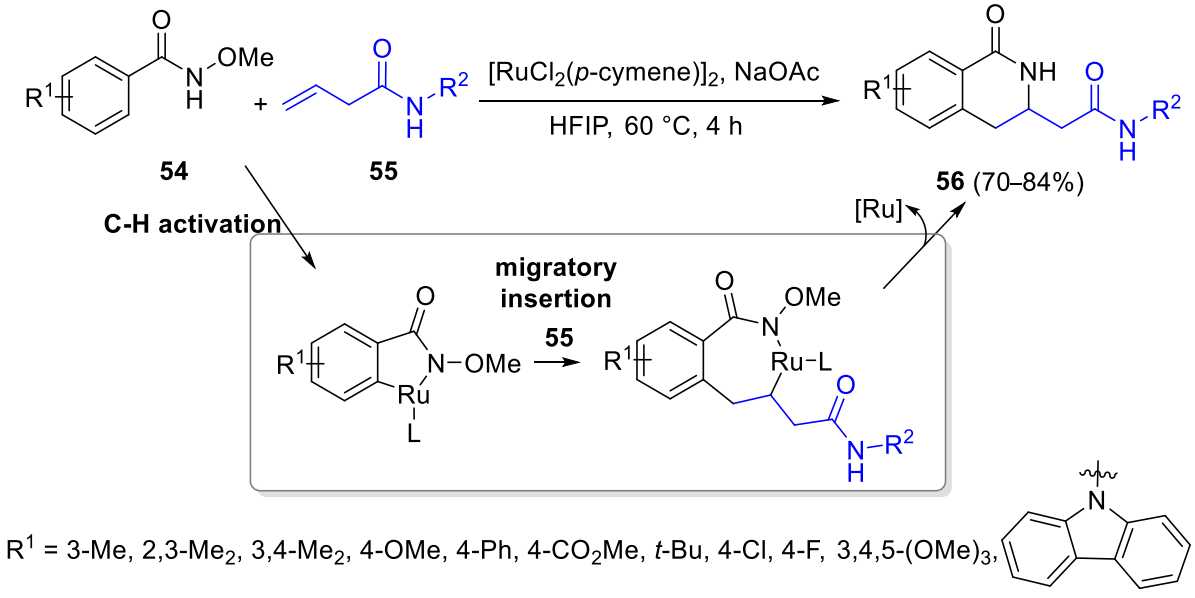


R^1 = H, F, Me R^2 = H, Me

R^3, R^4 = *n*-Pr, 4-*t*-BuC_6H_4, 4-MeOC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-F_3CC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-thiophenyl

Scheme 19. Synthesis of dihydrofuran-fused isoquinolones.

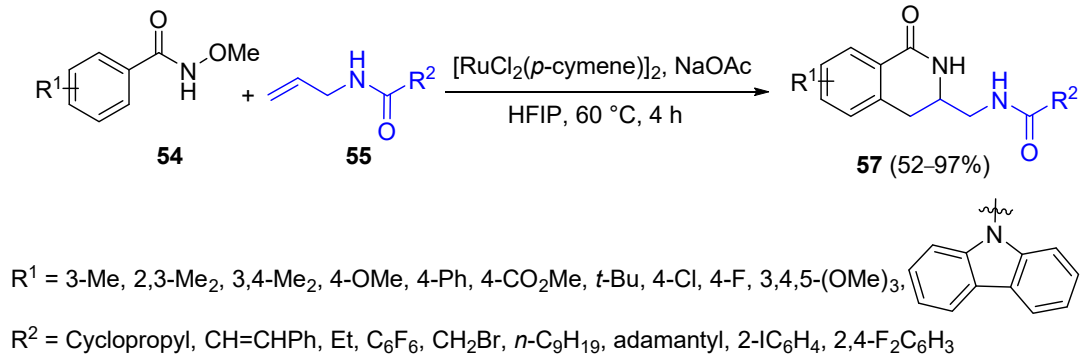
In another study, the amide source was aryl hydroxamic acid ester **54**, and alkyne was replaced with the alkene-amide **55**. Sequential Ru(II)-catalyzed C–H activation of reactant **54**, migratory insertion of alkene **55**, and reductive elimination resulted in good to high yields of dihydroisoquinolinone compounds **56** (Scheme 20) [59]. A similar reaction was conducted using amide **54** to obtain dihydroisoquinolinones **57** (Scheme 21) [60].



R^1 = 3-Me, 2,3-Me_2, 3,4-Me_2, 4-OMe, 4-Ph, 4-CO_2Me, *t*-Bu, 4-Cl, 4-F, 3,4,5-$(OMe)_3$,

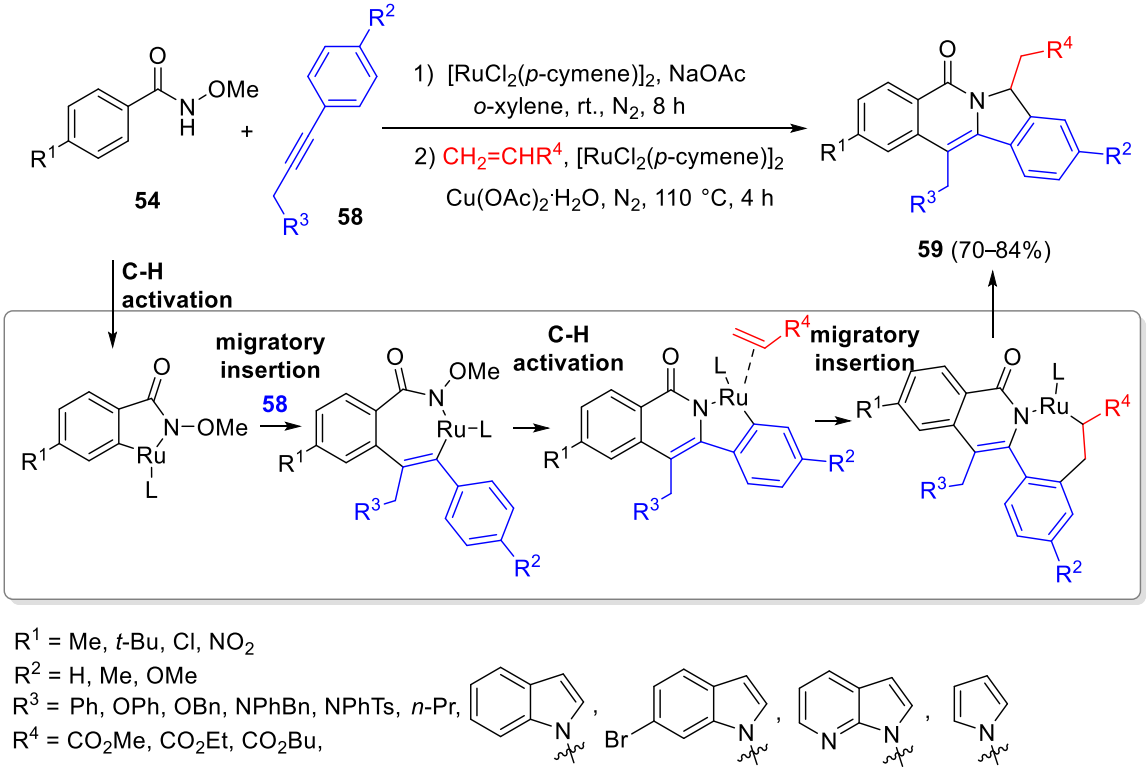
R^2 = 2,4,6-$Me_3C_6H_2$, 3,4,5-$(MeO)_3C_6H_2$, 1-naphthyl, CH_2Bn, CH_2(4-MeC_6H_4), CH_2-THF, CH(Me)Ph

Scheme 20. Synthesis of dihydroisoquinolinone compounds.



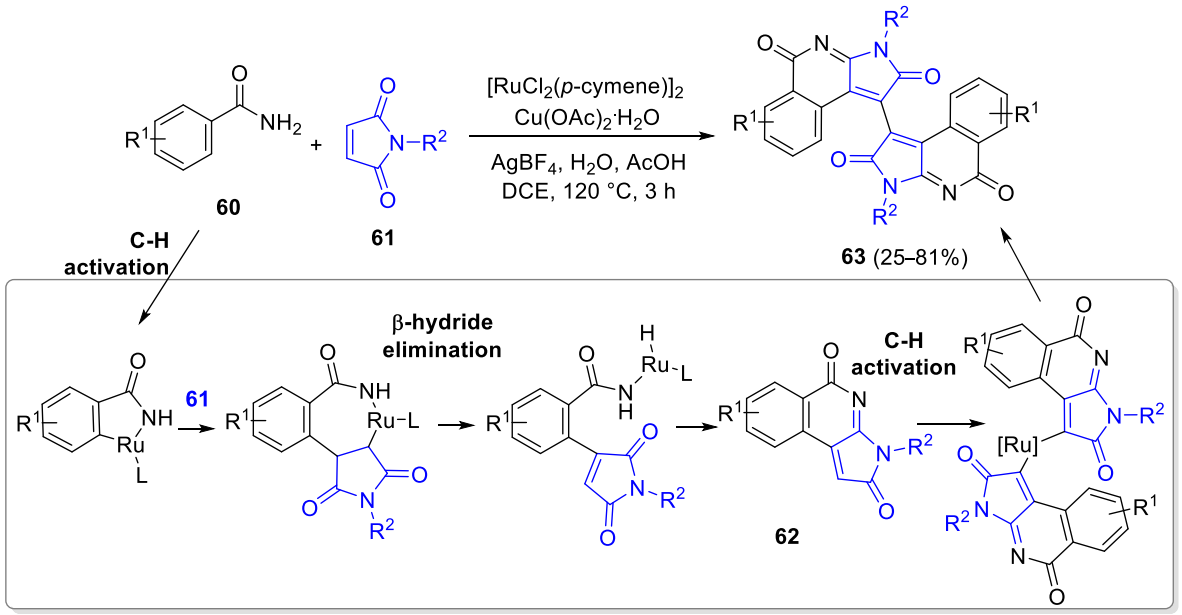
Scheme 21. Synthesis of dihydroisoquinolinones.

In a creative one-pot sequential approach, both alkynes **58** and alkenes reacted with aryl hydroxamic acid ester **54**, yielding isoindolo[2,1-*b*]isoquinolinone compounds **59**. The progress of this reaction depends on the double Ru(II)-based C–H activations (Scheme 22). It should be noted that unsymmetrical internal alkynes resulted in the formation of a single isomer [61].



Scheme 22. Synthesis of isoindolo[2,1-*b*]isoquinolinone compounds.

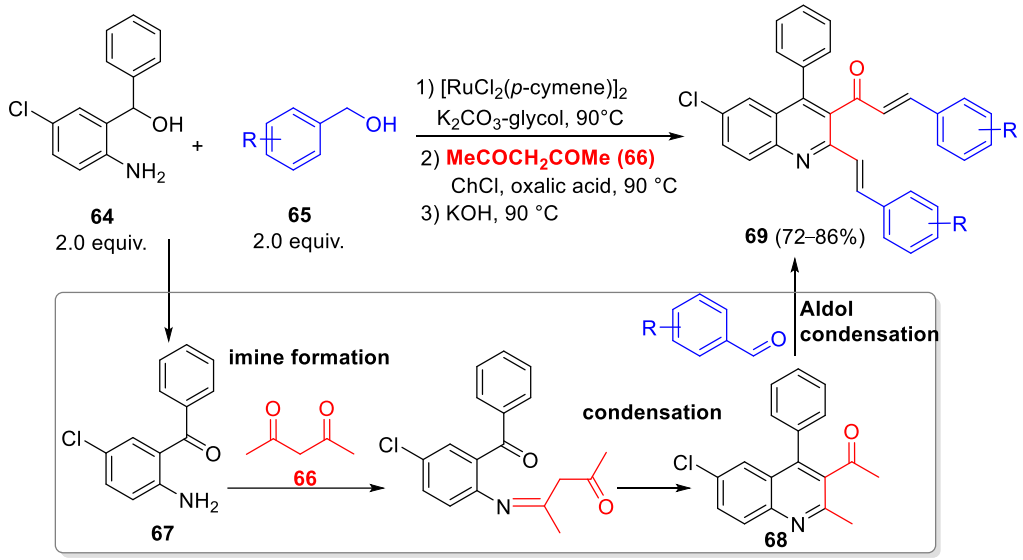
Consequently, a wide variety of quinolinone compounds can be designed by changing the aryl amide and alkene sources. Jaiswal et al. synthesized pyrrolo[2,3-*c*]isoquinoline-2,5-dione dimers **63** by the use of bezamides **60** and maleimides **61**. This reaction passed from intermediate **62**, which was subjected to a second C–H activation to give the dimer product **63** (Scheme 23). The dimeric bond of products **63** is breakable under UV irradiation, forming orange-red photoluminescence radical monomers. The products showed steady-state fluorescence emission with large Stokes shifts up to 5100 cm^{-1}. Moreover, a cyclic voltammetry study displayed redox properties of products **63** due to reductive processes and enol-keto conversions [62].



R^1 = H, 4-Me, 3-Me, 4-OMe, 4-F, 4-Cl, 3-Cl, 3-F, 3-Br, 4-CF_3, 4-Ph (positioned in the reactant)
R^2 = Me, Et, *i*-Pr, *n*-Bu, *n*-Hex, Bn

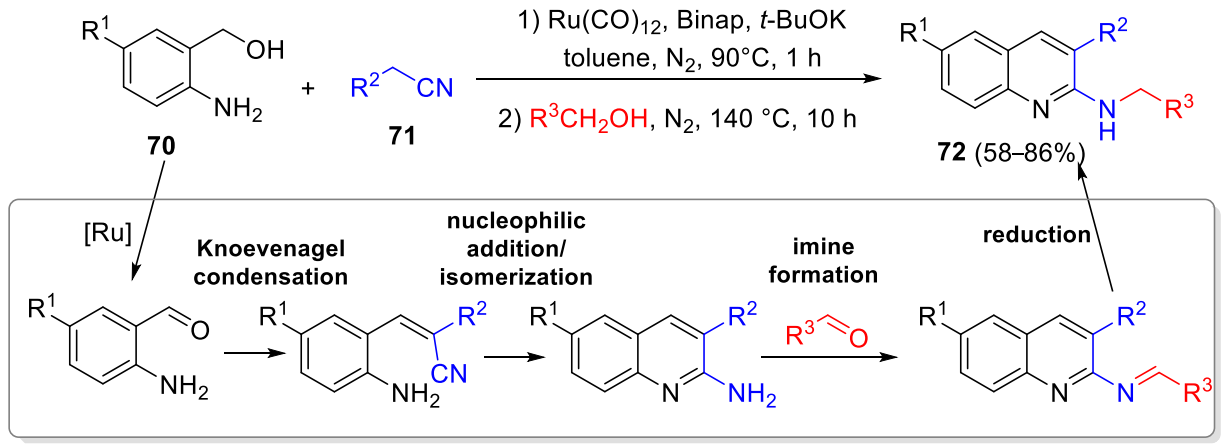
Scheme 23. Synthesis of 2*H*-pyrrolo[2,3-*c*]isoquinoline-2,5(3*H*)-diones.

As mentioned before in Scheme 15, alcohols are oxidized to their corresponding aldehydes or ketones in the presence of Ru(II) catalysts. Prameela and Khan used this fact to design a series of substituted quinolines **69** via the reactions of 2-aminobenzhydrol **64**, benzyl alcohols **65**, and acetyl acetone **66**. Consequently, 2-aminobenzhydrol **64** was oxidized to 2-aminobenzophenone **67**, which in turn reacted with acetyl acetone **66**, followed by an intramolecular condensation to give intermediate **68**. Finally, a crossed Aldol condensation between the latter and benzaldehyde derivatives, formed from the oxidation of benzyl alcohol **65**, led to the formation of fluorescent quinoline derivatives **69** (Scheme 24) [63]. In another study, 2-aminobenzhydrol **70** reacted with nitrile compounds **71** and alcohols to give 2-aminoquinoline **72** (Scheme 25) [64].



R = H, 2-Cl, 4-Cl, 4-Br, 4-CN, 4-Me, 4-OMe, 3,4-$(OMe)_2$, 2,3,4-$(OMe)_3$, 2,4,5-$(OMe)_3$, 2-NO_2, 4-NMe_2

Scheme 24. Synthesis of quinoline compounds.

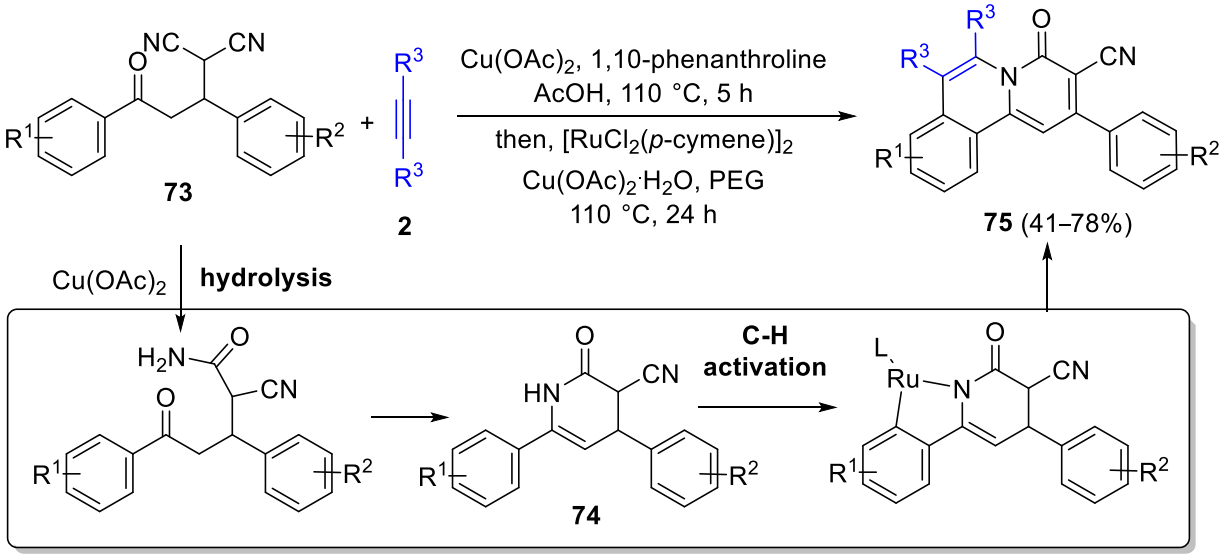


R^1 = H, Me, OMe, Cl
R^2 = Ph, 4-MeC_6H_4, 4-*t*-Bu,C_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, naphthyl
R^3 = CH_2Bn, *n*-Bu, 2-pyridyl, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4

Scheme 25. Synthesis of 2-aminoquinoline compounds.

2.8. Complicated Fused Heterocycles

Rakshit et al. used γ-keto malononitriles **73** to react with alkynes **2** in the presence of Ru(II)-catalytic system. One of the nitrile groups of reactant **73** was hydrolyzed in the presence of $Cu(OAc)_2$, followed by annulation to give intermediate **74**. C–H activation of the latter and migratory insertion of alkynes yielded the fluorescent fused isoquinolines **75** (Scheme 26) [65].

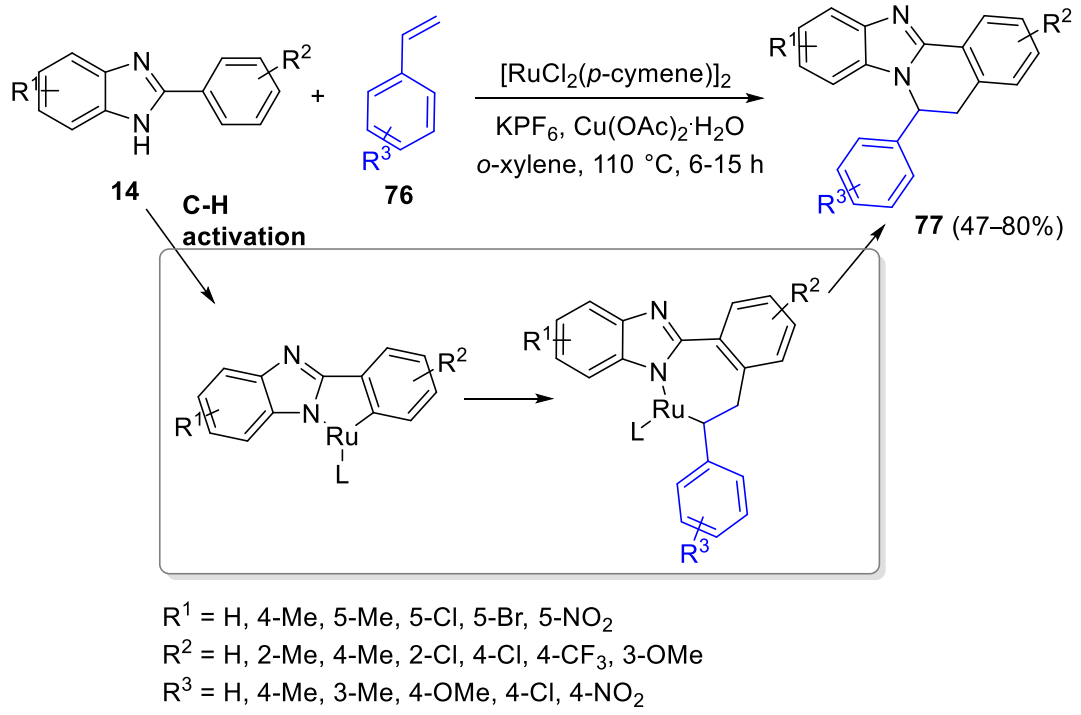


R^1 = 4-Me, 4-OMe, 4-CF_3, 4-F, 4-Cl, 4-Br, 4-NO_2
R^2 = 4-Me, 4-OMe, 4-SMe, 4-Ph, 4-Cl, 2-Br, 3-NO_2
R^3 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 3-ClC_6H_4, *n*-Pr

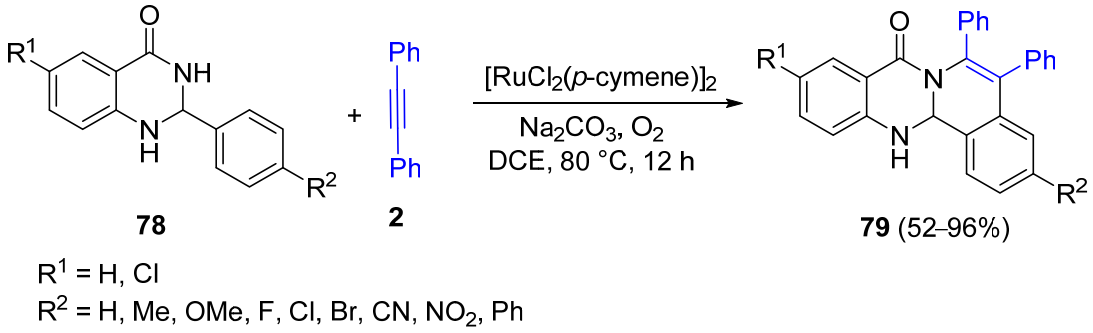
Scheme 26. Synthesis of isoquinoline compounds.

As mentioned before in Schemes 6, 8 and 9, the reaction of nitrogen-based heterocycles with olefins comprising electronegative groups, such as carboxylates, can afford five-membered fused heterocycles. In another study, the reaction between imidazoles **14** and styrenes **76** gave imidazo[2,1-*a*]isoquinoline compounds **77** due to a lack of electronegative groups, which prevented Michael addition, and forced participation of both olefin's carbon atoms in the annulation (Scheme 27) [66]. A similar pathway happened during the reaction

between dihydroquinazolinone **78** and alkynes, yielding isoquinolino[1,2-*b*]quinazolin-8-ones **79** (Scheme 28) [67].



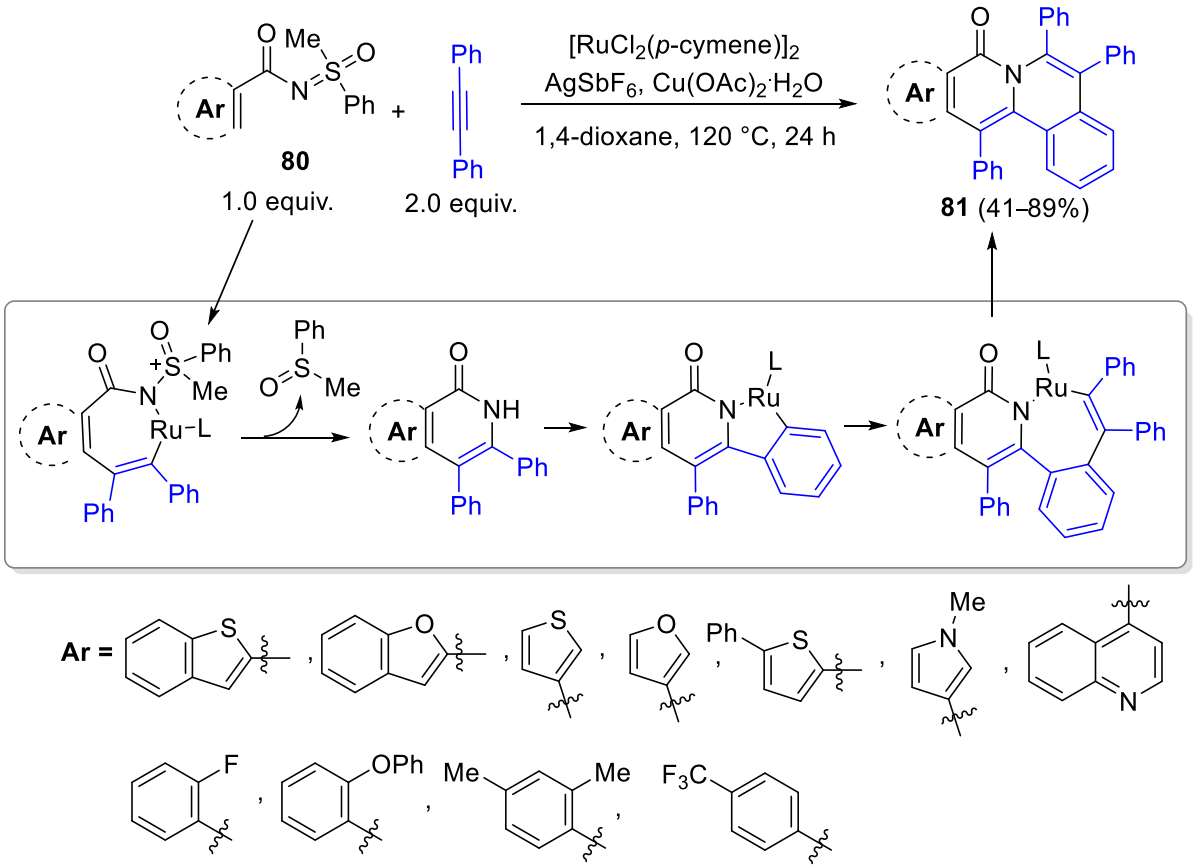
Scheme 27. Synthesis of imidazo[2,1-*a*]isoquinoline compounds.



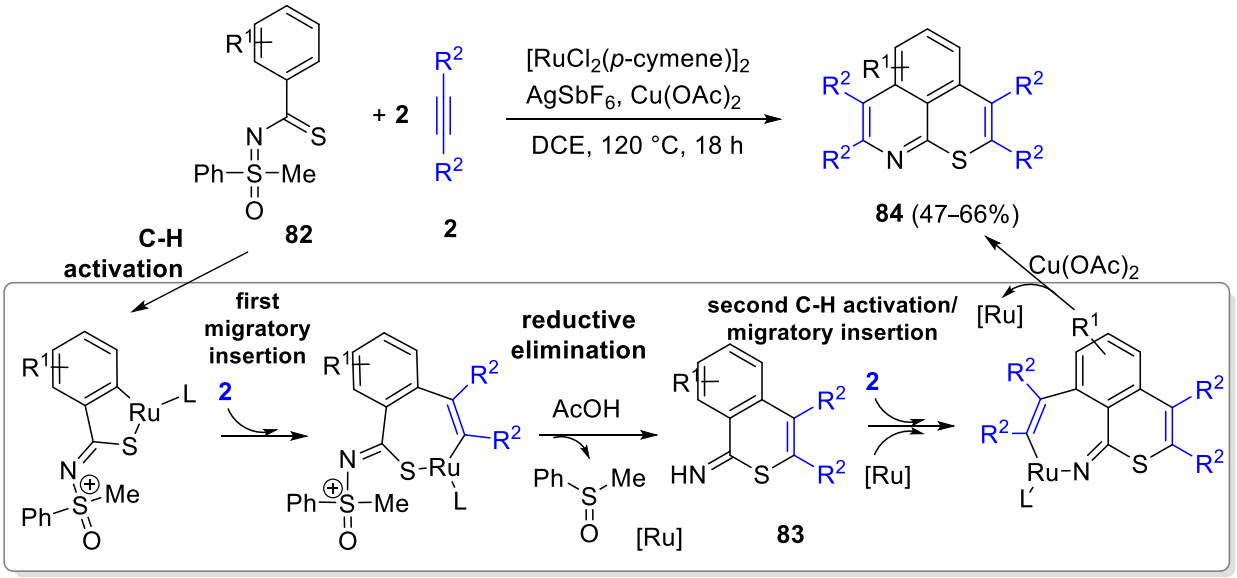
Scheme 28. Synthesis of isoquinolino[1,2-*b*]quinazolin-8-ones.

The applicability of sulfoximine groups in the annulation of heterocycles was previously shown in Scheme 19. The reaction of methylphenyl sulfoximine **80** with two equivalents of diphenylacetylene passed from a double Ru(II)-catalyzed annulation reaction to give fused pyrido[2,1-*a*]isoquinolin-4-ones **81** (Scheme 29) [68–70].

Shankar et al. used sulfoximine **82** in the reaction with alkynes to achieve fluorescent pyranoisoquinolines **84**. This reaction is based on a double annulation in which intermediate **83** was initially formed to follow the second C–H activation/migratory insertion of the alkyne (Scheme 30) [71,72]. A similar protocol was employed for the generation of fused oxepino-pyridines **86** using sulfoximine **85** (Scheme 31) [73]. Instead of two equivalents of alkynes, one equivalent of alkyne and one equivalent of olefins can be utilized to develop such a reaction. Mukherjee et al. designed fused spiro-isoquinolones **89** through the three-component reaction of sulfoximine **82**, alkyne, and quinone **87**. Formation of intermediate **88** promoted Michael addition, furnishing fused spiro-product **89** (Scheme 32) [74].

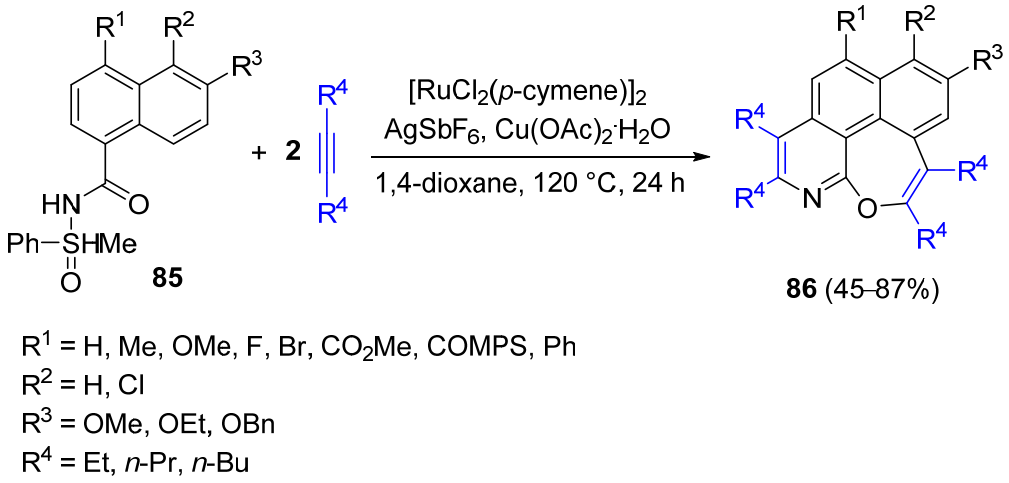


Scheme 29. Synthesis of fused pyrido[2,1-*a*]isoquinolin-4-ones.

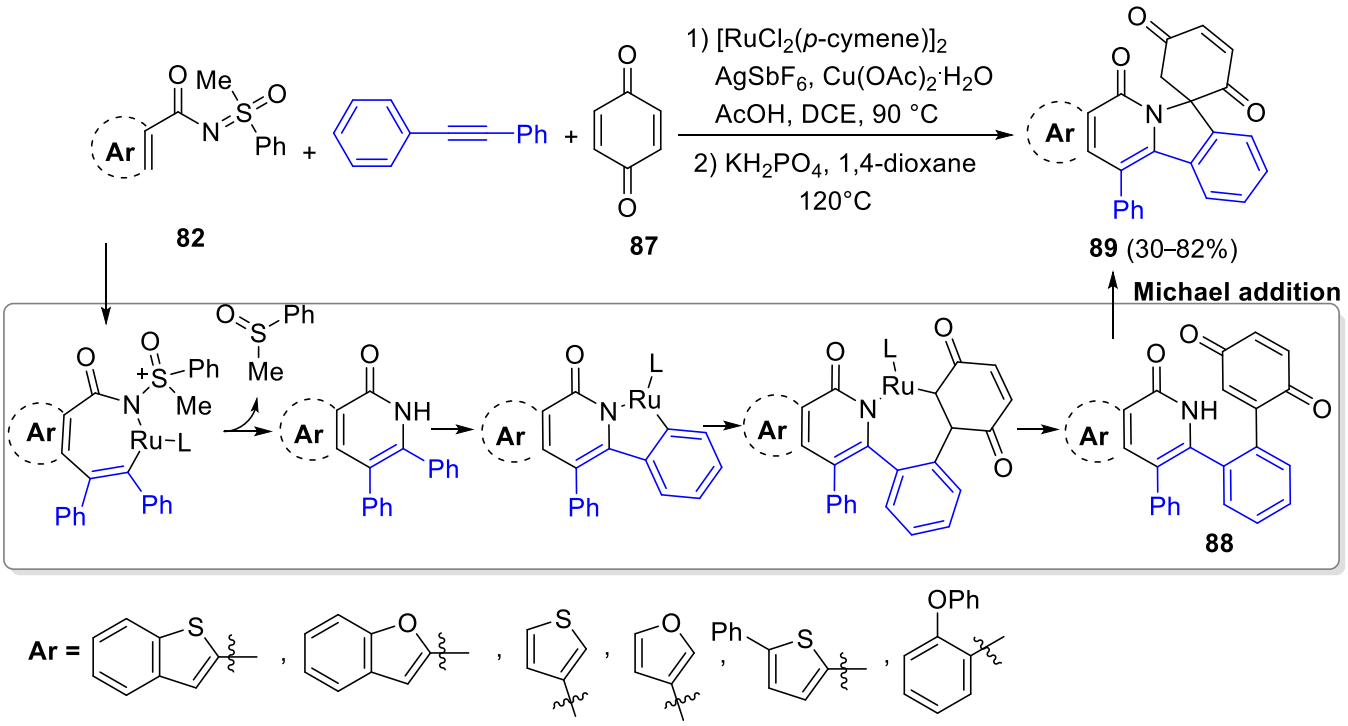


R^1 = 4-Me, 4-F, 4-CO_2Me (positioned in the reactant)
R^2 = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-*t*-BuC_6H_4, 3-MeC_6H_4, *n*-Bu

Scheme 30. Synthesis of pyranoisoquinolines.



Scheme 31. Synthesis of fused oxepino-pyridines.



Scheme 32. Synthesis of spiro-isoquinolones.

3. Conclusions

The interest in sequential catalysis of ruthenium complexes in organic transformations, especially C–H activations and annulations, is growing tremendously. Ru-complexes along with an oxidizer and an additive can catalyze sequential transformations in a one-pot manner. The key reagent in the Ru-catalyzed one-pot synthesis of heterocycles is olefins or alkynes that can react with aryl amines, aryl amides, aryl carboxylic acids, heterocycles, and phenols. As a result of a slight creative change in the structure of reactants, a new heterocycle is generated, which is highly important in green synthesis because the desired product can be obtained in a single reaction using the least amount of solvents and reagents. In years to come, sequentially one-pot Ru-catalyzed annulation reactions will become an appreciated tool for the prompt synthesis of bioactive heterocycles.

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