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Domino carbometalation/coupling reactions of *N*-arylpropiolamides: a novel and promising synthetic strategy toward stereocontrolled preparation of highly substituted 3-methyleneindolinones

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3-Methyleneindolinone derivatives are important structural motifs found in many compounds of natural occurrence and pharmacological significance. However, despite their wide importance, mild and highly efficient stereoselective synthesis of (*E*)- and (*Z*)-3-methyleneindolinones still remains to be a difficult problem. Therefore, the development of new synthetic methods for their stereocontrolled preparation is of prime importance in organic synthesis. In this mini review, we highlight the advances in stereoselective synthesis of mono- and disubstituted-3-methyleneindolinones through metal-catalyzed intramolecular cyclization of *N*-arylpropiolamides from 1988 to 2017.

1. Indolinone

2-Indolinones are privileged structural units not only in natural products[1] but also in several other fields such as medicinal,[2] agricultural,[3] and dye chemistry.[4] Fused ring heterocyclic compounds play an important role in the biological system and DNA molecule, antimalarial, anti-inflammatory, quantitative determination of bioorganic compounds and fluorescence properties.[5] 3-Methyleneindolinones are among the most important structural classes of 2-indolinones, which are present in numerous naturally occurring substances and biologically active compounds.[2,5] For example, sunitinib **1** with brand name of sutent is a receptor protein-tyrosine kinase inhibitor that marketed worldwide for the treatment of renal cell carcinoma and imatinib resistant GIST. It is the first anticancer drug to be simultaneously approved (in 2006) for two different indications.[6] Toceranib **2**, with trade name palladia, is a dog-specific

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anti-cancer drug. It works by killing tumor cells directly and by cutting off the tumor's blood supply.[7] It is interesting that toceranib is the first drug developed specifically for the treatment of cancer in dogs. Nintedanib **3** with brand names of Vargatef and Ofev is a kinase inhibitor that used for the treatment of idiopathic pulmonary fibrosis (IPF) and a type of non-small-cell lung cancer called adenocarcinoma.[8] SU4984 **4** is an inhibitor of tyrosine kinase activity of fibroblast growth factor receptor 1 (FGFR1) undergoing clinical trials for the treatment of human cancers.[9] Alkaloids isatinone A **5** and B **6**, which were isolated from ethanolic extracts of the herb *Isatis costata*, have significant antifungal activity.[10] As these examples show, 3-methyleneindolinone derivatives offer very attractive options for drug design of various pharmacological agents. However, despite their wide importance, highly stereoselective synthesis of (*E*)- and (*Z*)-3-methyleneindolinones still remains to be a formidable challenge (Fig. 1).

Over the past several years, *N*-propargyl-amines and -amides have received significant attention in organic synthesis owing to their easy availability, cost effectiveness, and versatility in the synthesis of a wide variety of nitrogen based heterocycles.[11] In this regard, the synthesis of 3-methyleneindolinones from *N*-arylpropiolamides have undergone very rapid growth in recent years. Cyclization of *N*-arylpropiolamide derivatives provide one of the most powerful one-step and atom-economic methods for the stereoselective synthesis of highly substituted 3-methyleneindolinones. These reactions were highlighted by Millemaggi and Taylor in their interesting review in 2010.[12] In continuation of our works,[11] our aim in this review is to try to provide a comprehensive and updated overview of recent developments in the (*E*)- and (*Z*)-selective synthesis of 3-methyleneindolinone derivatives from cyclization of *N*-arylpropiolamides through metal-catalyzed approaches with the emphasis on the mechanistic aspects of the reactions.

2. Synthesis of 3-methyleneindolinones from *ortho*-halo *N*-arylpropiolamides

The first example of transformation of *N*-phenylpropiolamides to 3-methyleneindolinones through a 5-*exo-dig* fashion was reported by the groups of Bowman, in 1988. They showed that intramolecular radical cyclization of *N*-(2-iodophenyl)-*N*-methyl-3-phenylpropiolamide **7** in the presence of Bu_3SnH/AIBN system in refluxing toluene gave *E*/*Z*-mixture of corresponding 3-alkenyl-indolinone **8** in 37% yield (Scheme 1).[13] Twelve years later, Brunton and Jones reinvestigated this reaction employing *N*-phenylpropiolamides bearing *tert*-butyldimethylsilyl (TBDMS) groups in the alkyne terminus as substrates. The corresponding indolinones were obtained in moderate yields and good (*Z*)-selectivity.[14]

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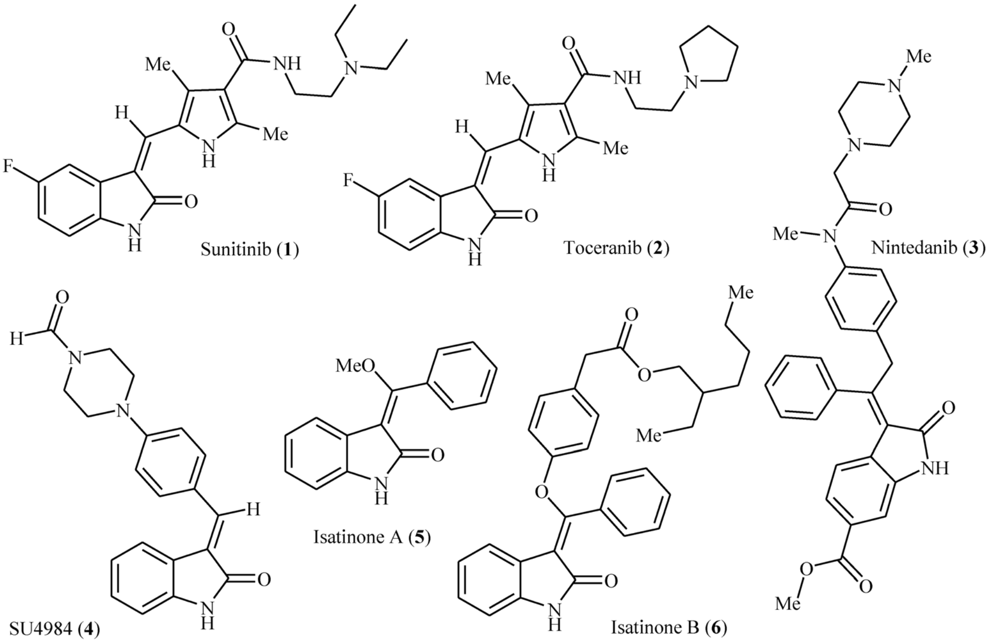
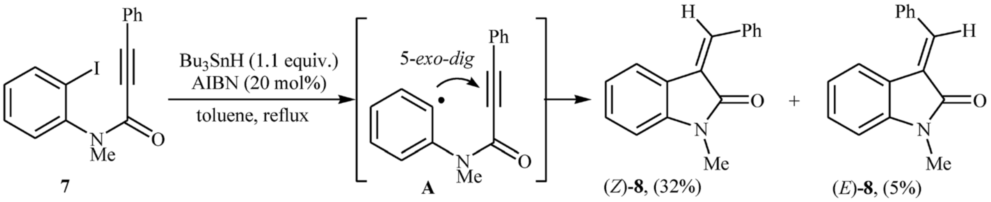


Fig. 1 Selected examples of 3-methyleneindolinone-based drugs (sunitinib, toceranib, nintedanib, SU4984) and natural products (isotinone A and B).

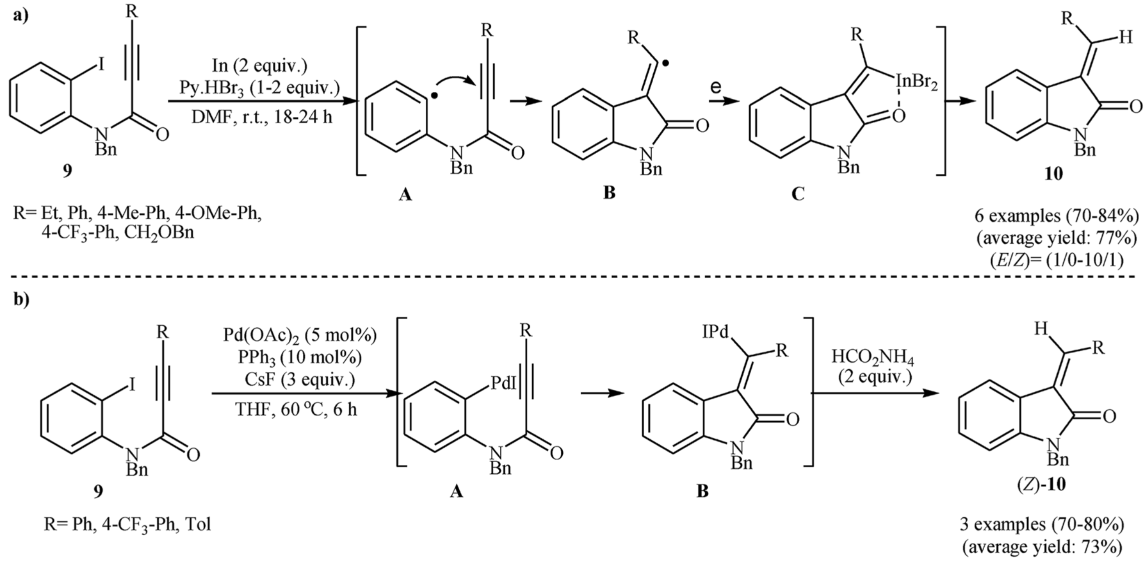


Scheme 1 Synthesis of 3-alkenyl-indolinones **8** *via* stannane mediated intramolecular cyclization of *N*-(2-iodophenyl)-*N*-methyl-3-phenylpropiolamide **7**.

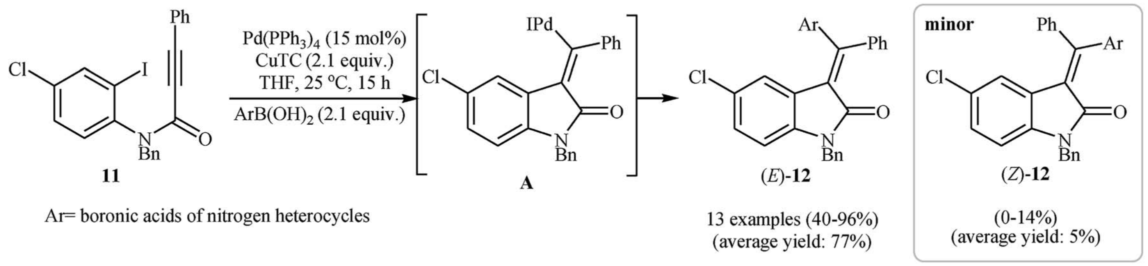
Subsequently, Takemoto and co-workers found that N-protected *N*-(2-iodophenyl)propiolamides **9** in the presence of In/Py + HBr_3/DMF system, underwent a reductive radical cyclization to afford corresponding (*E*)-3-alkylideneindolinones **10** in good to high yields with excellent stereoselectivity (Scheme 2a).[15] The (*E*)-selectivity of the reaction can be ascribed to the strong coordination of the indium atom to amide carbonyl oxygen of the intermediate **C**. It is worth noting that the *N*-(2-iodophenyl)propiolamides bearing an electron-withdrawing groups on the aryl ring failed to enter into the cyclization reactions and the substrates bearing electron-rich aryl rings gave very poor results. The same authors also were able to demonstrate that a range of disubstituted 3-alkylideneoxindoles could be obtained from the corresponding *N*-phenylpropiolamides through a tandem In-mediated reductive radical cyclization and Pd-catalyzed cross-coupling reaction.[16] Later, the same group showed that the treatment of internal aryl substituted *N*-(2-iodophenyl)propiolamides **9** with a catalytic amount of $Pd(OAc)_2$ and PPh_3 in the presence of cesium fluoride and ammonium formate in THF resulted in good yields of corresponding (*Z*)-3-alkylideneindolinones (*Z*)-**10** through an intramolecular Heck cyclization (Scheme 2b). However, *N*-phenylpropiolamides having alkyl groups in the alkyne terminus failed to participate in the reaction. The authors claimed that the key step of these reactions is the *syn* addition of arylpalladium halide **A** to the triple bond. They also successfully extended this chemistry to synthesis of further functionalized indolinones *via* palladium-catalyzed Heck/Suzuki–Miyaura, Heck/Heck, and Heck/carbonylation/Suzuki–Miyaura domino reactions using aforementioned catalytic system.[17]

Alongside this, Player and co-workers presented a palladium-catalyzed tandem Heck cyclization/Suzuki–Miyaura coupling of N–H free *N*-(2-iodophenyl)propiolamide **11** with arylboronic acids into (*E*)-3-(diarylmethylene)indolinones **12**. Thus, the careful analysis of the optimized reactions revealed that the optimum condition for this reaction was the addition of $Pd(PPh_3)_4$ (15 mol%), copper(I) thiophen-2-carboxylate (CuTC) (2.1 equiv.), and arylboronic acid (2.1 equiv.) at room temperature, to a solution of *N*-(2-iodophenyl)propiolamide in dry THF. Under optimized conditions, the reaction tolerates both electron-rich and electron-poor arylboronic acids and gave the corresponding 3,3-(diarylmethylene)indolinones **12** in moderate to high yields and good to excellent regioselectivity (Scheme 3).[18]

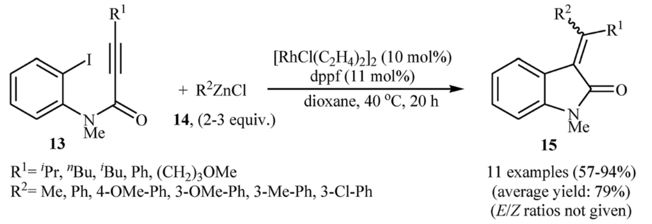
Shortly afterward, Shintani, Yamagami, and Hayashi extended the scope of electrophilic partners to organozinc



Scheme 2 (a) In-Mediated reductive radical cyclization of *N*-phenylpropiolamides **9**; (b) stereoselective synthesis of (*Z*)-3-alkylideneindolinones (*Z*)-**10** *via* palladium-catalyzed Heck cyclization of internal *N*-(2-iodophenyl)propiolamides **9**.

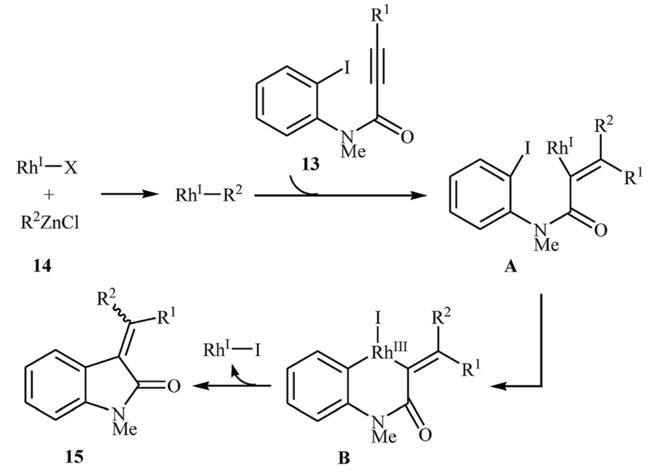


Scheme 3 Pd-Catalyzed tandem Heck cyclization/Suzuki–Miyaura coupling of N–H free *N*-(2-iodophenyl)propiolamide **11** with arylboronic acids.



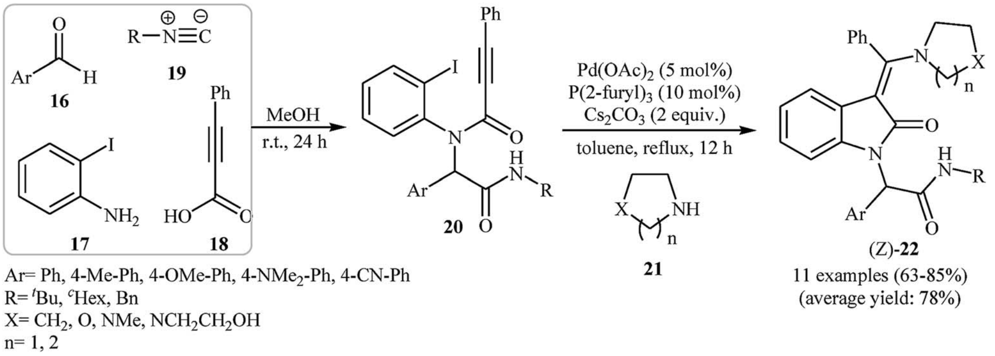
Scheme 4 Synthesis of 3,3-(diarylmethylene)indolinones **15** *via* Rh-catalyzed cascade reaction of *N*-(2-iodophenyl)propiolamides **13** and organozinc chlorides **14**.

chlorides **14**. They showed that treatment of *N*-methylated *N*-(2-iodophenyl)propiolamides **13** with organozinc chlorides **14** in presence of $[RhCl(C_2H_4)_2]_2$/dppf as catalytic system in dioxane resulted in corresponding 3,3-(diarylmethylene)indolinones **15** in good to high yields (Scheme 4). Mechanistically, in contrast to the palladium catalyzed processes, this reaction is believed to proceed through a carborhodation-oxidative addition-reductive elimination sequential process (Scheme 5).[19]

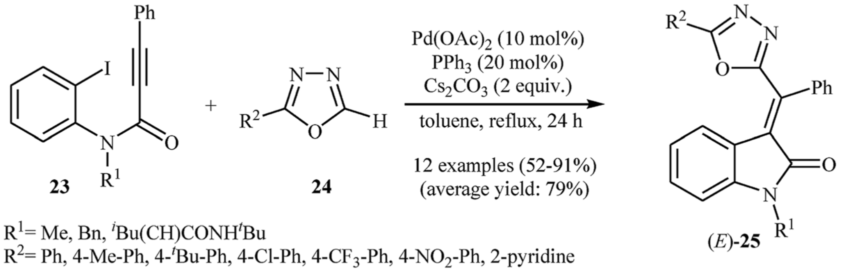


Scheme 5 Proposed mechanism for formation of **17**.

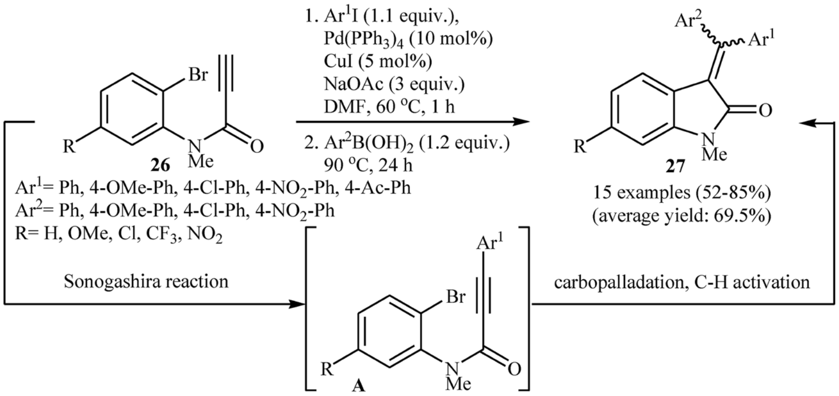
In 2011, Balalaie and co-workers developed the stereoselective synthesis of (*Z*)-3-(aminoarylmethylene)indolinones **22** *via* a tandem palladium-catalyzed carbopalladative cyclization-Buchwald reaction of Ugi-adducts **20** with amines **21**. Thus, in the presence of $Pd(OAc)_2/P(2\text{-furyl})_3/Cs_2CO_3$ as catalytic system in refluxing toluene, *N*-substituted phenylpropiolamides **20**,



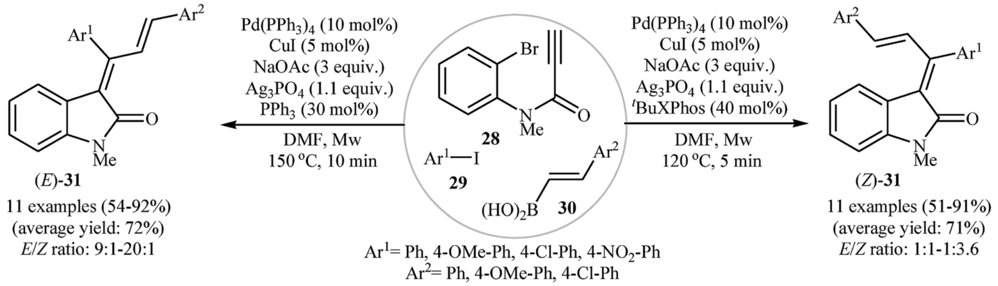
Scheme 6 Stereoselective synthesis of (*Z*)-3-(aminoarylmethylene)indolinones **22** *via* Ugi-carbopalladative cyclization-Buchwald reaction sequences developed by Balalaie.



Scheme 7 Pd-Catalyzed synthesis of (*E*)-3-((1,3,4-oxadiazol-2-yl)(aryl)methylene)indolinones **25** from *N*-propiolamides **23** and 1,3,4-oxadiazoles **24** described by Sharma.

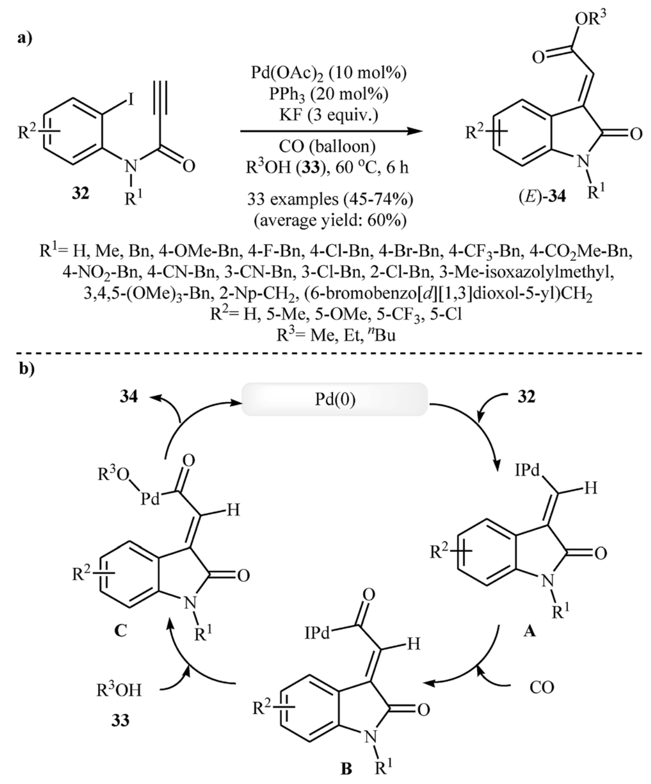


Scheme 8 Pd-Catalyzed Sonogashira/Heck/Suzuki–Miyaura combined reaction of *N*-(2-bromophenyl)propiolamides **26**.



Scheme 9 Three-component tandem reactions for the stereoselective synthesis of 3-(1,3-diarylallylidene)indolinones **31**.

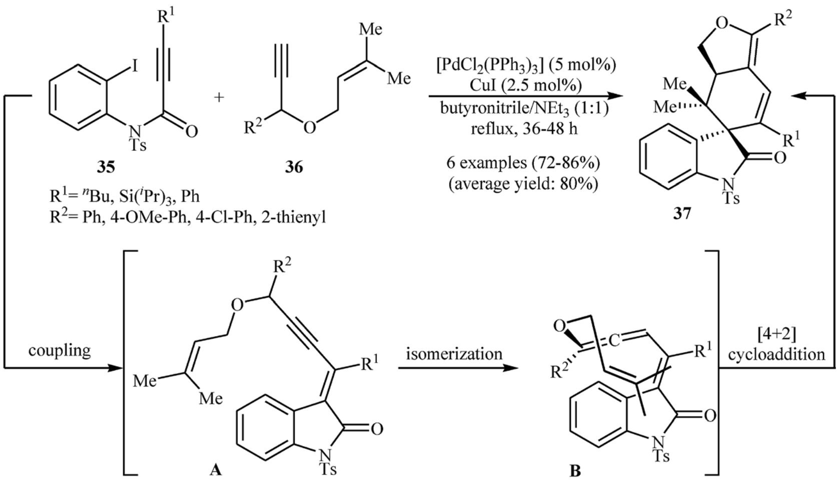
which were prepared from the reaction of benzaldehydes **16**, 2-iodoaniline **17**, phenylpropiolicacid **18**, and isocyanides **19**, were treated with secondary amines **21** to give (*Z*)-3-(amino-arylmethylene)indolinones **22** in good to high yields (Scheme 6).[20] Later, in a closely related investigation, U. Sharma, E. Eycken, and co-workers showed that 3-methyleneindolinones **25** were formed from *N*-propiolamide **23** and 1,3,4-oxadiazoles **24** (Scheme 7). This transformation requires the use of $Pd(OAc)_2$ as catalyst and PPh_3 as ligand under N_2 atmosphere. The reaction was run in refluxing toluene and leads to (*E*)-3-((1,3,4-oxadiazol-2-yl)(aryl)methylene)indolinones **27** through an intermolecular domino carbopalladative cyclization/C–H functionalization sequence of an *N*-propiolamide **25** and an 1,3,4-oxadiazole **26**.[21] These results indicated that the nature of ligands have a great impact on the stereoselectivity of products.



Scheme 10 (a) Pd-Catalyzed tandem Heck and alkoxycarbonylation reactions of *N*-substituted *N*-(2 iodophenyl)propiolamides **32** with CO and alcohols **33** developed by Li; (b) mechanism that accounts for the formation of **34**.

In 2013, a beautiful approach for the synthesis of 3,3-(diarylmethylene)indolinones **27** *via* a sequential Pd-catalyzed Sonogashira/Heck/Suzuki–Miyaura reactions of terminal *N*-(2-bromophenyl)propiolamides **26** with aryl iodides and arylboronic acids was demonstrated by Seo and coworkers. After studying a number of catalyst and bases, a combination of $Pd(PPh_3)_4$/CuI/NaOAc in DMF was found to be optimum with respect to the yield of product isolated (Scheme 8). The results demonstrated that under this reaction conditions electron poor aryl iodides lead to a strong preference for *Z*-products and electron rich aryl iodides resulting in a relatively weak preference for *E*-products.[22] Subsequently, the same group reinvestigated this reaction by displacing of *N*-(2-bromophenyl) propiolamides with 2-(propiolamido)phenyl triflates but lower yields than previously reported examples were observed.[23] Recently, the same authors improved the efficiency of this reaction in terms of the yield and reaction time by performing the process under microwave irradiation conditions employing $Pd(PPh_3)_4/PPh_3/CuI/NaOAc/Ag_3PO_4$ as catalytic system.[24]

In a recent study, the same research team extended their methodology to the highly stereoselective synthesis of (*E*)- and (*Z*)-isomers of 3-(1,3-diarylallylidene)indolinones **31**, through microwave-assisted three-component tandem Sonogashira/Heck/Suzuki–Miyaura reactions of *N*-(2-bromophenyl)propiolamide **28**, aryl iodides **29**, and vinyl boronic acids **30**. They found that the nature of the phosphine ligand, reaction temperature, and reaction time had a major impact on the *E*/*Z* ratio of products. Thus, reaction with PPh_3 at high temperatures and longer reaction times gave *E*-isomers with excellent stereoselectivity, whereas reaction with *t*-Bu XPhos at lower temperatures and



Scheme 11 Synthesis of spirocyclic indolones **37** through a Pd-catalyzed insertion/coupling/isomerization/Diels–Alder sequential process.

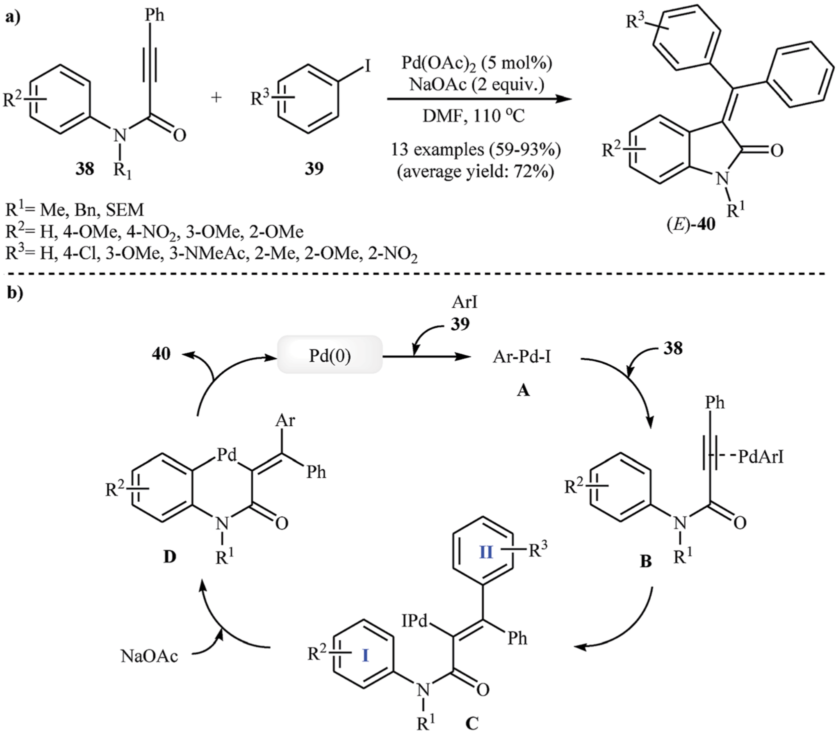
shorter reaction times lead to *Z*-isomers with moderate stereoselectivity (Scheme 9).[25]

In 2016, Li *et al.* developed a new methodology toward (*E*)-oxindolylidene acetates **34** through a Pd-catalyzed tandem Heck and alkoxycarbonylation reactions of *N*-substituted *N*-(2-iodophenyl)propiolamides **32** with CO and alcohols **33** (Scheme 10). They tested several catalysts, ligands, and additives, and the system $Pd(OAc)_2/PPh_3/KF$ was found to be optimal with respect to isolated product yield. The optimized protocol tolerated a variety of sensitive functional groups, such as nitro, cyano, fluoro, chloro, bromo, methoxyl, and ester functionalities on the aryl ring of propiolamides and gave final products in moderate to good yields (Scheme 10a). However, the scope of alcohols are limited to the small primary aliphatic alcohols. The author proposed mechanism for this cyclization, which is outlined in Scheme 10b. It is noted that the resulting products showed a growth inhibitory activity against a variety of human cancer cell lines.[26]

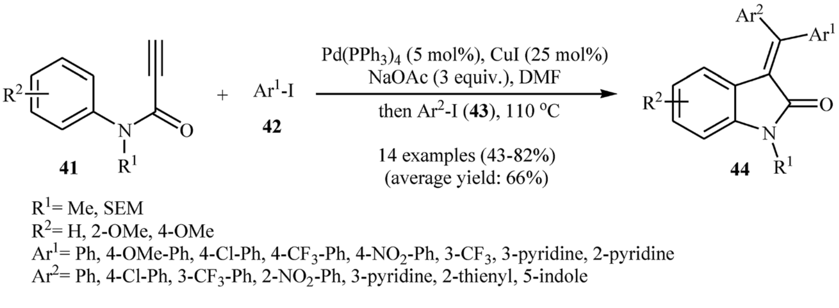
An interesting domino procedure for the synthesis of spirocyclic indolones **37** from internal N-protected *N*-(2-iodophenyl)propiolamides **35** and propargyl allyl ethers **36**, in which four new C–C bonds are formed, was developed by Müller *et al.* (Scheme 11). The electron-poor vinylpropargyl allyl ether **A**, which is generated from Pd-catalyzed coupling of **35** and **36**, undergoes a triethylamine-catalyzed propargyl-allene isomerization to give enallene **B**. A subsequent intramolecular [4 + 2] cycloaddition leads to the observed products **37**.[27]

3. Synthesis of 3-methyleneindolinones from *ortho*-unsubstituted *N*-phenylpropiolamides

The possibility of cyclization of *ortho*-unsubstituted *N*-phenylpropiolamides to indolinones was first realized by Zhu and coworkers, in 2006, who synthesized (*E*)-3-(diarylmethylene)

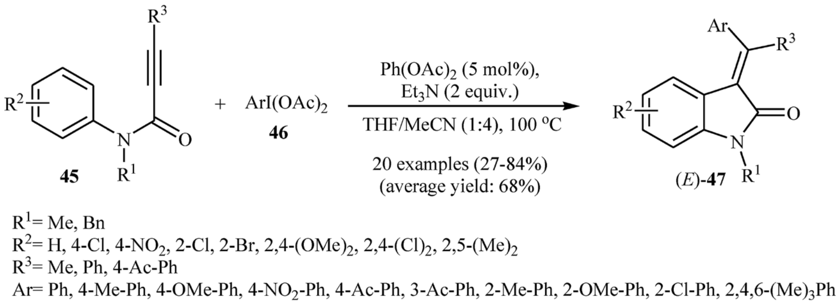


Scheme 12 (a) Synthesis of (*E*)-3-(diarylmethylene)indolinones **40** *via* Pd-catalyzed carbopalladation/C–H activation/C–C bond-forming cascade reaction of *N*-phenylpropiolamides **38** and aryl iodides **39**; (b) mechanism that accounts for the formation of **40**.

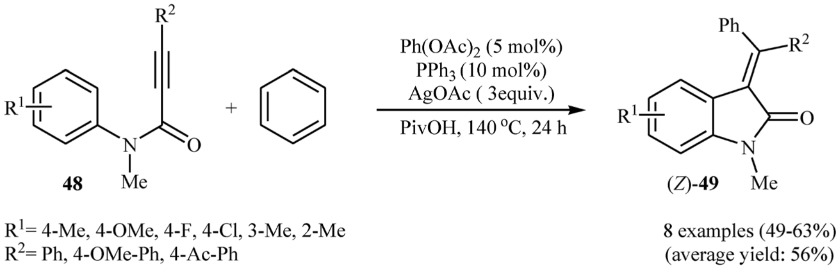


Scheme 13 Stereocontrolled three-component synthesis of unsymmetrically substituted 3-(diarylmethylene)indolinones **44** developed by Zhu.

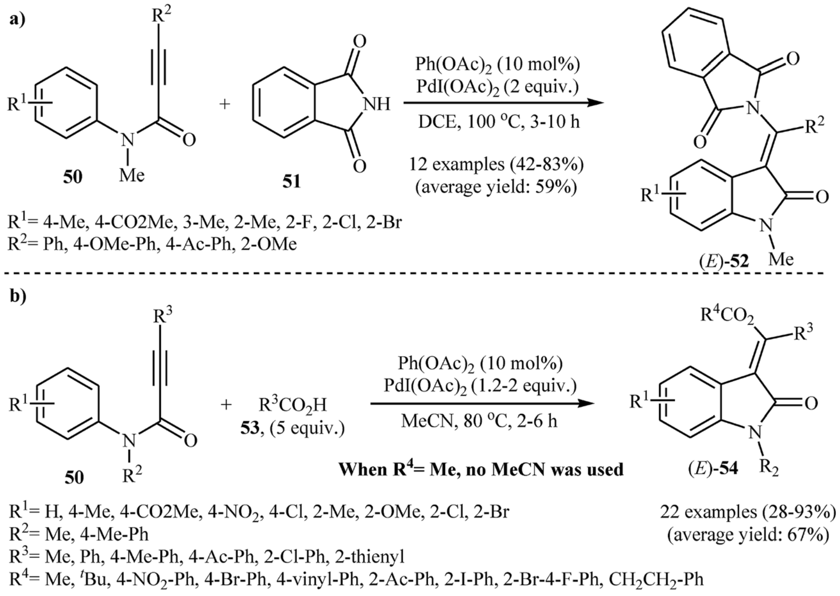
indolinones **40** from corresponding tertiary *N*-phenylpropiolamides **38** and aryl iodides **39** using Pd(OAc)$_2$/NaOAc/DMF system (Scheme 12a). This method is compatible with a large range of tertiary *N*-phenylpropiolamides, but it could not be extended to secondary *N*-phenylpropiolamides. Depending on the electronic effects of substituents on the aryl iodides, substrates with electron-withdrawing groups gave higher yields than those with electron-donating groups. The mechanism proposed to explain this reaction is shown in Scheme 12b and starts with the formation of arylpalladium(II) species **A** *via* oxidative addition of aryl iodide to palladium(0), and then coordination of **A** to the triple bond of propiolamide to give intermediate **B**, which undergoes a *syn* carbopalladation to produce vinylpalladium intermediate **C.** Subsequently, C–H activation of ring I gives six-membered palladacycle **D.** Finally, a reductive elimination affords the observed products **40**



Scheme 14 Synthesis of (*E*)-3-(diarylmethylene)indolinones **47** *via* Pd-catalyzed C–H functionalization of *N*-arylpropiolamides **45** with aryliodonium salts **46**.

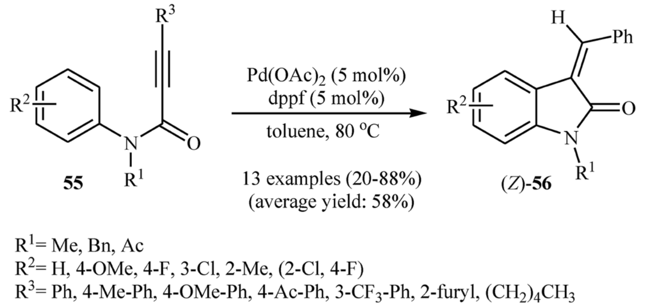


Scheme 15 Synthesis of (*Z*)-3-(diarylmethylene)indolinones **49** through a Pd-catalysed double C–H activation process.

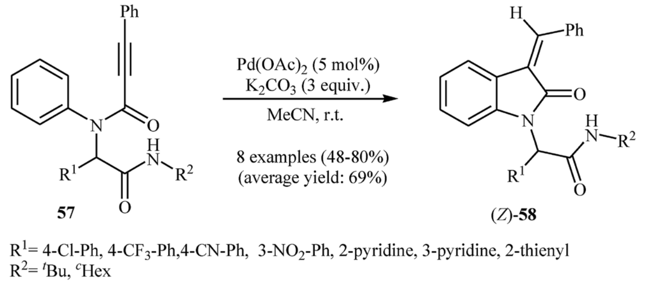


Scheme 16 (a) Li's synthesis of (*E*)-3-(phthalimido(aryl)methylene)indolinones **52**; (b) Li's synthesis of (*E*)-(2-indolinon-3-ylidene)methyl acetates **54**.

(Scheme 12b).[28] Shortly afterward, the same authors extended their methodology to the stereocontrolled three-component (external *N*-phenylpropiolamides **41**, aryl iodides **42** and **43**) synthesis of unsymmetrically substituted 3-(diarylmethylene) indolinones **44** through a domino Sonogashira/carbopalladation/C–H activation/C–C bond-forming sequence (Scheme 13).[29]



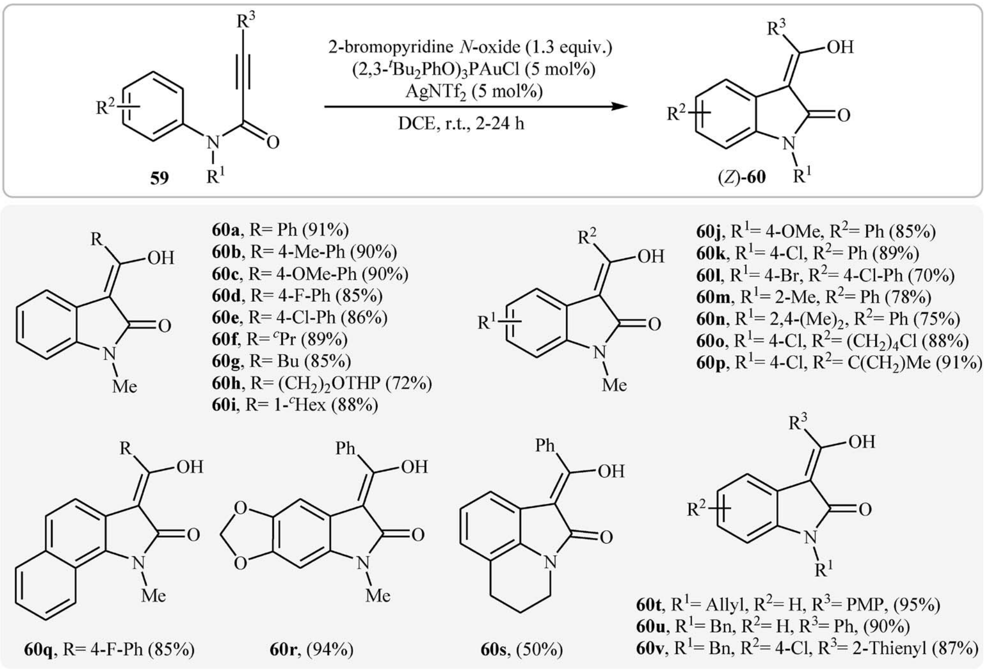
Scheme 17 Pd-Catalyzed hydroarylations of *N*-arylpropiolamides **55** developed by Li.



Scheme 18 Pd-Catalyzed hydroarylations of *N*-arylpropiolamides **57** reported by Balalaie.

Following these works, the Li group developed an analogous one-pot access to (*E*)-3-(diarylmethylene)indolinones **47** by the reaction of *N*-phenylpropiolamides **45** with aryliodonium salts **46** (Scheme 14). Several palladium sources, additives and solvents were tested, and the system $Pd(OAc)_2/Et_3N$/THF/MeCN (1 : 4) was found to be superior. However, N–H free and terminal propiolamides failed to participate in this reaction.[30] To overpass the limitation encountered by N–H free phenylpropiolamides, the same authors investigated the reaction of secondary *N*-phenylpropiolamides with aryl iodides in the presence of $Pd(OAc)_2$/CuI/*N*,*N*′-dimethylethane-1,2-diamine/K_2CO_3/DMF/MeCN (1 : 1.4) system and satisfactory results were obtained.[31] In a beautiful approach, Pinto, Neuville, and Zhu disclosed a one-pot, three-component version of the same reaction where the requisite *N*-phenylpropiolamides were prepared *in situ* from propiolamides and arylbromides.[32] With the objective of designing a comprehensive protocol to 3-(diarylmethylene) indolinones, the scope of coupling partners were extended to benzene. The $Pd(OAc)_2/PPh_3$/AgOAc combination was found to be optimal for this reaction. Under optimized conditions, the reaction tolerates electron-donating and electron-withdrawing substituents and gave the corresponding (*Z*)-3-(diarylmethylene) indolinones **49** in moderate yields (Scheme 15). However, *N*-phenylpropiolamides having alkyl groups in the alkyne terminus failed to participate in the reaction.[33]

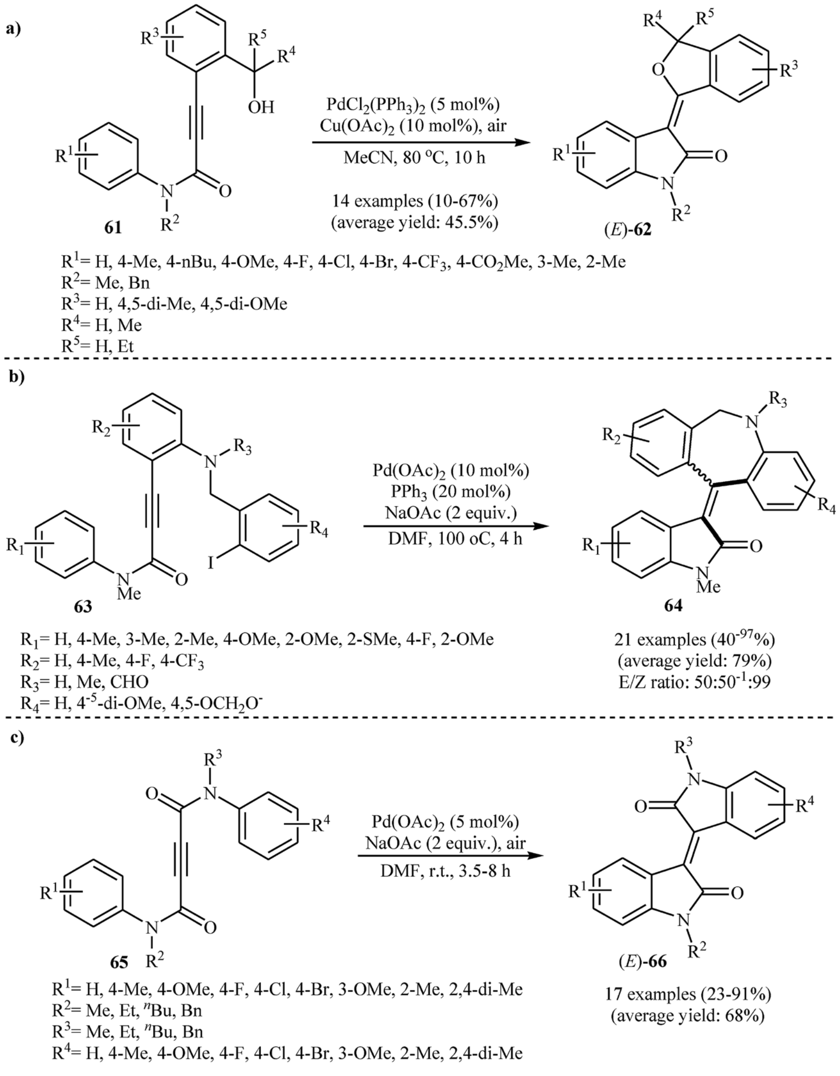
In 2008, Li and co-workers reported an efficient and beautiful protocol for the stereoselective synthesis of biologically important (*E*)-3-(phthalimido(aryl)methylene)indolinones **52** from the reaction between tertiary *N*-phenylpropiolamides **50** and phthalimide **51** through a palladium-catalyzed



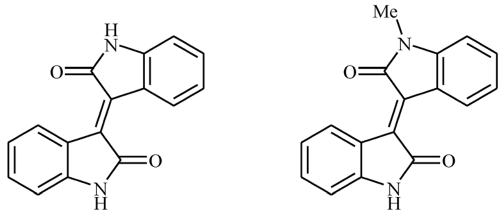
Scheme 19 Oxidation/C–H functionalization of *N*-arylpropiolamides **59**.

intermolecular aminopalladation/C–H activation strategy. They discovered that the reaction of 1 equiv. of *N*-phenylpropiolamides **50** with 3 equiv. of phthalimide **51** in DCE at 100 °C in the presence of catalytic amounts of $Pd(OAc)_2$ and over-stoichiometric amounts of $PdI(OAc)_2$ produced desired products **52** in moderate to good yields (Scheme 16a). The reaction, however, appears to be limited to *N*-phenylpropiolamides containing aryl groups in the alkyne terminus. Extension to alkyl subsumed internal phenylpropiolamides and external phenylpropiolamides were attempted, but the corresponding indolinones were isolated in very poor yields.[34] In a subsequent extension of the substrate scope of the methodology, it was shown that both aryl and alkyl-substituted internal *N*-phenylpropiolamides **50** could be treated with carboxylic acids **53** under the abovementioned reaction conditions to give corresponding (*E*)-(2-indolinon-3-ylidene)methyl acetates **54** (Scheme 16b). However, N–H free and *N*-acetylated phenylpropiolamides failed to give any of the desired indolinone derivative.[35]

The same authors were also able to demonstrate that a range of (*Z*)-3-(monosubstituted-methylene)indolinones **56** could be stereoselectively obtained from the palladium-catalyzed intramolecular hydroarylation of corresponding *N*-arylpropiolamides **55** through a 5-*exo-dig* fashion employing $Pd(OAc)_2$ as catalyst and dppf (1,1′-bis(diphenyphosphino)ferrocene) as ligand in toluene at 80 °C (Scheme 17). It should be mentioned that the (*E*)-isomers have been isolated in some cases as the minor products. Interestingly, at higher temperatures than 80 °C the yield of (*Z*)-isomers is decreased in favor of the (*E*)-isomers. When the cyclization was performed at 140 °C, the (*E*)-products were obtained in good to high yields (59–86%) with a mixture of (*Z*)-products (8–30%).[36] Later, Balalaie and co-workers reinvestigated this reaction using $Pd(OAc)_2/K_2CO_3$ combination as catalytic system. The reactions were run in acetonitrile at room



Scheme 20 (a) Intramolecular cyclization of 3-(2-(hydroxymethyl)aryl)-*N*-phenylpropiolamides **61** into (*E*)-3(isobenzofuran-3(1*H*)-ylidene) indolinones **62**; (b) synthesis of 3-[5*H*-dibenzo[*b*,*e*]azepin-11(6*H*)-ylidene]indolinones **64** *via* intramolecular annulation of 3-[2-(2-iodobenzylamino)aryl]-*N*-arylpropiolamides **63**; (c) synthesis of (*E*)-bisindolinones **66** in *via* intramolecular double annulation of N^1,N^4-diphenylbut-2-ynediamides **65**.



Isoindigo (**67**) Meisoindigo (**68**)

Fig. 2 Chemical structure of isoindigo **67** and meisoindigo **68**.

temperature and provided corresponding (*Z*)-3-(arylmethylene)-indolinones **58** in good to high yields (Scheme 18).[37]

Recently, Qian and Zhang demonstrated an elegant gold-catalyzed oxidation/C–H functionalization reaction of tertiary *N*-arylpropiolamides **59** into 3-acylindolinone derivatives **60** (Scheme 19). In most cases, the nature of the substituents had no influence on the results of this reaction. However, *N*-acylated substrates failed to participate in this cyclization.[38]

In 2009, Li's group elegantly applied palladium-catalyzed intramolecular C–H activation reactions of 3-(2-(hydroxymethyl) aryl)-*N*-phenylpropiolamides **61** in the syntheses of (*E*)-3-(isobenzofuran-3(1*H*)-ylidene)indolinones **62** (Scheme 20a). Among the various catalysts and oxidants examined, $PdCl_2(PPh_3)_2$ and $Cu(OAc)_2$/air emerged as the optimal choices for the cyclization. The reaction conditions allowed the use of substrates bearing a variety of important functional groups including chloro, bromo, methoxy, and ester.[39] Shortly afterwards, the same group disclosed that a series of potential biological active 3-[5*H*-dibenzo[*b*,*e*]azepin-11(6*H*)-ylidene]indolinones **64** could be synthesized from the corresponding 3-[2-(2-iodobenzylamino)aryl]-*N*-arylpropiolamides **63** through a sequential intramolecular arylation of the alkyne moiety with an aryl iodide/annulation of vinyl carbon with an arene C–H bond process (Scheme 20b). The reactions performed in DMF, and $Pd(OAc)_2/PPh_3$/NaOAc was used as the catalytic system.[40] Alongside this, more recently, Du *et al.* have reported an innovative approach for the synthesis of (*E*)-bisindolinones **66** in moderate to good yields *via* an intramolecular double annulation of N^1,N^4-diphenylbut-2-ynediamides **65** catalyzed by $Pd(OAc)_2$ under oxygen atmosphere at room temperature (Scheme 20c). They showed the application of this procedure for the high yielding syntheses of antileukemic drugs isoindigo **67** and meisoindigo **68** (Fig. 2).[41]

4. Summary and outlook

From this mini review, it is clear that metal (specially palladium)-catalyzed domino reactions of *N*-arylpropiolamides has emerged as a promising synthetic strategy toward stereocontrolled preparation of mono- and disubstituted-3-methyleneindolinones that has been successfully used in the synthesis of many important bioactive compounds, like isoindigo and meisoindigo. The nature of the catalysts, ligands, reaction temperatures and times have great influences on the *E*/*Z* ratio of products. We believed that more and more catalytic systems will be developed for the exclusively (*E*)- and (*Z*)-selective synthesis of biologically important and complex 3-methyleneindolinone-based natural products in the near future.

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