## **RSC Advances**



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### REVIEW

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Cite this: RSC Adv., 2017, 7, 19061

### 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.

Received 2nd February 2017 Accepted 8th March 2017

DOI: 10.1039/c7ra01371j

rsc.li/rsc-advances

### 1. Indolinone

2-Indolinones are privileged structural units not only in natural products<sup>1</sup> but also in several other fields such as medicinal,<sup>2</sup> agricultural,<sup>3</sup> and dye chemistry.<sup>4</sup> Fused ring heterocyclic

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<sup>b</sup>Department of Chemistry, Islamic Azad University, Tabriz Branch, Tabriz, Iran <sup>c</sup>Pharmaceutical Sciences Research Center, Department of Medicinal Chemistry, Mazandaran University of Medical Sciences, Sari, Iran. E-mail: reza\_bnia@yahoo. com; abekhradnia@mazums.ac.ir compounds play an important role in the biological system and DNA molecule, antimalarial, anti-inflammatory, quantitative determination of bioorganic compounds and fluorescence properties.<sup>5</sup> 3-Methyleneindolinones are among the most important structural classes of 2-indolinones, which are present in numerous naturally occurring substances and biologically active compounds.<sup>2,5</sup> 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.<sup>6</sup> Toceranib **2**, with trade name palladia, is a dog-specific



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Ahmad Shaabani in Shahid Beheshti University, Tehran, Iran. Now he is working at Tabriz Branch, Islamic Azad University, Tabriz, Iran as Associate Professor. His research interests include organic synthesis, catalyst, nano, organic and green chemistry. anti-cancer drug. It works by killing tumor cells directly and by cutting off the tumor's blood supply.<sup>7</sup> 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 nonsmall-cell lung cancer called adenocarcinoma.<sup>8</sup> 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.<sup>9</sup> Alkaloids isatinone A 5 and B 6, which were isolated from ethanolic extracts of the herb *Isatis costata*, have significant antifungal activity.<sup>10</sup> As these examples show, 3methyleneindolinone derivatives offer very attractive options for drug design of various pharmacological agents. However,



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University, Urmia, Iran, under the supervision of Prof. M. A. Farajzadeh in 1999. Kalhor completed his Ph.D. at Tabriz University, Tabriz, Iran, in 2005 under the supervision of Prof. M. H. Sorouraddin and Prof. M. R. Rashidi. His research interests include chemometrics, nano particles, nano composites, separation science, solid phase micro extraction, sample pretreatment, molecular spectroscopy, modelling and experimental design. 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.<sup>11</sup> In this regard, the synthesis of 3-methyleneindolinones from Narylpropiolamides 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,<sup>11</sup> 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<sub>3</sub>SnH/ AIBN system in refluxing toluene gave E/Z-mixture of corresponding 3-alkenyl-indolinone 8 in 37% yield (Scheme 1).<sup>13</sup> 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.<sup>14</sup>



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University-Tehran, Iran (2005). During his sabbatical period, he worked on the mechanism of transition metal-catalyzed crosscoupling reaction, both from an experimental and computational viewpoint under the supervision of Prof. Per-Ola Norrby in Gothenburg University, Sweden (2012–2013).



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-phenyl-propiolamide 7.

Subsequently, Takemoto and co-workers found that N-protected N-(2-iodophenyl)propiolamides 9 in the presence of In/Py + HBr<sub>3</sub>/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 Inmediated reductive radical cyclization and Pd-catalyzed crosscoupling reaction.<sup>16</sup> 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.<sup>17</sup>

Alongside this, Player and co-workers presented a palladiumcatalyzed 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<sub>3</sub>)<sub>4</sub> (15 mol%), copper(1) 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 electronrich 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).<sup>18</sup>

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 Rhcatalyzed cascade reaction of *N*-(2-iodophenyl)propiolamides 13 and organozinc chlorides 14.

chlorides **14**. They showed that treatment of *N*-methylated *N*-(2iodophenyl)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).<sup>19</sup>

In 2011, Balalaie and co-workers developed the stereoselective synthesis of (*Z*)-3-(aminoarylmethylene)indolinones **22** 



Scheme 5 Proposed mechanism for formation of 17.

*via* a tandem palladium-catalyzed carbopalladative cyclization-Buchwald reaction of Ugi-adducts **20** with amines **21**. Thus, in the presence of  $Pd(OAc)_2/P(2-furyl)_3/Cs_2CO_3$  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.



 $R^2$ = Ph, 4-Me-Ph, 4-<sup>t</sup>Bu-Ph, 4-Cl-Ph, 4-CF<sub>3</sub>-Ph, 4-NO<sub>2</sub>-Ph, 2-pyridine

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**, 2iodoaniline **17**, phenylpropiolicacid **18**, and isocyanides **19**, were treated with secondary amines **21** to give (*Z*)-3-(aminoarylmethylene)indolinones **22** in good to high yields (Scheme 6).<sup>20</sup> 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)<sub>2</sub>



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.

as catalyst and PPh<sub>3</sub> as ligand under N<sub>2</sub> atmosphere. The reaction was run in refluxing toluene and leads to (*E*)-3-((1,3,4oxadiazol-2-yl)(aryl)methylene)indolinones **27** through an intermolecular domino carbopalladative cyclization/C–H functionalization sequence of an *N*-propiolamide **25** and an 1,3,4oxadiazole **26**.<sup>21</sup> These results indicated that the nature of ligands have a great impact on the stereoselectivity of products.

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-(2bromophenyl)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<sub>3</sub>)<sub>4</sub>/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<sub>3</sub>)<sub>4</sub>/PPh<sub>3</sub>/CuI/NaOAc/Ag<sub>3</sub>PO<sub>4</sub> as catalytic system.<sup>24</sup>

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<sub>3</sub> 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).<sup>25</sup>

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)<sub>2</sub>/PPh<sub>3</sub>/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.<sup>26</sup> 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.<sup>27</sup>

# 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.

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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).<sup>28</sup> 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)



R<sup>1</sup>= Me, Bn, Ac R<sup>2</sup>= H, 4-OMe, 4-F, 3-Cl, 2-Me, (2-Cl, 4-F)

R<sup>3</sup>= Ph, 4-Me-Ph, 4-OMe-Ph, 4-Ac-Ph, 3-CF<sub>3</sub>-Ph, 2-furyl, (CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>

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



 $R^{1}$ = 4-Cl-Ph, 4-CF<sub>3</sub>-Ph,4-CN-Ph, 3-NO<sub>2</sub>-Ph, 2-pyridine, 3-pyridine, 2-thienyl  $R^{2}$ = <sup>*t*</sup>Bu, <sup>*c*</sup>Hex

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

indolinones 44 through a domino Sonogashira/carbopalladation/C-H activation/C-C bond-forming sequence (Scheme 13).<sup>29</sup>

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)<sub>2</sub>/Et<sub>3</sub>N/THF/MeCN (1:4) was found to be superior. However, N-H free and terminal propiolamides failed to participate in this reaction.<sup>30</sup> 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)<sub>2</sub>/CuI/N,N'-dimethylethane-1,2-diamine/K<sub>2</sub>CO<sub>3</sub>/ DMF/MeCN (1:1.4) system and satisfactory results were obtained.<sup>31</sup> 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)<sub>2</sub>/PPh<sub>3</sub>/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, Nphenylpropiolamides 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)<sub>2</sub> and over-stoichiometric amounts of PdI(OAc)<sub>2</sub> 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.<sup>34</sup> 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.<sup>35</sup>

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)<sub>2</sub> 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%).<sup>36</sup> Later, Balalaie and co-workers reinvestigated this reaction using Pd(OAc)<sub>2</sub>/K<sub>2</sub>CO<sub>3</sub> 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(1H)-ylidene) indolinones **62**; (b) synthesis of 3-[5H-dibenzo[b,e]azepin-11(6H)-ylidene]indolinones**64**via intramolecular annulation of <math>3-[2-(2-iodobenzy-lamino)aryl]-N-arylpropiolamides **63**; (c) synthesis of (*E*)-bisindolinones **66** in via intramolecular double annulation of  $N^1, N^4$ -diphenylbut-2-ynediamides **65**.



temperature and provided corresponding (*Z*)-3-(arylmethylene)indolinones **58** in good to high yields (Scheme 18).<sup>37</sup>

Recently, Qian and Zhang demonstrated an elegant goldcatalyzed 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.<sup>38</sup>

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(1H)-ylidene)indolinones 62 (Scheme 20a). Among the various catalysts and oxidants examined, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and Cu(OAc)<sub>2</sub>/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-[5H-dibenzo[b,e]azepin-11(6H)-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)<sub>2</sub>/PPh<sub>3</sub>/NaOAc was used as the catalytic system.<sup>40</sup> 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 3methyleneindolinone-based natural products in the near future.

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