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3-Alkenyl-oxindoles: Natural Products, Pharmaceuticals, and Recent Synthetic Advances in Tandem/Telescoped Approaches

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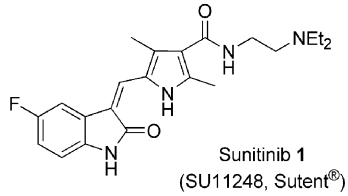
The structures and biological activities of naturally occurring 3-alkenyl-oxindoles are reviewed. Important man-made 3-alkenyl-oxindoles are covered, particularly those with pharmaceutical applications such as sunitinib (SU11248), the orally active receptor tyrosine kinase inhibitor marketed by Pfizer as Sutent®. Traditional synthetic approaches to 3-alkenyl-oxindoles are summarised and then recently developed tandem/telescoped synthetic routes are described.

1. Introduction

3-Alkenyl-oxindoles are at the heart of a range of medicinally and biologically important compounds, as well as a number of natural products. However, to the best of our knowledge, these compounds have not been reviewed (although there are recent reviews on oxindoles[1] and on 3,3-spirocyclic oxindoles[2]). A Beilstein database search on the 3-alkenyl-oxindole sub-structure, with free sites at every variable position, gives over 3900 hits, many of which exhibit potent biological activities, such as anticancer, antibacterial, antifungal, antiviral and antiangiogenic properties. Of particular significance is sunitinib (SU11248, **1**),[3] the orally active receptor tyrosine kinase (RTK) inhibitor marketed by Pfizer as Sutent®. Sunitinib (**1**) was approved by the FDA in 2006 for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumours, and was reported by the in-pharma technologist website to have generated $847m in global sales in 2008 alone.[4]



Sunitinib **1**
(SU11248, Sutent®)

This review summarises the structures of 3-alkenyl-oxindole natural products and pharmaceutical drugs/lead compounds, as well as their biological activities. Traditional synthetic approaches to 3-alkenyl-oxindoles are then reviewed together with novel approaches, including those from our own laboratory, reported more recently.

2. 3-Alkenyl-oxindoles Isolated from Natural Sources

Despite the large number of 3-alkenyl-oxindoles reported, a Beilstein database search limited to structures iso-

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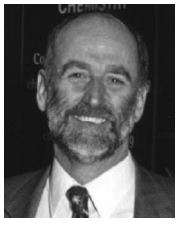
Alessia Millemaggi conducted her undergraduate studies at the University of Bologna, where she received her laurea in 2004. She stayed at the University of Bologna to join the research group of Dr. Mauro Panunzio, working on the synthesis of 1,3-aminols via hetero Diels–Alder reactions. In 2006, she joined DSM Research, Geleen, The Netherlands, working on the resolution of enantiomeric mixtures by preferential crystallisation. She is currently undertaking her Ph.D. within the group of Professor Richard Taylor at the University of York, working on the development of tandem reactions and their application in natural product synthesis.



Richard Taylor obtained B.Sc. and Ph.D. (Dr. D. Neville Jones) from the University of Sheffield. Postdoctoral periods with Dr. Ian Harrison and Professor Franz Sondheimer were followed by lectureships at the Open University and then UEA, Norwich. In 1993 he moved to the Chair of Organic Chemistry at the University of York. Taylor's research interests centre on the synthesis of bioactive natural products and the development of new synthetic methodology. His awards include the Royal Society of Chemistry's Pedler Lectureship (2007). Taylor is the current President of the International Society of Heterocyclic Chemistry, a past-President of the RSC Organic Division and an Editor of Tetrahedron.

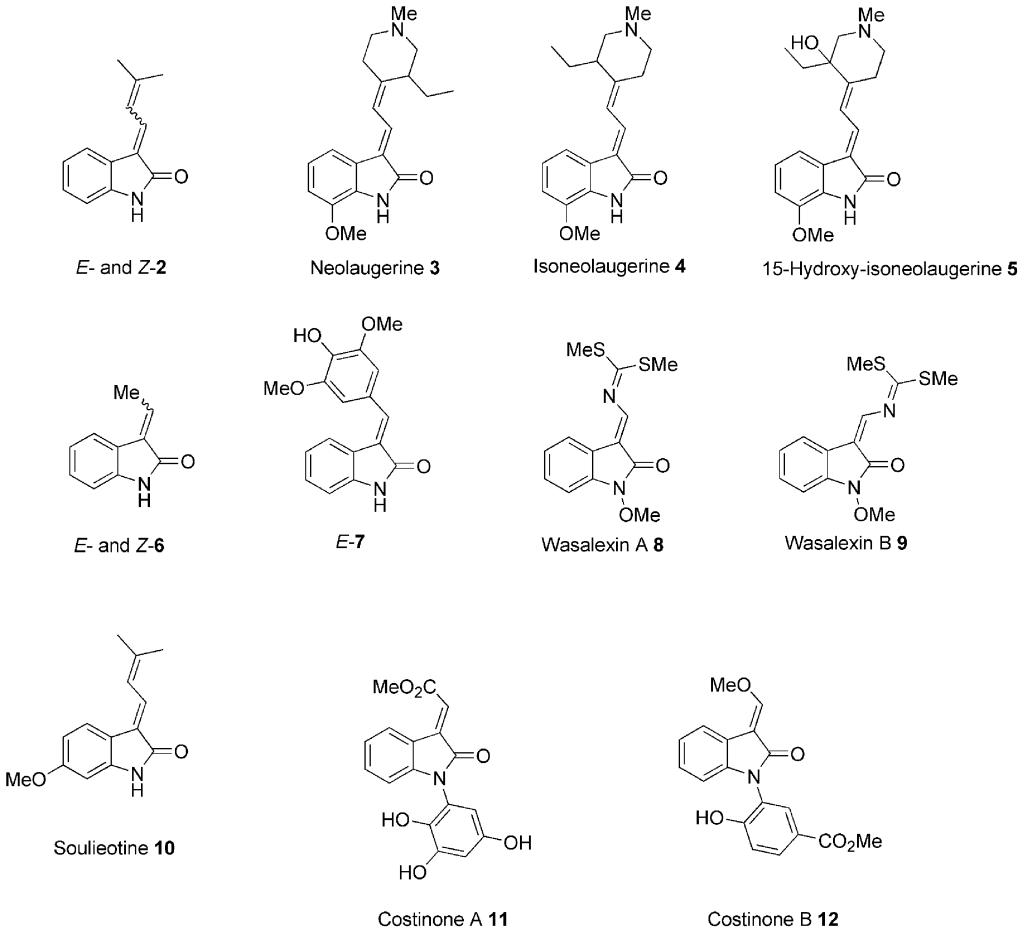


Figure 1. Natural products containing the 3-alkenyl-oxindole core with a trisubstituted 3-alkene.

lated from natural sources produced only 13 compounds with a trisubstituted 3-alkenyl unit (Figure 1, **2**–**12**). The first naturally occurring 3-alkenyl-oxindoles to be isolated were (*E*)- and (*Z*)-3-(3′-methyl-2′-butenylidene)-2-indolinones of type **2**. These two yellow pigments were isolated in 1978 from the rhizomes of *Cimicifuga dahurica*, a plant used in the Chinese traditional medicine "Bei Sheng Ma", and particularly known for its antipyretic properties.[5] However, it should be noted that the complete structure elucidation of compounds **2** was only reported in 1981 by the same authors.[6]

In 1993, three new oxindole alkaloids neolaugerine (**3**), isoneolaugerine (**4**), and 15-hydroxy-isoneolaugerine (**5**) (stereochemistries not fully elucidated) were isolated from the root bark of *Neolaugeria resinosa*, a small evergreen tree distributed throughout the Bahamas and West Indies.[7]

The very simple (*E*)- and (*Z*)-3-ethylidene-1,3-dihydroindol-2-ones **6** were isolated from the fungus *Colletotrichum fragariae* in 1996 and have been described as self-germination inhibitors.[8] The oxindole alkaloid *E*-**7** was isolated in 1997 from the roots of *Isatis indigotica*, a constituent of the widely used traditional Chinese medicine "Ban-Lan-Gen", mainly used for its antipyretic, antiviral and detoxifying properties.[9] In 1999, two phytoalexins, wasalexin A (**8**) and wasalexin B (**9**), were isolated from the foliar tissue of wasabi (*Wasabia japonica*, syn. *Eutrema wasabi*) and wasalexin A (**8**) exhibited antifungal activity against *Phoma lingam*.[10,11] The C-3′ nitrogen substituent and the *N*-methoxy-oxindole functionality are noteworthy in these examples.

Soulieotine (**10**) was reported in 2005, isolated from the rhizomes of *Souliea vaginata*, a plant employed as an anti-inflammatory analgesic in traditional Chinese medicine.[12] In 2006, costinone A (**11**) and costinone B (**12**) were isolated from the Pakistani herb *Isatis costata* and found to inhibit lipoxygenases and butylcholinesterases.[13] The *N*-aryl substitution in these compounds is of note, as is the presence of the 3′-oxygen substituent in costinone B.

Extending the structure search to include naturally occurring 3-alkenyl-oxindoles with a tetrasubstituted 3-alkenyl unit produced the compounds shown in Figure 2. The simplest examples (no additional rings) are the isatinones A and B (**13** and **14**), two new antifungal oxindole alkaloids that were isolated from the herb *Isatis costata* in 2007 (stereochemistry not defined in alcohol side chain).[14] The presence of the 3′-oxygen substituent in the isatinones is noteworthy (see costinone B, **12**).

There are a reasonable number (six) of 3-alkenyl-oxindole natural products in which the 3-alkenyl substituents are part of an additional ring (Figure 2, **15**–**20**). The purple

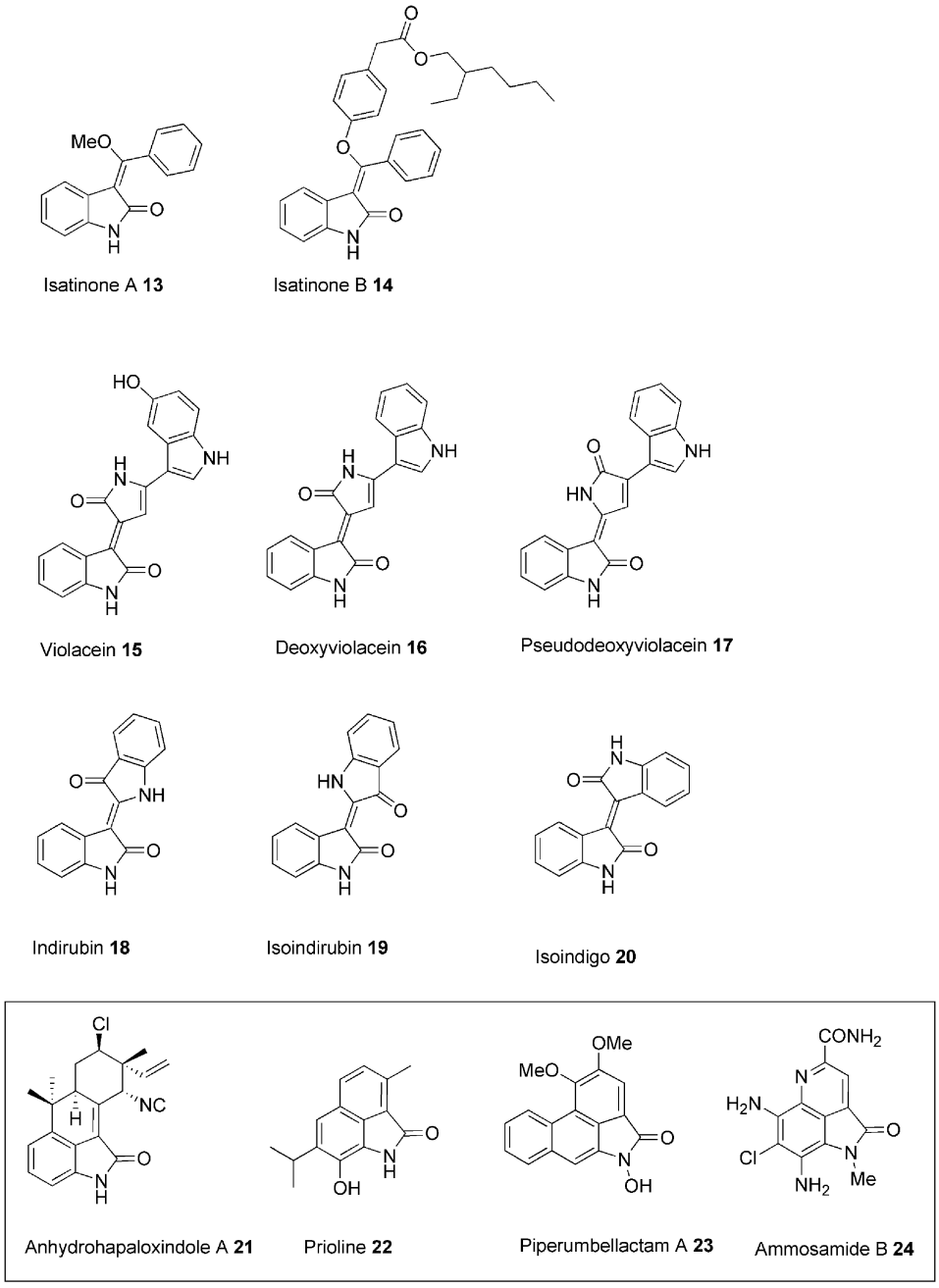


Figure 2. Natural products containing the 3-alkenyl-oxindole core with a tetrasubstituted 3-alkene.

pigment, violacein (**15**) was first isolated in 1934[15,16] from the Amazonian bacteria *Chromobacterium violaceum* and has been reported to possess multiple biological activities, including in vitro antitumour effects.[17] The parent compound deoxyviolacein (**16**) was isolated from the same source in 1958[18] and pseudodeoxyviolacein (**17**) was isolated from *Chromobacterium violaceum* in 1994.[19] Biosynthetic studies concerning violacein (**15**) and deoxyviolacein (**16**) have identified related 3-alkenyl-oxindoles as possible intermediates.[20] Indirubin (**18**) was first isolated from human blood plasma, urine and haemofiltrate of uraemic patients in 1986,[21] while its isomer isoindirubin (**19**) was isolated together with isoindigo (**20**) from the leaves of woad (*Isatis tinctoria*) in 2001.[22]

Although a comprehensive listing will not be provided here, it should be noted that a number of polycyclic compounds are known which contain the 3-alkenyl-oxindole moiety. Four examples, **21**–**24**, are shown in Figure 2 to illustrate these structural types. The only examples not involving additional aromatic rings are the anhydrohapaloxindoles (e.g., anhydrohapaloxindole A, **21**) which were isolated as minor alkaloids from a cultured strain of the terrestrial blue-green alga *Hapalosiphon fontinalis* in 1987.[23] Prioline (**22**), a novel alkaloid isolated in 2000 from *Salvia prionitis* Hance (Labiatae), a herbaceous plant employed in Chinese folk medicine for the treatment of tonsillitis, pharyngitis, pulmonary tuberculosis and bacillary dysentery, nicely illustrates a 3-alkenyl-oxindole in which the alkenyl

portion is incorporated into a phenyl ring.[24] A large family of aristolactams are known and the recently reported piperumbellactam A (**23**) isolated from *Piper umbellatum* is representative of these polycyclic aromatic analogues.[25] *Piper umbellatum* is a widely used herb in Cameroon traditional medicine for the treatment of poisoning, general pains and rheumatism and the piperumbellactams exhibited antioxidant, antifungal and glucosidase inhibitory properties.[25] Finally, ammosamide B (**24**) is a more complex 3-alkenyl-oxindole in which the additional ring is heterocyclic; **24** was recently isolated from the marine-derived *Streptomyces* strain CNR-698[26] and has been shown to possess cell cycle modulation properties via myosin inhibition.[27]

3. 3-Alkenyl-oxindoles in the Pharmaceutical Industry

The wide range of biological activities displayed by 3-alkenyl-oxindoles has stimulated considerable pharmaceutical interest. As mentioned earlier, the most successful example is the anticancer drug Sutent® (sunitinib, SU11248, **1**), which was discovered by Sugen and then developed and marketed by Pfizer. Sutent® is currently prescribed for the treatment of renal cell carcinoma and gastrointestinal stromal tumours and is undergoing clinical trial studies for the treatment of other solid tumours.[4] Sutent® is an orally active tyrosine kinase inhibitor and was the first cancer

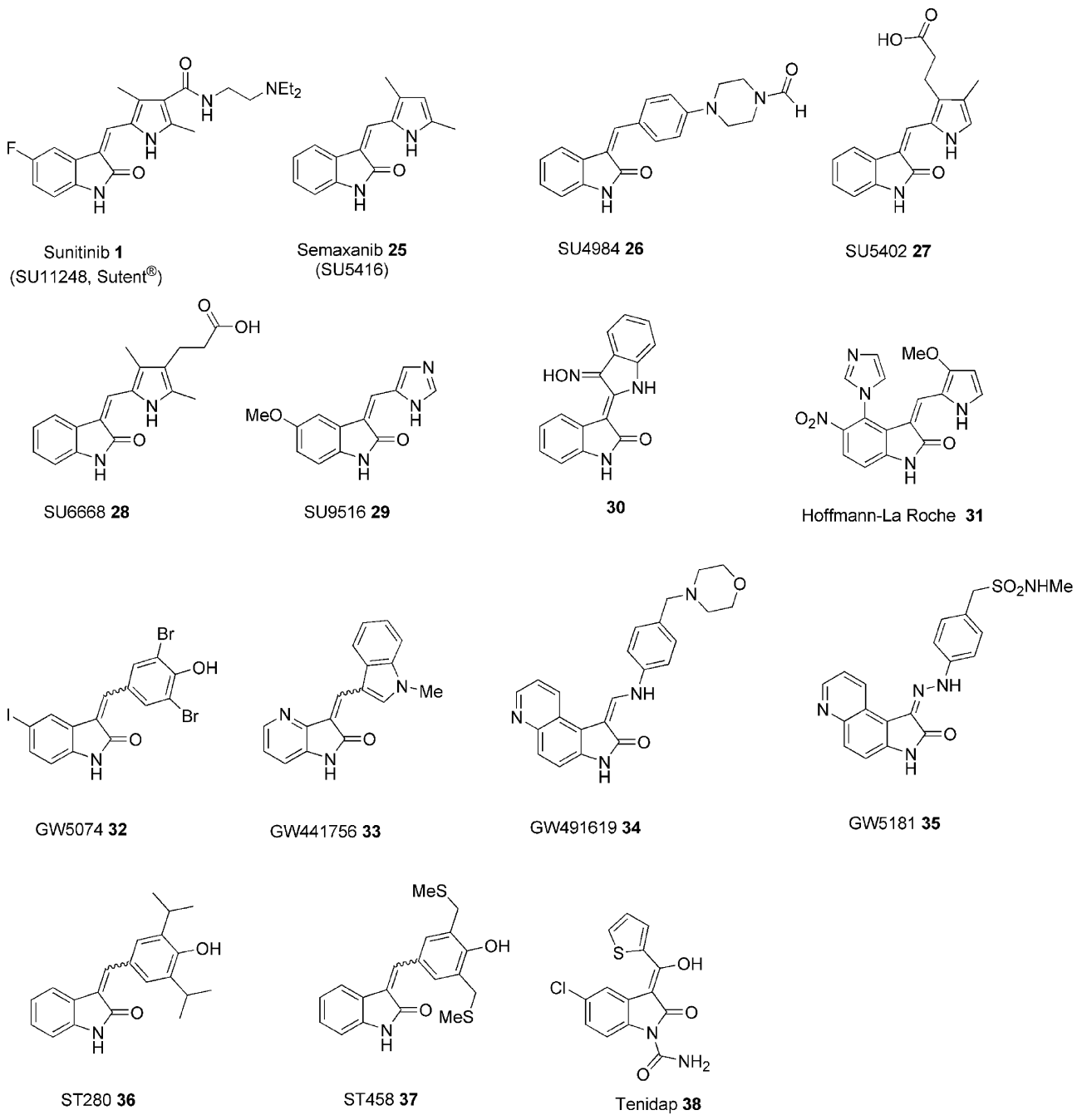


Figure 3. Pharmaceutically active 3-alkenyl-oxindoles.

drug to be simultaneously approved for two different indications. A number of related Sugent compounds deserve mention (Figure 3). Semaxanib (SU5416, **25**) is a related anticancer, antiangiogenic compound which succeeded as far as phase III clinical trials for colo-rectal cancer.[28] The mode of action of semaxanib, and of the related analogues SU4984 (**26**), SU5402 (**27**), SU6668 (**28**) and SU9516 (**29**), together with indirubin derivatives (e.g., the 3′-monoxime **30**), has been recently reviewed by Cerchiaro and Ferreira.[1]

As might be expected given the success of Sutent®, many related 3-alkenyl-oxindoles have been reported by other pharmaceutical companies, and two recent reviews[29] and a book[30] on cyclin-dependent kinase inhibitors have been published. Representative examples include the Hoffmann-La Roche oxindole derivative **31**,[31] the GlaxoSmithKline's 3-benzylideneindolinones such as GW5074 (**32**),[32] and the aza-oxindole GW441756 (**33**), a potent and highly selective, orally active tyrosine kinase A inhibitor.[32] In addition, 3-(arylaminomethylenyl)indolinones such as GW491619 (**34**),[33,34] and GW5181 (**35**)[29,30] have also been identified as potent kinase inhibitors.

The Kanegafuchi Chem. Ind. Co. reported the signal inhibitory properties of substituted 3-alkenyl-oxindoles such as ST280 (**36**) and ST458 (**37**).[35] Finally, mention must be made of tenidap (**38**), a potent cyclooxygenase inhibitor, developed by Pfizer for the treatment of rheumatoid arthritis and osteo-arthritis.[36–38] Despite the high expectations, it was not launched because of concerns about reduced bone mineral density.[38]

4. Classic Synthetic Routes to 3-Alkenyl-oxindoles

Due to their wide-ranging biological activities, a large number of synthetic approaches to 3-alkenyl-oxindoles have been reported in the literature. A Beilstein data-base search with 3-alkenyl-oxindoles as reaction products gave over 7000 hits in 2010, many of which have been reported in recent years. Given the constraints of space, a comprehensive review of 3-alkenyl-oxindole syntheses is therefore impossible. Instead, a brief overview of classic approaches to 3-alkenyl-oxindoles is given in this section, and more recent tandem and telescoped approaches will be covered in Section 5. The two most common approaches start from a preformed oxindole system, as illustrated in Figure 4, and they will be summarised in turn.

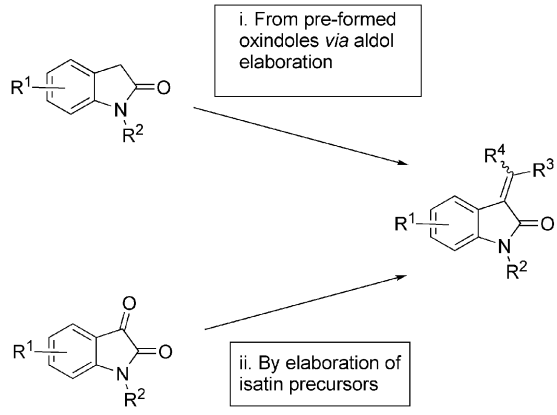
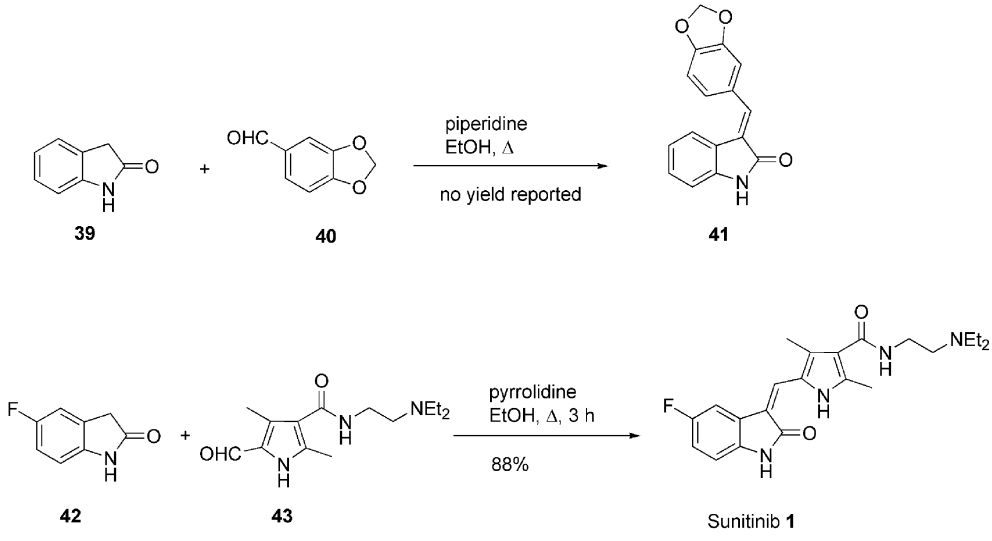


Figure 4. Classic approaches to 3-alkenyl-oxindoles.

4.1 Synthesis of 3-Alkenyl-oxindoles from Preformed 3-Unsubstituted Oxindoles via Aldol Condensation

The most often-used procedure involves the condensation of unsubstituted oxindoles with carbonyl compounds, and a Beilstein data-base search on this type of synthetic disconnection gives over 1500 results. To the best of our knowledge, this process was first reported by Wahl and Bayard in 1909 to prepare (3*E*)-3-(1,3-benzodioxol-5-ylmethylidene)-1,3-dihydro-2*H*-indol-2-one (**41**) via condensation of oxindole **39** with 1,3-benzodioxole-5-carbaldehyde (**40**) (Scheme 1).[39] In this example, only the *E*-isomer was obtained, presumably due to the steric bulk of the aryl group.

The simplicity of this aldol approach has resulted in it being widely adopted. Many of the 3-alkenyl-oxindole drug candidates have been prepared in this way. For example,



Scheme 1.

as disclosed in US patent 657329, sunitinib (Sutent®, **1**) is prepared by the condensation of the oxindole **42** with the pyrrolecarbaldehyde **43** (Scheme 1).[40] Sunitinib (**1**) is isolated exclusively as the *Z*-isomer with intramolecular H-bonding presumably being responsible for the high stereoselectivity.

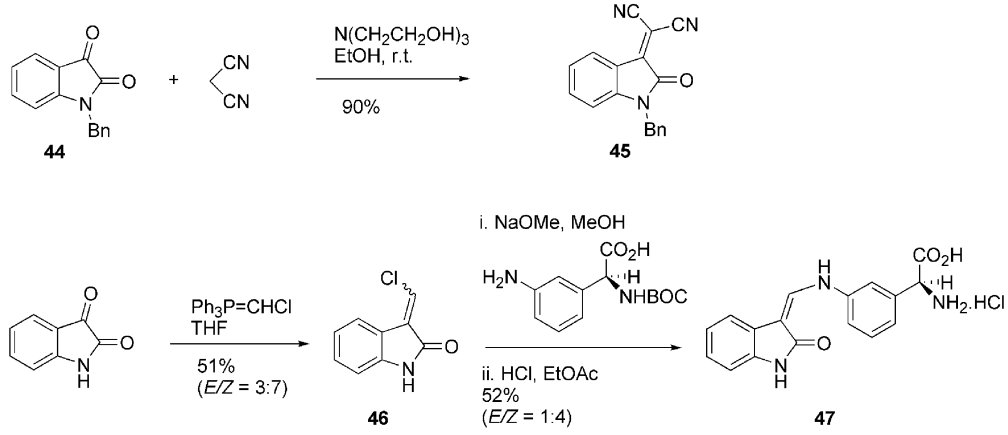
Despite the stereoselective nature of the two examples shown in Scheme 1, it should be noted that the aldol approach often produces 3-alkenyl-oxindoles as *E*/*Z*-mixtures.[41]

4.2 Synthesis of 3-Alkenyl-oxindoles by Elaboration of Isatin Precursors

Isatin (1*H*-indole-2,3-dione) and its derivatives are readily available and undergo enolate-type condensation regioselectively at C-3. The earliest use of such a condensation to prepare 3-alkenyl-oxindoles would seem to be the report by Walter in 1902 and utilised unprotected isatin and malononitrile.[42] Since this seminal publication, a Beilstein data-base search gives well over 500 results for the isatin to 3-alkenyl-oxindole transformation. A recent example using *N*-benzylisatin (**44**) for the preparation of the malononitrile adduct **45** is shown in Scheme 2,[43] as is a Wittig route from isatin to the 3-chloro-alkenyl-oxindole **46** and 3-amino-alkenyl-oxindoles such as **47**.[44]

5. Tandem/Telescoped Synthetic Routes to 3-Alkenyl-oxindoles

In recent years, the growing importance of 3-alkenyl-oxindoles has resulted in the design of a large number of new synthetic approaches, too many to be covered comprehensively. In this section, we have concentrated on one-pot preparations of 3-alkenyl-oxindoles in which the heterocyclic portion of the oxindole unit is formed as part of the synthetic process; such reactions can be classified as tandem (all reagents added at the outset) or telescoped (sequential addition of reagents). Even within this sub-section of synthetic approaches, we have not been able to provide compre-



Scheme 2.

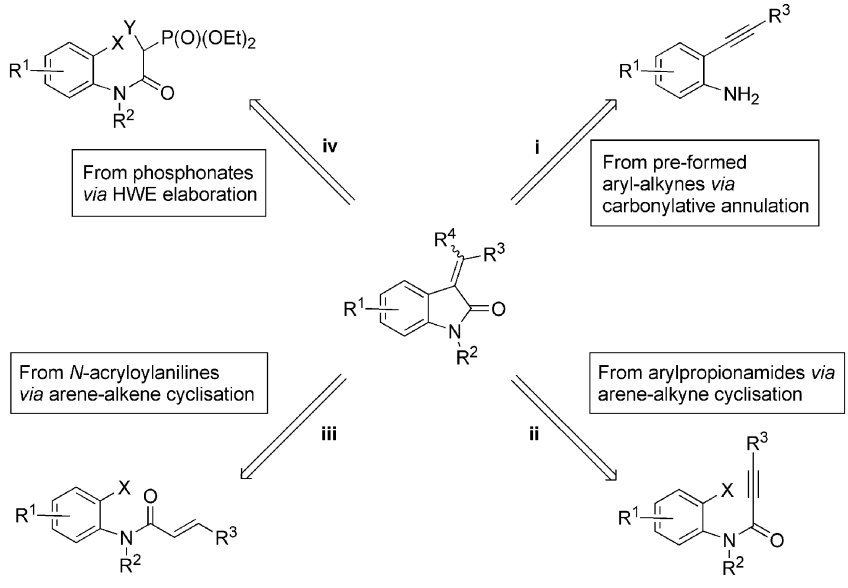
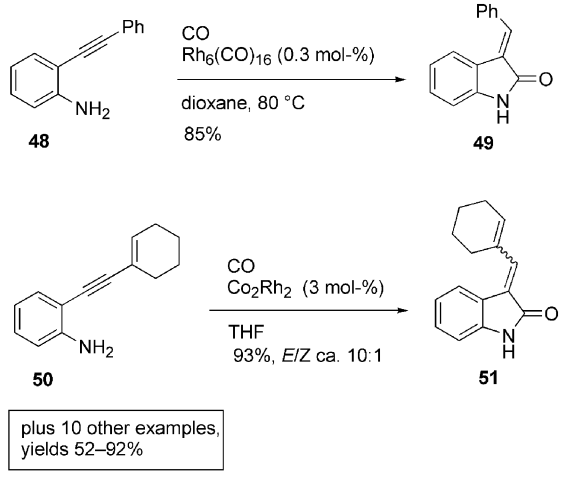


Figure 5. Tandem/telescoped approaches to 3-alkenyl-oxindoles.

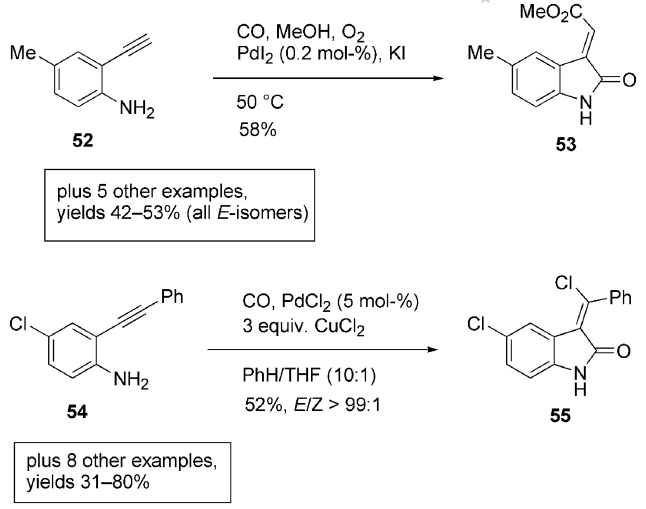
hensive coverage (and we apologise to the authors of papers we have not been able to include). We should also note that the page limitations of this Microreview mean that the mechanistic discussion has been curtailed; readers are referred to the original papers for more details. Adapting the classification proposed by Dai et al.,[45] the tandem/telescoped synthetic approaches used for the construction of the 3-alkenyl-oxindole motif have been collected into 4 main groups (Figure 5).

5.1 Synthesis of 3-Alkenyl-oxindoles from Pre-formed Arylalkynes via Carbonylative Annulation

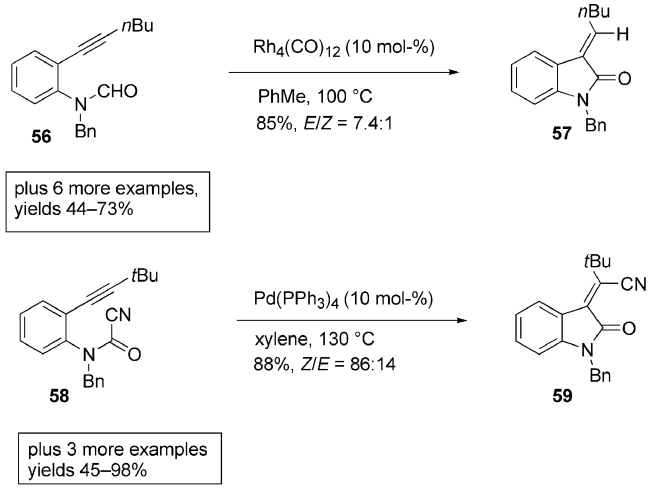
A number of groups have recently utilised the metal-catalysed carbonylative annulation of alkynyl-arylamines to prepare 3-alkenyl-oxindoles. One of the earliest examples of this process (Scheme 3, **48**→**49**) used a rhodium carbonyl catalyst[46] and this procedure has recently been generalised using a modified heterobimetallic cobalt/rhodium nanoparticulate catalyst (e.g., **50**→**51**).[47]



Scheme 3.



Scheme 4.



Scheme 5.

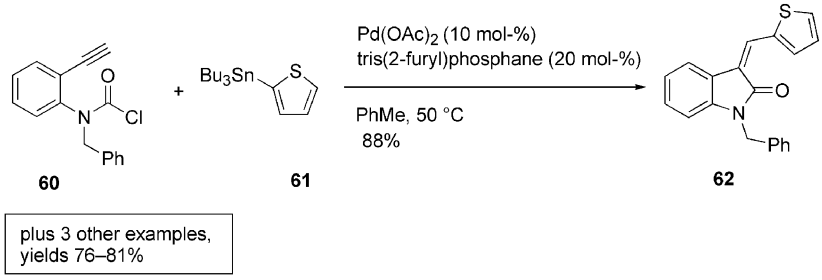
Subsequently, palladium-catalysed carbonylation approaches were developed for use in 3-alkenyl-oxindole synthesis (Scheme 4). Gabriele, Salerno and co-workers first prepared (methoxycarbonyl)methylene analogues such as **53** via an *E*-selective, double carbonylation process,[48] and in 2007, Li and co-workers developed a stereoselective palladium-catalysed carbonylative annulation of alkynyl-arylamines for the synthesis of vinyl chlorides **55** (Scheme 4).[49]

More recently, *N*-formyl, *N*-carboxyl and related analogues have been employed as starting materials to remove the need to use carbon monoxide. The Takemoto group has developed a rhodium-catalysed cyclisation of *N*-formyl anilides such as **56** to give the corresponding 3-alkenyl-oxindoles such as **57** in good yields as a mixture of *E*/*Z* isomers (Scheme 5).[50] In a similar vein, the palladium-catalysed intramolecular cyanoamidation of alkynyl-cyanoformamides **58** generated nitrile-substituted 3-alkenyl-oxindoles such as **59**.[51]

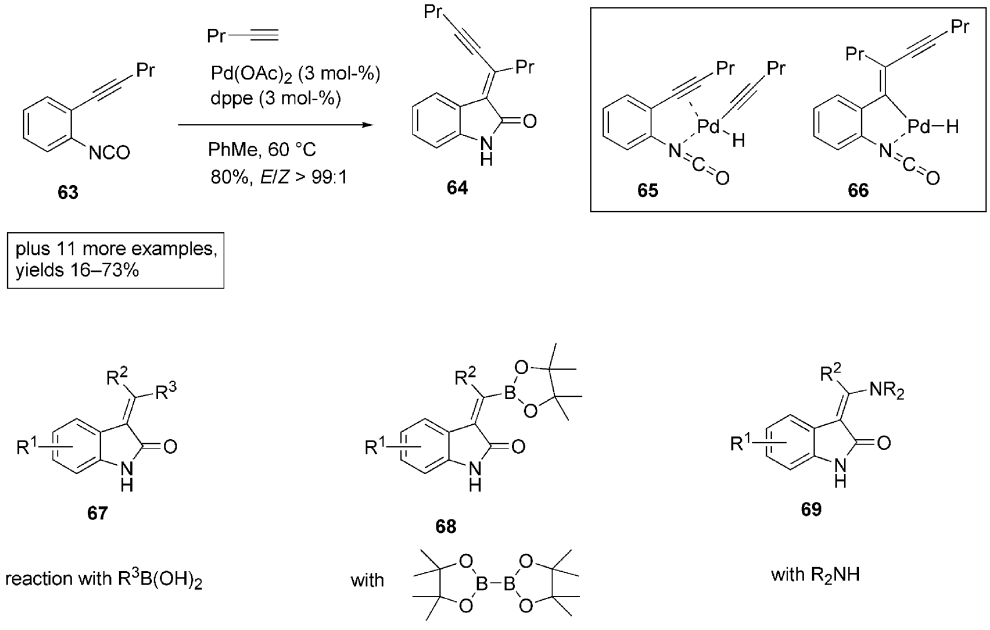
Grigg's group has pioneered the area of palladium-catalysed cyclisation-anion capture and a Stille coupling sequence, devised to convert carbamoyl chlorides such as **60** into oxindoles such as **62**, as illustrated in Scheme 6.[52]

More recently, Kamijo, Yamamoto, and co-workers developed a new approach to the synthesis of 3-enynyl-oxindoles **64** utilising the palladium-catalysed cyclisation of acetylenic aryl isocyanates **63** in the presence of terminal alkynes (Scheme 7).[53] The authors proposed that an "intramolecular nucleophilic vinylpalladation" mechanism was likely, proceeding by way of intermediates **65** and **66**, with alkene isomerisation occurring after oxindole formation.

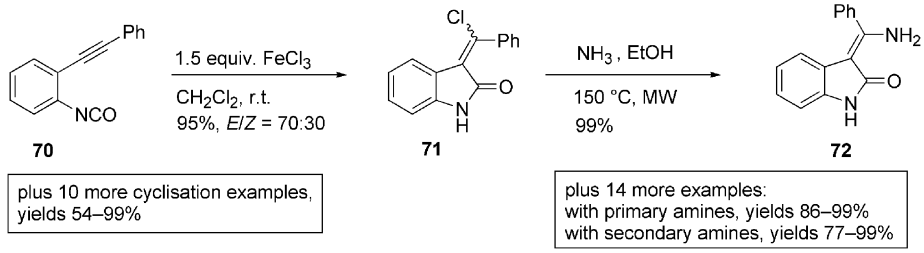
Subsequently, Murakami and co-workers exploited this isocyanate methodology to prepare a wide range of 3-alkenyloxindoles such as adducts **67** (trapping with boronic acids),[54] novel pinacolborane derivatives **68** [trapping with bis(pinacolato)diboron][55] and enamine derivatives **69** (trapping with amines/amides).[56] In all cases, using either rhodium or palladium catalysis, cyclisation occurred in a stereoselective manner with the newly introduced substituent *syn* to the oxindole carbonyl group.



Scheme 6.



Scheme 7.



Scheme 8.

Recently, Meyer, Cossy, and co-workers have further enhanced the isocyanate methodology by introducing an iron(III) chloride variant (Scheme 8).[57] The authors propose that a cationic cyclisation occurs to generate 3-(arylchloromethylene)oxindoles such as **71** which could be converted into (*Z*)-3-(aminomethylene)oxindoles such as **72** upon treatment with amines under microwave (MW). In all cases, products **72** are obtained exclusively as the *Z*-stereoisomer.

Finally, it should be recognised that approach (i) discussed in this section requires the initial formation of the precursor alkynyl-arylamines (often by a Sonogashira-type approach). By contrast, the approaches discussed in sections 5.2–5.4 all incorporate the formation of the C3–C4 bond as part of the annulation sequence.

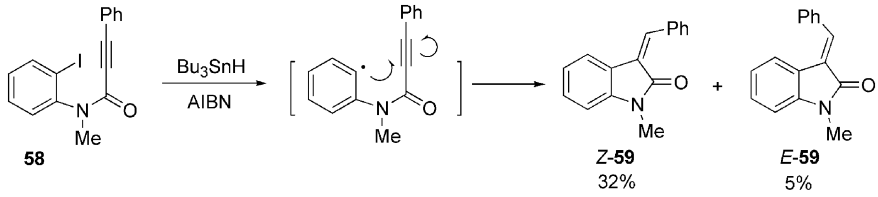
5.2 Synthesis of 3-Alkenyl-oxindoles from Arylpropionamides via Arene–Alkyne Cyclisation

(a) Halogenated Arylpropionamide Approaches

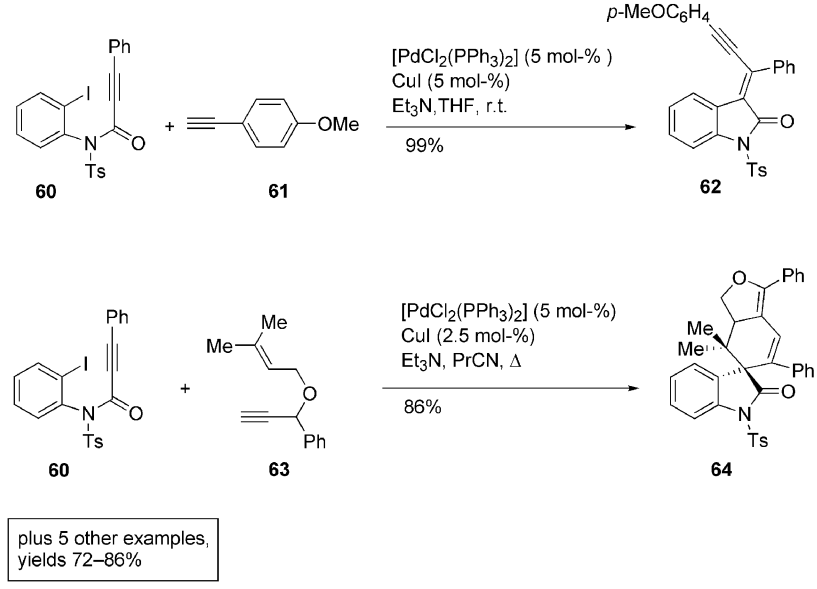
Halogenated arylpropionamides such as **58** are commonly employed for the synthesis of 3-alkenyl-oxindoles. One of the first approaches of this type, developed by Bow-

man, Heaney, and Jordan in 1988, involved tin hydride-AIBN initiated radical cyclisation (Scheme 9).[58] However, the cyclisation proceeded in low yield and gave an *E*/*Z*-mixture of 3-alkenyl-oxindoles **59**. Jones and Brunton subsequently expanded the scope of this reaction and proposed that the greater stability of the *Z*-vinyl radical intermediate is responsible for the observed *Z*-stereoselectivity.[59]

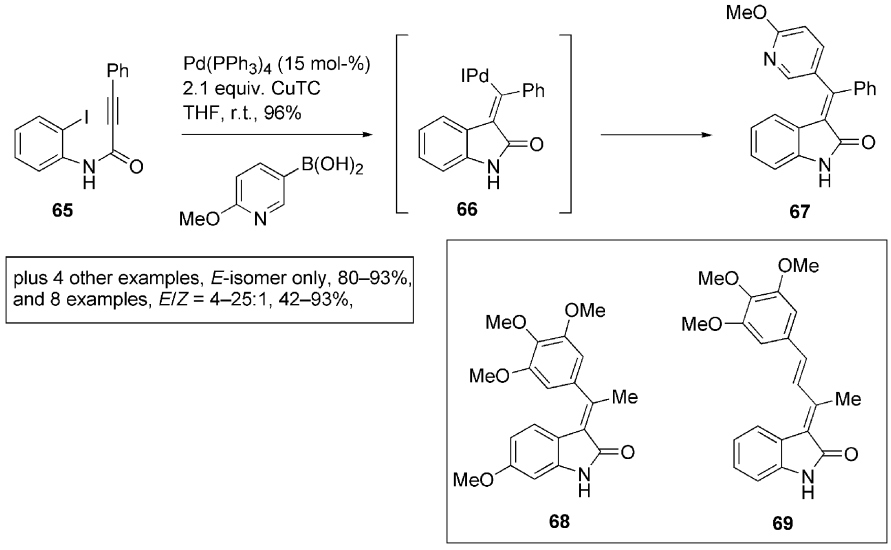
Much of the recent research in this area has involved palladium-catalysed cyclisation processes which allow much greater scope in terms of further elaboration. Possibly the first such example was reported by Müller's group in 2005 and utilised a tandem Heck carbocyclisation/Sonogashira cross-coupling approach for the stereoselective synthesis of 3-alkenyl-oxindole **62** (Scheme 10)[60]. Thus, treatment of *N*-(iodophenyl)alkynamide **60** and *p*-methoxyphenylacetylene (**61**) with catalytic $[PdCl_2(PPh_3)_2]$ and CuI gave product **62** in quantitative yield exclusively as the *E*-isomer in almost quantitative yield. Furthermore, by using the ω-alkenyl-



Scheme 9.



Scheme 10.



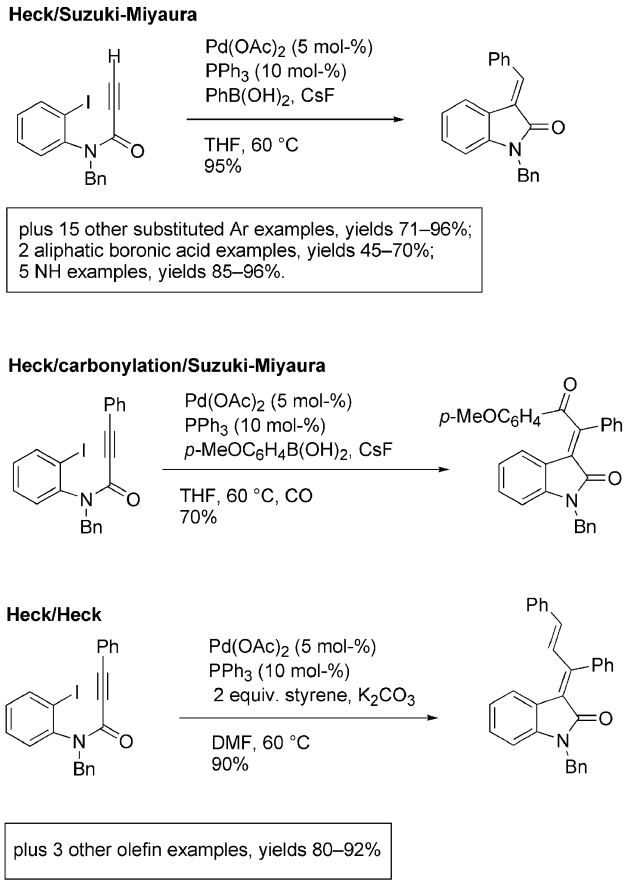
Scheme 11.

alkyne **63**, carbocyclisation/Sonogashira/Diels–Alder cascade sequence produced the spiro-oxindole **64** in excellent yield (Scheme 10).[60]

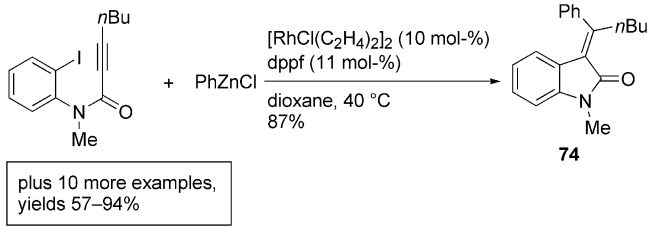
In 2005, Player and co-workers reported a tandem Heck/Suzuki–Miyaura coupling process for the synthesis of (*E*)-3,3-(diaryl)oxindoles **67** (Scheme 11).[61] Using catalytic tetrakis(triphenylphosphane)palladium(0) and copper(I) thiophene-2-carboxylate (CuTC), the tandem sequence proceeded in high yield and good to complete stereoselectivity via trapping of the *syn*-palladated intermediate **66** (Scheme 11). A related tandem Heck/Suzuki–Miyaura sequence was subsequently employed by Arthuis et al. to prepare novel constrained combretastatin A-4 analogues such as **68** and **69**.[62] As combrestatin A-4 is known for its ability to selectively target the vascular system of tumours, analogues such as **68** and **69**, are currently undergoing biological evaluation.[62]

Also in 2005, Takemoto and co-workers reported a palladium-catalysed Heck/Suzuki–Miyaura process and also introduced a carbonylative version, as well as a Heck/Heck sequence for the stereoselective synthesis of a range of 3-alkenyl-oxindoles (Scheme 12).[63]

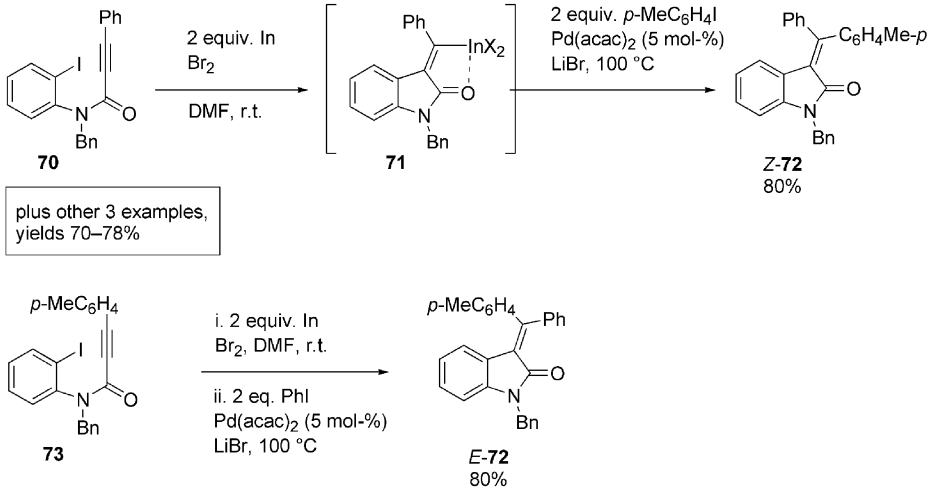
Takemoto and co-workers have also utilised *N*-arylpropionamides **70** in a tandem indium-mediated carbometallation/Pd-catalysed cross-coupling sequence for the stereoselective formation of 3-alkenyl-oxindoles **72** (Scheme 13). The key step was the formation of a vinyl-indium intermediate, **71**, which ensure complete stereocontrol due to the strong coordination of the indium cation to the amide carbonyl oxygen to the metal centre, ensured the complete stereocontrol observed in the process. Therefore, use of the phenylalkyne **70** and tolyl iodide as the trapping agent gave exclusively *Z*-**72** whereas with tolylalkyne **73** and iodobenzene, *E*-**72** was the only product.[64,65] In addition, a related Rh-catalysed organozinc coupling was reported by Shintani, Yamagami, and Hayashi in 2006 producing alkenyl-oxindoles **74** (Scheme 14).[66]



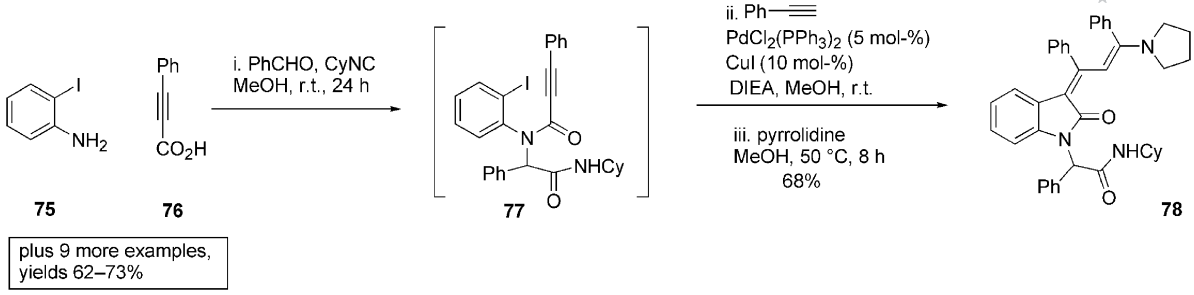
Scheme 12.



Scheme 14.

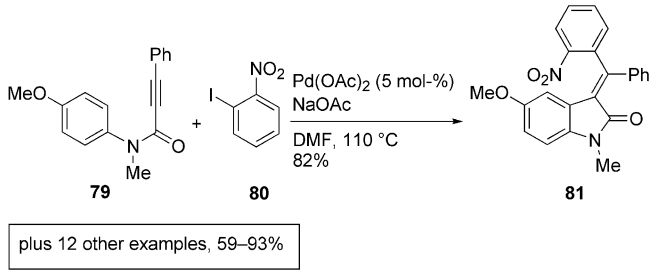


Scheme 13.



Scheme 15.

Finally in this part, in 2010 Balalaie and co-workers reported a sequential one-pot, six-component process for the preparation of 3-arylidene-oxindoles **78** (Scheme 15).[67] Their approach involved an initial Ugi four-component coupling to transform iodoaniline into arylpropionamides **77**. In situ addition of a palladium catalyst and phenylacetylene then promoted a tandem Heck carbocyclisation/Sonogashira sequence (see Scheme 10) and finally Michael-type addition of pyrrolidine generated the complex 3-methylene-oxindole **78** in reasonable yield and with complete *Z*-selectivity.

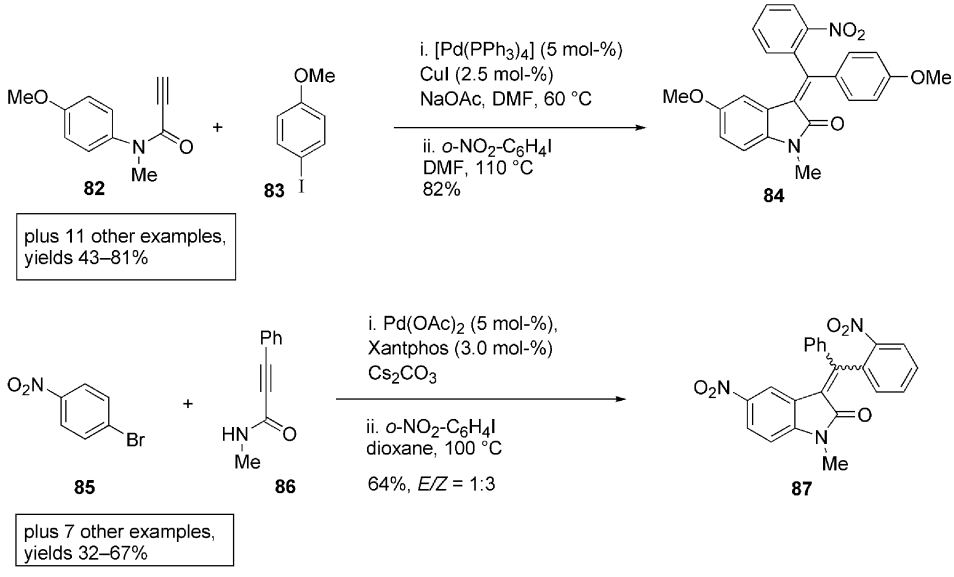


Scheme 16.

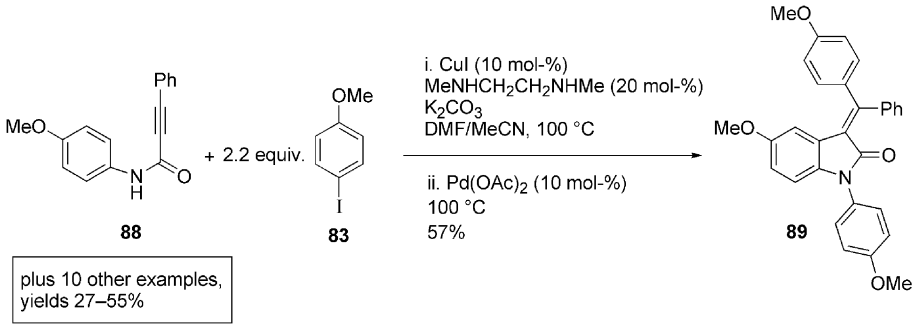
(b) Aryl C–H Activation Approaches

More recently, C–H activation has allowed for arylpropionamide cyclisation variants to be carried out without the need for an α-halogeno-anilide by utilising aryl C–H activation. For example, Zhu and co-workers developed an efficient tandem process for the conversion of amides such as **79** and aryl iodides **80** into unsymmetrically substituted 3-alkenyl-oxindoles **81** (Scheme 16).[68] The proposed mechanism involves an oxidative addition of Pd^0 into the aryl iodide followed by a regioselective *syn*-carbopalladation across the alkyne then aryl C–H activation adjacent to the amide substituent and a reductive elimination to construct the new C–C bond.

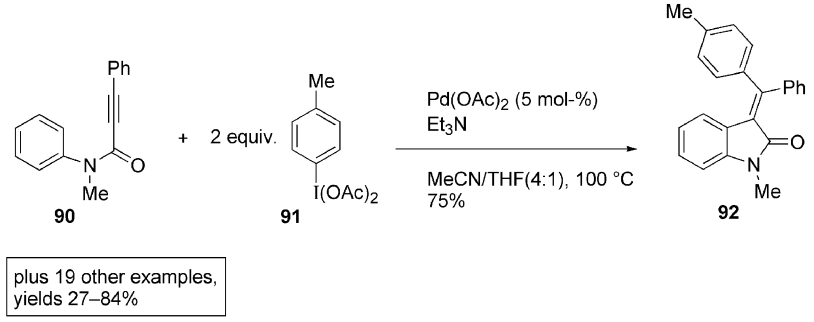
Subsequent to this report, Zhu's group developed two different three-component variants of the above methodology for the preparation of unsymmetrically substituted 3-(diarylmethylene)oxindoles (Scheme 17).[69,70] In the first example, a terminal alkyne **82** initially undergoes an in situ Sonogashira coupling with aryl iodide **83**, and upon addition of a second aryl iodide, the previously described carbopalladation/C–H activation sequence operates to generate alkenyl-oxindole **84** stereoselectively and in high yield.[69] In the second variant, palladium-catalysed *N*-arylation is carried out as the first step followed by the carbopalladation/cyclisation sequence.[70] Thus, aryl halide **85** and *N*-alkylpropriolamide **86**, followed by addition of *or-*



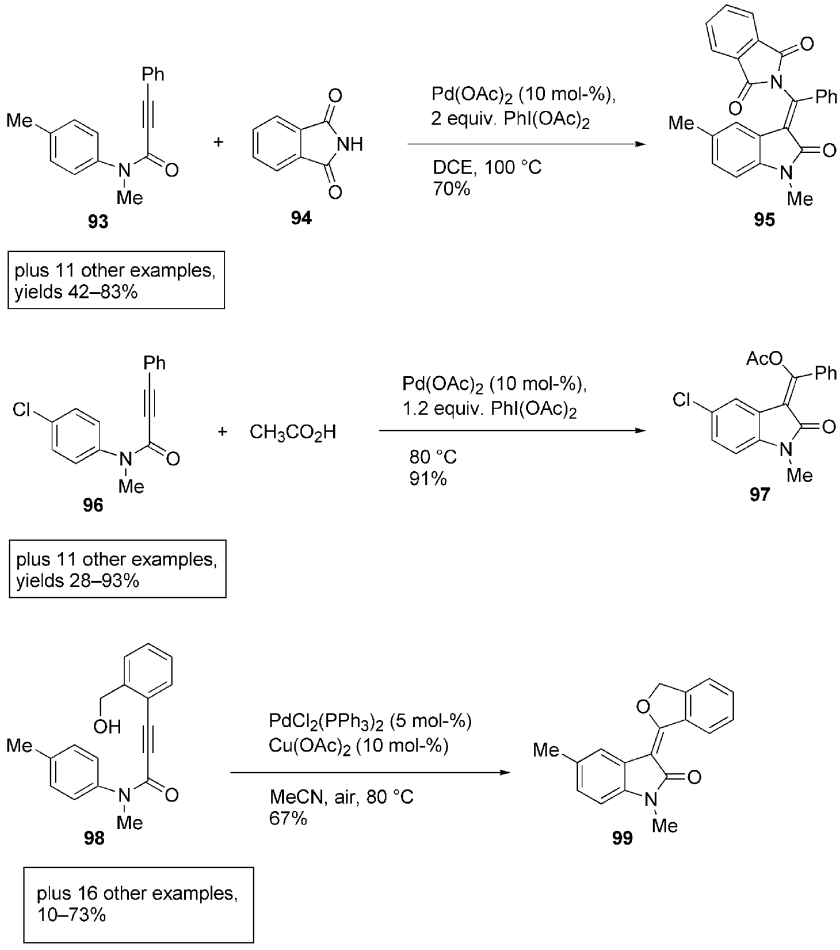
Scheme 17.



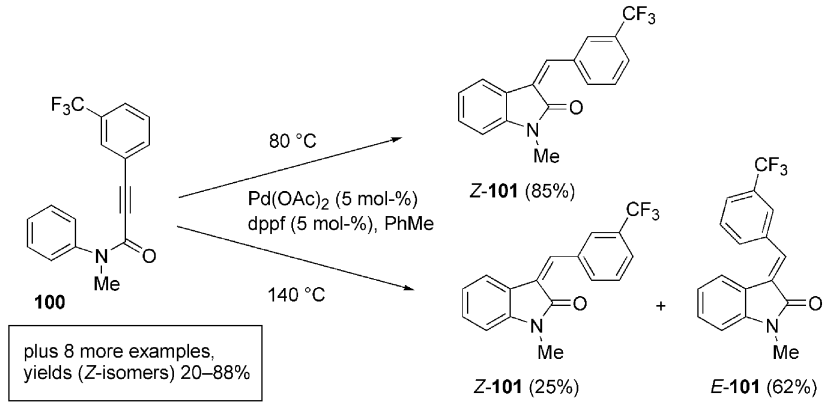
Scheme 18.



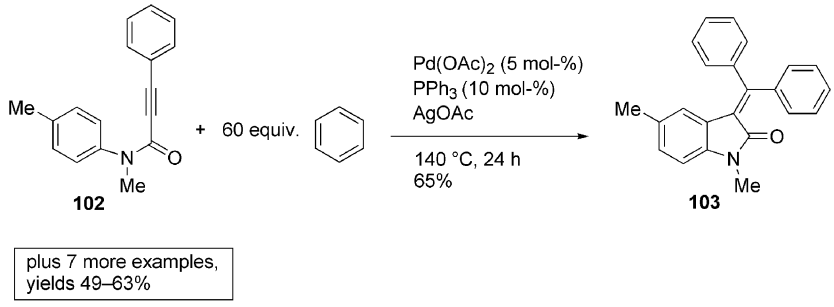
Scheme 19.



Scheme 20.



Scheme 21.



Scheme 22.

tho-nitro-iodobenzene, produce the tetrasubstituted 3-methylene-oxindole derivative **87** in reasonable yield and stereoselectivity. In this variant, it should be noted that an *E*/*Z*-mixture **87** is formed; the authors propose that the presence of the Xanthos ligand (used to facilitate *N*-arylation) slows down the C–H activation step allowing isomerisation of the intermediate vinyl-palladium species to occur.[70]

Li's group has reported a similar arylpropionamide three component cyclisation route to unsymmetrically substituted 3-alkenyl-oxindoles (Scheme 18). This one-pot process involves the copper-catalysed arylation of amide **88**, which is followed by a palladium-catalysed *syn*-carbopalladation/aryl C–H activation sequence to give 3-alkenyloxindole **89** in moderate yield.[71]

Li's group next developed a palladium-mediated C–H activation process in which the aryl-donor is provided by an aryliodonium salt (Scheme 19).[72] Thus, the arylpropionamide **90** and tolyliodonium salt **91** generate the 3-alkenyl-oxindole **92**. The authors suggest that, in the presence of triethylamine, the hypervalent iodine reagent is converted into the corresponding aryl iodide which then participates in the palladium-mediated cascade as described above.

Perhaps of greater utility, in 2008 Li and Wang showed that treatment of an arylpropionamide with phthalimide in the presence of a Pd^{II} catalyst and $PhI(OAc)_2$ (as an oxidant), generates amino-functionalised (*E*)-3-alkenyl-oxindoles such as **95** (Scheme 20).[73] In a similar manner, the use of carboxylic acids gives oxygen-functionalised (*E*)-3-alkenyl-oxindoles (e.g. **96**→**97**, Scheme 20).[74] Li and co-workers have also utilised this C–H activation methodology, but with air as the oxidant, to prepare (*E*)-3-[isobenzofuran-3(1*H*)-ylidene]indolin-2-ones such as **99** as potential tyrosine kinase inhibitors.[75]

In 2009, Li's group reported a stereoselective palladium-catalysed C–H activation cyclisation procedure for the conversion of arylpropionamides **100** into monosubstituted 3-methylene-oxindoles **101** (Scheme 21).[76] The stereoselectivity of the reaction is controlled by the temperature; at 80 °C the *Z*-isomers are formed with high or complete stereoselectivity, whereas at 140 °C, equilibration is observed producing a predominance of the thermodynamically preferred *E*-isomer.

Finally in this section, Li and co-workers have recently described a palladium-catalysed double C–H activation route to aryl phenyl-substituted 3-methylene-oxindoles **103** in which benzene provides a phenylpalladium(II) species which initiates the *syn*-carbopalladation/aryl C–H activation sequence (Scheme 22).[77] In the presence of pivalic acid, oxindole formation is suppressed and 3-aryl-quinolones are formed preferentially.[77]

5.3 Synthesis of 3-Alkenyl-oxindoles from *N*-Acryloyl Anilines via Arene–Alkene Cyclisation

(a) Halogenated N-Acryloylaniline Approaches

Following on from early work using nickel catalysis,[78] in 1979 Terpko and Heck[79] and Mori and Ban[80] independently described the palladium-catalysed preparation

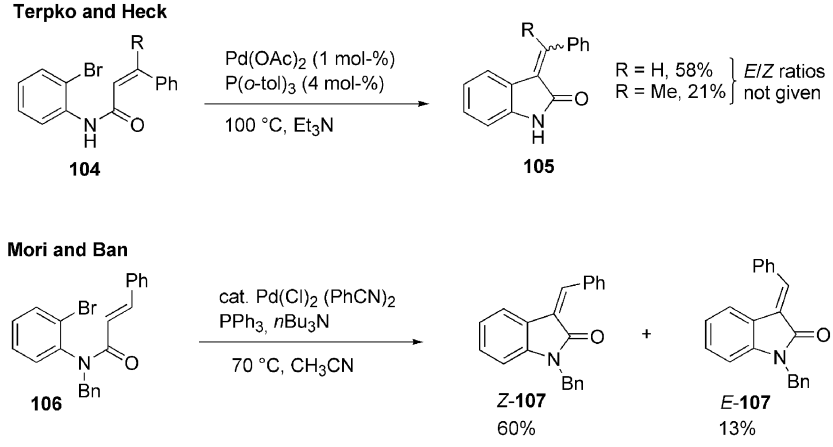
of 3-alkenyl-oxindoles from *N*-acryloyl-2-haloanilines (Scheme 23). Ever since then, the Heck approach has been a mainstay of 3-alkenyl-oxindole synthesis, and its utility for the preparation of highly complex spiro-oxindoles has been recently reviewed.[2a]

In terms of more recent developments in the Heck cyclisation approach to 3-alkenyl-oxindoles, Balasubramanian and co-workers developed a solid-phase synthesis of 3-alkenyl-oxindoles utilising the Heck cyclisation (Scheme 24).[81] Commencing with resin-bound *N*-acryloyl-*ortho*-iodoaniline **108**, palladium-mediated Heck cyclisation produced the resin-bound 3-ethylidene-oxindole **109**, as a mixture of isomers, in 88% mass recovery. Cleavage from the resin with TFA gave oxindole **110** in 92% yield.

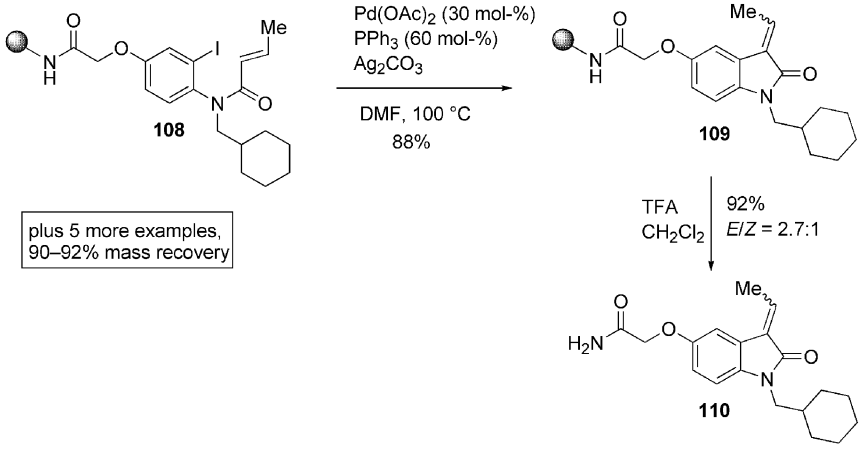
Hirama and co-workers also used an intramolecular Heck reaction for the synthesis of 3-alkenyl-oxindole **112** during the total synthesis of TMC-95A (**113**), a potent and selective proteasome inhibitor.[82] As shown in Scheme 25, the intramolecular Heck reaction of *N*-Boc-protected aniline **111** gave 3-alkenyl-oxindole **112** in 86% yield, selectively as the *Z*-isomer (the stereoselectivity was rationalised by a *syn*-addition/bond rotation/*syn*-elimination sequence).[83]

TMC-95A has been used as a proving ground for the various routes to 3-alkenyl-oxindoles. In their successful total syntheses, the Danishefsky group employed the aldol approach with oxindole **114** and aldehyde **115**,[84] and Williams' group proceeded via a Julia elaboration of isatin **116** using benzothiazole sulfone **117** (Scheme 25).[85] In addition, Takemoto and co-workers applied their indium-mediated cyclisation procedure on the *N*-alkylpropriolamide **118** to prepare the alkenyl-oxindole core of the natural product.[65]

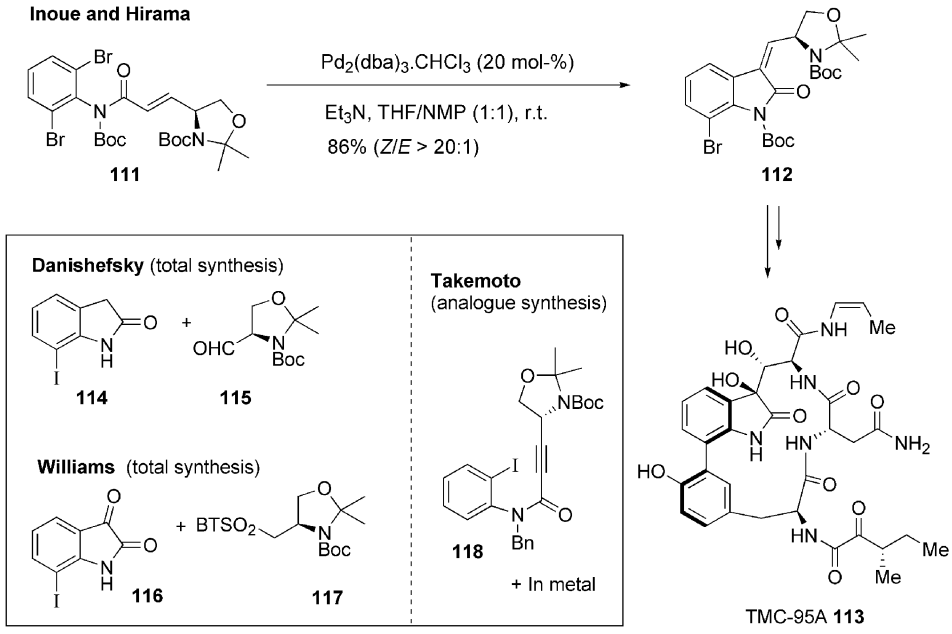
Moving on to more recent developments in tandem/telescoped approaches involving *N*-acryloyl-*ortho*-haloanilines, Umkehrer et al. reported a one-pot synthesis of



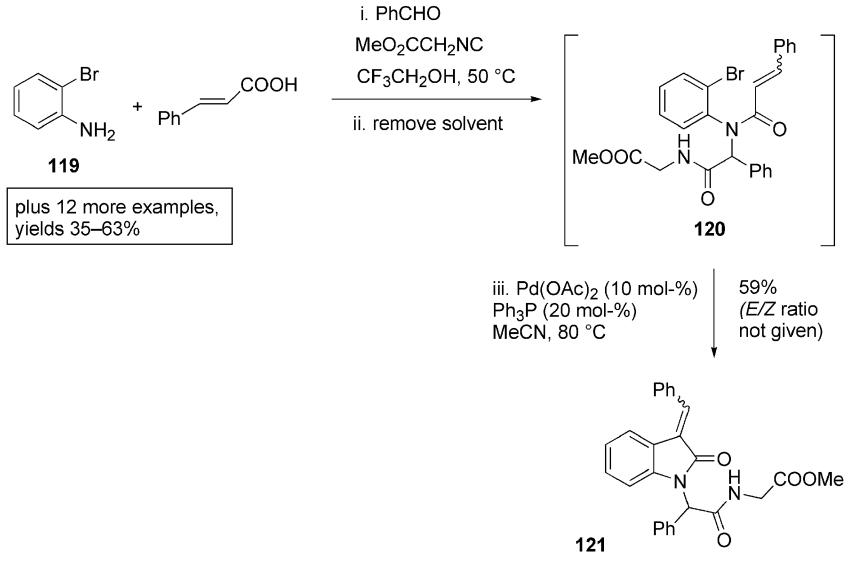
Scheme 23.



Scheme 24.



Scheme 25.



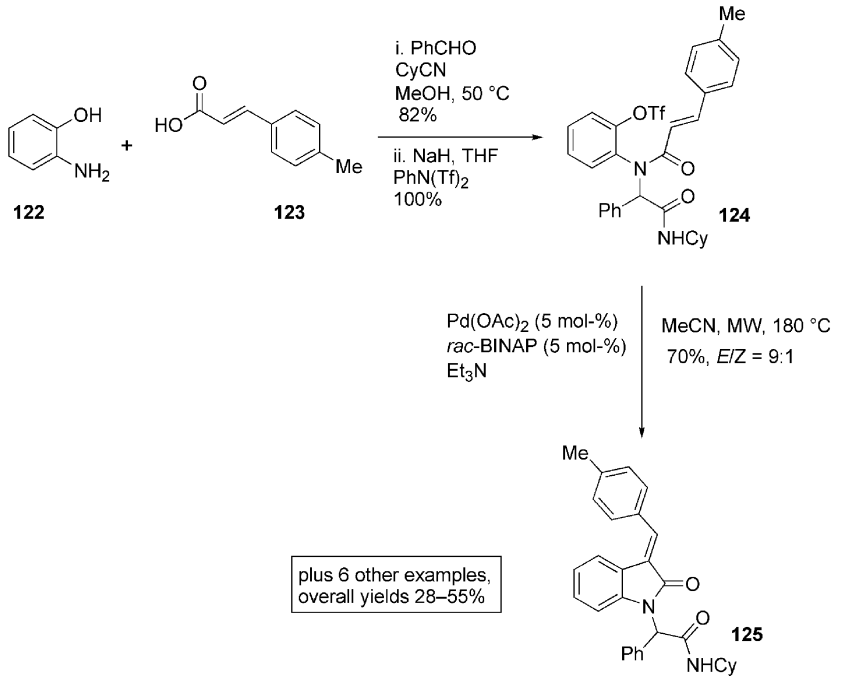
Scheme 26.

3-alkenyl-oxindoles starting from *ortho*-bromoanilines (Scheme 26).[86] Their approach involved an initial Ugi four-component coupling process to transform the aniline **119** into amide **120**. A solvent change followed by addition of palladium acetate then promoted Heck cyclisation to give the monosubstituted 3-methylene-oxindole **121** in reasonable yield as a mixture of stereoisomeric alkenes.

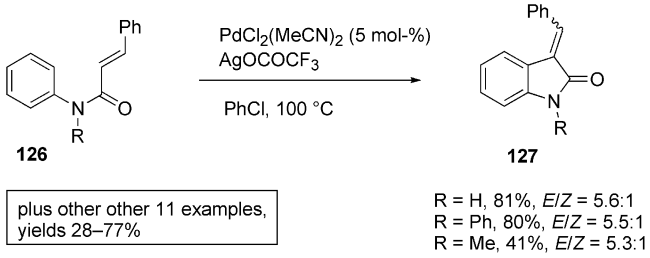
In a similar manner, Dai's group employed the Ugi four-component coupling reaction and intramolecular Heck cyclisation for the synthesis of 3-alkenyl-oxindoles **125** starting from phenols **122** (Scheme 27).[45]

(b) Aryl C–H Activation Approaches

Finally, and very recently, Nagasawa and co-workers reported a facile synthesis of 3-alkenyl-oxindoles by palladium-catalysed aromatic C–H activation/Heck reaction starting from simple *N*-acryloylanilines **126** (Scheme 28).[87] This reaction could be employed to prepare oxindoles **127** in which the nitrogen atom is unsubstituted or bears an aryl or alkyl group. More developments in related C–H activation approaches to 3-alkenyl-oxindoles can be expected in the near future.



Scheme 27.



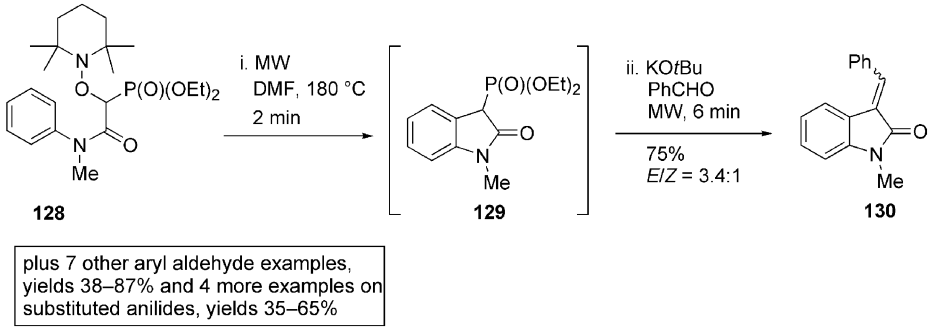
Scheme 28.

5.4 Telescoped and Tandem HWE Approaches to 3-Alkenyl-oxindoles

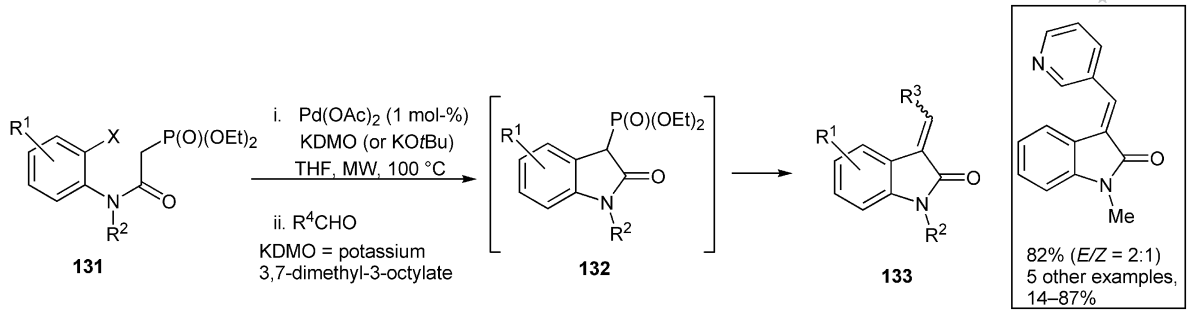
In 2004, Studer and co-workers reported an ingenious, one-pot telescoped route to 3-alkenyl-oxindoles involving tandem radical generation then homolytic aromatic substitution and finally Horner–Wadsworth–Emmons olefination (Scheme 29).[88] Microwave induced nitroxide cleavage was employed to initiate the cyclisation process, and a range of aryl aldehydes were then employed in the HWE olefination, which was also accelerated using MW irradiation. Although the radical precursors **128** have to be synthesised in advance, the cyclisation process does not require an α-halogenated aniline as is often the case.

A related telescoped, one-pot procedure was recently developed by the Taylor group in York for the streamlined conversion of α-haloanilides **131** into 3-alkenyl-oxindoles **133**, as shown in Scheme 30.[89] The amidophosphonates **131** were subjected to palladium-catalysed, base-mediated intramolecular enolate arylation to give the cyclised intermediates **132**; subsequent addition of an aldehyde in the presence of the base then initiated HWE olefination to generate the target alkenyl-oxindoles **133** in a regiocontrolled manner. This procedure, which utilises readily available cyclisation precursors **131** and a very low loading of palladium acetate, was successfully utilised to prepare a range of 3-alkenyl-oxindoles **133** derived from aromatic, heteroaromatic and aliphatic aldehydes.

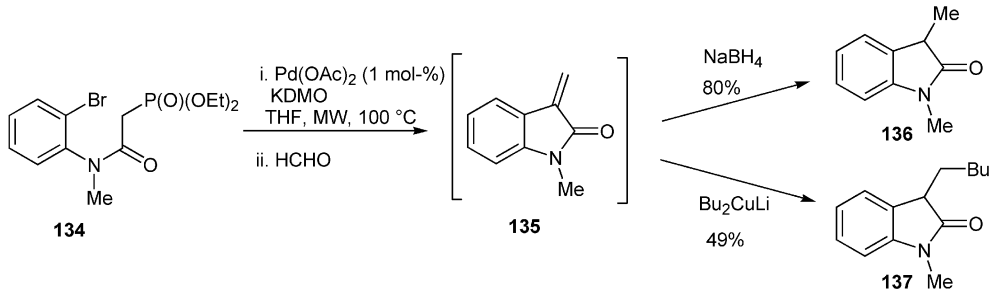
Formaldehyde could also be employed as trapping agent, but α-methylene-amide **135** is unstable and has to be trapped in situ (Scheme 31). The addition of sodium



Scheme 29.



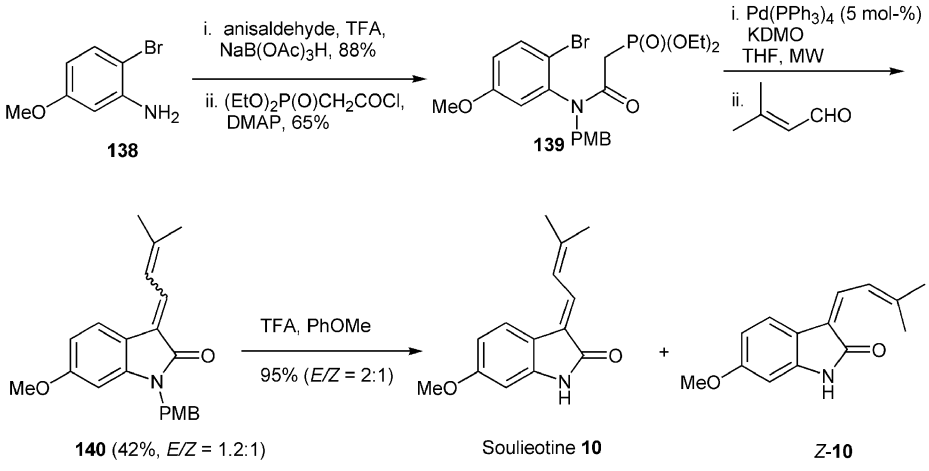
Scheme 30.



Scheme 31.

borohydride gave 3-methyl-oxindole **136** in excellent yield over the three step, one-pot process, and lithium dibutylcuprate generated the corresponding 3-pentyl-oxindole **137**.[89,90]

This enolate arylation/HWE sequence was also employed for the first synthesis of the simple natural product soulieotine **141** (Scheme 32). Soulieotine **10** was isolated from the rhizomes of *Souliea vaginata*, a plant employed as an anti-inflammatory, analgesic in traditional Chinese medicine. The PMB-protected cyclisation precursor **139** was easily obtained from aniline **138** and application of the enolate arylation/HWE sequence with 3-methylbutenal as the trapping agent gave the expected adduct **140** in 42% unoptimised yield as an isomeric mixture of alkenes. It should be noted that the enolate arylation was unsuccessful using $Pd(OAc)_2$, presumably due to palladium(II)-mediated PMB deprotection, but proceeded with tetrakis(triphenylphosphane)palladium. TFA deprotection then produced a mixture of *E*-**10** and *Z*-**10** (2:1) which were separated by chromatography and the major isomer was confirmed as soulieotine by NMR studies and X-ray crystallography.[89]



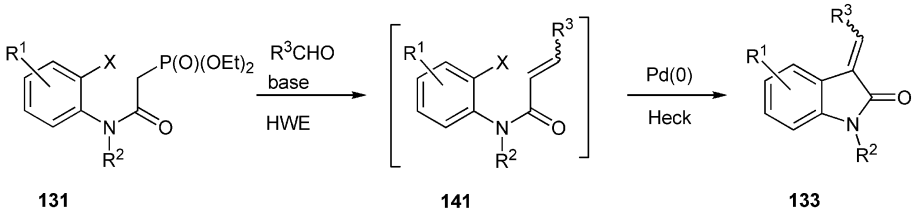
Scheme 32.

The HWE approaches discussed above (see Schemes 29, 30, 31, and 32) involve one-pot telescoped sequences but are not true tandem processes (the aldehyde is added after the arylation process has reached completion). However, the York group subsequently developed a tandem HWE/Heck approach to 3-alkenyl-oxindoles as shown in Scheme 33. In this procedure, the phosphonate **131**, aldehyde, base and Pd^0 catalyst are mixed together and the first-formed HWE product **141** then undergoes Heck cyclisation in situ to produce 3-alkenyl-oxindoles **133**.[91]

This tandem HWE/Heck sequence was first applied to *N*-Me systems (Scheme 34) and was successful with a range of aromatic, heteroaromatic and aliphatic aldehydes. The 3-alkenyl-oxindole products were usually obtained as mixtures of stereoisomers with the *E*-isomers predominating, although in certain cases (e.g., **142a**) the *E*-isomer was produced exclusively.[91]

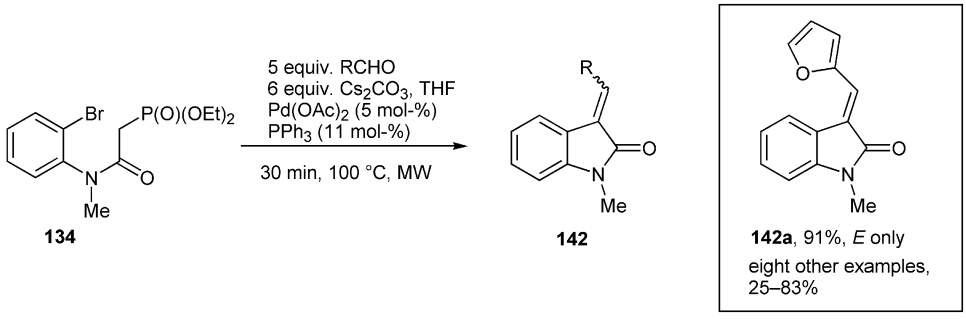
A major advantage of the tandem HWE/Heck sequence is that it is compatible with *N*-unprotected anilides (Scheme 35). In such cases, it was demonstrated that the best catalyst for the Heck reaction was tetrakis(triphenylphosphane)palladium, and that the iodo-phosphonate **144** often gave higher yields than the corresponding bromide **143**. This method was utilised with a range of aryl and heteroaryl aldehydes but was unsuccessful with aliphatic aldehydes[91] (the *N*-Me procedure is preferred for these processes).

To illustrate the value of the tandem HWE/Heck sequence, it was applied to a simple, one-pot preparation of



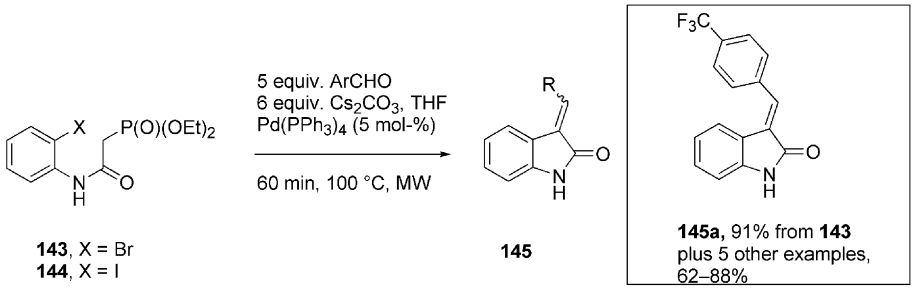
131 **141** **133**

Scheme 33.



134 **142**

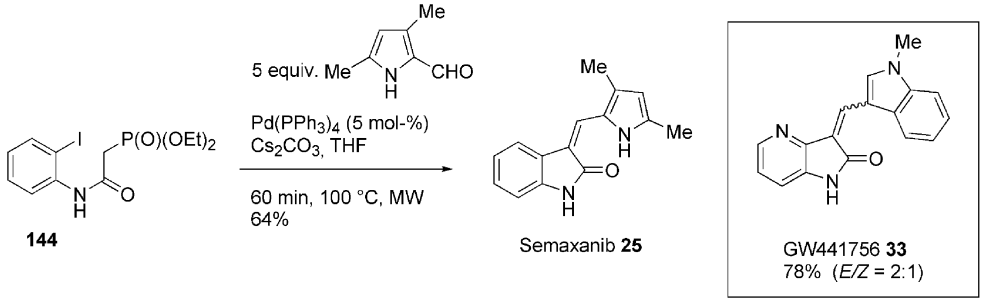
Scheme 34.



143, X = Br
144, X = I

145

Scheme 35.

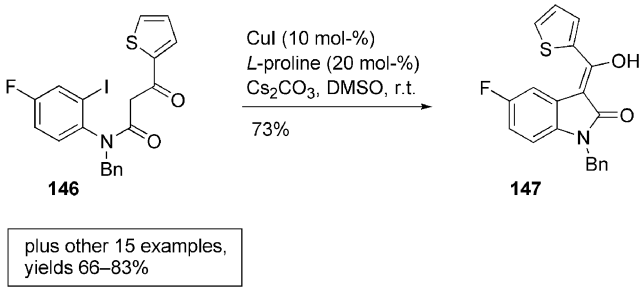


144 Semaxanib **25**

Scheme 36.

the anticancer agent semaxanib (**25**) and the Trk A inhibitor GW441756 (**33**, Scheme 36).[91] In the optimal procedure, using the standard HWE/Heck sequence, iodide **144** was converted into semaxanib (**25**) in a one-pot process in 64% yield solely as the required *Z*-stereoisomer. In a similar manner, the 3-alkenyl-aza-oxindole GW441756 (**33**) was prepared by a tandem HWE/Heck procedure (Scheme 36).[90] This is apparently the shortest synthesis of GW441756 (**33**) published to date.

Finally, because it involves an enolate arylation (see Schemes 30, 31, and 2), the copper-catalysed coupling route to 3-acyloxindoles, such as **147**, developed by Lu and Ma is included (Scheme 37).[92] Thus, treatment of β-keto-2-iodoanilide **146** with Cu/proline in DMSO at room temperature gives oxindole **147**, which bears a close structural resemblance to the cyclooxygenase inhibitor, tenidap (**38**).



Scheme 37.

6. Summary and Outlook

There are a number of natural products based on 3-alkenyl-oxindoles but it is in the development of new biological tools and novel pharmaceutical leads where the 3-alkenyl-oxindole unit comes into its own. This is illustrated by the discovery and development of, sunitinib (**1**) (SU11248), the orally active receptor tyrosine kinase inhibitor marketed by Pfizer as Sutent® which is reputed to have generated over $800m in global sales in 2008 alone. Traditional synthetic approaches to 3-alkenyl-oxindoles (e.g. aldol condensations of unsubstituted oxindoles and Wittig-type reactions of isatins) have been employed for many years but these often involve many synthetic operations and they can be low-yielding and exhibit poor stereoselectivity. Over the past 5–10 years, the synthetic chemistry community has therefore used considerable imagination and ingenuity to devise a number of novel and efficient routes to 3-alkenyl-oxindoles, many of which give excellent stereoselectivity. Many of these new procedures use tandem/telescoped protocols in which the oxindole ring is constructed at the same time as the alkenyl unit is installed, and this dramatically shortens the synthetic route. The use of metal catalysis (especially palladium) features large in these new procedures and, in the past year or two, methods which incorporate aromatic C–H activation have been developed, thereby simplifying the preparation of the starting materials. These new routes to 3-alkenyl-oxindoles should greatly facilitate the drug discovery process and should soon translate into new families of man-made compounds for biological screening, and new synthetic routes to complex natural products.

Acknowledgments

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