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Tandem Horner–Wadsworth–Emmons/Heck procedures for the preparation of 3-alkenyl-oxindoles: the synthesis of Semaxanib and GW441756

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Dedicated to Professor Steve Ley to celebrate the award of the Tetrahedron Prize and to acknowledge his scientific inspiration – and his enduring friendship and support

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ABSTRACT

A tandem sequence involving Horner–Wadsworth–Emmons (HWE) olefination followed by a palladium-catalysed intramolecular Heck reaction has been developed to provide rapid access to 3-alkenyl-oxindoles from α-halo-anilides. This one-pot microwave accelerated process proceeds with catalytic palladium(II) acetate or tetrakis(triphenylphosphine)palladium, and has been used to prepare a range of adducts derived from aromatic, heteroaromatic and aliphatic aldehydes. The procedures can be used to prepare *N*-unprotected oxindoles directly and the applicability of the process has been established by carrying out one-pot syntheses of Semaxanib, an angiogenesis signalling inhibitor, and GW441756, an aza-oxindole Trk A inhibitor.

1. Introduction

3-Alkenyl-oxindoles and 3-alkenyl-aza-oxindoles are present in many compounds of medicinal and biological importance as well as in a number of natural products.[1–3] In terms of pharmaceuticals, mention should be made of the *anti*-angiogenic/*anti*-cancer pyrrolylidene oxindoles Semaxanib (SU5416) **1**[4] and Sunitinib (SU11248) **2**,[5] Tenidap **3**, a cyclooxygenase inhibitor used for the treatment of rheumatoid arthritis and osteo-arthritis,[6] and the aza-oxindole GW441756 **4**, a potent and highly selective, orally active tyrosine kinase (Trk) A inhibitor.[7] In terms of natural products, Soulieotine **5**[8] and Ammosamide B **6**[9] are representative examples (Fig. 1). Soulieotine **5** was isolated from *Souliea vaginata*, which is employed as an *anti*-inflammatory in traditional Chinese medicine[8] and Ammosamide B **6** was recently obtained from the marine-derived *Streptomyces* strain CNR-698 and shown to inhibit myosin.[9] In addition, 3-alkenyl-oxindoles have been widely employed as building blocks in natural product and target synthesis.[10]

As part of a programme to develop efficient and practical tandem/telescoped procedures to heterocyclic systems,[11,12] we recently designed a telescoped, one-pot procedure for the streamlined conversion of α-halo-anilides **7** into 3-alkenyl-oxindoles **9**, as shown in Scheme 1.[11] The amidophosphonates **7** were subjected to palladium-catalysed intramolecular enolate arylation to give the cyclised intermediates **8**; subsequent addition of an aldehyde in the presence of base then initiated Horner–Wadsworth–Emmons (HWE) olefination to generate the target alkenyl-oxindoles **9** in a regiocontrolled manner. This procedure was successfully utilised to prepare a range of 3-alkenyl-oxindoles **9** derived from aromatic, heteroaromatic and aliphatic aldehydes and formaldehyde and employed for the first synthesis of Soulieotine **5**.[11]

Although successful, the sequence illustrated in Scheme 1 still possesses some drawbacks:

i. It did not prove possible to carry out the process in a tandem manner – the aldehyde had to be added after the arylation process had reached completion.

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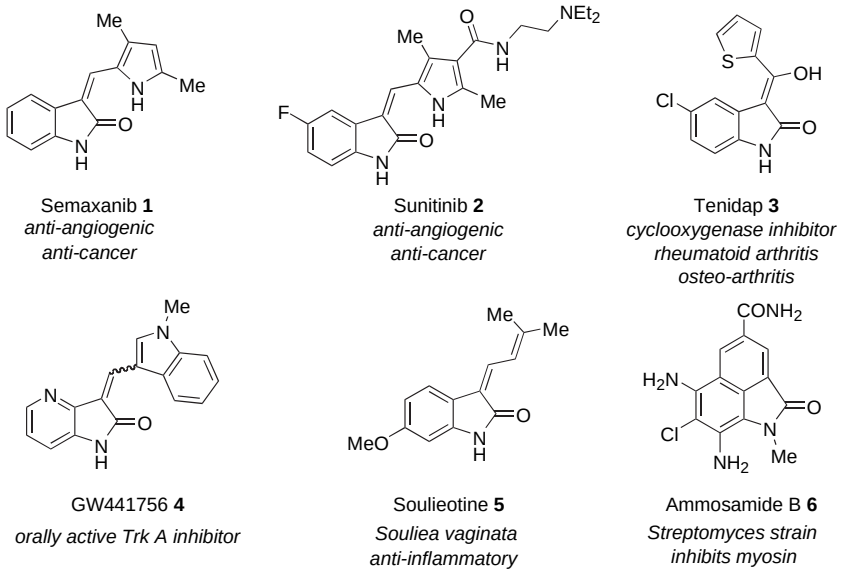
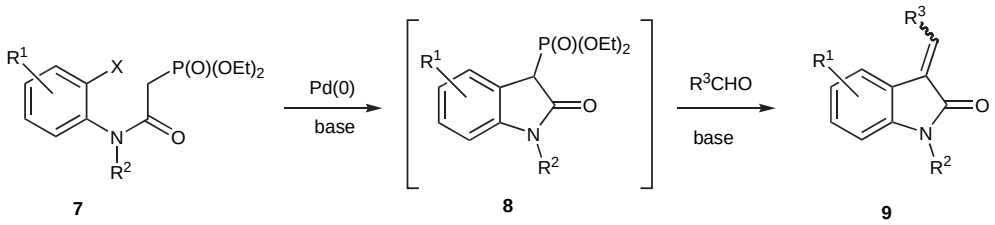


Figure 1. Representative 3-alkenyl-oxindoles.



Scheme 1.

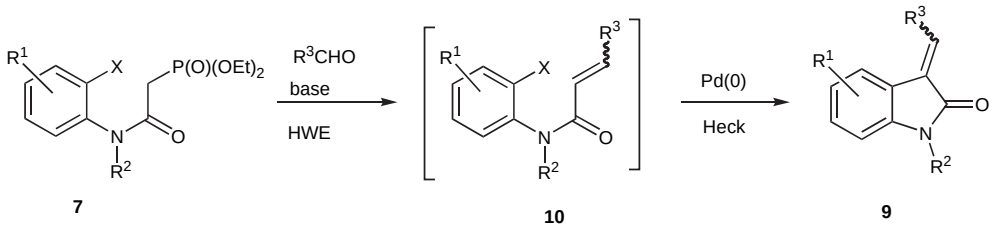
ii. It was not possible to carry out the enolate arylation/HWE procedure on unprotected anilides **7** (R^2=H); this necessitated the use of *N*-protected oxindoles (**9**, $R^2 \neq H$) and an additional deprotection step was required to produce the free oxindoles.

In the search for an improved procedure for the overall annulation we investigated the complementary HWE/Heck approach to 3-alkenyl-oxindoles **9** (Scheme 2) in a 'one-pot' microwave irradiation process. Heck reactions leading to 3-alkenyl-oxindoles **9** are well known[13–18] but, to our knowledge, they have not been combined with in situ generation of the cyclisation precursors **10**.[17] In addition, in some cases, Heck routes to oxindoles have been shown to be compatible with unprotected nitrogen substituents.[18]

In order to evaluate the sequence shown in Scheme 2, we initially investigated the individual steps (Table 1) before moving on to the one-pot process. These initial investigations used the *N*-methyl phosphonate **11**, excess benzaldehyde and a number of different bases to promote the HWE reaction. A smaller excess of the aldehyde could be employed but longer reaction times were then required.

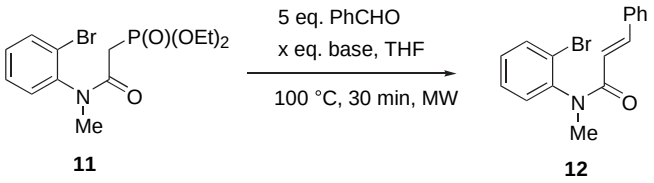
The use of potassium 3,7-dimethyl-3-octylate (KDMO)[11] and KO^tBu in THF (entries i and ii) gave the expected alkene **12** albeit in disappointing yield with a number of side-products being evident. However, with Cs_2CO_3 as base the required reaction proceeded in essentially quantitative yield (entry iii). The optimum conditions used 6 equiv of Cs_2CO_3 and 5 equiv of benzaldehyde at high concentration (300 mM with respect to phosphonate) with microwave acceleration.

Encouraged by these results, we next investigated the second step of the one-pot sequence, the Heck reaction (Table 2). Several different palladium sources were screened unsuccessfully but the expected 3-alkenyl-oxindole **13a** was observed using tetrakis (triphenylphosphine)palladium (entry i), $Pd_2(dba)_3$ (entry ii), and palladium(II) acetate (entry iii). However, the best yield by far was



Scheme 2.

Table 1
HWE reactions of the N-methylated phosphonate **11**



11 **12**

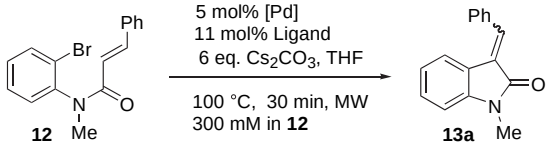
Entry	Base	Eq. base	Conc. 11 [mM]	Yield 12[a] [%]
i	KDMO	2.5	100	61
ii	KO^{t}Bu	2.5	100	40
iii	Cs_2CO_3	6	300	98[b,c]

[a] *E*/*Z* >95:5.
[b] Repeating this reaction but with 2.5 equiv Cs_2CO_3 gave **12** in 22% yield.
[c] Repeating this reaction with 2.5 equiv Cs_2CO_3 at a concentration of 100 mM gave **12** in 80% yield.

observed using 5 mol % $Pd(OAc)_2$ and 11 mol % triphenylphosphine. With these conditions the N-methylated oxindole **13a** was isolated in 91% yield (entry iv).

With the parameters for the individual reactions defined, the one-pot tandem HWE/Heck reactions of N-methylated phosphonate **11** was explored (Table 3). Starting with benzaldehyde (entry i), we were delighted to observe that on mixing all of the reagents for both processes together, the desired 3-alkenyl-oxindole **13a** was

Table 2
Heck reactions of the N-methylated alkene **12**[a]



12 **13a**

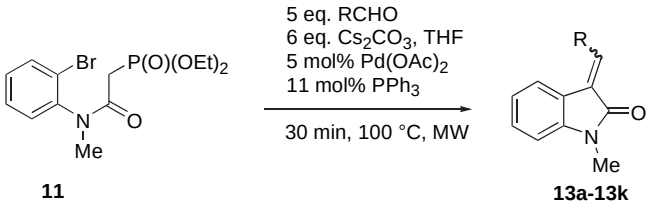
Entry	[Pd][b]	Ligand	Yield 13a (%)	*E*/*Z* ratio
i	$Pd(PPh_3)_4$	—	41	4:1
ii	$Pd_2(dba)_3$	—	31	3:1
iii	$Pd(OAc)_2$	—	22	4:1
iv	$Pd(OAc)_2$	PPh_3[c]	91	1:1

[a] The chloride and iodide corresponding to bromide **12** were also investigated. The chloride proved unreactive in the Heck reaction whereas the iodide underwent smooth cyclisation; however, the iodide proved to be unstable to storage and so bromide **12** was used preferentially.
[b] With $PdCl_2$, $[Pd(PPh_3)_2Cl_2]$ and $[Pd(CH_3CN)_2Cl_2]$ no reaction was observed.
[c] Repeating this reaction but with P(*o*-Tol)$_3$ or $P(C_6F_5)_3$ gave **13a** in 85% and 21% yield, respectively.

obtained in 83% overall yield. It should be noted that, in the absence of microwave irradiation, oxindole formation was not observed using a 30 min reaction time.

This tandem HWE/Heck sequence was then applied to a range of aromatic and heteroaromatic aldehydes (entries ii–vii). As can be seen, electron-deficient aryl compounds reacted moderately well (entries ii–iv) but with 4-methoxybenzaldehyde the yield of 3-alkenyl-oxindole **13e** was disappointing under these standard conditions (entry v), presumably due to mesomeric deactivation of the aldehyde group. It is worth emphasising that the reaction conditions employed in Table 3 were optimised for benzaldehyde and the yields with the other aldehydes could well be improved by further study (the Heck cyclisation is always the difficult step). With pyridine-3-carboxaldehyde and 2-furaldehyde good yields of the oxindole products were obtained under the standard conditions (entries vi and vii). Aliphatic aldehydes also gave good results in this tandem sequence (entries viii and ix). As is normal in

Table 3
The tandem HWE/Heck route to 3-alkenyl-oxindoles **13a–j**



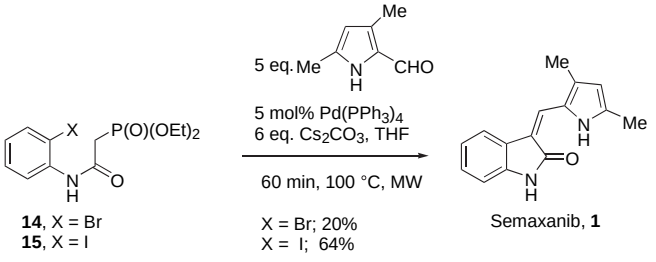
11 **13a-13k**

Entry	Aldehyde	Product, Yield (%)	*E*/*Z* ratio
i	PhCHO	13a, 83[a]	1:1
ii	4-NO_2–C_6H_4–CHO	13b, 45	1:1
iii	4-Cl–C_6H_4–CHO	13c, 58	*E*-only
iv	4-CF_3–C_6H_4–CHO	13d, 57	*E*-only
v	4-MeO–C_6H_4–CHO	13e, 25	1.3:1
vi	Pyridine-3-CHO	13f, 98	1.6:1
vii	2-Furaldehyde	13g, 99	*E*-only
viii[b]	3-Methylbutyraldehyde	13h, 71	1:1
ix[b]	CyCHO	13i, 71	2.6:1

[a] Other solvents can also be employed: THF–PhMe (1:1, 35%), DME (61%), CH_3CN (70%).
[b] No 3-alkenyl-oxindole was observed using pivaldehyde and HCHO gave a complex mixture of products; hexanal gave the expected product in >60% yield but it was not possible to obtain an analytically pure sample.

reactions of this type producing 3-alkenyl-oxindoles,[19] mixtures of stereoisomers (often rich in the *E*-isomers) were normally obtained (unless intramolecular hydrogen bonding is present to favour the *Z*-isomer – see compound **1** in Scheme 3). The *E*/*Z* ratio was also sensitive to solvent, choice of phosphine and palladium catalyst, catalyst concentration and reaction time.

Having developed a satisfactory tandem procedure for preparing N-methylated 3-alkenyl-oxindoles, we proceeded to investigate the use of the *N*-unprotected phosphonate **14** in the tandem HWE/Heck sequence. Analysis of the individual steps as before revealed that the HWE reaction was slower in the un-



14, X = Br
15, X = I

X = Br; 20%
X = I; 64%

Semaxanib, **1**

Scheme 3.

protected system, that the best catalyst for the Heck reaction was tetrakis(triphenylphosphine)palladium, and that the iodophosphonate **15** often gave higher yields than the corresponding bromide **14**. It was also established that the one-pot process was more efficient than the two step sequence, possibly due to synergistic effects.[20]

With the knowledge gleaned from the above investigations, a range of aldehydes were studied in this *N*-unprotected HWE/Heck sequence (Table 4). As before, benzaldehyde and electron-deficient analogues gave 3-alkenyl-oxindoles in good to excellent yields (entries i and ii) but, by contrast to the N–Me system, 4-methoxybenzaldehyde also gave an excellent 82% yield of oxindole **16c** under these standard conditions (entry iii, presumably a reflection of the longer reaction time). However, 4-chloro-benzaldehyde reacted

sluggishly in the sequence using bromide **14** and the iodide **15** was needed to obtain a reasonable yield of adduct **16d** (entry iv). With pyridine-3-carboxaldehyde and 2-furaldehyde, good yields of the oxindole products were also obtained starting from iodide **15** (entries v and vi). However, in the N–H series, reactions with aliphatic aldehydes gave only poor conversion (entry vii); the N–Me procedure is preferred for these processes. In terms of stereoselectivity, the *E*/*Z* ratios for the NMe (Table 3) and NH (Table 4) examples vary but in an unpredictable manner (some reaction are more selective, some less, in the NH systems). We ascribe these differences to the small changes in product structures (NMe vs NH), and the longer reaction times in the NH examples.

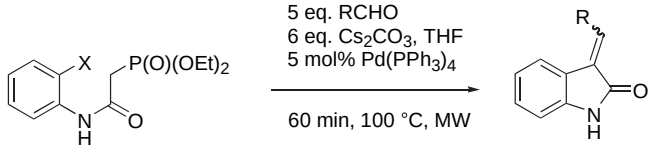
To illustrate the value of the tandem HWE/Heck sequence, it was applied to a simple, one-pot preparation of the *anti*-cancer agent Semaxanib **1** as shown in Scheme 3. Semaxanib, a small molecule angiogenesis signalling inhibitor, was designed to block the VEGF-R in blood vessels, thereby inhibiting the blood supply to the tumour.[4] Thus, in the optimum procedure, using the standard HWE/Heck sequence, iodide **15** was converted into Semaxanib **1** in a one-pot process in 64% yield solely as the required *Z*-stereoisomer (intramolecular H-bonding being responsible for the high stereoselectivity).

Buoyed by the successful preparation of Semaxanib **1**, we moved on to explore the use of the tandem HWE/Heck process for one-pot approaches to 3-alkenyl-aza-oxindoles, as exemplified by the Trk A inhibitor GW441756 **4** (Scheme 4). Aza-oxindoles display a wide range of biological properties including *anti*-viral, *anti*-arthritis and *anti*-tumour activities.[3,7]

The bromopyridine precursor **17** was readily prepared and proved to be an excellent substrate for the HWE/Heck sequence. With benzaldehyde as trapping agent, aza-oxindole **18**[21] was formed in 70% yield. With *N*-methylindole-3-carboxaldehyde, the reaction gave the Trk A inhibitor **4** in up to 78% yield (DME gave slightly higher yields than THF in this case) as a mixture of isomers (the compound is marketed as an *E*/*Z*-mixture). To our knowledge, this is the shortest synthesis of GW441756 **4** published to date.

In summary, we have developed a new tandem sequence involving HWE olefination followed by a palladium-catalysed intramolecular Heck reaction which provides rapid access to 3-alkenyl-oxindoles from readily available α-halo-anilides and aldehydes. The one-pot, MW accelerated process is fast (30–60 min) and can be employed with a range of aldehyde trapping reagents. N-Alkylated and NH oxindoles can be prepared using this sequence, which can also be extended to prepare 3-alkenyl-aza-oxindoles. The applicability of the tandem HWE/Heck sequence has been demonstrated by carrying out one-pot syntheses of the *anti*-cancer agent Semaxanib, and of GW441756, a potent aza-oxindole Trk A inhibitor.

Table 4
The tandem HWE/Heck route to unprotected 3-alkenyl-oxindoles **16a–g**



14, X = Br
15, X = I

16a-16g

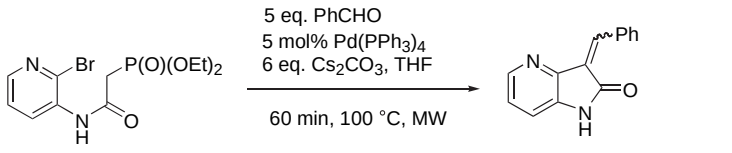
Entry	X	Aldehyde	Product, yield (%)	*E*/*Z* ratio
i	Br	PhCHO	16a, 82[a]	2:1
ii	Br	4-CF_3–C_6H_4–CHO	16b, 91	5:1
iii	Br	4-MeO–C_6H_4CHO	16c, 82	3:1
iv	I	4-Cl–C_6H_4–CHO	16d, 78[b]	*E*-only
v	I	Pyridine-3-CHO	16e, 88	2.3:1
vi	I	2-Furaldehyde	16f, 62	2:1
vii	Br	CyCHO[c]	16g, 12	1:1

[a] A 54% yield was obtained using the $Pd(OAc)_2$ conditions as in Table 3 in a one-step process; in a two step process the overall yield was 73% with a combined reaction time of 90 min.
[b] Yield of **16d** from **14** was 35%.
[c] Pivaldehyde and hexanal underwent efficient HWE elaboration but gave low yields of oxindole products (10–40%) and the hexanal product could not be fully purified; no oxindole products were observed with acetaldehyde and formaldehyde (which gave a polymeric material).

2. Experimental

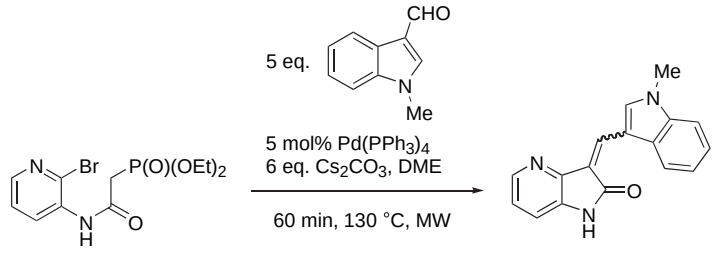
2.1. General details

All reagents were purchased from commercial sources and used without further purification. All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen or argon atmosphere using standard syringe and septum techniques unless otherwise stated. THF were freshly distilled from sodium/



17

18, 70% (*E*:*Z* = 3.8:1)



17

GW441756 **4**, 72-78% (*E*:*Z* = 2:1)

Scheme 4.

benzophenone. Thin layer chromatography was performed on pre-coated 0.2 mm Merck Kieselgel 60 F_{254} silica plates and compounds were visualized under 245 nm ultraviolet irradiation followed by staining in alkaline potassium permanganate. Flash column chromatography was performed using Fluka Kieselgel 60 F (220–440 mesh) with the indicated solvents. Petroleum ether refers to the fractions with boiling range 40–60 °C. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded with a Thermo-Nicolet IR100 spectrophotometer as thin films between sodium chloride plates. ^{1}H and ^{13}C NMR spectra were obtained using either a JEOL 400 MHz spectrometer operating at either 400 MHz or 100 MHz or a Bruker AMX 500 spectrometer operating at 500 MHz or 125 MHz, respectively. Data are expressed in parts per million downfield shift from tetramethylsilane as an internal standard or relative to $CDCl_3$. All *J* values are given in Hertz. Assignments are made with the aid of DEPT 135, COSY and HSQC experiments. Mass spectra were recorded using a Fisons Analytical VG Autospec spectrometer operating in chemical ionization (CI), electron ionisation (EI) or fast atom bombardment (FAB) mode or on a Bruker Daltronics microTOF spectrometer operating in electrospray ionisation (ESI) mode. All microwave reactions were performed in a CEM Discover system (50 W, closed vessel mode, 100 °C; the set temperature was reached in 10 min and maintained for the remainder of the experiment). 2-Bromo-anilides **11**[11] and **15**[22] were prepared using literature procedures. The following products are known: **13a**,[23] **13b**,[23] **13d**,[23] **13e**,[23] **13f**,[24] **16a**,[25] **16b**,[26] **16c**,[25] **16d**,[25] **16e**,[25] **16e**[27] and **16f**.[19] With 3-alkenyloxindoles **13** and **16**, the *E*/*Z* ratios were determined using NMR spectroscopy on the unpurified reaction mixtures. The individual *E*- and *Z*-isomers were easily distinguished using NMR spectroscopy (the chemical shift of the vinyl =CH is observed at higher parts per million values for the *E*-isomer compared to the *Z*-isomer).[11,23] In addition, the *Z*-isomer is usually less polar and is eluted first during column chromatography.[11,23]

2.2. (*E*)-*N*-(2-Bromophenyl)-*N*-methylcinnamamide 12

A solution of the 2-bromo-*N*-methylanilide **11** (100 mg, 0.27 mmol), Cs_2CO_3 (373 mg, 1.64 mmol) and benzaldehyde (160 μL, 1.37 mmol) in THF (1 mL) under an Ar atmosphere was heated with MW irradiation at 100 °C (CEM Discover, 50 W max.) for 30 min. The reaction mixture was treated with dist. H_2O (3 mL) and the aqueous layer was extracted with EtOAc (3×3 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo and purified by flash chromatography (SiO_2, petrol/EtOAc, 10:1) to give the title compound **12** (85 mg, 98%, *E*-isomer only), as a colourless oil, R_f 0.47 (petrol/EtOAc, 10:1); IR (neat) 3437, 3005, 2925, 2853, 1658, 1616, 1582, 1477, 1450, 1420, 1370, 1289, 1248, 1216, 1133, 1060, 1030, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.73–7.69 (m, 2H), 7.42 (ddd, *J*=1.5, 7.3, 7.8 Hz, 1H), 7.34–7.27 (m, 7H), 6.12 (d, *J*=15.5 Hz, 1H,), 3.31 (s, 3H, N–Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=166.0, 142.4, 142.2, 135.0, 133.9, 130.2, 129.8, 129.6, 128.9, 128.6, 127.8, 123.5, 117.8, 36.2 (N–Me) ppm MS (ESI) 316 ([M+H]$^+$, 100); HRMS (ESI): Found, 316.0332. $C_{16}H_{15}{}^{79}BrNO$ requires 316.0333 (−0.4 ppm error).

2.3. General procedure for the HWE/Heck sequence using N–Me protected phosphonates

A solution of 2-bromo-*N*-methylanilide **11**[11] (100 mg, 0.27 mmol), Cs_2CO_3 (373 mg, 1.64 mmol), $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), PPh_3 (7.9 mg, 0.03 mmol) and benzaldehyde (160 μL, 1.37 mmol) in THF (1 mL) under an Ar atmosphere was heated under MW irradiation at 100 °C (CEM Discover, 50 W max.) for 30 min. The reaction mixture was treated with dist. H_2O (3 mL) and the aqueous layer was extracted with EtOAc (3×3 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo and purified by flash chromatography (SiO_2, petrol/EtOAc, 10:1).

2.4. (*E*)-3-(4-Chlorobenzylidene)-1-methylindolin-2-one 13c

Yellow solid (21.3 mg, 58%, *E*-isomer only), mp 107–109 °C; R_f 0.27 (petrol/EtOAc, 10:1); IR (neat) 3424, 1704, 1608, 1488, 1377, 1339, 1092, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.77 (s, 1H), 7.58 (m, 3H), 7.44 (m, 2H), 7.28 (ddd, *J*=1.1, 7.7, 7.7 Hz, 1H), 6.90 (ddd, *J*=1.1, 7.7, 7.7 Hz, 1H), 6.86 (br d, *J*=7.7 Hz, 1H), 3.27 (s, 3H, N–Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.7, 144.7, 135.8, 133.7, 130.9, 130.3, 129.2, 128.7, 127.9, 122.9, 122.2, 121.0, 108.5, 25.9 (N–Me) ppm; MS (ESI) 270 ([M+Na]$^+$, 100); HRMS (ESI): Found, 270.0680. $C_{16}H_{13}{}^{35}ClNO$ requires 270.0674 (2.2 ppm error).

2.5. (*E*)-3-(Furan-2-ylmethylene)-1-methylindolin-2-one 13g

Yellow solid (28 mg, 99%, *E*-isomer only), mp 124–128 °C; R_f 0.42 (petrol/EtOAc, 5:1); IR (neat) 3116, 1702, 1629, 1604, 1470, 1489, 1420, 1379, 1341,1254, 1127, 1106, 1021, 745 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ=8.42 (d, *J*=7.5 Hz, 1H), 8.18 (d, *J*=1.8 Hz, 1H), 7.43 (s, 1H), 7.36 (ddd, *J*=1.1, 7.5, 7.5 Hz, 1H), 7.30 (d, *J*=3.5 Hz, 1H), 7.09 (ddd, *J*=1.1, 7.5, 7.5 Hz), 7.05 (br d, *J*=7.5 Hz, 1H), 6.81 (dd, *J*=1.8, 3.5 Hz, 1H), 3.21 (s, 3H, N–Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.7, 151.8, 146.0, 144.2, 129.6, 125.1, 122.5, 122.3, 121.7, 120.6, 119.9, 113.3, 107.9, 25.9 (N–Me) ppm; MS (ESI) 326 ([M+H]$^+$, 100); HRMS (ESI): Found, 326.0863. $C_{14}H_{12}NO_2$ requires 326.0866 (−1.0 ppm error).

2.6. (*E*/*Z*)-1-Methyl-3-(3-methylbutylidene)indolin-2-one 13h

Colourless oil (44.8 mg, 71%, *E*/*Z*=1:1, separated by column chromatography, petrol/EtOAc), R_f 0.38 (*E*)/0.61 (*Z*) (petrol/EtOAc, 9:1); IR (neat) 3406, 1696, 1650, 1613, 1469, 1380, 1335, 1257, 1122, 1090, 1022, 745 cm^{-1}.

E-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.41 (d, *J*=7.7 Hz, 1H), 7.26 (ddd, *J*=1.2, 7.7, 7.7 Hz, 1H), 7.02 (ddd, *J*=1.0, 7.7, 7.7 Hz, 1H), 6.90 (t, *J*=7.9 Hz, 1H), 7.09 (br d, *J*=7.7, 1H), 3.22 (s, 3H, N–Me), 2.92 (dd, *J*=6.9, 7.9 Hz, 2H), 1.87 (m, 1H), 1.01 (d, *J*=6.7 Hz, 6H) ppm.

Z-isomer: ^{1}H (400 MHz, $CDCl_3$) δ=7.56 (d, *J*=7.5 Hz, 1H), 7.27 (m, 1H), 7.09–7.02 (m, 2H), 6.82 (br d, *J*=7.8 Hz, 1H), 3.23 (s, 3H, N–Me), 2.56 (t, *J*=7.3 Hz, 1H), 1.96 (m, 1H), 1.03 (d, *J*=6.7 Hz, 6H) ppm; ^{13}C NMR (100 MHz, CD_3CN, *Z*-isomer) δ=169.4, 144.6, 143.7, 130.8, 129.6, 125.1, 123.8, 121.1, 110.1, 37.8, 30.4, 26.7, 23.5 ppm; MS (ESI) 216 ([M+H]$^+$, 100); HRMS (ESI): Found, 216.1383. $C_{14}H_{17}NO$ requires 216.1382 (0.2 ppm error).

2.7. (*E*/*Z*)-3-(Cyclohexylmethylene)-1-methylindolin-2-one 13i

Yellow solid (45.7 mg; 71%, *E*/*Z*=2.6:1, separated by column chromatography, petrol/EtOAc), mp 115–117 °C; R_f 0.31 (*E*)/0.17 (*Z*) (petrol/EtOAc, 10:1); IR (neat) 2924, 2851, 1704, 1612, 1470, 1380, 1257, 1089, 745 cm^{-1}.

E-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.38 (d, *J*=7.4 Hz, 1H), 7.25 (ddd, *J*=1.2, 7.7, 7.7 Hz, 1H), 7.01 (ddd, *J*=1.0, 7.7, 7.7 Hz, 1H), 6.78 (br d, *J*=7.7 Hz, 1H), 6.68 (d, *J*=10.0 Hz, 1H), 3.84 (m, 1H), 3.28 (s, 3H, N–Me), 1.83–1.70 (m, 4H), 1.53–1.37 (m, 2H), 1.29–1.11 (m, 4H) ppm.

Z-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.51 (d, *J*=7.7 Hz, 1H), 7.27 (ddd, *J*=1.0, 7.7, 7.7 Hz, 1H), 7.04 (ddd, *J*=1.0, 7.7, 7.7 Hz, 1H), 6.91 (d, *J*=9.8 Hz, 1H), 6.82 (br d, *J*=7.8 Hz, 1H), 3.23 (s, 3H, N–Me), 2.94 (m, 1H), 1.83–1.70 (m, 4H), 1.53–1.37 (m, 2H), 1.29–1.11 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.8, 147.4, 143.9, 128.9,

126.0, 123.5, 122.3, 122.2, 108.2, 37.9, 31.4, 25.8, 25.5, 25.3 ppm; MS (ESI) 242 ([M+H]$^+$, 100); HRMS (ESI): Found, 242.1539. $C_{16}H_{20}NO$ requires 242.1536 (1.2 ppm error).

2.8. 1,3-Diethyl 2-(2-bromophenylamino)-2-oxoethylphosphonate 14

A solution of 2-bromoaniline (2 g, 11.8 mmol) in dry dichloromethane (15 mL) was cooled to 0 °C, and then 2-chloro-1-methylpyridinium iodide (9 g, 35.4 mmol), triethylamine (6 g, 59 mmol) and 2-(diethoxyphosphoryl)acetic acid (3.5 g, 17.7 mmol) were added. After 30 min the reaction mixture was treated with 10% HCl (10 mL), extracted with dichloromethane (3×30 mL) and the organic layers were washed with brine (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo and purified by flash chromatography (SiO_2, 5% MeOH/EtOAc) to give the title compound **14** (3.36 g, 81%) as a colourless oil, R_f 0.57 (EtOAc/MeOH, 10:1); IR (neat) 3444, 2985, 1692, 1592, 1531, 1438, 1304, 1246, 1026, 973, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.83 (br s, 1H), 8.28 (d, J=8.3 Hz, 1H), 7.55 (m, 1H), 7.32–7.26 (m, 1H), 7.01–6.97 (m, 1H), 4.24–4.16 (m, 4H), 3.06 (d, J=8.3 Hz, 2H), 1.35 (t, J=7.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=162.8 (d, J(C-P)=4.1 Hz), 135.9, 132.7, 128.3, 125.7, 122.5, 113.8, 63.8 (d, J(C-P)=6.5 Hz), 36.6 (d, J(C-P)=130.4 Hz), 15.9 (d, J(C-P)=6.0 Hz) ppm; MS (ESI) 350 ([M+H]$^+$, 100); HRMS (ESI): Found, 350.0151. $C_{12}H_{18}{}^{79}BrNO_4P$ requires 350.0145 (1.9 ppm error).

2.9. General procedure for the HWE/Heck sequence using N–H unprotected phosphonates

A solution of 2-bromo-anilide **14** (100 mg, 0.29 mmol), Cs_2CO_3 (390 mg, 1.72 mmol), $Pd(PPh_3)_4$ (16.5 mg, 0.014 mmol) and benzaldehyde (145 μL, 1.43 mmol) in THF (1 mL) under an Ar atmosphere was heated using MW irradiation at 100 °C (CEM Discover, 50 W max.) for 60 min. The reaction mixture was treated with dist. H_2O (3 mL) and the aqueous layer was extracted with EtOAc (3×3 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo and purified by flash chromatography (SiO_2, petrol/EtOAc, 5:1). A similar procedure was employed using the iodo-anilide **15**.

2.10. (*E*/*Z*)-3-(Cyclohexylmethylene)indolin-2-one 16g

Yellow film (8 mg, 12%, E/Z=1:1, separated by column chromatography, petrol/EtOAc), mp 92–94 °C, R_f 0.30, 0.35 (petrol/EtOAc, 10:1); IR (neat) 3238, 2926, 2849, 1703, 1641, 1614, 1463, 1332, 1216, 741 cm^{-1}.

E-isomer: ^{1}H NMR (400 MHz, CD_3CN) δ=9.10 (br s, 1H), 7.44 (d, J=7.7 Hz, 1H), 7.15 (ddd, J=1.1, 7.7, 7.7 Hz, 1H), 6.96 (ddd, J=1.0, 7.7, 7.7 Hz, 1H), 6.85 (m, 2H), 2.88 (m, 1H), 1.83–1.79 (m, 5H), 1.37–1.22 (m, 5H) ppm.

Z-isomer: ^{1}H NMR (400 MHz, CD_3CN) δ=8.40 (br s, 1H), 7.58 (m, 1H), 7.23 (ddd, J=1.2, 7.7, 7.7 Hz, 1H), 7.01 (ddd, J=1.1, 7.7, 7.7 Hz, 1H), 6.90 (d, J=9.8 Hz, 1H), 6.70 (br d, J=7.7 Hz, 1H), 2.97 (m, 1H), 1.85–1.77 (m, 4H), 1.51–1.41 (m, 3H), 1.35–1.28 (m, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ=168.6, 145.9, 141.8, 128.9, 126.4, 123.8, 122.3, 121.8, 119.8, 37.7, 31.4,25.6, 25.3 ppm; MS (ESI) 228 ([M+H]$^+$, 100); HRMS (ESI): Found, 228.1383. $C_{15}H_{18}NO$ requires 228.1375 (3.6 ppm error).

2.11. (*Z*)-3-((3,5-Dimethyl-1*H*-pyrrol-2-yl)methylene)indolin-2-one 1[19]

Yellow solid (38.5 mg, 64%, *Z*-isomer only), mp 220–222 °C, lit.[19] mp 221–222 °C; R_f 0.29 (petrol/EtOAc, 1:1); IR (neat) 3170, 1672, 1556, 1464, 1340, 1289, 784, 734 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ=13.38 (s, 1H), 10.80 (s, 1H), 7.72 (d, J=7.7 Hz, 1H), 7.56 (s, 1H), 7.10 (ddd, J=1.1, 7.7, 7.7 Hz, 1H), 6.98 (ddd, J=1.1, 7.7, 7.7 Hz, 1H), 6.87 (br d, J=7.7 Hz, 1H), 6.01 (d, J=2.5 Hz, 1H), 2.32 (s, 3H), 2.30 (s, 3H) ppm; ^{13}C (100 MHz, DMSO-d_6) δ=169.3, 138.0, 135.5, 131.5, 126.5, 125.8, 125.6, 123.3, 120.7, 117.9, 112.6, 112.4, 109.2, 13.4, 11.2 ppm; MS (ESI) 239 ([M+H]$^+$, 100); HRMS (ESI): Found, 239.1179. $C_{15}H_{15}N_2O$ requires 239.1179 (−0.1 ppm error). These data were consistent with those published.[19]

2.12. Diethyl 2-(2-bromopyridin-3-ylamino)-2-oxoethylphosphonate 17

White solid (3.36 g, 81%), mp 68–70 °C; R_f 0.42 (MeOH/EtOAc, 10:1); IR (neat) 3230, 2985, 1688, 1578, 1529, 1452, 1392, 1300, 1229, 1053, 1025, 975, 799 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.98 (br s, 1H), 8.62 (dd, J=1.8, 8.2 Hz, 1H), 8.11 (dd, J=1.8, 4.6 Hz, 1H), 7.27 (m, 1H), 4.25–4.17 (m, 4H), 3.07 (d, J=20.7 Hz, 2H), 1.36 (t, J=7.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=163.4 (d, J(C-P)=4.2 Hz), 145.2, 133.9, 133.5, 129.5, 123.5, 63.0 (d, J(C-P)=6.5 Hz), 37.2 (d, J(C-P)=130.7 Hz), 16.0 (d, J(C-P)=5.9 Hz) ppm; MS (ESI) 352 ([M+H]$^+$, 100); HRMS (ESI): Found, 351.0104. $C_{11}H_{17}{}^{79}BrN_2O_4P$ requires 351.0107 (−1.0 ppm error).

2.13. (*E*/*Z*)-3-Benzylidene-1*H*-pyrrolo[3,2-*b*]pyridin-2(3*H*)-one 18

Yellow solid (70%, E/Z=3.8:1, inseparable), mp 212–214 °C lit.[21] (mixture) mp 206–208 °C; R_f 0.43 (petrol/EtOAc, 1:1); IR (neat) 2919, 1704, 1610, 1569, 1409, 1176, 768 cm^{-1}; ^{1}H (400 MHz, DMSO-d_6, E/Z mixture) δ=10.85 (s, 1H, *E*), 10.79 (s, *Z*), 8.81 (m, 2H, *Z*), 8.52 (m, 2H, *E*), 8.30 (dd, J=2.6, 3.8 Hz, 1H, *Z*), 8.16 (dd, J=1.8, 4.4 Hz, 1H, *E*), 8.06 (s, 1H, *E*), 7.73 (s, 1H, *Z*), 7.53 (m, 3H, *E*), 7.28 (m, 3H, *Z*), 7.21 (m, 2H, *E*), 7.05 (m, 3H, *Z*) ppm (data consistent with those published[21]); ^{13}C (100 MHz, DMSO-d_6, E/Z mixture) δ=168.3 (C2), 166.3 (C2′), 144.6 (C7a′), 142.8 (C7a), 142.3 (C7′), 142.2 (C7), 140.8 (C3a), 139.7 (C3a′), 138.9 (C5), 136.3 (C5′), 134.3 (C6), 133.8 (C6′), 133.7 (C14, 10), 133.1 (C14′, 10′), 131.9 (C3), 131.9 (C3′), 129.0 (C13, 11), 128.8 (C13′,11′), 125.9 (C12′), 125.4 (C12), 124.3 (C9), 123.9 (C9′), 116.7 (C8), 116.0 (C8′) ppm; MS (ESI) 223 ([M+H]$^+$, 100); HRMS (ESI): Found, 223.0866. $C_{14}H_{11}N_2O$ requires 223.0863 (1.4 ppm error).

2.14. (*E*/*Z*)-3-((1-Methyl-1*H*-indol-3-yl)methylene)-1*H*-pyrrolo[3,2-*b*]pyridin-2(3*H*)-one 4

Yellow film (56.5 mg, 72%, E/Z=2:1, inseparable), mp 181–183 °C; R_f 0.35 (petrol/EtOAc, 1:2); IR (neat) 3402, 2923, 1685, 1597, 1515,1472, 1389, 1333, 1195, 1122 cm^{-1}; ^{1}H NMR (400 MHz, MeOD-d_4, E/Z mixture) δ=10.13 (s, 1H), 9.48 (s, 1H), 8.64 (s, 1H), 8.39 (dd, J=1.5, 5.1 Hz, 1H), 8.29 (s, 1H), 8.14 (dd, J=1.5, 5.1 Hz, 1H), 8.06 (m, 1H), 7.98 (m, 1H), 7.57 (m, 2H), 7.36 (m, 4H), 7.28 (m, 2H), 7.20–7.14 (m, 2H), 4.03 (s, 3H), 4.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, E/Z mixture) δ=190.7, 179.0, 145.0, 142.6, 142.2, 140.8, 140.7, 139.8, 135.1, 132.6, 132.4, 132.3, 132.2, 132.0, 131.6, 128.8, 128.7, 123.5, 123.4, 123.3, 122.4, 122.3, 121.1, 120.9, 119.1, 118.9, 116.8, 115.0, 112.4, 110.3, 33.8, 33.7 ppm; MS (ESI) 276 ([M+H]$^+$, 100); HRMS (ESI): Found, 276.1131. $C_{17}H_{14}N_3O$ requires 276.1129 (−2.0 ppm error).

For further characterization, **4**·HCl salt (E/Z ratio 2:1) was prepared, mp 260–262 °C; Sigma–Aldrich (E/Z ratio 8:1) mp ≥270 °C.

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