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Telescoped Enolate Arylation/HWE Procedure for the Preparation of 3-Alkenyl-Oxindoles: The First Synthesis of Soulieotine

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A telescoped sequence involving palladium-catalysed intramolecular enolate arylation followed by an in situ HWE olefination has been developed to provide rapid access to 3-alkenyl-oxindoles. This "one-pot" process, which is greatly accelerated by microwave irradiation, proceeds with low loadings of palladium(II) acetate (0.2–1.0 mol-%), and has been used to prepare a range of adducts derived from aromatic, heteroaromatic and aliphatic aldehydes as well as formaldehyde. In addition, further elaboration of the formaldehyde adducts are described. The applicability of the process has been established by carrying out the first synthesis of Soulieotine, a constituent of a traditional Chinese medicine.

3-Alkenyl-oxindoles form the cornerstone of a range of medicinally and biologically important compounds as well as a number of natural products.[1] Illustrative examples are shown in Figure 1. In terms of pharmaceuticals, mention should be made of the pyrrolylidene oxindoles Semaxanib (SU5416) (**1**)[2] and Sunitinib (SU11248) (**2**),[3] both of which display antiangiogenic and anticancer activity, and Tenidap (**3**), a potent inhibitor of cyclooxygenase, used for the treatment of rheumatoid arthritis and osteo-arthritis.[4] With respect to oxindole-containing natural products, Soulieotine (**4**) and Ammosamide B (**5**) are representative examples. Soulieotine (**4**) was isolated from *Souliea vaginata* which is employed as an antiinflammatory analgesic in traditional Chinese medicine.[5] Ammosamide B (**5**) was recently obtained from the marine-derived *Streptomyces* strain CNR-698[6] and shown to possess cell cycle modulation properties by myosin inhibition.[7] Furthermore, 3-alkenyl-oxindoles are versatile precursors for further synthetic manipulation and have been employed widely in natural product total synthesis[8] and for the preparation of novel "unnatural" adducts.[9,10]

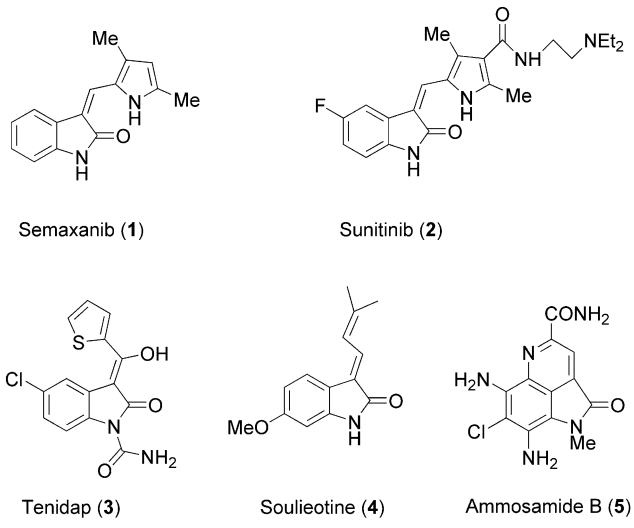

Figure 1. Representative 3-alkenyl-oxindoles.

As part of a programme to develop efficient and practical tandem/telescoped procedures to heterocyclic systems,[11] we became interested in bioactive 3-alkenyl-oxindoles such as those shown in Figure 1. On the basis of our recent development of a telescoped Michael addition/HWE olefination sequence leading to α-methylene-γ-butyrolactones,[11b] we designed a telescoped, one-pot procedure for the streamlined conversion of acylated halo-anilines **6** into 3-alkenyl-oxindoles **8**, as shown in Scheme 1. Thus, the amidophosphonates **6** would be subjected to palladium-catalysed intramolecular enolate arylation to give the cyclised intermediates **7**; subsequent addition of an aldehyde in the presence of base should initiate Horner–Wadsworth–Emmons (HWE) olefination to generate the target alkenyl-oxindoles **8** in a regiocontrolled manner.

Palladium-catalysed amide enolate arylation approaches to "simple" oxindoles are precedented,[12–14] although the published approaches seem to require relatively high loadings of palladium and the use of bulky, electron-rich phosphane, N-heterocyclic carbene or relatively expensive BINAP or dppf ligands. Our aim was to successfully accomplish the telescoped enolate arylation/HWE sequence

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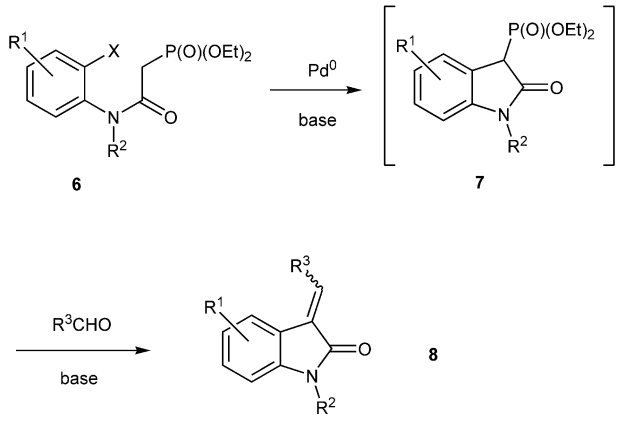


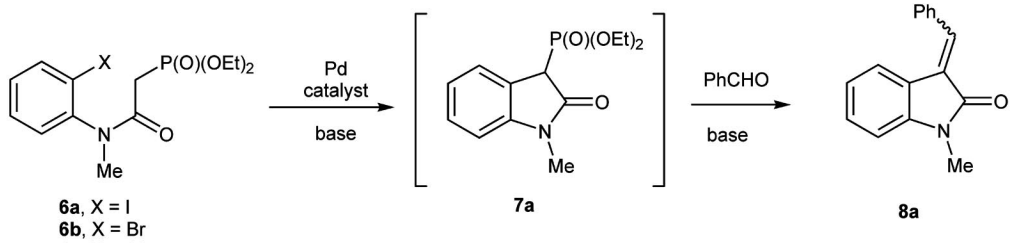
Scheme 1.

shown in Scheme 1 using commercially available reagents and low catalyst loadings. To this end, preliminary studies were carried out using the 2-haloaniline derivatives **6a**–**c** (readily prepared from commercially available diethyl phosphonoacetic acid and the corresponding 2-haloanilines), potassium *tert*-butoxide and benzaldehyde as shown in Table 1. In the first attempt, using iodide **6a**, KO*t*Bu and 5 mol-% $Pd(PPh_3)_4$, followed by addition of benzaldehyde after TLC analysis indicated that the arylation had gone to completion, we were delighted to obtain the desired styrenyl-oxindole **8a** in 81% overall yield (Entry i). The corresponding bromide **6b** gave a similar yield (Entry ii) but the arylation step was considerably slower; the corresponding aryl chloride **6c** did not undergo coupling under these conditions (Entry iii). Although successful with **6a** and **6b**, the duration of both arylation and olefination processes was unacceptable (2–24 h and then 24 –76 h in THF at reflux). Variations in solvent, base and catalyst were therefore explored to accelerate this telescoped sequence but without any major improvement [although it was found that potassium 3,7-dimethyl-3-octylate (KDMO), ca. 3 M in heptanes, provided a more reliable and convenient source of base].

Gratifyingly, the use of microwave irradiation resulted in a dramatic reduction in reaction times (Entries iv–vii). Treatment of aryl bromide **6b** with 5 mol-% $Pd(PPh_3)_4$ and KDMO followed by microwave heating gave complete arylation in just 10 min and HWE olefination with benzaldehyde was complete in 30 min producing adduct **8a** in 78% isolated yield (Entry iv). Reducing the $Pd(PPh_3)_4$ loading from 5 mol-% to 1 mol-% had no deleterious effect on time or yield (Entry v), although the aryl chloride **6c** still reacted sluggishly under these conditions. (Entry vi).

Given the greater availability and stability, and lower cost, of aryl bromides compared to aryl iodides, we decided to optimise the bromide procedure in terms of the palladium catalyst used to mediate enolate arylation. Success was found with the use of 1 mol-% palladium(II) acetate (Entry vii) which produced adduct **8a** in 87% yield. Not

Table 1. Preliminary studies on the conversion of anilides **1** into 3-styrenyl-oxindole **8a**.[a]



6a, X = I
6b, X = Br
6c, X = Cl

7a

8a

Entry	Anilide	Conditions	Heat (Δ) or MW	Yield **8a** (%)[b]
i	**6a**	(i) $Pd(PPh_3)_4$ (5 mol-%), KO*t*Bu, 2 h (ii) 70 h	Δ	81
ii	**6b**	(i) $Pd(PPh_3)_4$ (5 mol-%), KDMO, 24 h (ii) 24 h	Δ	78[c]
iii	**6c**	$Pd(PPh_3)_4$ (5 mol-%), KDMO, 4 d	Δ	0
iv	**6b**	(i) $Pd(PPh_3)_4$ (5 mol-%), KDMO, 10 min (ii) 30 min	MW	78[d]
v	**6b**	(i) $Pd(PPh_3)_4$ (1 mol-%), KDMO, 10 min (ii) 30 min	MW	82
vi	**6c**	(i) $Pd(PPh_3)_4$ (5 mol-%), KDMO, 10 min (ii) 30 min	MW	22
vii	**6b**	(i) $Pd(OAc)_2$ (1 mol-%), KDMO, 10 min (ii) 30 min	MW	87[e,f, g]

[a] All reactions were carried out as follows unless otherwise noted: **6** (ca. 0.3 mmol) in THF (3 mL), base (2.5 equiv.) then PhCHO (5 equiv.). Reactions carried out in THF at reflux or under MW irradiation at 100 °C (CEM Discover, 50 W max.). [b] *E*/*Z* ratio 5:1. [c] Identical yield using KO*t*Bu (no product with LHMDS). [d] In the absence of the palladium catalyst no arylation was observed. [e] Repeating this reaction exactly but with 0.2 mol-% $Pd(OAc)_2$ gave a 46% yield of **8a**. [f] Repeating this reaction in THF at reflux (no MW) gave a 65% yield of **8a** after 46 h. [g] With PhCHO (1.2 equiv.), the HWE reaction required 1.5 h giving **8a** in 73% yield.

only is $Pd(OAc)_2$ relatively inexpensive, it is easy to handle, oxidatively stable and has an excellent "shelf-life". It should also be emphasised that this coupling proceeded without the need for phosphane additives. It was also established that the catalyst loading could be reduced to as little as 0.2 mol-% $Pd(OAc)_2$. In the majority of the reactions, an excess of benzaldehyde (5 equiv.) was employed but it was found that the sequence could be performed with a stoichiometric quantity, although a longer HWE reaction time was required. In general, where the aldehyde is of low value, the use of 1 mol-% $Pd(OAc)_2$ and 5 equiv. of aldehyde seems to be optimum.

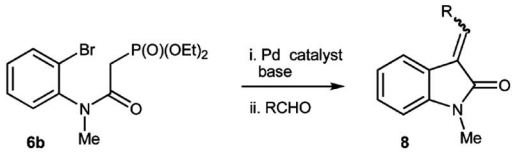
Following on from the optimisation studies, we went on to investigate the scope of the enolate arylation/HWE sequence using aryl bromide **6b** in terms of the aldehyde component (Table 2).

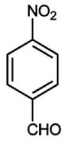
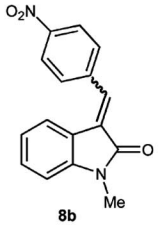
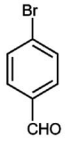
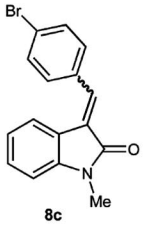
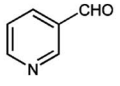
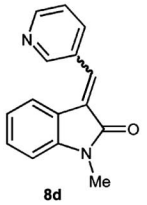
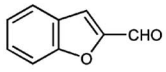
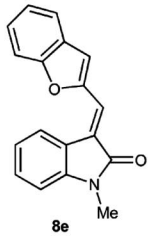
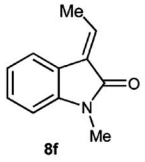
As can be seen, in addition to benzaldehyde used in the optimisation study, 4-nitro- and 4-bromobenzaldehyde reacted in the expected manner giving the corresponding adducts **8b** and **8c** in moderate to good yields (Entries i and ii). Heteroaromatic aldehydes were also successful (Entries iii and iv); thus, pyridine-3-carboxaldehyde gave adduct **8d** in 82% yield, and 2-formylbenzofuran gave the novel adduct **8e** in 59% yield as a single stereoisomer (tentatively assigned as the *E*-isomer shown on the basis of NOESY studies). Finally, the use of enolisable aliphatic aldehydes and ketones was investigated; under the standard conditions, only acetaldehyde gave the expected product **8f**, albeit in low yield (Entry v). It should be noted that all of the reactions in Table 2 were carried out using the conditions optimised for benzaldehyde; it may well be that additional optimisation for each substrate would improve yields.

In addition to the aldehydes shown in Table 2, trapping with formaldehyde was also explored (Scheme 2). It is known that the expected intermediate **8g** is unstable and has to be trapped in situ.[10] By using formaldehyde in the palladium-catalysed intramolecular enolate arylation/HWE sequence and then adding sodium borohydride, we were able to isolate the 3-methyl-oxindole **9**[15] in excellent yield over the three step, one-pot process. In a similar manner, enone **8g** could be intercepted with lithium dibutylcuprate to generate the corresponding 3-pentyl-oxindole **10**.[16] To establish the generality of this one-pot elaboration sequence, the benzaldehyde adduct **8a** was reacted in situ with lithium dibutylcuprate followed by iodomethane; this four step sequence (enolate arylation/HWE/conjugate addition/alkylation) gave the 3,3′-dialkylated oxindole **11** in reasonable, unoptimised yield.

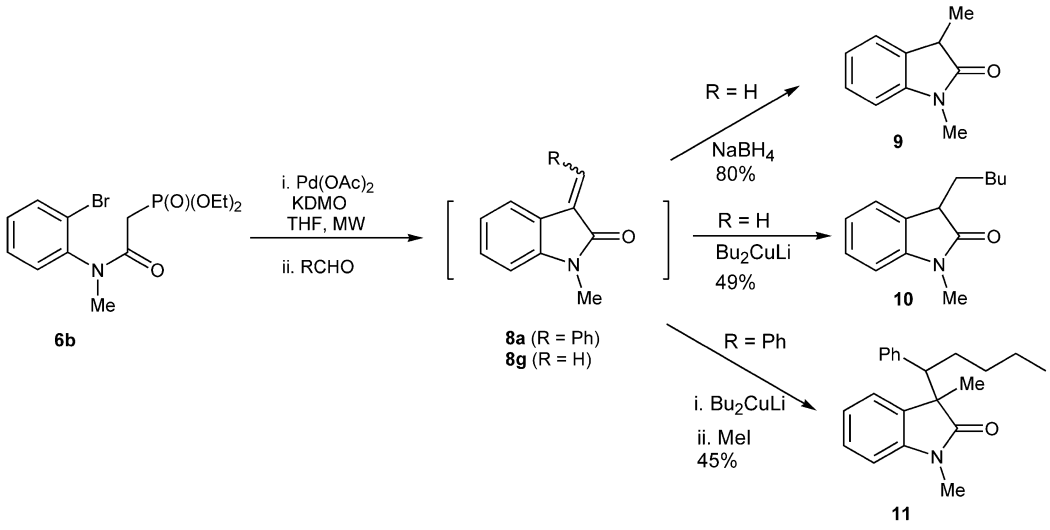
Finally, our attention turned to a simple natural product target with which to validate the utility of the enolate arylation/HWE sequence. Soulieotine (**4**) was isolated from the rhizomes of *Souliea vaginata*, a plant employed as an anti-inflammatory analgesic in traditional Chinese medicine.[5] As Soulieotine (**4**) has not yet been prepared by total synthesis, and as there is some doubt about the alkene stereochemistry (see later), we embarked upon its preparation. To construct an oxindole such as **4**, in which the nitrogen is unsubstituted, it was necessary to employ an easily removable protecting group. We therefore commenced with the readily prepared amine **12**[17] and prepared the PMB-protected cyclisation precursor **13** as shown in Scheme 3. Ap-

Table 2. Variation of the aldehyde in the enolate arylation/HWE sequence.[a]

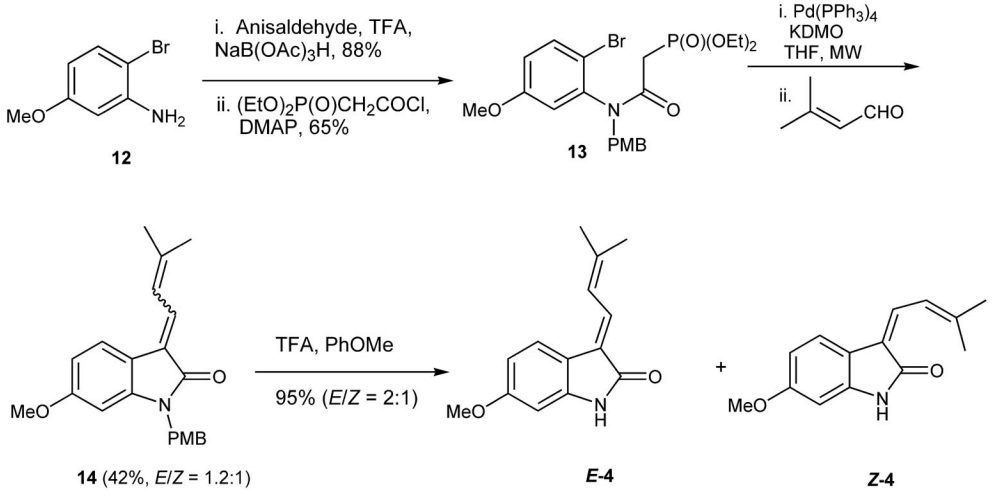


Entry	Aldehyde	Product	Yield / % (*E*/*Z*)
i			54 (1.25:1)
ii			78 (2.5:1)
iii			82 (2:1)
iv			59 (*E* only)
v[b]	MeCHO		14 (*E* only)

[a] All reactions were carried out using **6b** (ca. 0.3 mmol) in THF (3 mL), $Pd(OAc)_2$ (1 mol-%), KDMO in heptanes (2.5 equiv.) for 10 min then RCHO (5 equiv.) for 30 min; both steps carried out under MW irradiation at 100 °C (CEM Discover, 50 W max.). [b] No adducts obtained using pivaldehyde and cyclohexanone.



Scheme 2.



Scheme 3.

plication of the enolate arylation/HWE sequence to substrate **13** using 3-methylbutenal as the trapping agent gave the expected adduct **14** 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 (this effect was also observed with other N-PMB analogues). TFA deprotection then produced a mixture of *E*-**4** and *Z*-**4** (2:1) which were separated by chromatography (although they readily interconvert; the 2:1 ratio is re-established after one hour in $CHCl_3$ at room temp.). The major isomer was established as *E*-**4** by NOE studies and by comparison of NMR spectroscopic data with related systems.[18] The data for *E*-**4** corresponded well with those published[5] for Soulieotine, removing any uncertainty concerning the stereochemistry of the exocyclic alkene. (In the publication outlining the isolation of Soulieotine **4**,[5] the natural product was described as the *E*-isomer but the *Z*-isomer was drawn in error.) Finally, unambiguous proof of the structure of *E*-**4** was established by X-ray crystallography (Figure 2).

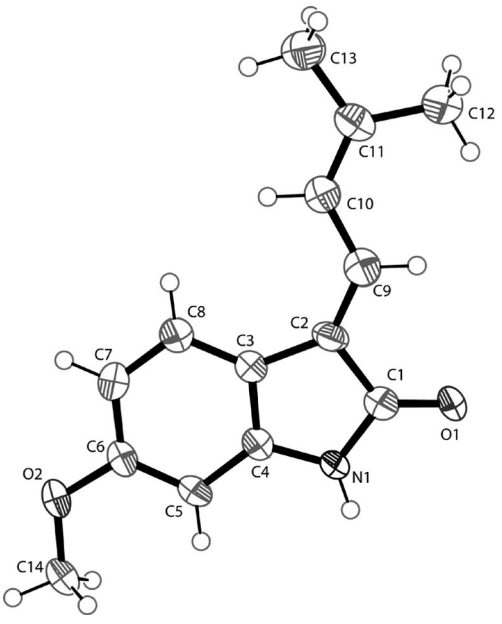


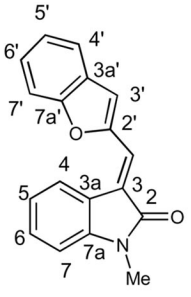
Figure 2. X-ray structure of *E*-**4** depicted using ORTEP-3.

Summary

A telescoped palladium-catalysed enolate arylation/HWE olefination sequence has been developed to provide rapid access to 3-alkenyl-oxindoles from readily available bromoanilines. This "one-pot" process is greatly accelerated by microwave irradiation, and proceeds with low loadings of palladium(II) acetate (0.2–1.0 mol-%). In terms of the HWE process, aromatic, heteroaromatic and aliphatic aldehydes have all been successsfully employed. In addition, formaldehyde can be utilised in the HWE reaction and the resulting α-methylene lactam further elaborated in situ. Soulieotine, isolated from the rhizomes of *Souliea vaginata*, has been prepared to illustrate the potential of this telescoped process and structural clarification has been provided [Soulieotine is predominantly (*E*)-6-methoxy-3-(3′-methyl-2′-butenylidene)-2-indolinone, *E*-**4**].

Experimental Section

(*E*)-3-(Benzofuran-2′-ylmethylidene)-1-methyl-2-indolinone (8e): A solution of aryl bromide **6b** (110 mg, 0.30 mmol), KDMO (2.7 M in heptanes, 0.28 mL, 0.75 mmol), and $Pd(OAc)_2$ (0.7 mg, 0.003 mmol) in THF (3 mL) under Ar was heated under MW irradiation at 100 °C (CEM Discover, 50 W max.) for 10 min. After this time 2-benzofurancarboxaldehyde (220 mg, 1.51 mmol) was added in one portion and the resulting solution was heated under MW irradiation at 100 °C for 30 min. The reaction mixture was treated with satd. NH_4Cl (3 mL) and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, petroleum ether/EtOAc, 95:5), gave **8e** (49 mg, 59%) as a yellow solid, m.p. 173–174 °C (from CH_2Cl_2/pentane); R_f = 0.2 (petroleum ether/EtOAc, 80:20).



8e

IR (neat): ṽ = 1702, 1624, 1601, 1467, 1450, 1377, 1291, 1256, 1145, 1096, 1024, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, J = 7.5 Hz, 1 H, 4-H), 7.66–7.60 (m, 2 H, 4′-H, 6′-H), 7.56 (s, 1 H, 3′-H), 7.43 (ddd, J = 10.0, 7.5, 1.0 Hz, 1 H, 5′-H), 7.36–7.27 (m, 2 H, 7′-H, 6-H), 7.18 (s, 1 H, CH=), 7.14 (ddd, J = 7.5, 7.5, 1.0 Hz, 1 H, 5-H), 6.83 (d, J = 7.5 Hz, 1 H, 7-H), 3.28 (s, 3 H, N-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (C-2), 156.5 (C-7a′), 153.1 (C-2′), 144.7 (C-3a), 130.2 (C-7′), 128.5 (C-3), 127.2 (C-5′), 125.9 (C-4), 125.1 (C-3a′), 123.9 (C-6), 122.5 (C-4′), 122.2 (C-5), 121.4 (C-7a), 120.8 (C-3′), 115.7 (CH=), 111.7 (C-6′), 108.0 (C-7), 25.9 (N-Me) ppm. MS (ESI): *m*/*z* (%) = 298 (100) $[M + Na]^+$. HRMS (ESI): found 298.0833. $C_{18}H_{13}NNaO_2$ calcd. 298.0838 (δ =1.9 ppm error).

CCDC-723953 (for *E*-**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Full characterisation data for compounds **6b**, **6c**, **11**, **13**, **14**, *E*-**4** and *Z*-**4**.

Acknowledgments

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