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Three-component bimetallic (Pd/In) mediated cascade allylation of C = X functionality
Part 1. Scope and Class 1 examples with aldehydes and ketones

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Abstract

A new general three-component Pd/In bimetallic cascade reaction with four synthetic variants involving aryl iodides, allenes and C = X compounds affording homoallylic alcohols/amines as products is described and exemplified for Class 1 processes (intermolecular Pd–intermolecular In steps). Remarkable increases in yield and reaction rates were observed in the presence of amine additives. Excellent diastereoselection is exhibited when 2-hydroxycyclohexanone is employed, and semi-empirical and ab initio calculations are used to rationalise the observed *syn*:*anti* diastereoselectivity.

Keywords: Bimetallic; Cascade allylation; Aldehydes; 1,2-Diones

1. Introduction

π-Allylpalladium(II) complexes are important intermediates in a plethora of catalytic reactions including allylic substitutions [1], allylic oxidation [2] and 1,4-oxidation of conjugated dienes [3]. These reactions all involve nucleophilic attack of carbon or heteroatomic nucleophiles on the π-allyl moiety. We and others have been involved in generating π-allylpalladium(II) intermediates via aryl/heteroaryl iodides and allenes or substituted allenes in the presence of palladium(0) [4–8] and we have utilised this methodology in multi-component cascade processes [9].

Here, we describe how the natural electrophilic reactivity of π-allylpalladium complexes **1** generated from aryl iodides and allenes can be reversed by reductive transmetallation with indium powder. The resultant umpolung allylindium species **2** subsequently adds to the C = X compound affording homoallylic alcohols/amines **3** (Scheme 1) [10–12]. Palladium catalysts are tolerant towards a wide range of functional groups including carbonyls and imines. This bimetallic cascade process allows the synthetic flexibility to access reactions of these usually immune functionalities.

Transmetallation of allenylpalladium(II) [13] and conventionally generated π-allylpalladium(II) species by indium salts have also been reported by others [14,15].

Allylation of carbonyl compounds or imines giving the corresponding homoallylic alcohols or amines is an important synthetic transformation and numerous reagents have been developed for this purpose [16]. Indium has emerged as the metal of choice to mediate the reaction because of its environmentally benign properties allied with a high degree of *chemo*-, *regio*- and *diastereo*-selectivity [17,18].

We have identified four synthetic variants of the Pd/In bimetallic three-component process depending on whether the Pd-catalysed step and the In-mediated allylation are *inter*- or *intra*molecular (Table 1). Class

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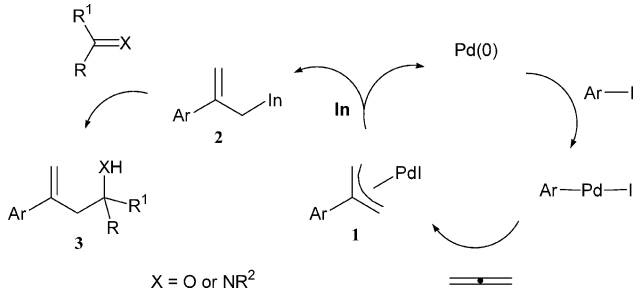


Scheme 1.

Table 1
Variants of Pd/In cascade

Class	Pd step	In step
1	Intermolecular	Intermolecular
2	Intermolecular	Intramolecular
3	Intramolecular	Intermolecular
4	Intramolecular	Intramolecular

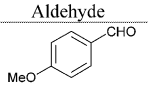
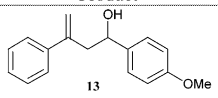
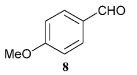
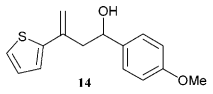
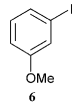
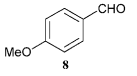
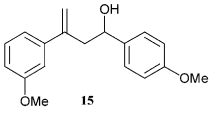
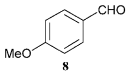
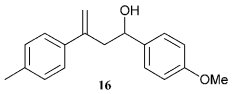
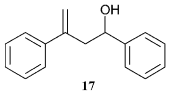
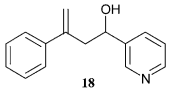
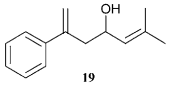
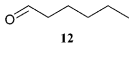
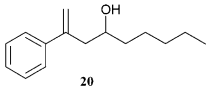
1 processes require both the Pd and In steps to be intermolecular and this paper will disclose full experimental details of this class utilising aldehydes and ketones as electrophiles. Subsequent papers in this series will deal with Classes 2–4 and other electrophiles [10–12,15,19].

2. Results and discussion

Initial studies focused on reactions employing iodobenzene (1.5 mmol), *p*-anisaldehyde (1.0 mmol), allene (1 bar) and indium powder(1.0 mmol) with a catalytic system comprising $Pd(OAc)_2$ (10 mol%) which is reduced in situ to Pd(0) and tris(2-furyl)phosphine (20 mol%) in DMF in a Schlenk tube. Temperatures below 80 °C or the use of triphenylphosphine resulted in incomplete conversion of the starting materials. To achieve complete and reproducible consumption of the aldehyde 1.5 mmol of indium powder was required affording the desired homoallylic alcohol **13** in 64% isolated yield after aqueous work-up. Blank experiments conducted in the absence of In or Pd(0) proved that the presence of both metals is required for the cascade to proceed. Encouraged by these results, a variety of aryl and heteroaryl iodides **4**–**7** were screened using the optimised conditions and all were successfully incorporated into the reaction (Table 2).

Aromatic, heteroaromatic, aliphatic and α-β-unsaturated aldehydes **8**–**12** were also reacted under the same conditions with iodobenzene and allene gas affording homoallylic alcohols in yields ranging from 43 to 70% (Table 2).

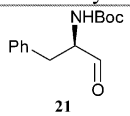
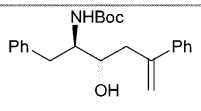
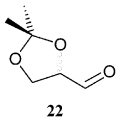
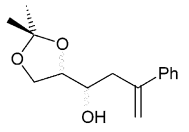
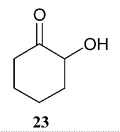
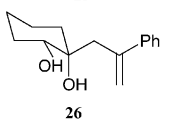
Table 2
Class 1 bimetallic cascades

Aryl iodide	Aldehyde	Product	Yield(%)[a]
 4	 8	 13	64
 5	 8	 14	66
 6	 8	 15	60
 7	 8	 16	40
 4	 9	 17	43
 4	 10	 18	65
 4	 11	 19	70[b]
 4	 12	 20	65

[a]Isolated yield [b]Alcohol : triene 2:1

We have also briefly studied the effect of chelating groups α to the aldehyde, as have others, such as nitrogen [21], hydroxyl [22] and alkoxy [23], on the stereochemical outcome of the reaction of iodobenzene and allene following the general procedure (Table 3). The products were obtained in comparable yield and

Table 3
Effect of chelating groups on Class 1 cascades

Carbonyl	Product	Syn:Anti	Yield(%)[a]
 21	 24	1:1	75
 22	 25	5:1	55
 23	 26	96:4	67

[a]Isolated yield

with the same degree of diastereoselectivity as observed in the corresponding aqueous indium-mediated Barbier reactions.

In the case of 2-hydroxycyclohexanone **23**, a 96:4 mixture of diastereoisomers of **26** was observed. The relative stereochemistry of the major isomer was assigned on the basis that the large 2-phenylallyl substituent would adopt an equatorial position. The conformer with the 2-phenylallyl group axial is ca. 5 kcal mol^{-1} higher in energy according to MM2 calculations [24].

The $^{3}J_{HH}$ coupling constants of the proton at δ 3.34 ppm (H^{1}_{ax}) are characteristic of an axial proton (Fig. 1). The *syn* relationship of the two hydroxyl groups was confirmed by n.O.e. data (Fig. 1) in accordance with Paquette's observations on the addition of allylindium to 2-hydroxycyclohexanone [10,22].

A transition state involving metal chelation has been previously proposed to account for the *syn*-diastereoselectivity of additions of allyl indium to 2-alkoxy- and 2-hydroxy cyclohexanones [10]. In order to investigate the observed stereochemical trends in the present additions, we have used both semi-empirical and ab initio calculations [25] to model the transition states for the two extreme cases involving additions to **21** (i.e. no selectivity) and **23** (i.e. highly *syn* selective).

For additions to aldehyde **21**, the four possible Zimmerman–Traexler, chair-like transition states (**A**–**D**, Scheme 2) have been modelled using semi-empirical calculations [25]. These correspond to additions of the allyl indium intermediate to either the *re* or *si* face of the aldehyde, each of which can involve two possible chair-like arrangements (Scheme 2).

Although these data indicate that this reaction should proceed preferentially via transition states **A** (giving *syn*-**24**) and **C** (giving *anti*-**24**), at this level of approximation, these have essentially the same heats of formation and so would indicate no preference for either type of diastereoisomer in keeping with our experimental observations. For **A**, the structure was actually observed to be in a twist-boat arrangement so placing the substituent into a pseudo-equatorial conformation. Interestingly, transition structures **A** and **D** do not involve any chelation of the urethane moiety to the indium centre, despite both possessing the required orientation relative to the metal (although this would involve a seven-membered ring chelate), and in both structures, the urethane group is oriented away from the metal centre.

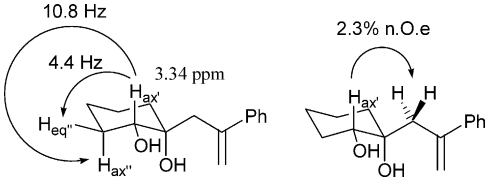


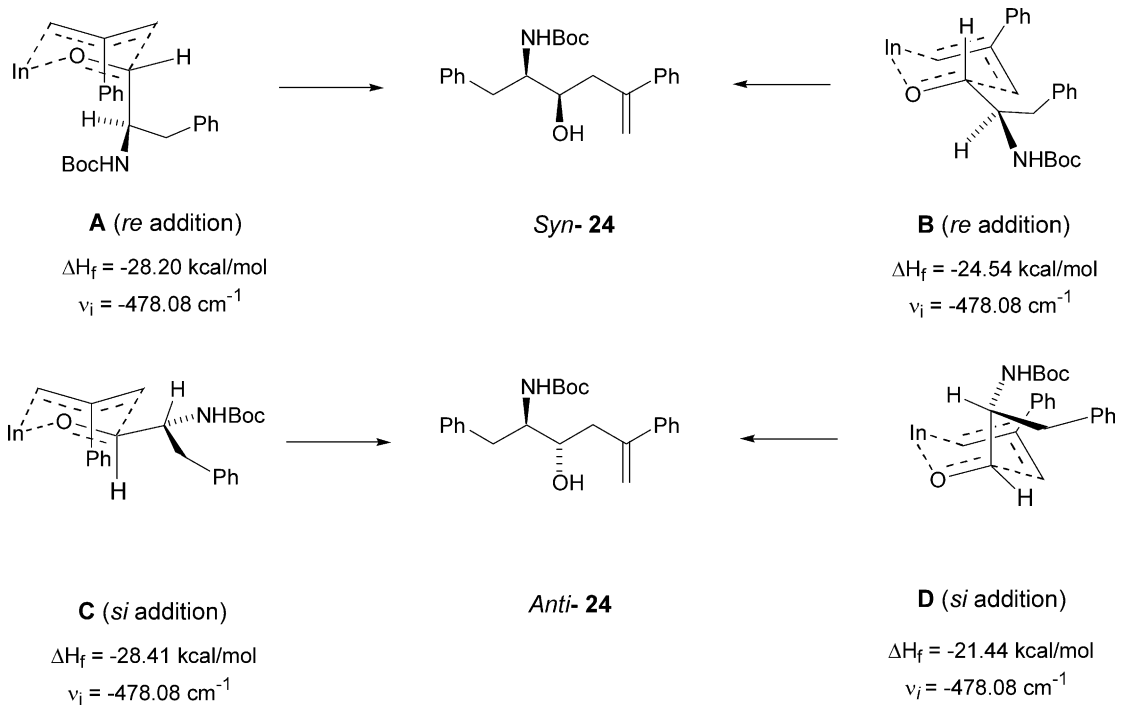
Fig. 1. Coupling constant and n.O.e. data for **26**.

For additions to 2-hydroxy cyclohexanone **23**, the number of possible chair-like transition states doubles as there now four possible chair-like conformations (due to the presence of two spiro-fused six-membered rings) for each of the *re* and *si* addition modes respectively. The transition structures (**E**–**L**) corresponding to all of these were also estimated using semi-empirical calculations [25] (Scheme 3).

These calculations reveal that transition structures **F**, **H**, and **I** all involve chelation of the hydroxyl to the indium atom and all are lower in energy than the remaining five alternative structures. Transition structure **I** ($\Delta H_f = -19.42$ kcal mol^{-1}, leading to the *anti* product) has the lowest energy overall, but is closely followed by transition structure **F** (($\Delta H_f = -18.07$ kcal mol^{-1}, leading to the *syn* product). Although these gas-phase semi-empirical calculations add support to the proposed chelation model [20], they do not adequately explain the observed preference for the *syn* diastereoisomeric diol. We have therefore used ab initio calculations to locate the transition structures corresponding to **F** and **I** in order to enable a more precise estimation of their relative energies. These now reveal that transition state **F** (ΔH_f (321 − *G*) = −6439.94305 au) is lower in energy than structure **I** (ΔH_f (321 − *G*) = −6439.93805 au) by 0.005 au which corresponds to 3.14 kcal mol^{-1}. It was also noted that structure **F** has a larger electronic dipole moment (7.86 D) than that of **I** (7.65 D) and so may be expected to be favoured in polar solvents. In order to estimate the possible role of solvent dielectric on the relative energies of **F** and **I**, we wished to perform semi-empirical calculations in a simulated solvent dielectric corresponding to DMF (dielectric constant 36.7). In order to simplify the calculations, these were performed for **F** and **I** using aluminium in place of indium and substituting the phenyl ring for hydrogen [25]. These solvent-based calculations also favour transition structure type **F** over that of type **I** by 3 kcal mol^{-1} and again predict a preference for the *syn* product.

Clearly, although a small preference for the observed diastereoselectivity has been revealed, it needs to be borne in mind, particularly for the semi-empirical calculations, that for simplicity, the environment around the metal atom has been approximated by involving only two attached ligands.

We next turned our attention to studying reactive ketones, such as 1,2-diones [26], as electrophiles in the three-component cascade reaction to expand the diversity available from the process. *N*-Methylisatin **29** was found to be a suitable component reacting with iodobenzene and allene following the protocol described above to afford 3-hydroxyoxindole **33** in 61% yield (Table 4). Various other aryl and heteroaryl iodides



Scheme 2. Heats of formation (ΔH_f) and imaginary vibrational frequencies (ν_i) for transition states corresponding to additions to aldehyde **21**.

were successfully incorporated with similar yields. A range of α-keto esters **30**–**32** were also employed in the reaction affording α-hydroxy esters **38**–**40** as products in 51–65% yield.

Although the Pd/In bimetallic cascade process is a potentially much more powerful variant of the Barbier reaction, it frequently suffers from modest yields. In seeking to remove this constraint we have been surveying the effect of additives on the rate and yield of the bimetallic cascade. Thus, we recently observed that the addition of one equivalent of piperidine to the reaction of iodobenzene, allene and benzaldehyde dramatically increased the yield of **17** from 43% to 83% whilst reducing the reaction time from 16 to 2 h.

Encouraged by this observation, a series of amine additives were examined and the results are summarised in Table 5. For strict comparison purposes a standard protocol was adopted: iodobenzene (1.5 mmol), benzaldehyde (1 mmol), additive (1 mmol, one equivalent), In (1.5 equivalents), $Pd(OAc)_2$ (10 mol%) and tri(2-furyl) phosphine (20 mol%) were reacted in DMF at 80 °C for 2 h (Schlenk tube).

Under these conditions the reaction fails to occur in the absence of the additive (Table 5, entry 1). It is mechanistically informative to note that, in the presence of secondary amine additives, aldehyde capture by the allylindium species **2** occurs preferentially over amine capture **1** → **41** of the π-allylpalladium(II) species except when two equivalents of piperidine or piperazine are used (Table 5, entries 3 and 6) and that capture of the allylindium species **2** by iminium ion **42** is not observed (Scheme 4). With 0.5 equivalent of piperidine a substantially lower yield is observed compared to when one equivalent is used (Table 5, entry 4).

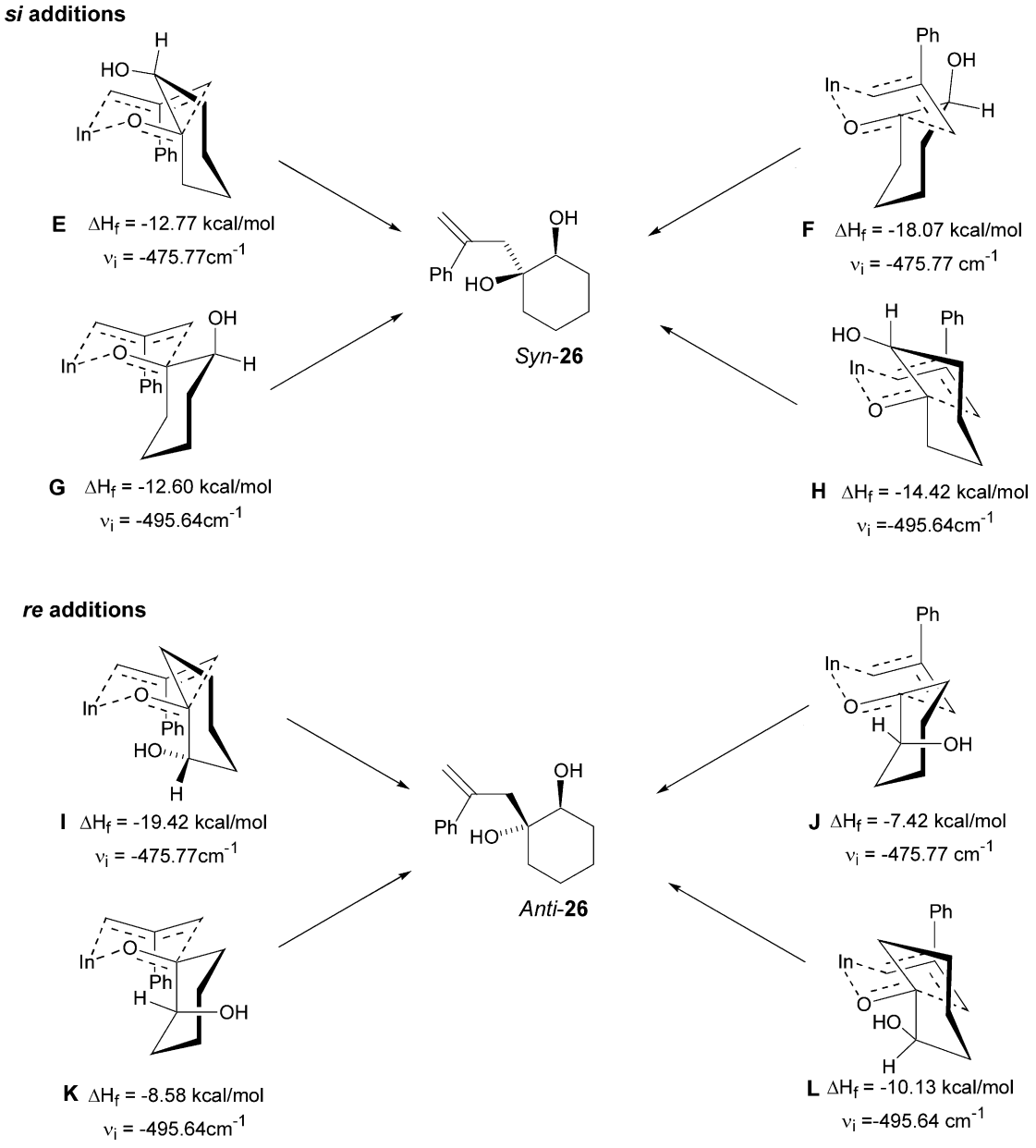
The increase in yield exhibited by each of the additives shows no correlation with pK_a values. Piperidine, pyrrolidone and pyridine (Table 5, entries 2, 10 and 16) exhibit a wide range of pK_a values yet all dramatically increase the yield.

All the cyclic amines effect an improvement in yield. Acyclic amines have little or no effect (Table 5, entries 12–15); except for (*S*)-1-phenylethylamine (Table 5, entry 21) suggesting steric effects are important. This is reinforced by the use of 2,2,6,6,-tetramethyl piperidine (Table 5, entry 5), where only trace amounts of product are observed.

Pyridine and to a lesser extent DMAP (Table 5, entries 16 and 17) both show rate acceleration, again illustrating that pK_a is not the important issue.

Interestingly, certain cyclic amides promote the reaction (Table 5, entries 10 and 11), although with methyl (*S*)-(+)-pyrrolidinone-5-carboxylate as the additive no chirality was induced in the final product (chiral HPLC). (*S*)-2-Methoxymethyl-pyrrolidine, (*S*)-prolinamide and (*S*)-1-phenylethylamine gave 85, 80 and 70% yield of the racemic homoallylic alcohol respectively (Table 5, entries 19, 20 and 21).

The failure of the amines to compete effectively with In for the π-allylpalladium(II) species and the absence of the iminium ion derived product **43** provides clear



Scheme 3. Heats of formation (ΔH_f) and imaginary vibrational frequencies (ν_i) for transition states corresponding to additions to ketone **23**.

evidence of substantial rate differences between the three potentially competing processes in Scheme 2.

It is possible that the additives play a role in solubilising the indium powder, thereby increasing its concentration in solution and accelerating the transmetallation. To test this hypothesis, two standard Barbier reactions were performed (Scheme 5) [27]. To a solution of allylindium, formed from stirring allyl bromide and indium in DMF, was added one equivalent of piperidine along with the aldehyde. A blank experiment was also conducted without any piperidine. The NMR spectra of the crude reaction products indicate that after 1 h reaction time, a higher conversion of aldehyde to product is obtained in the presence of piperidine. Thus the ratio of **9**:**45** is 1:1.5 with piperidine and 5:1 in its absence.

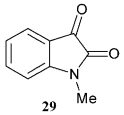
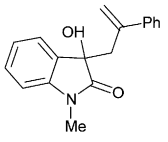
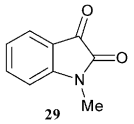
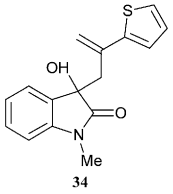
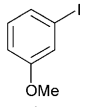
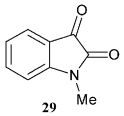
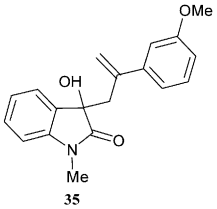
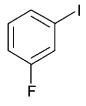
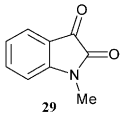
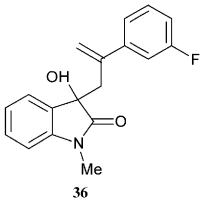
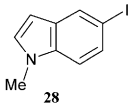
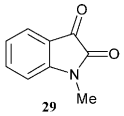
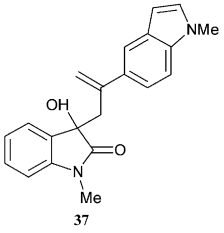
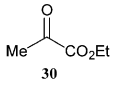
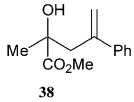
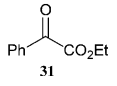
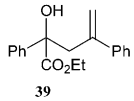
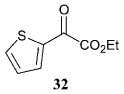
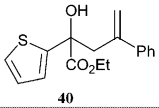
Another possible explanation, based on Table 5, is that the positive effects of the additives are due to a protective effect on the catalytically active Pd species allowing a higher catalytic turnover whilst increasing the yield and decreasing the reaction time.

The generality of the additive effect was demonstrated for a variety of aldehydes and aryl iodides using piperidine as the additive (Table 6). A substantial improvement in yield was noted in all cases.

In conclusion, the Class 1 three-component Pd/In cascade reaction is a versatile process allowing rapid access to a range of substituted homoallylic alcohols.

Amine additives have made the process much more attractive by dramatically increasing yields and shortening reaction times. Further work to elucidate the nature of the allylindium intermediate [28] and the exact role of the additives is in progress.

Table 4
Class 1 cascades with 1,2-diones

Aryl iodide	1,2-dione	Product	Yield(%)[a]
 4	 29	 33	61
 5	 29	 34	58
 6	 29	 35	60
 27	 29	 36	63
 28	 29	 37	53
 4	 30	 38	65
 4	 31	 39	53
 4	 32	 40	51

[a] Isolated yield

Table 5
Effect of additives on the yield of **3a**

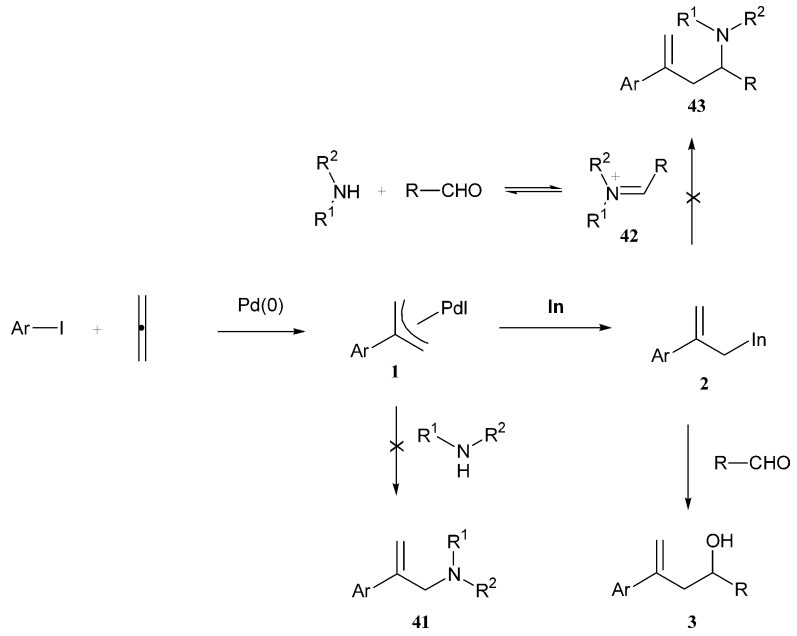
Entry	Amine additive	Yield [a] (%)	pK_a [b]
Cyclic six-membered amines			
1	None	< 10 [c]	–
2	Piperidine	83	11.24
3	Piperidine, 2 equiv.	28 [d]	11.24
4	Piperidine, 0.5 equiv.	< 20 [c]	11.24
5	2,2,6,6-Tetramethylpiperidine	< 7 [c]	11.49
6	Piperazine	28, 34 [d]	9.90
7	Morpholine	70	8.97
Cyclic five-membered amines/amides			
8	Pyrrolidine	47	11.26
9	3-Hydroxy pyrrolidine	69	10.28
10	Pyrrolidinone	78	16.62
11	Methyl (*S*)-(+)-pyrrolidinone carboxylate	88	14.65
Acyclic amines			
12	Triethylamine	0	10.62
13	Diethylamine	< 25 [c]	10.76
14	Diisopropylamine	0	10.76
15	1,1,3,3-Tetramethyl guanidine	0	15.20
Aromatic additives			
16	Pyridine	74	5.23
17	DMAP	41	9.52
18	Phenol	< 20 [c]	9.86
Chiral amines			
19	(*S*)-2-Methoxymethyl-pyrrolidine	85	10.55
20	(*S*)-Prolinamide	80	9.45
21	(*S*)-1-Phenylethylamine	70	9.75

[a] Isolated yields of **3a** after column chromatography unless otherwise stated.
[b] pK_a calculated using Acd pK_a predictor.
[c] Yields calculated from the NMR of the crude product.
[d] Amine captured product.

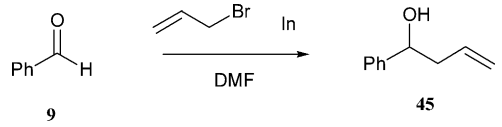
3. Experimental

3.1. General

Nuclear magnetic resonance spectra were recorded on Bruker DPX250, Bruker DPX300 and DPX500 instruments operating at 250, 300 and 500 MHz respectively. Chemical shifts are given in parts per million (δ) downfield from Me_4Si as internal standard. Coupling constants are given in Hertz (Hz). Unless otherwise stated, deuteriochloroform was used as solvent. Melting points were determined on a Kofler hot stage and are uncorrected. Mass spectral data were obtained from a VG Autospec instrument operating at 70 eV (EI) or ZD 2000 electrospray instrument (ES). Microanalyses were obtained using a Carbo Erba MOD11016 instrument and IR spectra were determined on a Nicolet Magna FT-IR 560 spectrometer, as a thin film on sodium chloride plates, prepared by evaporation of a solution of the compound in CH_2Cl_2 directly onto the plates. Column chromatography was performed using flash silica gel 60 and TLC plates were silica gel 60 F254 with plastic backing (Merck). Solvents were dried according



Scheme 4.



Scheme 5.

to established methods [29], unless purchased from Aldrich in sure-seal bottles. The term petrol refers to the 40–60 °C boiling point fraction of petroleum ether. All the compounds are named according to the IUPAC system and were obtained using the ACD/iLAB web service.

3.2. General procedure for the Pd/In bimetallic cascade allylation

The carbonyl compound (1 mmol), aryl iodide (1.5 mmol), indium powder (100 mesh) (1.5 mmol), tris-(2-furyl)phosphine (0.2 mmol), palladium(II) acetate (0.1 mmol) and DMF (10 cm^3) were added to a Schlenk tube which was then sealed, subjected to two freeze, pump, thaw cycles followed by addition of allene gas (~ 1 bar). The flask was allowed to warm to room temperature (r.t.) then heated at 80 °C for 18 h. The reaction mixture was cooled to r.t., vented, diluted with Et_2O (10 cm^3) and then quenched with 5% aqueous HCl (10 cm^3). The layers were separated and the aqueous layer extracted with Et_2O (3×20 cm^3). The combined extracts were washed with water (45 cm^3), dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with mixtures of petrol–EtOAc or petrol–ether affording the products **13**–**20**, **24**–**26**, **33**–**40** and **47**.

3.3. General procedure for the amine accelerated cascade

The same general protocol as above was followed for the amine accelerated process with the addition of 1 mmol of additive. The reactions were stirred at 80 °C for 2 h.

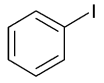
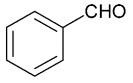
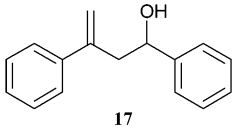
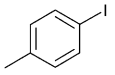
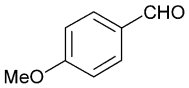
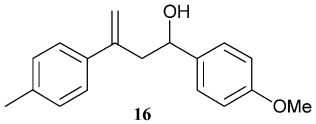
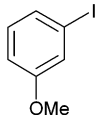
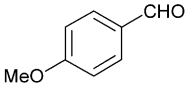
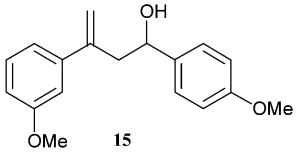
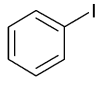
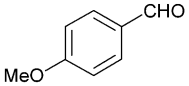
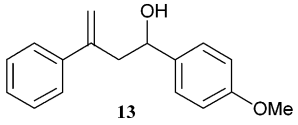
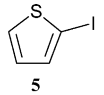
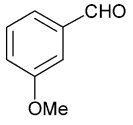
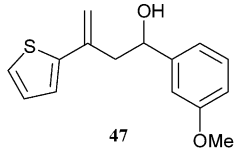
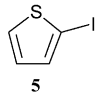
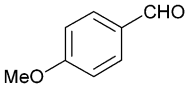
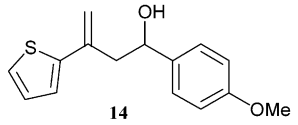
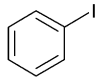
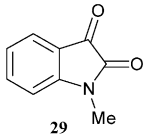
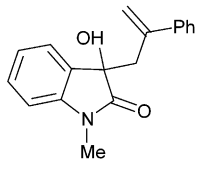
3.3.1. 3-Phenyl-1-(4-methoxyphenyl)-but-3-en-1-ol (*13*)

Procedure **B**. Purification by flash chromatography eluting with 1:1 v/v ether–petrol afforded the product (205 mg, 84%) as a colourless oil. Found: C, 80.10; H, 7.10; $C_{17}H_{18}O_2$ requires C, 80.30; H, 7.20%. δ_H (300 MHz) 2.09 (d, 1H, $J = 2.5$ Hz, OH), 2.86 (dd, 1H, $J =$ 8.7, 14.2 Hz, CH*H*CHOH), 2.95 (ddd, 1H, $J = 14.2$, 4.7 and 1.0 Hz, C*H*HOH), 3.78 (s, 3H, OCH_3), 4.66 (m, 1H, C*H*OH), 5.13 (d, 1H, $J = 1.0$ Hz, CH=C*H*H), 5.38 (d, 1H, $J = 1.4$ Hz, CH=CH*H*), 6.85 (d, 2H, $J = 8.7$ Hz, ArH), 7.25–7.44 (m, 7H, ArH). *m/z* (%) 237 [$M^+ -$ OH, 100], 159 (9), 137 (57), 129 (19). ν_{max} (film)/cm^{-1} 3413, 3000, 2834, 1612, 1514, 1303.

3.3.2. 1-(4-Methoxyphenyl)-3-thiophen-2-yl-but-3-en-1-ol (*14*)

Procedure **B**. Purification by flash chromatography eluting with 4:6 v/v ether–petrol afforded the product (245 mg, 94%) as a colourless oil. Found: C, 68.90; H, 6.15; S, 12.10; $C_{15}H_{16}O_2S$ requires C, 69.20; H, 6.20; S, 12.30%. δ_H (300 MHz) 2.10 (d, 1H, $J = 2.72$ Hz, OH), 2.80 (dd, 1H, $J = 14.2$ and 9.0 Hz, C*H*HOH), 2.89 (dd, 1H, $J = 14.1$ and 4.3 Hz, CH*H*OH), 3.81 (s, 3H, OCH_3),

Table 6
Effect of piperidine in the yield of Class 1 processes

Arl	Carbonyl	Product	Yield %[a] (%)[b]
 **4**	 **9**	 **17**	83 (43)
 **7**	 **8**	 **16**	80 (40)
 **6**	 **8**	 **15**	89 (60)
 **4**	 **8**	 **13**	84 (64)
 **5**	 **46**	 **47**	73 (-)
 **5**	 **8**	 **14**	94 (66)
 **4**	 **29**	 **33**	73 (61)

[a] Isolated yield with 1 eq. piperidine, 2 h reaction time, [b] Isolated yield with no added piperidine, 16 h reaction time.

4.87 (ddd, 1H, $J = 8.8$, 4.3 and 2.2 Hz), 5.04 (s, 1H, C=CHH, C*H*OH), 5.52 (s, 1H, C=CHH), 6.90 (d, 2H, $J =$ 8.7 Hz, ArH), 7.01 (dd, 1H, $J = 5.0$ and 3.7 Hz, Thiophene-H), 7.11 (d, 1H, $J = 3.5$ Hz, Thiophene-H), 7.22 (d, 1H, $J = 5.0$ Hz, Thiophene-H), 7.32 (d, 2H, $J =$ 8.64, ArH). *m*/*z* (%) 260 [M, 28], 243 [$M^+ - OH$, 100], 159 (84), 110.6 (95). ν_{max} (film)/cm^{-1} 3438, 2931, 1682, 1611, 1512, 1248.

3.3.3. 1-(4-Methoxyphenyl)-3-(3-methoxyphenyl)-but-3-en-1-ol (*15*)

Procedure **B**. Purification by flash chromatography eluting with 1:1 v/v ether–petrol afforded the product (254 mg, 89%) as a colourless oil. Found: C, 75.90; H, 7.30; $C_{18}H_{20}O_3$ requires C, 76.00; H, 7.10%. δ_H (300 MHz) 1.99 (d, 1H, $J = 2.5$ Hz, OH), 2.85 (dd, 1H, $J =$ 14.5, 8.6 Hz, CH*H*CHOH), 2.93 (dd, 1H, $J = 4.6$ and 1.0 Hz, C*H*HCHOH), 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.69 (ddd, 1H, $J = 8.6$, 4.6 and 2.4 Hz, C*H*OH), 5.16 (s, 1H, C=C*H*H), 5.40 (s, 1H, C=CH*H*), 6.84–6.89 (m, 3H, ArH), 6.96 (m, 1H, ArH), 7.03 (dd, 1H, $J = 7.7$ and 1.0 Hz, ArH), 7.28–7.31 (m, 3H, ArH). *m*/*z* (%): 267 [$M^+ - OH$, 100], 159 (81). ν_{max} (film)/cm^{-1} 3418, 2937, 2834, 1609, 1576, 1513.

3.3.4. 1-(4-Methoxy-phenyl)-3-p-tolyl-but-3-en-1-ol (*16*)

Procedure **B**. Purification by flash chromatography eluting with 1:3 v/v ether–petrol afforded the product (214 mg, 80%) as a colourless oil. Found: C, 80.50; H,

7.55; $C_{18}H_{20}O_2$ requires C, 80.60; H, 7.50%. δ_H (300 MHz): 2.00 (s, 1H, OH), 2.36 (s, 3H, Ar-CH_3), 2.83 (dd, 1H, $J = 14.3$ and 8.7 Hz, CH*H*CHOH), 2.96 (ddd, 1H, $J = 14.3$, 4.4 and 1.0 Hz, C*H*HCHOH) 3.81 (s, 3H, OCH_3) 4.68 (ddd, 1H, $J = 14.3$, 4.4 and 1.8Hz, C*H*OH), 5.11 (s, 1H, CH=C*H*H), 5.38 (s, 1H, CH=CH*H*), 6.88 (d, 2H, $J = 8.6$ Hz, ArH), 7.17 (d, 2H, $J = 7.9$ Hz, ArH), 7.28 (d, 2H, $J = 8.6$ Hz, ArH), 7.34 (d, 2H, $J = 8.1$ Hz, ArH). *m/z* (%) 251 [$M^+ - OH$, 98], 159 (77), 143 (100). ν_{max} (film)/cm^{-1} 3418, 2998, 2920, 2834, 1612, 1514.

3.3.5. 2,4 diphenyl-pent-4-en-2-ol (*17*)

Procedure **B**. Purification by flash chromatography eluting with 1:3 v/v ether–petrol afforded the product (185 mg, 83%) as a colourless oil. Found: C, 85.40; H, 7.30; $C_{16}H_{16}O$ requires C, 85.70; H, 7.20%. δ_H (300 MHz) 2.05 (d, 1H, $J = 2.3$ Hz, OH), 2.86 (dd, 1H, $J =$ 14.2 and 9.1 Hz, C*H*HCHOH), 3.02 (dd, 1H, $J = 14.2$ and 4.3 Hz, CH*H*CHOH), 4.72 (ddd, 1H, $J = 9.1$, 4.2 and 2.3 Hz, C*H*OH), 5.17 (s, 1H, C=C*H*H), 5.42 (s, 1H, C=CH*H*), 7.39–7.28 (m, 8H, ArH), 7.45 (m, 2H, ArH). *m/z* (%) 207 [$M^+ - OH$, 100], 129(98), 120(24). ν_{max} (film)/cm^{-1} 3407, 3029, 1628, 1494, 1454, 1027.

3.3.6. 3-Phenyl-1-pyridin-3-yl-but-3-en-1-ol (*18*)

Procedure **A**. Purification by flash chromatography eluting with 9:1 v/v ethyl acetate–petrol afforded the product (147 mg, 65%) as a colourless oil. Found: C, 79.7; H, 6.95; N, 6.05; $C_{15}H_{15}NO$ requires C, 80.0; H, 6.70; N, 6.20%. δ_H (250 MHz): 2.66 (bs, 1H, OH), 2.91 (dd, 1H, $J = 14.1$, 9.8 Hz, C*H*HCHOH), 3.01 (dd, 1H, $J = 14.1$, 5.6 Hz, CH*H*CHOH), 4.73–4.78 (m, 1H, C*H*OH), 5.15 and 5.42 (2d, 21H, $J = 1.3$ Hz, C=CH_2), 7.26–7.44 (m, 6H, ArH), 7.69 (d, 1H, $J = 7.9$ Hz, ArH) and 8.45 (m, 2H, ArH). *m/z* (%): 226 [$M+H^+$, 1], 180 (1), 128 (2), 117 (18) and 115 (100). ν_{max} (film)/cm^{-1} 3275, 3057, 2941, 1631, 1581 and 1429 cm^{-1}.

3.3.7. 6-Methyl-2-phenylhepta-1,5-dien-4-ol (*19*)

Procedure **A**. Purification by flash chromatography eluting with 6:4 v/v petrol–ether afforded the product (126 mg, 47%) as a colourless oil. Found: C, 83.0; H, 9.0; $C_{14}H_{18}O$ requires C, 83.2; H, 9.0%. δ_H (250 MHz): 1.55 and 1.69 (2d, 23H, $J = 1.3$ Hz, 2Me), 1.61 (bs, 1H, OH), 2.68–2.73 (m, 2H, CH_2C=C), 4.41 (dt, 1H, $J = 8.3$, 5.5Hz, C*H*OH), 5.19 (dq, 1H, $J = 8.3$, 1.3 Hz, C*H*=CMe_2), 5.17 and 5.40 (2d, 21H, $J = 1.5$ Hz, C=CH_2) and 7.26–7.44 (m, 5H, ArH). *m/z* (%): 184 [$M^+ - H_2O$, 18], 169 (46), 155 (27), 128 (55), 103 (88) and 77 (100). ν_{max} (film)/cm^{-1} 3337, 3082, 2932, 1676 and 1628 cm^{-1}.

3.3.8. Phenylnon-1-en-4-ol (*20*)

Procedure **A**. Purification by flash chromatography eluting with 3:1 v/v petrol–ether afforded the product (142 mg, 64%) as a colourless oil. Found: C, 82.5; H, 9.9; $C_{15}H_{22}O$ requires C, 82.5; H, 10.2%. δ_H (250 MHz): 0.87 (t, 3H, $J = 6.5$ Hz, Me), 1.20–1.38 (m, 6H, $3CH_2$), 1.40–1.55 (m, 2H, CH_2CH_2CHOH), 1.66 (d, 1H, $J = 3.0$ Hz, CH*H*CHOH), 3.57–3.70 (m, 1H, C*H*OH), 5.17 (s, 1H, C=C*H*H), 5.41 (d, 1H, $J = 1.4$ Hz, C=CH*H*) and 7.20–7.50 (m, 5H, ArH). *m/z* (%): 218 [M^+, 1], 200 [$M - H_2O$, 10], 143 (35), 129 (41) and 118 (100). ν_{max} (film)/cm^{-1} 3353, 2930, 2858, 1627, 1574 and 1495 cm^{-1}.

3.3.9. (2-t-Butoxycarbonylamino)-1,5-diphenylhex-5-en-3-ol (*24*)

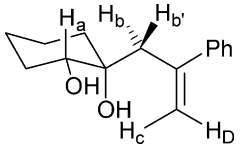
Procedure **A**. Purification by flash chromatography eluting with 3:1 v/v petrol–EtOAc afforded Isomer 1, (70 mg, 20%), Isomer 2, (91 mg, 25%) and mixed fractions: (ca 1:1 mixture of isomers, 115 mg, 31%). Overall yield 76%. Found: C, 74.9; H, 7.95; N, 3.8; $C_{23}H_{29}NO_3$ requires C, 75.2; H, 7.95; N, 3.8%. Isomer 1, colourless amorphous solid m.p. 125–130 °C. δ_H (500 MHz): 1.41 (s, 9H, 3Me), 2.64 (dd, 1H, $J = 14.0$, 9.0 Hz, C*H*HCHOH), 2.75 (dd, 1H, $J = 14.0$, 4.2 Hz, C*H*HCHOH), 2.81 (dd, 1H, $J = 13.4$, 7.9 Hz, PhC*H*HCHN), 2.89 (dd, 1H, $J = 13.4$, 5.6 Hz, PhCH*H*CHN), 3.66–3.67 (m, 1H, C*H*OH), 3.82 (q, 1H, $J = 7.9$ Hz, CHN), 5.13 and 5.38 (2s, 21H, C=CH_2) and 7.15–7.33 (m, 10H, ArH). Isomer 2, colourless amorphous solid m.p. 110–115 °C. δ_H (250 MHz): 1.32 (s, 9H, 3Me), 2.57–2.67 (m, 2H, CH_2CHOH), 2.75–2.99 (m, 2H, PhCH_2CHN), 3.60–3.80 (m, 2H, C*H*NH and NH), 4.68–4.71 (m, 1H, C*H*OH), 5.20 and 5.43 (2s, 21H, C=CH_2) and 7.13–7.39 (m, 10H, ArH). *m/z* (%) (mixture): 367 [M^+, < 1], 267 (7), 202 (100), 158 (40), 120 (36) and 91 (93). ν_{max} (film)/cm^{-1} 3440, 3354, 2975, 2933, 1688 and 1503 cm^{-1}.

3.3.10. 1-(2-2-Dimethyl-1,3-dioxolan-5-yl)-3-phenylbu-3-en-1-ol (*25*)

Procedure **A**. Purification by flash chromatography eluting with 1:1 v/v petrol–ether afforded the product (136 mg, 55%, ca. 5:1 mixture of diastereoisomers) as a pale yellow oil. Found: C, 72.4; H, 8.1; $C_{15}H_{20}O_3$ requires C, 72.6; H, 8.10%. Major isomer (from spectrum of mixture) δ_H (250 MHz): 1.35 and 1.41 (2s, 2Me), 2.00 (d, 1H, $J = 2.6$ Hz, OH), 2.56 (dd, 1H, $J =$ 9.8, 4.5 Hz, C*H*HCHOH), 2.88 (dd, 1H, $J = 9.8$, 1.2 Hz, CH*H*CHOH), 3.61–3.82 (m, 1H, C*H*OH), 3.94–4.03 (m, 3H, CH_2OCMe_2 and $CHOMe_2$), 5.19 and 5.35 (2d, 21H, $J = 1.1$ Hz, C=CH_2) and 7.26–7.45 (m, 5H, ArH). Minor isomer (from spectrum of mixture) δ_H (250 MHz): 1.35 and 1.41 (2s, 2Me), 2.00 (d, 1H, $J = 2.6$ Hz, OH), 2.63 (dd, 1H, $J = 14.1$, 7.9 Hz, C*H*HCHOH), 2.79 (dd, 1H, $J = 14.1$, 5.2 Hz, CH*H*CHOH), 3.71–3.77 (m, 1H, C*H*OH), 3.94–4.03 (m, 3H, CH_2OCMe_2 and $CHOMe_2$), 5.16 and 5.41 (2d, 21H, $J = 1.1$ Hz, C=CH_2) and 7.24–7.32 (m, 5H, ArH). *m/z* (%): 248 [M^+, 9], 233 (12), 130 (67), 101 (86) and 43 (100).

*3.3.11. syn-1-(2-Phenylallyl)-cyclohexane-1,2-diol (**26**)*

Procedure **A**. Purification by flash chromatography eluting with 2:1 v/v EtOAc–petrol afforded the product (155 mg, 67%) as colourless needles m.p. 78–80 °C. Found: C, 77.4; H, 8.85; $C_{15}H_{20}O_2$ requires C, 77.5; H, 8.70%. δ_H (500 MHz): 1.11–1.21 (m, 2H, CH_2 cyclohexane), 1.30–1.34 (m, 1H, cyclohexane), 1.39–1.44 (m, 1H, cyclohexane), 1.50–1.71 (m, 4H, cyclohexane), 1.78 and 1.98 (2bs, 21H, 2OH), 2.77 and 2.97 (2d, 21H, J = 13.0, 0.8 Hz, C=CCH_2), 3.34 (dd, 1H, $J_{ax-ax} = 10.8$, $J_{ax-eq} = 4.4$ Hz, C*H*OH), 5.17 (s, 1H, C=C*H*H), 5.37 (d, 1H, $J = 1.8$ Hz, C=CH*H*), 7.29 (t, 1H, $J = 7.0$ Hz, ArH), 7.35 (t, 2H, $J = 8.7$ Hz, ArH) and 7.42 (d, 2H, $J = 7.0$ Hz, ArH). *m/z* (%): 214 [$M^+ - H_2O$, 6], 118 (69), 115 (100), 97 (26) and 91 (21). ν_{max} (film)/cm^{-1} 3438, 3104, 2937, 1732, 1547 and 1344 cm^{-1}.



*3.3.12. 3-Hydroxy-1-methyl-3-(2-phenyl-2-propenyl)-1,3-dihydro-2H-indol-2-one (**33**)*

Procedure **B**. Purification by flash chromatography eluting with 3:1 v/v petrol–EtOAc afforded the product (203 mg, 73%) as colourless prisms, m.p. 146–149 °C. Found: C, 77.4; H, 6.1; N, 5.0; $C_{18}H_{17}NO_2$ requires C, 76.45; H, 6.1; N, 5.05%. δ_H (250 MHz) 2.85 (s, 3H, NMe), 3.11 (s, 1H, OH), 3.22 (d, 1H, $J = 13.2$, C*H*H), 3.30 (d, 1H, $J = 13.2$ Hz, CH*H*), 4.97 (s, 1H, C=CH_2), 5.06 (d, 1H, $J = 0.9$ Hz, C=CH_2), 6.65 (d, 1H, $J = 7.5$ Hz, ArH), 6.90 (t, 1H, $J = 7.5$ Hz, ArH) and 7.01–7.26 (m, 6H, ArH). *m/z* (EI, %); 279 [M^+, 12] and 162 (100). ν_{max} (nujol)/cm^{-1} 3308 (OH), 1693 (C=O), 1614 and 1097.

*3.3.13. 3-Hydroxy-1-methyl-3-[2-(2-thienyl)-2-propenyl]-1,3-dihydro-2H-indol-2-one (**34**)*

Procedure **A**. Purification by flash chromatography eluting with 3:1 v/v petrol-EtOAc afforded the product (165 mg, 58%) as colourless prisms, m.p. 134–136 °C. Found: C, 67.0; H, 5.4; N, 4.6; $C_{16}H_{15}NO_2S$ requires C, 67.35; H, 5.3; N, 4.9%. δ_H (500 MHz); 3.03 (s, 3H, NMe), 3.14 (d, 1H, $J = 13.5$ Hz, C*H*H), 3.17 (d, 1H, J = 13.5 Hz, CH*H*), 3.52 (bs, 1H, OH), 4.86 and 5.29 (2s, 21H, C=CH_2), 6.71 (d, 1H, $J = 7.8$ Hz, ArH), 6.72–6.84 (m, 2H, ArH), 6.94 (t, 1H, $J = 7.4$ Hz, ArH), 7.02 (m, 1H, ArH) and 7.21–7.27 (m, 2H, ArH). *m/z* (ES, %); 308 [$M^+ + Na$, 30] and 184 (100). ν_{max} (film)/cm^{-1} 3300 (OH), 1690 (C=O) and 1600 (Ph).

*3.3.14. 3-Hydroxy-3-[2-(3-methoxyphenyl)-2-propenyl]-1-methyl-1,3-dihydro-2H-indol-2-one (**35**)*

Procedure **A**. Purification by flash chromatography eluting with 1:1 v/v petrol–EtOAc afforded the product (186 mg, 60%) as colourless prisms, m.p. 108–110 °C. Colourless prisms (60%) from EtOAc, m.p. 108–110 °C. Found: C, 73.65; H, 6.2; N, 4.65; $C_{19}H_{19}NO_3$ requires C, 73.75; H, 6.2; N, 4.55%. δ_H (250 MHz); 2.90 (s, 3H, NMe), 3.19 (d, $J = 13.6$ Hz, 2H, C*H*H), 3.30 (d, $J = 13.6$ Hz, 2H, CH*H*), 3.34 (s, 1H, OH), 3.74 (s, 3H, OMe), 4.97 and 5.07 (2s, 21H, C=CH_2), 6.49–7.37 (m, 8H, ArH). *m/z* (EI, %); 309 [M^+, 12], 162 (100) and 148 (60). ν_{max} (nujol)/cm^{-1} 3230 (OH), 1699 (C=O) and 1377.

*3.3.15. 3-[2-(3-Fluorophenyl)-2-propenyl]-3-hydroxy-1-methyl-1,3-dihydro-2H-indol-2-one (**36**)*

Procedure **A**. Purification by flash chromatography eluting with 3:1 v/v petrol–EtOAc afforded the product (187 mg, 63%) as colourless prisms, m.p. 148–150 °C. Found: C, 72.4; H, 5.45; N, 4.8; $C_{18}H_{16}FNO_2$ requires C, 72.7; H, 5.4; N, 4.7%. δ_H (250 MHz); 2.95 (s, 3H, NMe), 3.23 (d, 2H, $J = 13.1$ Hz, CH_2), 3.27 (s, 1H, OH), 5.02 and 5.08 (2s, 21H, C=CH_2) and 6.66–7.26 (m, 8H, ArH). *m/z* (EI, %); 297 [M^+, 4], 281 [$M^+ - H_2O$, 3%] and 162 (100). ν_{max} (nujol)/cm^{-1} 3300 (OH), 1694 (C=O) and 1080.

*3.3.16. 3-Hydroxy-1-methyl-3-[2-(1-methyl-1H-indol-5-yl)-2-propenyl]-1,3-dihydro-2H-indol-2-one (**37**)*

Procedure **A**. Purification by flash chromatography eluting with 3:1 v/v petrol–EtOAc afforded the product (176 mg, 53%) as colourless prisms, m.p. 160–163 °C. Found: C, 76.0; H, 75.9; N, 8.15; $C_{21}H_{20}N_2O_2$ requires C, 75.9; H, 6.1; N, 8.4%. δ_H (250 MHz) 2.45 (s, 3H, NMe), 3.29 (d, 1H, $J = 13.2$ Hz, C*H*H), 3.39 (d, 1H, J = 13.2 Hz, CH*H*), 3.74 (s, 3H, NMe), 3.92 (bs, 1H, bs, OH), 4.90 (s, 1H, C=CH_2), 5.04 (s, 1H, C=CH_2), 6.37 (d, 1H, $J = 2.4$ Hz, Ar-H), 6.62 (d, 1H, $J = 7.7$ Hz, Ar-H), 6.87–7.29 (m, 7H, Ar-H). *m/z* (FAB, %) 332 [M^+, 65], 315 (20), 172 (100) and 162 (50). ν_{max} (film)/cm^{-1} 3363 (OH), 1701 (C=O), 1615, 1470 and 1091.

*3.3.17. Methyl 2-hydroxy-2-methyl-4-phenyl-4-pentenoate (**38**)*

Procedure **A**. Purification by flash chromatography eluting with 9:1 v/v petrol–EtOAc afforded the product (143 mg, 65%) as a colourless oil. Found: C, 70.65; H, 7.2; $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%. δ_H (250 MHz) 1.45 (3H, s, Me), 2.79 (dd, 1H, $J = 13.8$, 0.8 Hz, C*H*H), 3.08 (d, 1H, $J = 13.8$, CH*H*), 3.11 (s, 1H, OH), 3.25 (s, 3H, CO_2Me), 5.17 (dd, 1H, $J = 1.7$, 0.8 Hz, C=CH_2), 5.33 (d, 1H, $J = 1.7$ Hz, C=CH_2) and 7.29 (5 H, m, Ar-H). *m/z* (EI, %) 220 [M^+, 7], 161 [$M^+ - CO_2$Me, 45] and 118. ν_{max} (film)/cm^{-1} 3527 (OH), 2952, 1734 (C=O) and 1214.

*3.3.18. Ethyl 2-hydroxy-2,4-diphenyl-4-pentenoate (**39**)*

Procedure **A**. Purification by flash chromatography eluting with 9:1 v/v petrol–EtOAc afforded the product (157 mg, 53%) as a colourless oil. Found: C, 76.7; H, 6.85; $C_{19}H_{20}O_3$ requires C, 77.0; H, 6.8 0%. δ_H (500 MHz) 1.08 (t, 3H, $J = 7.2$ Hz, Me), 3.08 (d, 1H, $J = 14.1$ Hz, CH_2), 3.57 (d, 1H, $J = 14.1$ Hz, CH_2), 3.69 (dq, 1H, $J = 10.7$, 7.2 Hz, CH_2Me), 3.69 (1 H, s, OH), 3.92 (dq, 1H, $J = 10.7$, 7.2 Hz, CH_2Me), 5.25 (s, 1H, C=CH_2), 5.35 (s, 1H, C=CH_2), 7.24–7.38 (m, 8H, Ar-H) and 7.64–7.66 (m, 2H, Ar-H). *m/z* (EI, %) 296 [M^+, 1], 179 (30), 118 (25) and 105 (100). ν_{max} (film)/cm^{-1} 3509 (OH), 2981, 1727 (C=O), 1447 and 1212.

*3.3.19. Ethyl 2-hydroxy-4-phenyl-2-(2-thienyl)-4-pentenoate (**40**)*

Procedure **A**. Purification by flash chromatography eluting with 9:1 v/v petrol–EtOAc afforded the product (154 mg, 51%) as a colourless oil. Found: C, 67.55; H, 6.0; $C_{17}H_{18}O_3S$ requires C, 67.5; H, 6.0%. δ_H (500 MHz) 1.08 (t, 3H, $J = 7.2$ Hz, Me), 3.15 (d, 1H, $J = 14.0$, C*H*H), 3.49 (d, 1H, $J = 14.0$ Hz, CH*H*), 3.66 (dq, 1H, $J = 10.7$, 7.2 Hz, CH_2Me), 3.94 (dq, 1H, $J = 10.7$, 7.2 Hz, CH_2Me), 3.94 (bs, 1H, OH), 5.26 (s, 1H, C=CH_2), 5.35 (s, 1H, C=CH_2) and 6.94–7.36 (m, 8H, Ar-H). *m/z* (ES, %); 325 [$M^+ + Na$, 100], 271 (35) and 207 (10). ν_{max} (film)/cm^{-1} 3502 (OH), 1727 (C=O), 1444 and 1212.

*3.3.20. 1-(3-methoxyphenyl)-3-thiophen-2-yl-but-3-en-1-ol (**47**)*

Procedure **B**. Purification by flash chromatography eluting with CH_2Cl_2 afforded the product (190 mg, 73%) as a pale yellow oil. Found: C, 69.1; H, 6.10; S, 12.15; $C_{15}H_{16}O_2S$ requires C, 69.20; H, 6.20; S, 12.30%. δ_H (300 MHz) 2.17 (s, 1H, OH), 2.78 (dd, 1H, $J = 14.3$, 9.1 Hz, C*H*H), 2.92 (ddd, 1H, $J = 14.3$, 3.9, 0.8 Hz, CH*H*), 3.82 (s, 3H, OCH_3), 4.88 (dd, 1H, $J = 9.1$, 3.9 Hz, C*H*OH), 5.06 (s, 1H, C=C*H*H), 5.53 (s, 1H, C=CH*H*), 6.82 (ddd, 1H, $J = 8.2$, 2.5, 0.8 Hz, ArH), 6.97 (m, 2H, ArH), 7.01 (dd, 1H, $J = 5.1$, 3.6 Hz, Thiophene-H), 7.11 (dd, 1H, $J = 3.6$, 0.8 Hz, Thiophene-H), 7.21 (dd, 1H, $J = 5.1$, 0.8 Hz, ArH), 7.24–7.30 (m, 1H, ArH). *m/z* (ES, %); 260 [M^+, 86], 243 [$M^+ - OH$, 67], 125 (52), 112 (100). ν_{max} (film)/cm^{-1} 3412, 3054, 2762, 1602, 1421, 1265.

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