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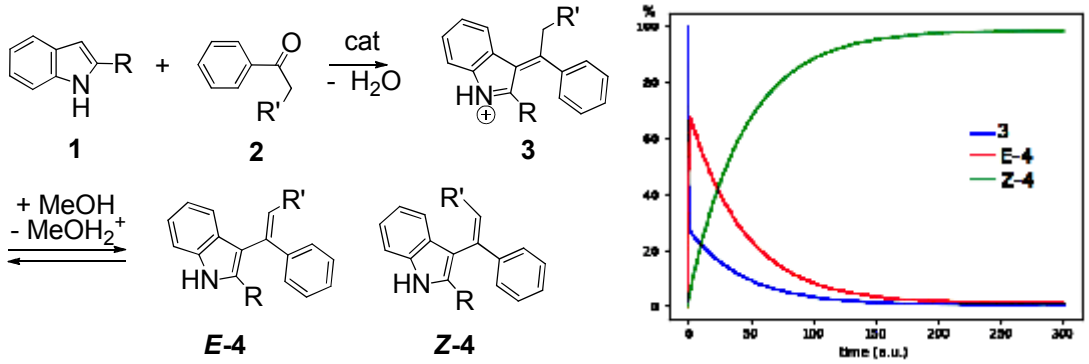

reaction diastereoselectivity depends on C-2 substitution of indole!

DIASTEREOSELECTIVE SYNTHESIS OF 3-(α-ARYL)ALKENYLINDOLES FROM THE DIRECT DEHYDRATIVE COUPLING OF INDOLES AND KETONES: A SYNTHETIC AND THEORETICAL STUDY

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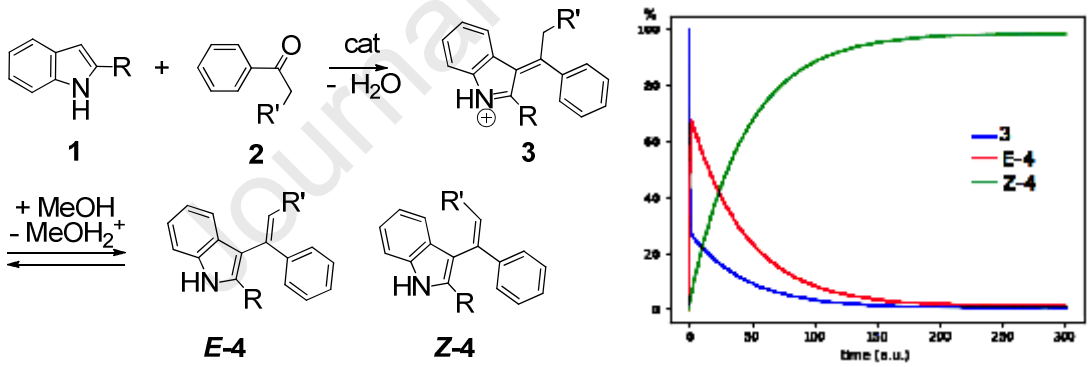
Graphical abstract:



reaction diastereoselectivity depends on C-2 substitution of indole!

Abstract:

A representative library of 3-(α-aryl)alkenylindoles has been prepared via a Brønsted-acid catalysed dehydrative coupling reaction between alkyl aryl ketones and some indoles. An interesting diastereoselectivity has been observed and has been explained from a mechanistic point of view.

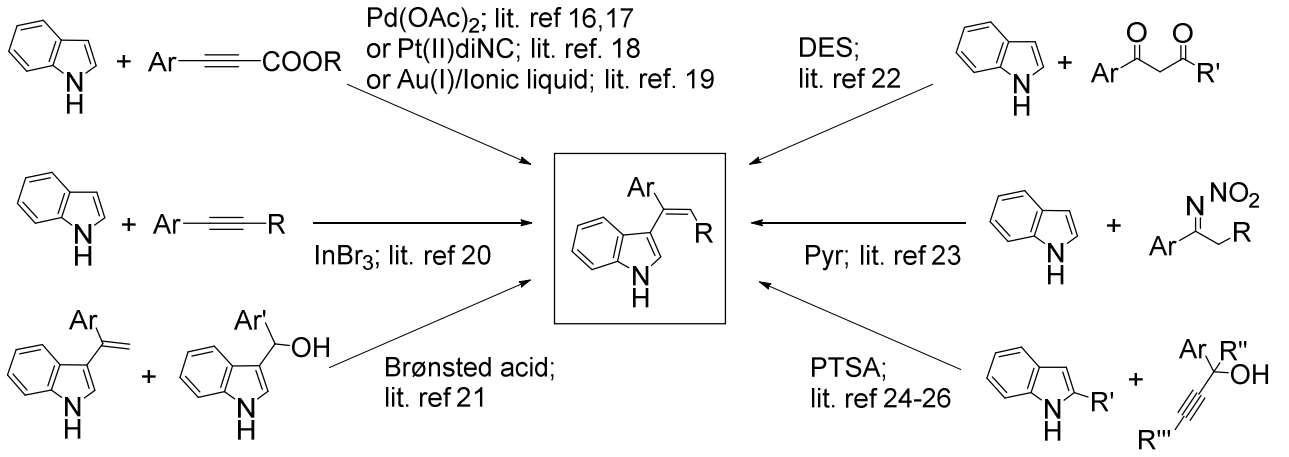
Keywords:

3-(α-aryl)alkenylindoles; diastereoselective reaction; dehydrative coupling; DFT calculations; indole functionalisation

1. Introduction

Indole is one of the most widespread heterocycles to be found in natural products, often endowed with biological activity;[1-7] therefore the synthesis and functionalisation of indole and its derivatives are fundamental processes and still challenging goals in synthetic studies. Limiting our references to even just the most recent reviews, indole alkaloids, carbazole and other indole-based heterocycles syntheses have been reported starting from 2- or 3-vinylindoles,[8, 9] as isolated or in situ formed intermediates. Furthermore, 3-vinylindole derivatives display interesting biological activities.[10-12]

The alkenyl group can be introduced on the indole ring using indirect or direct approaches, the former requiring and the second avoiding a previous indole functionalisation. Oxidative alkenylation, however, is the most commonly exploited synthetic procedure to introduce the α-unsubstituted alkenyl group directly on heterocycle rings.[13-15] Conversely, few reports deal with the synthesis of α-aryl substituted 3-alkenylindoles through the direct functionalisation of indole. These include hydroarylations of alkynoates which have been catalysed by palladium,[16, 17] platinum,[18] gold complexes in ionic liquids,[19] or hydroarylation of alkynes catalysed by indium bromide.[20] Other procedures involve a dehydrative coupling of 3-indolylmethanols,[21] an indole alkenylation with 1,3-dicarbonyl compounds in DES,[22] a metal-free cross-coupling with nitrimines,[23] and a Brønsted acid catalysed reaction with tertiary propargylic alcohols on 2-substituted indoles.[24-26]



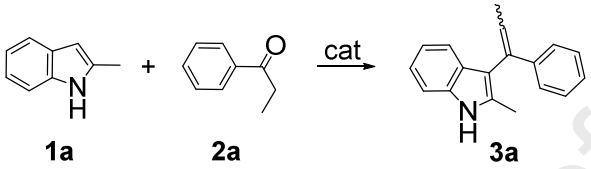
Scheme 1: **Previous synthetic approaches to the synthesis of 3-(α-aryl)alkenylindoles**

Dehydrative coupling of indoles with ketones (or aldehydes) is a simple method for direct C-3 alkenylation, although it can exploit subsequent intramolecular cyclisations.[14, 27-30] To the best of our knowledge, the papers most relevant to our research described the dehydrative coupling of indoles with ketones catalysed by Brønsted acidic ionic liquids,[31] or with benzyl aryl ketones under conventional and microwave conditions,[32] and, finally, the above-mentioned metal-free coupling of indoles with ketone derived nitrimines.[23] In those works, the authors tested some aryl alkyl ketones and, when the alkyl was the ethyl or benzyl group, they normally obtained the expected dehydrative coupling products as predominant or exclusive *E* diastereomers.[31]

Recently, we described a carbocation catalysed direct dehydrative coupling reaction between methyl aryl ketones (or cyclic ketones) and indoles,[33] a simple and straightforward way of achieving a 3-(α-aryl)vinylindole scaffold which is a versatile building block for the construction of complex structures. With the aim of extending our research to a 3-(α-aryl)alkenylindole synthesis, we decided to expand the above synthetic procedure to the reaction of indoles with some representative alkyl aryl ketones in the presence of different acid catalysts.

2. Results and discussion

As a model reaction, we decided to begin the study by reacting 2-methylindole (**1a**) with propiophenone (**2a**) to afford dehydrative coupling product **3a** in the presence of different catalysts, at variable temperatures and solvents (Scheme 2). We started our screening conditions using commercially available protic acid catalysts, namely methanesulfonic acid and *p*-toluenesulfonic acid, later moving on to the Lewis acid catalyst previously employed (Table 1).[33]



Scheme 2: Model reaction between 2-methylindole (**1a**) with propiophenone (**2a**)

Table 1: trial reactions

entry	**1a**:**2a**	solvent	Cat (mol %)	T (°C)	t (h)	Yield % (dr)[a]
1	1:1	MeOH	CH_3SO_3H (5)	rt	3	slow incomplete reaction
2	1:1	MeOH	CH_3SO_3H (5)	65	2	81 (92:8)
3	1:1	MeOH	*p*-TosOH (5)	65	5	[b]
4	1:1.1	MeOH	*p*-TosOH (5)	65	1	89 (92:8)
5	1:1.1	MeOH	*p*-TosOH (5)	65	1	93 (92:8)[c]
6	1:1.1	MeOH	*p*-TosOH (5)	rt	5	86 (92:8)
7	1:1.1	MeCN	*p*-TosOH (5)	rt	24	85 (90:10)
8	1:1.1	MeCN	*p*-TosOH (5)	65	10	89 (90:10)
9	1:1.1	-	*p*-TosOH (5)	rt	10	79 (95:5)
10	1:1.1	-	*p*-TosOH (5)	65	1[d]	55 (92:8)
11	1:1.1	-	*p*-TosOH (0.5)	rt	30	[e]
12	1:1	MeOH	**4** (5)	rt	24	Incomplete reaction
13	1:1.1		**4** (5)	65	2	83 (88:12)
14	1:1.1	MeOH	-	65	48	Only traces
15	1:1.1	-	-	rt	24	[e]
16	1:1	-	-	90	24	Minimal traces

[a] The reactions were run on a 2 mmol scale. Yields refer to pure isolated product. Diastereomeric ratio (dr) calculated from ^{1}H NMR spectra of isolated **3a**.

[b] Unreacted indole present in not negligible amount.

[c] The reaction was run on a 10 mmol scale.

[d] The reaction was stopped in the absence of indole **1a**.

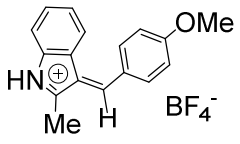
[e] No traces of product were detected.

The progress of the reaction was monitored by TLC, GC and GC-MS analyses. When using methanesulfonic acid as the catalyst, the GC and GC-MS analyses clearly showed the immediate formation of two diastereomeric products (M^+ 247; Table 1, entries 1 and 2). The first eluting product became rapidly predominant with respect to the second one, which prevailed at the beginning of the reaction but readily converted into the other. An attempt was made to stop the observed diastereomers conversion by varying the catalyst amount, reaction time and temperature, but this was unsuccessful. Even stopping the reaction at its onset, when the GC analysis revealed that the second diastereomer was slightly predominant (in the presence of the majority of unreacted reagents), the reaction work-up furnished only the first eluting diastereomer in low yield. With the reaction completed, product **3a** was isolated in 81% yield in 92:8 diastereomeric ratio (Table 1, entry 2).

Subsequently, *p*-toluenesulfonic acid was tested by screening different solvent and solvent-less conditions, catalyst amount and reaction temperature (Table 1, entries 3–11). The same evolution in product formation was observed as for methanesulfonic acid. The reagent ratio was optimised to **1a**:**2a** = 1:1.1, the better conversion was observed by heating to 65°C in methanol and in the presence of 5 mol% of catalyst (Table 1, entry 4); product **3a** was isolated in 85% yield (dr 92:8). Furthermore, the scale-up of the reaction was confirmed on a 10 mmol scale (Table 1, entry 5). Unsatisfactory results were obtained when using acetonitrile as the solvent (Table 1, entries 7 and 8) and in neat conditions (Table 1, entries 9–11), both at room temperature and under reflux heating.

Finally, we decided to evaluate the Lewis acid **4** used in our previous work dealing with dehydrative coupling between indoles and acetophenones (Table 1, entries 12 and 13).[33] The reaction required heating conditions with respect to the above Brønsted acids, but the same trend in

product formation/isomerisation and the same unsuccessful efforts to stop the reaction as the first diastereomer were unfortunately confirmed.



4

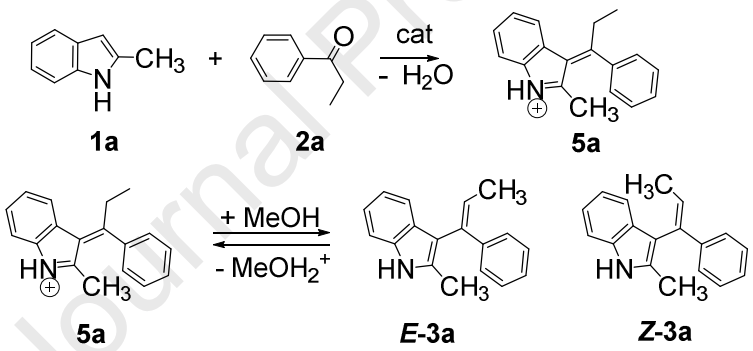
Figure 1: (4-Methoxyphenyl)(2-methylindol-3-yl)methylium tetrafluoroborate (4).

A blank reaction was eventually run in the absence of any catalyst in methanol and in neat conditions; no reaction was observed (Table 1, entries 14-15); furthermore, only traces of products were detected by heating to 90°C neat reagents for 24 hours (Table 1, entry 16).

In all reaction conditions, we isolated product **3a** in the virtually identical diastereomeric ratio. In order to establish the configuration of the prevalent diastereomer, spectral analyses were initially completed. Quite unexpectedly, ^{1}H NMR spectrum of **3a** showed a diastereomer ratio of 92:8, in favour of the *Z* isomer, by unambiguous comparison with NMR spectra reported in literature. Alkene **3a** was obtained by Mattson in a diastereomeric ratio *E*:*Z* = 6:1,[23] along with another three diastereomeric indole derivatives in predominant *E* configuration. The most distinctive signals are the vinylic proton quadruplet and the olefinic methyl doublet, which are centred at 6.35 ppm and 1.70 ppm, respectively, for the *Z* diastereomer, and centred at 5.94 ppm and 1.94 ppm for the *E*.

In order to rationalise this outcome, the reaction mechanism was studied via the computational method (the details are reported in the Supplementary Data). As the reaction mechanism is assumed to be the same as that previously studied for a similar system,[33] only the last step of the reaction was analysed (Scheme 3). The catalysed addition of **2a** to **1a** and dehydration generates the cation **5a**. This intermediate is deprotonated by the solvent methanol, yielding the final product **3a**. The structures of the transition states and the product complexes (**3a** and the protonated methanol) were optimised for the two diastereomers. For both of them, 12 conformations were found (see Tables 5aS and 5bS in the Supplementary Data). The free energy barriers for the deprotonation range from 14.6 and 18.2 kcal mol^{-1} for the generation of the *E* diastereomer and

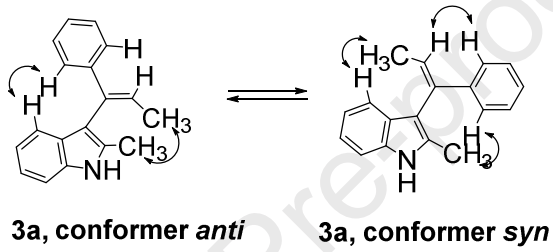
from 17.0 and 19.4 kcal mol^{-1} for the generation of the *Z* diastereomer. As one of the reactants is the solvent, the application of the Eyring equation is questionable; therefore, we cannot confidently calculate the absolute values of the reaction rate constants k_E and k_Z. However, here, we are only interested in the comparison between the two pathways so that we can calculate the rate between k_E and k_Z which is found to be 26. The formation of the *E* diastereomer is faster. However, the most stable complex of the diastereomer *Z* of **3a** is more stable than that of the *E* diastereomer by 1.5 kcal mol^{-1}. Moreover, the formation of both products is only slightly thermodynamically favoured (-1.9 and -0.4 kcal mol^{-1}, respectively). Therefore, we can hypothesise that, due to the long reaction time (at least 2 hours), the thermodynamic controls the final outgoing. From the reaction free energies reported above we can calculate a diastereomeric ratio of 83:17 in favour of the *Z* product, in agreement with the experimental findings.



Scheme 3: Key steps in the reaction mechanism of 1a and 2a yielding the *E* and *Z* diastereomers of 3a.

Furthermore, in order to confirm the predominant configuration of **3a**, NOE experiments were performed (see Figure 1 in the Supplementary Data). Different selective excitations of methyl protons in position 2 of the indole, of the methyl protons on the double bond and of the vinylic proton made it possible for the *Z* configuration to be assigned to **3a**. Selective excitation of methyl protons in 2 of the indole ring showed an NOE effect on phenyl protons in *ortho* position and on proton bound to indole nitrogen. Selective excitation of methyl protons bound to the double bond showed an NOE effect with the vinylic proton and the indole proton in 4 position. Finally, selective

excitation of vinylic proton showed an NOE on methyl protons in 2 and on phenyl protons in *ortho* position. A weak NOE effect was, moreover, observed between protons of the two methyl groups, and between phenyl protons in *ortho* position with indole proton in 4 position, which can presumably be ascribed to conformational equilibriums between *anti* and *syn* conformers (Figure 2). Calculations (see Table 6S in the Supplementary Data) confirm this hypothesis: the conformer *syn* is less stable than the *anti* by only 0.3 kcal mol^{-1} in terms of free energy and the rotational barrier along the styryl sp^2–sp^2 single bond is 5.0 kcal mol^{-1}, so the interconversion is expected to be very fast even at room temperature.



3a, conformer *anti* **3a, conformer *syn***

Figure 2: conformational equilibrium between 3a conformers.

In effect, because of the steric hindrance, the two conformations of **3a** are not fully planar so they both present an axially chiral styrene motif, where fairly large substituents could prevent rotation about the styryl sp^2–sp^2 single bond.[34-39] ~~Immediately, optical rotatory power was tested in different solvents and concentrations: however, no significant value was observed. This is coherent with~~ Free energy barriers were calculated for the R/S interconversion in the two conformers, which are 15 and 16 kcal mol^{-1} for conformers *anti* and *syn*, respectively (see Table 6S in the Supplementary Data). From these values we can estimate the interconversion rate constants of $8•10^2$ and $3•10^2$ sec^{-1}, which are fast enough to prevent the isolation of the enantiomers.

Finally, **3a** configuration was examined by X-ray analysis. Crystals suitable for X-ray diffraction were obtained for three specimens of **3a**; these were obtained directly after chromatographic purification the first by using **4** as the catalyst and the second by using *p*-TosOH, and the third after re-crystallisation from dichloromethane/petroleum ether (using *p*-TosOH as the catalyst). The three collected structures are the same and confirm the *Z* configuration of compound **3a**. In this paper, the

data for the second specimen were reported. The asymmetric unit contains the whole molecule (Figure 3). The molecule is composed of two planar fragments, one containing the atoms C1 and the indole moiety (rmsd = 0.011 Å) and the second containing the atoms from C10 to C18 (rmsd = 0.102 Å). The two planes form a twist angle of 77 degrees around the C3-C12 bond, as expected due to the steric hindrance of the aromatic moieties. ~~Thus, the molecule in the solid state is chiral (with an *S* configuration) and, since it crystallises in the acentric space group $P2_1$, the single crystal should show optical rotatory power. The structure determined for the three data collections show the same enantiomer for the molecule, so we can suspect that this one alone is formed during crystallisation.~~ Thus, the molecule in the solid state is chiral (with an *S* configuration) and it crystallises in the acentric space group $P2_1$; furthermore, the structure determined for the three data collections show the same enantiomer for the molecule.

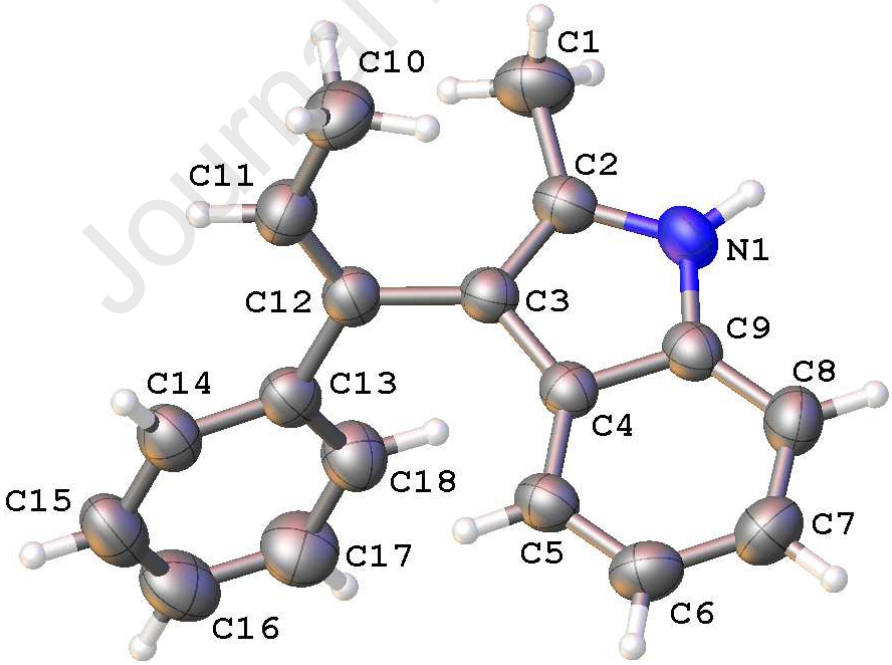


Figure 3. Asymmetric unit of compound 3a.

In order to exclude any hypothesis that the powder of the compound **3a** is a mixture of crystals with *E* and *Z* configurations, the powder pattern was collected and compared to the one calculated from the crystal structure (Figure 4): only the presence of the *Z* diastereomer was found, since the

structure with *E* configuration must show a completely different position and relative intensities of the peaks.

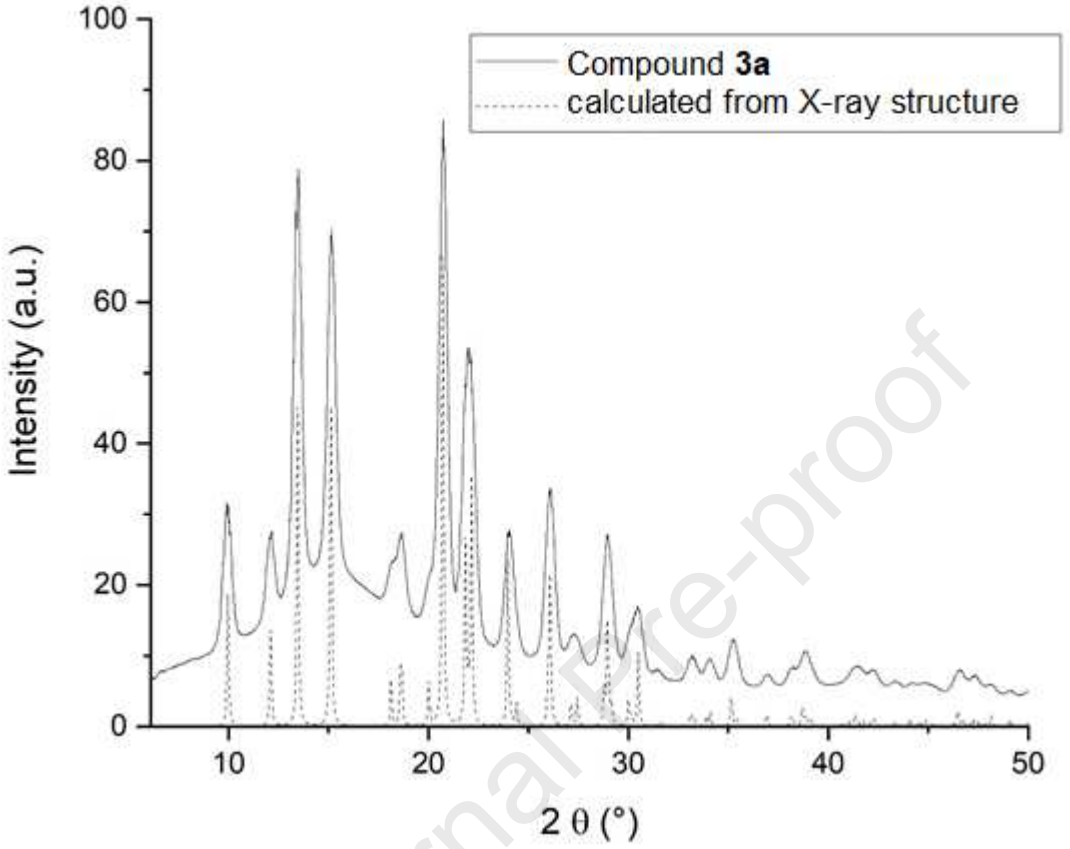
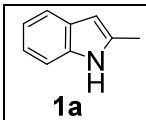
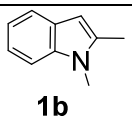
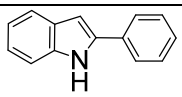
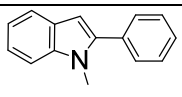
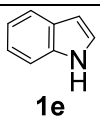
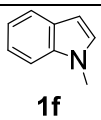
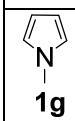
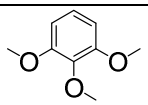
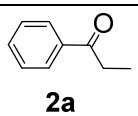
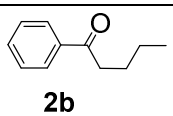
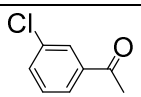
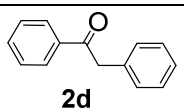


Figure 4. X-ray powder pattern of compound 3a compared with the one calculated from the crystal structure.

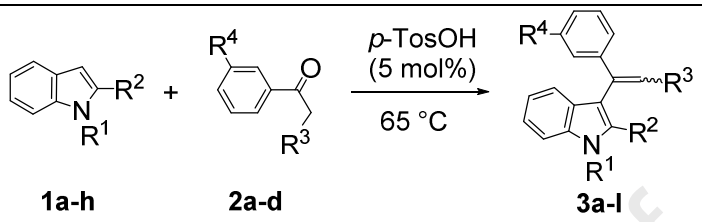
With the optimised reaction conditions in our hands, we decided to explore the scope of the reaction to some other activated nucleophiles and alkyl aryl ketones; they are reported in reagent Chart 1.

Chart 1: Nucleophiles 1a-h and alkyl aryl ketones 2a-d.

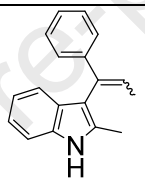
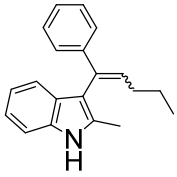
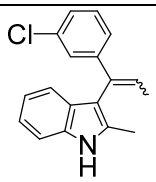
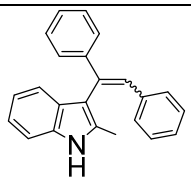
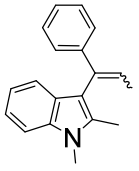
 **1a**	 **1b**	 **1c**	 **1d**	 **1e**	 **1f**
 **1g**	 **1h**	 **2a**	 **2b**	 **2c**	 **2d**

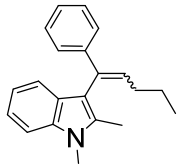
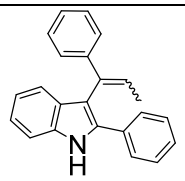
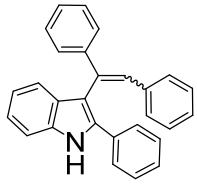
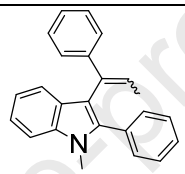
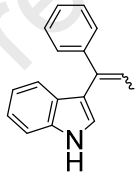
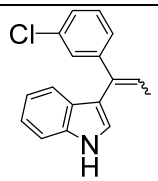
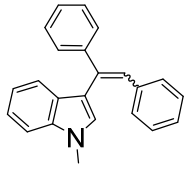
All the products we were able to prepare are listed in Table 2 along with all experimental details, product yields and diastereomeric ratios.

Table 2: reaction details and scope



1a-h **2a-d** **3a-l**

Entry	Reagents and products				Reagents		t (h)	Products 3; Yield %[a]		dr (Z:E)	Lit. dr (E:Z)
	R^1	R^2	R^3	R^4	1	2					
1	H	Me	Me	H	**1a**	**2a**	1		**3a**; 85	92:8	6:1[23]
2	H	Me	Pr	H	**1a**	**2b**	2		**3b**; 80	90:10	
3	H	Me	Me	Cl	**1a**	**2c**	1		**3c**; 87	98:2	20:1[23]
4	H	Me	Ph	H	**1a**	**2d**	2		**3d**; 79	92:8	Z[32] 6:94[20] 5:1[23] E[31] (by comparison with ref.30)
5	Me	Me	Me	H	**1b**	**2a**	2		**3e**; 82	94:6	

6	Me	Me	Pr	H	**1b**	**2b**	3		**3f**; 80	92:8	
7	H	Ph	Me	H	**1c**	**2a**	48		**3g**; 73[b]	99:1	
8	H	Ph	Ph	H	**1c**	**2d**	48		**3h**; 24[c]	96:4	Z>99[20]
9	Me	Ph	Me	H	**1d**	**2a**	24		**3i**; 80	95:5	E (dr not reported)[31]
10	H	H	Me	H	**1e**	**2a**	7		**3j**; 58	37:63	No data[16]
11	H	H	Me	Cl	**1e**	**2c**	7		**3k**; 43	35:65	*E* (but dr not done) or *Z*[23]
12	Me	H	Ph	H	**1f**	**2d**	24		**3l**; 78	40:60	90:10[20]

[a] The reactions were run on a 2 mmol scale, in a molar ratio **1**:**2**=1:1.1, in anhydrous methanol (5 mL), without exclusion of air or moisture, at 65 °C. Reaction details (time and yield) are reported for each product. Yields refer to pure isolated products. Diastereomeric ratios (dr) were calculated from ^{1}H NMR spectra or GC analyses of isolated products. See experimental section for details.

[b] Reaction was carried out in the presence of 10 mol% cat

[c] Reaction was carried out in the presence of 15 mol% cat

First of all, 2-methylindole (**1a**) was reacted with valerophenone (**2b**); product **3b** was isolated in 80% yield and a dr *Z*:*E* = 90:10, on the grounds of chemical shifts of the diastereomer vinylic

proton (Table 2, entry 2). By reaction with *m*-chloropropiophenone (**2c**), product **3c** was obtained in a dr *Z*:*E* = 98:2 based on a comparison with literature spectral data (Table 2, entry 3).[23]

Reaction with benzyl phenyl ketone (**2d**) afforded product **3d** (Table 2, entry 4) in 87% yield, which was assigned the *Z* configuration by Perumal,[20] and the *E* configuration by Mattson[23] and Gu.[31] The assignment of Gu is made by comparison with Srinivasan's work; in this work, however, the authors reported the X-ray structure of the product condensation between 2-methylindole (**1a**) with benzyl *p*-tolyl ketone and this structure had a *Z* configuration.[32] Furthermore Perumal's paper on hydroarylation of alkynes with indoles demonstrated that the E/Z ratio of the products was a result of the substitution of indole in position 2: unsubstituted indoles chiefly afforded *E* diastereomers, whilst 2-substituted indoles, on the contrary, gave mainly *Z* diastereomers. This statement was confirmed by an X-ray diffraction analysis of **3d** (obtained form 2-substituted indole **1a**; isolated in a 94:6 *Z/E* diastereomeric ratio) and of **3l** (obtained from 2-unsubstituted indole **1f**; isolated in a *Z/E* diastereomeric ratio 10:90). These findings were rationalised based on the thermodynamic stability of the final products; the proposed mechanism involved an isomerisation of a carbocationic intermediate. In our conditions, product **3d** was obtained in a dr *Z*:*E* = 92:8, as confirmed by comparison with literature data.

Subsequently, 1,2-dimethylindole (**1b**) was reacted with ketones **2a** and **2b** (Table 2, entries 5 and 6): products **3e** and **3f** were obtained in good yields in a diastereomeric ratio in favour of *Z* based on vinylic proton chemical shifts with respect to similar products **3a** and **3b**.

Reactions of 2-phenylindole (**1c**) with ketones **2a** and **2d** (Table 2, entry 7 and 8) turned out to be much slower than the above reactions: a strong steric effect can be ascribed to the phenyl substituent in 2, enhanced by the additional phenyl group in ketone **2d**. Nevertheless, products **3g** and **3h** were obtained and the diastereomeric ratio was in favour of the *Z* diastereomer by comparing literature findings and chemical shifts of their vinylic proton with that of known compounds **3a** and **3c**.[20, 23] Thereafter, 1-methyl-2-phenylindole (**1d**) was tested in the reaction with propiophenone (**2a**); as expected, the reaction took more time than less hindered indoles, but the

yield was good. The dr of product **3i** by ^{1}H NMR spectroscopy is in favour of the *Z* isomer, as assigned above (Table 2, entry 9).

~~Incidentally, the optical rotatory power of both **3h** and **3i** was tested, as for **3a**; however, although the steric hindrance should reasonably be higher and prevent racemisation, no significant values were observed.~~

Thereafter, 2-unsubstituted indoles **1e** and **1f** were tested in dehydrative coupling reactions with **2a, 2c** and **2d**. The reaction of indole **1e** with ketones **2a** and **2c** gave products **3j** and **3k**, respectively, in low yields and with longer reaction times (Table 2, entries 10 and 11). The unsatisfactory yields could be explained, although only in part, by the well-known acid-catalysed indole trimerisation.[40-42] Indole **1f** and ketone **2d** gave product **3l** in good yield, but in the same diastereomeric ratio as the above reactions with indole **1e**. Reacting 2-unsubstituted indoles, the diastereomeric ratios were slightly in favour of the *E* diastereomer, as evidenced by the comparison of their NMR spectra with those of authentic specimens, when available,[20, 23] or with those of similar compounds reported here; this assignment accords with Perumal's claims.[20]

Finally, we tried to expand the scope of the reaction to activated nucleophiles other than indoles, namely 1-methylpyrrole (**1g**) and 1,2,3-trimethoxybenzene (**1h**); in our conditions, however, the corresponding dehydrative coupling products were not obtained.

3. Conclusions

In conclusion, we studied a Brønsted-acid catalysed direct dehydrative coupling reaction between alkyl aryl ketones and some indoles from a synthetic and mechanistic point of view. The results obtained are interesting also when compared with the few known literature reports. A representative library of 3-(α-aryl)alkenylindoles has been prepared; currently, our research interest is focused on the functionalisation of these reactive useful intermediates for the synthesis of complex scaffolds present in natural products endowed with biological activity.

4. Experimental

4.1. General Information

All reactions were conducted in open air vials using analytical grade reagents, and were monitored by TLC and GC analyses, GC-MS spectrometry and NMR spectroscopy. GC-MS spectra were recorded on a mass selective detector connected to a GC with a cross-linked methyl silicone capillary column. Mass spectra were recorded on a mass spectrometer equipped with an ElectroSpray Ionization source (ESI). IR spectra were recorded on an IR PerkinElmer UATR Two. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL ECZR600 spectrometer at 600 MHz and 150 MHz, respectively. The data are reported as follows: chemical shifts in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constants (Hz), and integration. In ^{1}H NMR spectra, distinctive signals for *Z* and *E* diastereomers are reported; signals are however often indistinguishable in the aromatic region. TLC were performed on silica gel TLCPET foils GF 254, 2–25 μm, layer thickness 0.2 mm, medium pore diameter 60 Å. Plates were visualised using UV light (254 nm). Column chromatography was carried out using SiO_2 (pore size 70 Å, 70–230 mesh). Petroleum ether refers to the fraction boiling in the 40–60 °C range and is abbreviated as PE. Commercially available reagents and solvents were used without purification or distillation prior to use. Room temperature (20–25 °C) is abbreviated as rt. Yields for pure (GC, GC-MS, TLC, ^{1}H NMR) isolated products are listed in Table 2. Diastereomeric ratio (dr) were calculated from ^{1}H NMR spectra when feasible or from GC analyses of purified products. The structure and purity of all new products were determined by elemental analyses, ESI, ^{1}H and ^{13}C NMR and DEPT spectra. The structure and purity of known products were confirmed by comparing their physical and spectral data (MS, ^{1}H and ^{13}C NMR) with those reported in the literature.

Single crystal X-ray diffraction (XRD). X-ray diffraction data for **3a** were collected at room temperature using an Oxford Diffraction Gemini R Ultra diffractometer equipped with AtlasS2

detector. Data were collected with mirror monochromatized Cu-Kα radiation (1.5418 Å). The CrysAlisPro[43] package was used for data collection and integration, SHELXT[44] for resolution, SHELXL[44] for refinement and Olex2[45] for graphics.

Crystal Data: M = 247.32 g/mol, monoclinic, space group $P2_1$ (no. 4), a = 8.0148(1) Å, b = 9.7768(1) Å, c = 9.7130(2) Å, β = 114.121(2)°, V = 694.65(2) Å^3, Z = 2, T = 298.7(3) K, μ(Cu-Kα) = 0.519 mm^{-1}, *Dcalc* = 1.182 g/cm^3, 11071 reflections measured (9.978 ≤ 2Θ ≤ 133.966), 2460 unique (R_{int} = 0.0231, R_{sigma} = 0.0199) which were used in all calculations. The final R_1 was 0.0389 (I > 2σ(I)) and wR_2 was 0.0906 (all data).

The interested reader can find further details of crystal data, data collection, least-squares refinements and bond lengths and angles in the Supporting Information (Tables S1, S2). CIF file was deposited in the Cambridge Crystallographic Database (CCDC 2003357).

4.2. Dehydrative Coupling: representative procedure for the synthesis of products 4.

To a solution of indole 1 (2.0 mmol) and alkyl aryl ketone 2 (2.2 mmol) in anhydrous methanol (5 mL), *p*-toluenesulfonic acid was added as the catalyst (0.019 g, 5 mol%) under stirring. The reaction mixture was then stirred in an air atmosphere, at reflux temperature (65 °C), as reported in Table 2. Upon completion, the reaction mixture was treated with H_2O/DCM (1:1, 40 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure and the crude product was purified by column chromatography.

*4.2.1. 2-Methyl-3-[1-phenylprop-1-enyl]-1H-indole (**3a**).*[23]

Chromatographic purification (PE/Acetone 90:10) gave **3a** as a pale yellow solid; 0.42 g (85% yield); dr *Z:E* = 92:8; mp 114.0–115.0 °C (DCM/PE); ^{1}H NMR (600 MHz, $CDCl_3$) predominant *Z* diastereomer δ 1.70 (d, *J* = 6.9 Hz, 3H), 2.22 (s, 3H), 6.35 (q, *J* = 6.9 Hz, 1H), 6.98 (td, *J* = 7.5, 0.9 Hz, 1H), 7.10 (td, *J* = 7.3, 0.8 Hz, 2H), 7.17 (tt, *J*=7.1, 1.3 Hz, 1H), 7.20-7.24 (m, 2H), 7.27-7.32

(m, 3H), 7.96 (br s, 1H); distinctive signals for the *E* diastereomer δ 1.94 (d, *J* = 6.8 Hz, 3H), 2.19 (s, 3H), 5.94 (q, *J* = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.6 (CH_3), 16.2 (CH_3), 110.2 (CH), 111.8 (C), 119.5 (CH), 119.7 (CH), 121.1 (CH), 126.0 (CH), 126.6 (CH), 126.7 (2 x CH), 128.2 (2 x CH), 128.8 (C), 132.9 (C), 134.7 (C), 135.5 (C), 142.8 (C). IR ν (cm^{-1}) 3424, 2909, 1591, 1214, 746, 700. MS m/z (%) 247 [M^+](100), 232 (25), 218 (85).

*4.2.2. 2-Methyl-3-[1-phenylpent-1-enyl]-1H-indole (**3b**).*

Chromatographic purification (PE/Acetone 90:10) gave **3b** as a yellow solid; 0.44 g, (80% yield);dr *Z:E* = 90:10; mp 89.7–90.9 °C (DCM/PE); ^{1}H NMR (600 MHz, $CDCl_3$) predominant *Z* diastereomer δ 0.85 (t, *J* = 7.4 Hz, 3H), 1.40–1.46 (m, 2H), 2.00–2.05 (m. 2H), 2.22 (s, 3H), 6.28 (t, *J* = 7.2 Hz, 1H), 6.97–7.00 (m, 1H), 7.08–7.12 (m, 1H), 7.15–7.18 (m, 2H), 7.20–7.24 (m, 2H), 7.29–7.31 (m, 3H), 7.95 (br s, 1H); distinctive signals for the *E* diastereomer δ 0.96 (t, *J* = 7.4 Hz, 3H), 2.20 (s, 3H), 5.85 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.5 (CH_3), 14.0 (CH_3), 22.9 (CH_2), 32.3 (CH_2), 110.1 (CH), 112.3 (C), 119.5 (CH), 119.6 (CH), 121.1 (CH), 126.6 (CH), 126.7 (CH), 128.2 (CH), 129.0 (C), 132.2 (CH), 132.7 (C), 133.6 (C), 135.5 (C), 142.8 (C). IR ν (cm^{-1}) 3376, 2957, 1458, 1214, 748, 694. MS m/z (%) 275 [M^+](100), 260 (85), 246 (88). Anal. Calcd for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.09. Found C, 87.18; H, 7.62; N, 5.03.

*4.2.3. 2-Methyl-3-[1-(3-chlorophenyl)prop-1-enyl]-1H-indole (**3c**).*[23]

Chromatographic purification (PE/Acetone 90:10) gave **3c** as an oil; 0.49 g, (87% yield); dr *Z:E* = 98:2; ^{1}H NMR (600 MHz, $CDCl_3$) predominant *Z* diastereomer δ 1.71 (d, *J* = 6.9 Hz, 3H), 2.21 (s, 3H), 6.37 (q, *J* = 6.9 Hz, 1H), 6.98–7.03 (m, 1H), 7.11–7.17 (m, 5H), 7.32 (d, *J*=8.1 Hz, 2H), 8.07 (br s, 1H); distinctive signals for the *E* diastereomer δ 1.95 (d, *J* = 7.1 Hz, 3H), 2.19 (s, 3H), 5.98 (q, *J* = 7.1 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.6 (CH_3), 16.3 (CH_3), 110.4 (CH), 111.07 (C), 119.5 (CH), 119.6 (CH), 121.2 (CH), 125.0 (CH), 126.6 (CH), 126.7 (CH), 127.4 (CH), 128.6 (C),

129.4 (CH), 133.1 (C), 133.8 (C), 134.1 (C), 135.6 (C), 144.9 (C). IR ν (cm^{-1}) 3399, 2910, 1589, 1214, 740, 695. MS m/z (%) 281 [M^+](100), 266 (30), 252 (35), 230 (33), 217 (50).

*4.2.4. 2-Methyl-3-[1,2-diphenyleth-1-enyl]-1H-indole (**3d**).*[23, 31, 32]

Chromatographic purification (PE/Acetone 90:10) gave **3d** as a white solid; 0.49 g, (79% yield); dr *Z:E* = 92:8; mp 158–159 °C (DCM/PE); ^{1}H NMR (600 MHz, $CDCl_3$) predominant *Z* diastereomer δ 1.97 (s, 3H), 6.97 (t, *J* = 7.4 Hz, 1H), 7.07–7.10 (m, 2H), 7.11–7.16 (m, 6H), 7.30–7.34 (m, 4H), 7.45–7.47 (m 2H), 7.85 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.6 (CH_3), 110.3 (CH), 111.9 (C), 119.7 (CH), 120.1 (CH), 121.3 (CH), 126.5 (CH), 127.4 (CH), 127.5 (CH), 128.2 (CH), 128.4 (CH), 128.6 (C), 128.8 (CH), 129.6 (CH), 133.2 (C), 135.2 (C), 135.8 (C), 138.7 (C), 143.2 (C). IR ν (cm^{-1}) 3408, 3051, 1594, 1218, 742, 693. MS m/z (%) 309 [M^+](100), 294 (50), 217(45).

*4.2.5. 1,2-Dimethyl-3-[1-phenylprop-1-enyl]indole (**3e**).*

Chromatographic purification (PE/EE 99:1) gave **3e** as a white solid; 0.43 g, (82% yield); dr *Z:E* = 94:6; mp 94.7–96.0 °C (DCM/PE); ^{1}H NMR (600 MHz, $CDCl_3$) predominant *Z* diastereomer δ 1.71 (d, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 3.74 (s, 3H), 6.38 (q, *J* = 7.2 Hz, 1H), 6.99–7.02 (m, 1H), 7.15–7.18 (m, 2), 7.18–7.21 (m, 2H), 7.23–7.26 (m, 2H), 7.30–7.33 (m, 3H); distinctive signals for the *E* diastereomer δ 1.99 (d, *J* = 7.2 Hz, 3H), 2.44 (s, 3H), 3.67 (s, 3H), 5.94 (q, *J* = 7.1 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.3 (CH_3), 16.3 (CH_3), 29.8 (CH_3), 108.6 (CH), 111.0 (C), 119.1 (CH), 119.7 (CH), 120.6 (CH), 125.9 (CH), 126.6 (CH), 126.8 (2XCH), 127.8 (C), 128.2 (2XCH), 134.7 (C), 135.2 (C), 136.9 (C), 143.1 (C). IR ν (cm^{-1}) 3017, 1552, 1233, 750, 697. MS m/z (%) 261 [M^+](100), 246 (30), 232 (70). Anal. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found C, 87.27; H, 7.29; N, 5.30.

*4.2.6. 1,2-Dimethyl-3-[1-phenylpent-1-enyl]indole (**3f**).*

Chromatographic purification (PE/EE 95:5) gave **3f** as a white solid; 0.46 g, (80% yield); dr *Z:E* = 92:8; mp 73.8–74.2 °C (DCM/PE); ^{1}H NMR (600 MHz, $CDCl_3$) predominant *Z* diastereomer δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.47–1.54 (m, 2H), 2.06–2.11 (m, 2H), 2.27 (s, 3H), 3.76 (s, 3H), 6.35 (t, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.4, 1H), 7.20–7.24 (m, 3H), 7.29–7.25 (m, 2H), 7.34–7.38 (m, 3H); distinctive signals for the *E* diastereomer δ 1.04 (t, *J* = 7.5 Hz, 3H), 1.58–1.64 (m, 2H), 2.40–2.44 (m, 2H), 2.47 (s, 3H), 3.69 (s, 3H), 5.89 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.3 (CH_3), 14.1 (CH_3), 23.0 (CH_2), 29.8 (CH_3), 32.4 (CH_2), 108.6 (CH), 111.5 (C), 119.2 (CH), 119.6 (CH), 120.7 (CH), 126.6 (CH), 126.8 (2XCH), 128.1 (C), 128.2 (2XCH), 132.2 (CH), 134.1 (C), 134.6 (C), 136.7 (C), 143.1 (C). IR ν (cm^{-1}) 2952, 1540, 1233, 759, 697. MS m/z (%) 289 [M^+](100), 274 (40), 260 (75). Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found C, 87.10; H, 7.93; N, 4.80.

*4.2.7. 2-Phenyl-3-[1-phenylprop-1-enyl]-1H-indole (**3g**).*

Chromatographic purification (PE/Acetone 90:10) gave **3g** as a yellow waxy solid; 0.45 g, (73% yield); dr *Z:E* = 99:1; mp 65.0–68.0 °C (DCM/PE); ^{1}H NMR (600 MHz, $CDCl_3$) predominant *Z* diastereomer δ 1.51 (d, *J* = 6.6 Hz, 3H), 6.40 (q, *J* = 6.6 Hz, 1H), 7.03–7.06 (m, 1H), 7.18–7.26 (m, 6H), 7.32–7.35 (m, 2H), 7.39–7.43 (m, 3H), 7.61 (d, *J* = 7.1 Hz, 2H), 8.32 (br s, 1H); distinctive signals for the *E* diastereomer δ 1.91 (d, *J* = 7.2 Hz, 3H), 5.93 (q, *J* = 7.1 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9 (CH_3), 110.8 (CH), 112.2 (C), 120.1 (CH), 120.5 (CH), 122.6 (CH), 126.5 (CH), 126.6 (CH), 126.8 (CH), 126.9 (CH), 127.6 (CH), 128.3 (CH), 128.9 (CH), 129.1 (CH), 129.6 (C), 133.1 (C), 134.9 (C), 136.2 (C), 142.2 (C). IR ν (cm^{-1}) 3406, 3053, 1601, 1227, 739, 691. MS m/z (%) 309 [M^+](100), 294 (75). Anal. Calcd for $C_{23}H_{19}N$: C, 89.28; H, 6.19; N, 4.53. Found C, 89.22; H, 6.15; N, 4.49.

*4.2.8. 2-Phenyl-3-[1,2-diphenyleth-1-enyl]-1H-indole (**3h**).*[20]

Chromatographic purification (PE/Acetone 90:10) gave **3h** as a yellow waxy solid; 0.18 g, (24% yield); dr *Z:E* = 96:4; mp 65.0–68.0 °C (DCM/PE); ^{1}H NMR (600 MHz, $CDCl_3$) predominant *Z* diastereomer δ 6.93–7.00 (m, 5H), 7.00–7.04 (m, 1H), 7.15–7.20 (m, 5H), 7.20–7.23 (m, 5H), 7.40–7.44 (m, 3H), 7.50–7.52 (m, 2H), 8.30 (br s, 1H); distinctive signal for the *E* diastereomer δ 8.23 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 110.9 (CH), 112.5 (C), 120.3 (CH), 120.6 (CH), 122.7 (CH), 126.5 (CH), 126.9 (CH), 127.1 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.1 (C), 130.9 (CH), 132.5 (C), 135.0 (C), 135.1 (C), 136.4 (C), 138.1 (C), 142.89. IR ν (cm^{-1}) 3460, 3025, 1598, 1217, 761, 695. MS m/z (%) 371 [M^+](100), 294 (35).

*4.2.9. 1-Methyl-2-phenyl-3-[1-phenylprop-1-enyl]indole (**3i**).*[31]

Chromatographic purification (PE/EE 99:1) gave **3i** as a white solid; 0.51 g, (80% yield); dr *Z:E* = 95:5; mp 153.2–153.7 °C (DCM/PE; lit. mp 79-81 °C for *E* diastereomer); ^{1}H NMR (600 MHz, $CDCl_3$) predominant *Z* diastereomer δ 1.43 (d, *J* = 6.8 Hz, 3H), 3.78 (s, 3H), 6.20 (q, *J* = 6.9 Hz, 1H), 7.08 (t, *J* = 7.4, 1H), 7.16–7.19 (m, 1H), 7.21–7.25 (m, 3H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.31–7.33 (m, 1H), 7.35–7.37 (m, 6H), 7.43 (d, *J* = 8.2 Hz, 1H); distinctive signals for the *E* diastereomer δ 1.78 (d, *J* = 7.1 Hz, 3H), 3.63 (s, 3H), 5.80 (q, *J* = 6.9 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.1 (CH_3), 31.4 (CH_3), 109.5 (CH), 112.4 (C), 119.7 (CH), 120.6 (CH), 121.9 (CH), 126.4 (CH), 126.5 (CH), 126.7 (2xCH), 127.8 (CH), 128.0 (C), 128.1 (2xCH), 128.3 (2xCH), 130.1 (2xCH), 132.4 (C), 134.7 (C), 137.8 (C), 139.3 (C), 143.2 (C). IR ν (cm^{-1}) 3052, 1603, 1238, 740, 696. MS m/z (%) 323 [M^+](100), 308 (40).

*4.2.10. 3-[1-Phenylprop-1-enyl]-1H-indole (**3j**).*[16]

Chromatographic purification (PE/Acetone 80:20) gave **3j** as an oil; 0.27 g, (58% yield); dr *Z:E* = 37:63; ^{1}H NMR (600 MHz, $CDCl_3$) predominant *E* diastereomer δ 1.87 (d, *J* = 7.0 Hz, 3H), 6.28 (q,

J = 7.0 Hz, 1H), 6.81 (d, *J* = 2.5 Hz, 1H), 7.03–7.06 (m, 1H), 7.10–7.12 (m, 2H), 7.18–7.22 (m, 3H), 7.24–7.29 (m, 3H), 7.31–7.38 (m, 5H), 7.40–7.42 (m, 2H), 7.48–7.51 (m, 1H), 7.59–7.61 (m, 1H), 8.23 (br s, 1H); distinctive signals for the *Z* diastereomer δ 1.85 (d, *J* = 7.0 Hz, 3H), 6.32 (q, *J* = 7.0 Hz, 1H), 8.02 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.4 (and 16.3, CH_3), 111.2 (CH), 111.4 (CH), 114.9 (C), 118.9 (CH), 119.7 (CH), 120.0 (C), 120.2 (CH), 120.8 (C), 121.2 (CH), 121.5 (CH), 122.0 (CH), 122.2 (CH), 123.7 (CH), 124.4 (CH), 125.4 (C), 126.7 (CH), 126.8 (CH), 127.2 (CH), 127.5 (C), 127.7 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 128.9 (CH), 130.0 (CH), 135.2 (C), 136.1 (C), 136.5 (C), 136.8 (C), 141.0 (C), 143.5 (C). IR ν (cm^{-1}) 3408, 3054, 1596, 1206, 741, 698. MS m/z (%) 233 [M^+](100), 217 (30).

*4.2.11. 3-[1-(3-Chlorophenyl)prop-1-enyl]-1H-indole (**3k**).*[23]

Chromatographic purification (PE/Acetone 80:20) gave **3j** as an oil; 0.23 g, (43% yield); dr *Z:E* = 35:65; ^{1}H NMR (600 MHz, $CDCl_3$) predominant *E* diastereomer δ 1.81 (d, *J* = 7.1 Hz, 3H), 6.29 (q, *J* = 7.1 Hz, 1H), 6.81 (br s, 1H), 7.02–7.05 (m, 1H), 7.09–7.11 (m, 1H), 7.12 (br s 1H), 7.14–7.16 (m, 2), 7.17–7.21 (m, 4H), 7.29–7.31 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 8.07 (br s, 1H); distinctive signals for the *Z* diastereomer δ 1.83 (d, *J* = 6.9 Hz, 3H), 6.25 (q, *J* = 6.9 Hz, 1H), 8.26 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.3 (and 16.3, CH_3), 111.2 (CH), 111.4 (CH), 114.3 (C), 119.7 (C), 119.8 (CH), 120.2 (CH), 120.6 (CH), 122.1 (CH), 122.2 (CH), 122.3 (CH), 123.6 (CH), 124.3 (CH), 125.4 (CH), 125.7 (C), 126.6 (CH), 126.7(CH), 127.0 (CH), 127.1 (CH), 127.3 (C), 128.2 (CH), 129.3 (CH), 129.4 (CH), 129.9 (CH), 133.9 (C), 134.0 (C), 134.1 (C), 135.2 (C), 136.1 (C), 136.7 (C), 142.9 (C), 145.4 (C). IR ν (cm^{-1}) 3403, 3055, 1590, 1201, 740, 694. MS m/z (%) 267 [M^+](100), 230 (30).

*4.2.12. 3-[1,2-Diphenyleth-1-enyl]-1-methylindole (**3l**).*[20]

Chromatographic purification (PE/EE 895:5) gave **3l** as a white solid; 0.48 g, (78% yield); dr *Z:E* = 40:60; mp 178-182 °C (DCM/PE); ^{1}H NMR (600 MHz, $CDCl_3$) predominant *E* diastereomer δ 3.73 (s, 3H) 6.77 (s, 1H), 6.89–6.96 (m, 2H), 7.02–7.14 (m, 9H), 7.17–7.21 (m, 2H), 7.24–7.35 (m, 10H), 7.42–7.44 (m, 1H), 7.71 (d, *J* = 8.0 Hz, 1H); distinctive signal for the *Z* diastereomer δ 3.77 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 32.9 (and 33.0, CH_3), 109.2 (CH), 109.6 (CH), 113.9 (C), 119.3 (C), 119.4 (CH), 120.0 (CH), 121.1 (CH), 121.3 (CH), 121.7 (CH), 122.1 (CH), 124.4 (CH), 125.9 (CH), 126.2 (C), 126.4 (CH), 127.4 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 129.2 (CH), 129.3 (CH), 129.7 (CH), 129.8 (CH), 130.3 (CH), 135.4 (C), 137.1 (C), 137.8 (C), 138.1 (C), 138.5 (C), 141.4 (C), 144.3 (C). IR ν (cm^{-1}) 3025, 1532, 1206, 734, 694. MS m/z (%) 309 [M^+](100), 293 (45).

Supporting Data

Supplementary data for this article can be found online and include copies of the ^{1}H and ^{13}C NMR spectra, crystal data, X-ray data collection and structure refinement, bond lengths and angles from X-ray diffraction, tables of calculated relative energies, discussion on steric and electronic effects, pictures of calculated structures, calculated absolute energies and Cartesian coordinates.

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- 3-(α-Aryl)alkenylindoles can be easily prepared via a direct dehydrative coupling reaction between alkyl aryl ketones and some indoles, in the presence of a Brønsted-acid catalyst.

- The observed good diastereoselectivity depending on indole substitution has been explained by a computational method.

- The synthesized compounds are reactive intermediates, useful for the synthesis of indole alkaloids, carbazole and other indole-based heterocycles.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: