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A simple, direct synthesis of 3-vinylindoles from the carbocation-catalysed dehydrative cross-coupling of ketones and indoles. A combined experimental and computational study.

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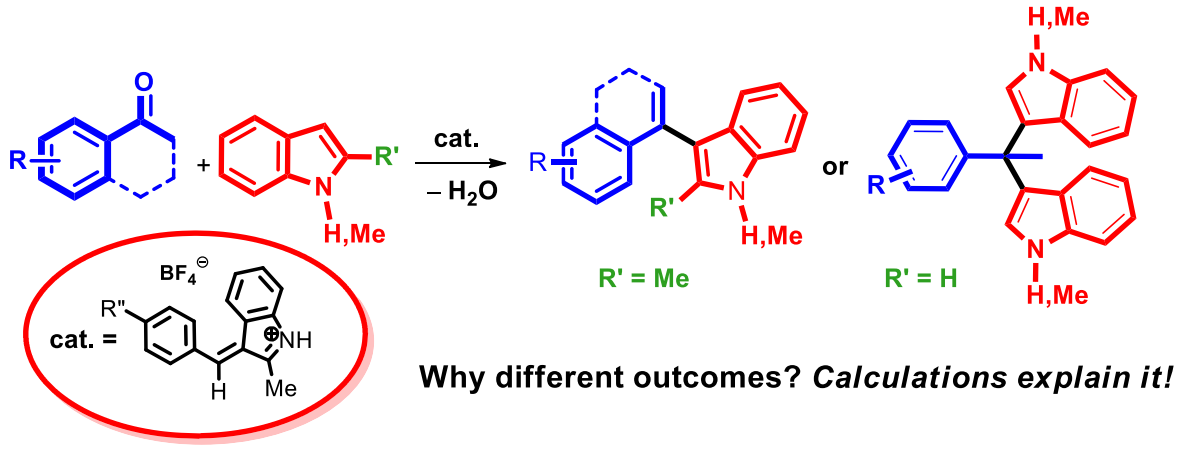
Graphical abstract:



Abstract: A straightforward synthesis of a library of largely new 3-vinylindoles via a clean dehydrative coupling reaction between ketones and indoles has been developed. Highly stable, non-nucleophilic aryl(2-methylindol-3-yl)methylium salts have been used as efficient Lewis acid catalysts. The advantages of the reaction are the use of equimolar amounts of inexpensive and easily available reagents, the low catalyst amount, high atom efficiency, the production of only one

molecule of water as a by-product and the mild reaction conditions. Computational studies of two specific reaction mechanism instances show that both steric and electronic effects heavely influence the nature of the final products, whether a methyl group in position 2 of the indole is present or absent.

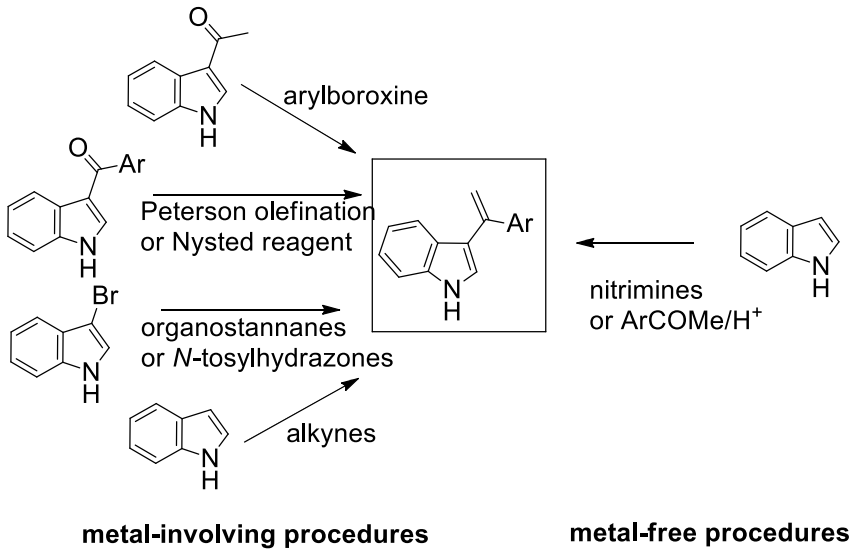
Keywords: Stable carbocations, Lewis acid catalysis, Dehydrative coupling, 3-Vinylindoles, DFT calculations

1. Introduction

Indoles are one of the most widespread heterocycles to be found in natural products and are often endowed with biological activity.[1-5] The synthesis and functionalization of indole derivatives are still challenging goals with these species being referred to as "privileged structures",[6] in a large number of drugs.[7-17] One of these structure groups, 3-(α-aryl)vinylindoles, features the 1-aryl-1-heteroarylethene scaffold, which is often found in molecules that show strong biological activity.[18,19] Furthermore, 3-vinylindole and its derivatives have been used as elaborate building blocks in the asymmetric synthesis of substituted indoles.[20]

Most of the methods for the synthesis of 1-aryl-1-(indol-3-yl)ethenes involve expensive reagents or metal-catalysed procedures and preformed 3-acylindoles or 3-bromoindoles (Scheme 1). The most recent metal-involving methods include the alkenylation of 3-bromoindoles with proper organostannanes,[21] indole gold- or indium-catalysed alkenylation with alkynes,[22,23] the nickel-catalysed addition of arylboron reagents to ketones,[24] the use of Nysted reagent and the Peterson olefination of indolyl ketones,[25] and the Suzuki–Miyaura coupling of 1-indolylvinyl phosphates,[26] while the most general protocols are based on the addition of Grignard reagents to ketones, followed by dehydration, or on Wittig olefination by methyl triphenylphosponium ylide.[27] On the

contrary, metal-free procedures comprehend the dehydrative coupling of indoles with ketones catalysed by Brønsted acid[28] or Brønsted acidic ionic liquids[29] and the metal-free formal C(sp^2)–C(sp^2) cross-coupling of indoles with nitrimines.[30] 3-Vinylindoles have also been formed as key intermediates in multicomponent reactions between indoles, ketones and a nucleophile,[31-34] and in multistep reactions.[35,36]



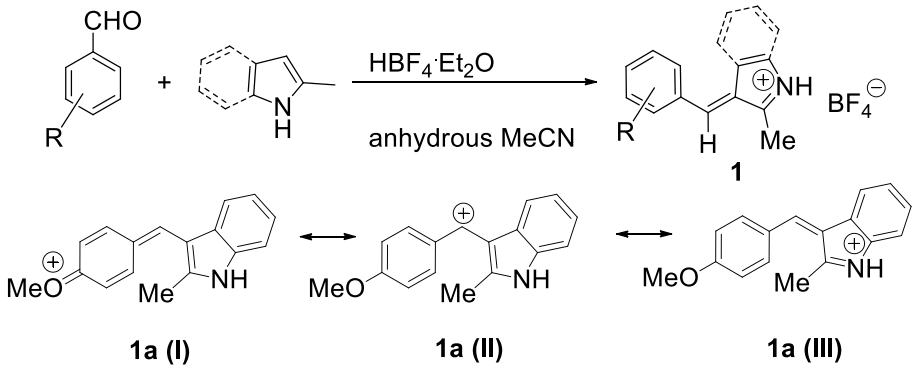
Scheme 1: Previous procedures for the synthesis of 3-(α-aryl)vinylindoles.

Our research interest in indole[37-39] and carbocation chemistry[40-43] has driven us to explore the synthetic potential of highly stabilised benzhydrylic cations, which we have recently reported on,[41,40] as Lewis acid catalysts in indole functionalisation. Like all other Lewis acids, carbocations have a low-lying empty p_C orbital, that can accept electrons and therefore activate an electrophile towards nucleophilic attack.

Mukaiyama and co-workers reported the very first carbocation-catalysed reactions,[44] and stable carbocations, such as tritylium ions, have been frequently investigated for use as organic Lewis acid catalysts eversince. The most recent applications of this type of catalysts are: intramolecular carbonyl-ene cyclization and [2+2]cycloaddition,[45] the hydrothiolations of di- and trisubstituted olefins,[46] the three component redox-neutral α-arylation of amines,[47] the Michael-type Friedel–Crafts reaction of indoles with α,β-unsaturated carbonyl compounds,[48] the chiral anion directed

asymmetric Diels–Alder reaction,[49] asymmetric latent carbocation catalysis in Friedel−Crafts alkylation, hetero-Diels−Alder and carbonyl-ene reactions,[50] the Povarov reaction,[51] carbonyl/olefin oxo-metathesis,[52] oxa-Diels–Alder reactions,[53] and heterocycle synthesis.[54,55] Comprehensive reviews on earlier works have been published by Franzen,[56,57] who mentioned the use of tritylium salts as Lewis acids in Mukaiyama aldol and Sakurai allylation reactions, as well in Diels–Alder, aza Diels–Alder and Michael reactions.

Tritylium salts were either used as commercially available reagents or generated *in situ* in the above-mentioned reports. As an alternative to these options, we have decided to test our air-stable aryl (2-methylindol-3-yl)methylium salts, which can be easily prepared in high yields and stored for significant amounts of time without decomposition (some months at 5°C) (Scheme 2). The diarylcarbenium ion can be stabilized by positive charge resonance delocalization both onto the phenyl and the indole rings, as reported for salt **1a** in Scheme 2. Bond distances obtained by X-ray analysis of **1a** clearly agree with the resonance structure III. The resonance structure II is however responsible of the reactivity of these species, as previously reported by us in an organocatalysed asymmetric α–alkylation of aldehyde[43] and in a diastereoselective alkylation of cyclic silyl enol ethers.[42]

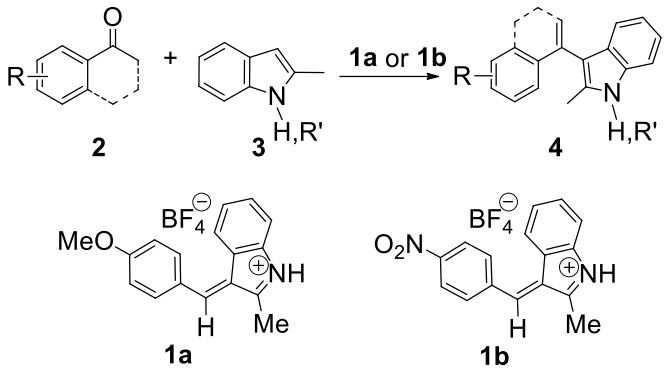


Scheme 2: Synthetic procedure for preparing salts **1** and resonance structures of salt **1a**.

The great stability of these indolyl-stabilised carbocations has also been confirmed by their electrophilicity values, as tabulated by Mayr.[58]

Indole alkyation normally occurs via electrophilic aromatic substitution and predominantly affords 3-alkyl derivatives. We have previously reported on a triarylmethane synthesis that was performed via a Brønsted acid-catalysed bisarylation (or bisheteroarylation) of activated aryl aldehydes. The reaction followed a multistep Friedel–Crafts type hydroxyalkylation in which the diarylmethanol intermediate immediately reacted with another equivalent of the arene, giving rise to a bisarylation product.[37] We herein report a new synthesis of 3-(α-aryl)vinylindoles that is based on a clean dehydrative coupling reaction between simple, cheap ketones **2** and nucleophilic aromatics **3** in the presence of catalytic amounts of either (4-methoxyphenyl) or (4-nitrophenyl)(2-methyl-3-indolyl)methylium tetrafluoroborate as Lewis acid catalysts (**1a** and **1b**, respectively, **Scheme 3**).[40] This direct coupling approach has only been reported once in the literature, giving excellent results in the presence of catalytic amounts of Brønsted acid ionic liquids that contained a sulfonic group.[29]

Scheme 3: Dehydrative coupling reaction of ketones 2 with nucleophiles 3



The dehydrative coupling products **4** were isolated in good yields in most cases. The reaction also benefits from high atom efficiency and produces only one molecule of water as a by-product.

2. Results and discussion

We decided that the reference reaction would be the coupling of 4-nitroacetophenone (**2a**) and 2-methylindole (**3a**) in a 1:1 molar ratio, in the presence of catalytic amounts of the above salts (**1a** or

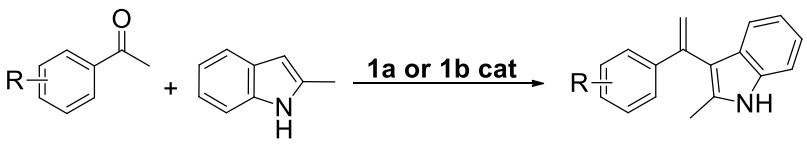
1b) and varying experimental conditions (Table 1). The variables taken into consideration are solvent, temperature, reaction time, and catalyst type and amount.

Neat conditions were initially tested and were found to be quite advantageous, although the formation of a very thick reaction mixture led to incomplete reactions both at rt (even after prolonged reaction times) and under heating (Table 1, entries 1–6). Furthermore, the catalyst amount was varied from 3 to 5 mol% (entries 2 and 3); no significant differences in the use of salts **1a** (entries 1–3) and **1b** (entries 4–6) were observed. Neat conditions were then extended to the reactions of **3a** with some representative acetophenones, namely **2b**, **2f** and **2g** (entries 7–10). While the results were unsatisfactory, except for the reaction of **2b** (entry 7), they highlighted the strong substituent effect and confirmed that, in the reaction of unactivated **2g**, the two catalysts showed identical performance (entries 9 and 10).

Then, the reference reaction was run in a solvent. Only traces of product were detected in dichloromethane under reflux in the presence of 10 mol% of salt **1b** (Table 1, entry 11). Finally, the model reaction was performed in MeOH in order to achieve reaction completion, as it is well-known that protic solvents stabilize carbocations. The reaction went to completion in 6 h at room temperature and furnished product **4a** under milder conditions and in better yield than previous reactions (entry 12).

A pilot run in methanol without catalyst did not give reaction (entry 13).

Table 1: Optimisation conditions of the dehydrative coupling reaction of ketones 2 with 2-methylindole (3a)[a] :



2a, R=4-NO_2 **3a** **4a, R=4-NO_2**
2b, R=4-CN **4b, R=4-CN**
2f, R=H **4h, R=H**
2g, R= 4-Me **4i, R= 4-Me**

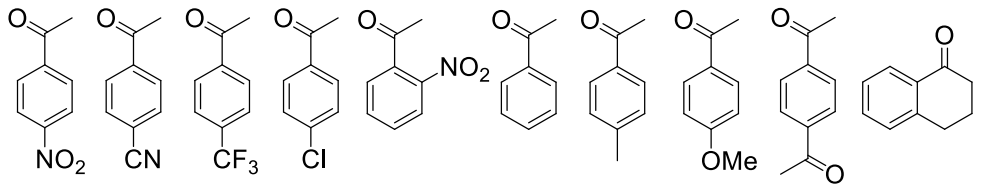
Entry	Ketone	Catalyst (mol%)	solvent	t(h)	T(°C)	Yield (%)[b]
1	**2a**	**1a (3)**	neat	24	rt	**4a**; 60[c]
2	**2a**	**1a (3)**	neat	1	90	**4a**; 70[c]
3	**2a**	**1a (5)**	neat	1	110	**4a**; 51
4	**2a**	**1b (3)**	neat	24	rt	**4a**; 70[c]
5	**2a**	**1b (3)**	neat	1	60	**4a**; 58
6	**2a**	**1b (3)**	neat	1	90	**4a**; 74[c]
7	**2b**	**1a (3)**	neat	1	90	**4b**; 74
8	**2f**	**1a (5)**	neat	7	90	**4h**; traces
9	**2g**	**1a (3)**	neat	24	60	**4i**; 30
10	**2g**	**1b (3)**	neat	24	60	**4i**; 30
11	**2a**	**1b (10)**	DCM	10	reflux	**4a**; traces
12	**2a**	**1a (5)**	anhydrous MeOH	6	rt	**4a**; 76
13	**2a**	**-**	anhydrous MeOH	24	rt	**-**

[a] Reaction conditions: **2**:**3** =1:1, on a 2 mmol scale.
[b] Yields refer to isolated products purified by column chromatography (eluent PE/acetone 85:15)
[c] Incomplete reaction.

The optimised reaction conditions (catalyst **1a**, 5 mol%, anhydrous methanol as solvent) were then applied to a number of acetophenones (substituted and not) and other representative ketones.

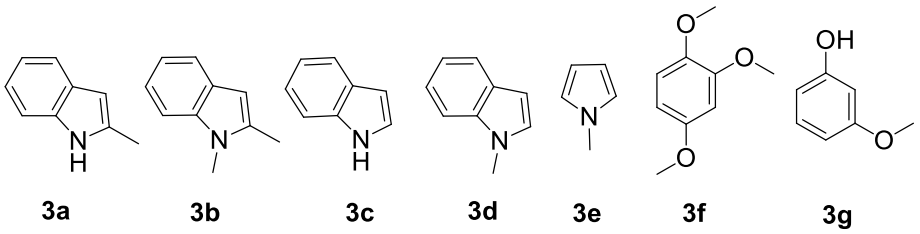
The list of tested acetophenones **2a**–**i**, and cyclic ketone **2j**, is reported in Chart 1, while that of aromatic and heteroaromatic compounds that reacted as nucleophiles can be found in Chart 2. Finally, Table 2 reports the results of the tested reactions, purified products **4a**–**4l**, reaction conditions and isolated yields.

Chart 1: Ketones 2a–j tested in the dehydrative coupling reaction.



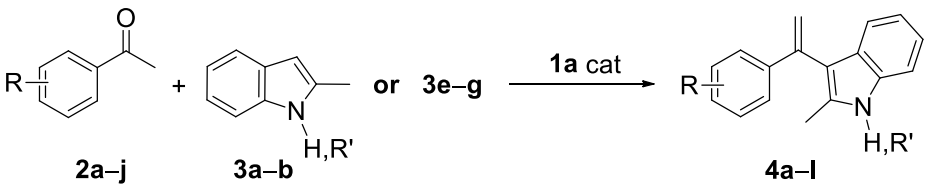
2a **2b** **2c** **2d** **2e** **2f** **2g** **2h** **2i** **2j**

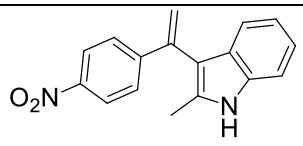
Chart 2: Aromatic and heteroaromatic compounds 3a–g tested as nucleophiles in the dehydrative coupling reaction with ketones 2.

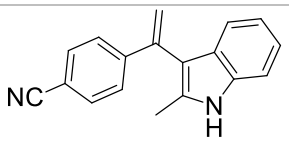
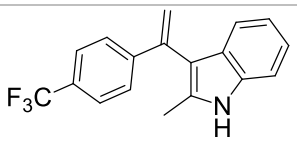
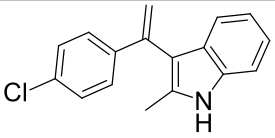
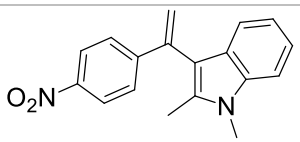
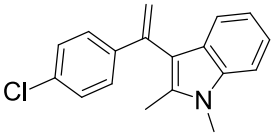
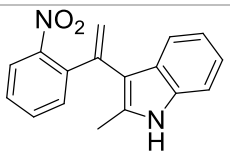
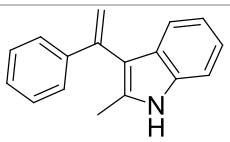
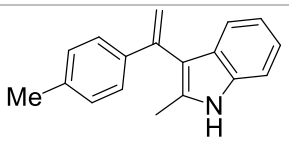
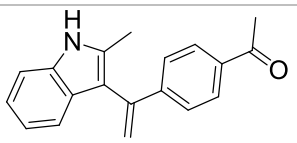


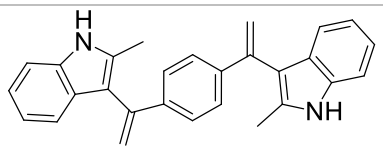
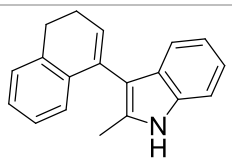
As observed in the trial runs, the reactions with 2-methylindole (**3a**) proceeded under milder reaction conditions in the presence of electron-withdrawing subtituents than when electron-donating groups were present. The effect that substituents have on the activation of the carbonyl group towards nucleophilic attack is noticeable. In fact, products **4a**–**d** were obtained in good yields at rt (yield range 70–85%; Table 2, entries 1–4), whereas the reactions of the less activated ketones **2f**–**g** needed to be heated at reflux and gave modest yields of **4h** and **4i** (59 and 54%, respectively; entries 8–9). The reaction of ketone **2g** was also carried out in the presence of salt **1b**, although no yield improvements were observed. In addition to the low reactivity shown by ketone **2g**, the nucleophilic solvent was observed to have attacked the catalyst **1b** (entry 9; see further in the discussion).

Table 2: Dehydrative coupling reaction of ketones 2 with nucleophiles 3 in the synthesis of 3-(α-aryl)vinylindoles 4.



Entry	Ketones **2**	Nucleophiles **3**	T °(C)	T (h)	Products **4** and yields (%)[a]
1	**2a**	**3a**	rt	6	 **4a**; 76%

2	**2b**	**3a**	rt	4.5	 **4b**; 85%
3	**2c**	**3a**	rt	4	 **4c**; 78%
4	**2d**	**3a**	rt	6.5	 **4d**; 70%
5	**2a**	**3b**	rt	4.5	 **4e**; 85%[b]
6	**2d**	**3b**	rt	4	 **4f**; 65%[b]
7	**2e**	**3a**	65	30	 **4g**; 65%[c]
8	**2f**	**3a**	65	5.5	 **4h**; 59%
9	**2g**	**3a**	65	4	 **4i**; 54%[d]
10	**2h**	**3a**	65	24	-[e]
11	**2i**	**3a**	rt	2.5	 **4j**; 65%[f]

12	**2i**	**3a**	rt	24	 **4k**; 34%[g]
13	**2j**	**3a**	65	8	 **4l**; 68%
14	**2a**	**3e**	rt	6	-[e]
15	**2a**	**3e**	65	4	-[h]
16	**2a**	**3f**	rt	3	-[e]
17	**2a**	**3f**	65	6	-[e]
18	**2a**	**3g**	rt	20	-[e]

[a] Reactions were performed on a 2 mmol scale in a molar ratio **2**:**3** =1:1 in the presence of catalyst **1a** (5% mol with respect to **2**, unless otherwise stated), in anhydrous methanol (5 mL), without the exclusion of air or moisture. Reaction conditions (time, temperature and yield) for each vinylindole **4** are reported. Yields refer to products purified by column chromatography. See experimental section for details.
[b] Product separated from the reaction mixture. The solid washed thoroughly with PE was virtually pure.
[c] Reaction was carried out at rt but with less satisfactory results.
[d] Reaction was carried out at a molar ratio **2**:**3** = 1:1.2. Furthermore, the reaction was run in the presence of **1b** as the catalyst, but without giving a better yield; furthermore, the nucleophilic solvent was observed to have attacked the catalyst **1b**; see text for details.
[e] No products **4** were obtained. GC-MS analyses showed the formation of 4-nitroacetophenone dimethylacetal.
[f] The molar ratio was **2**:**3**=2:1. Traces of **4k** were also isolated.
[g] The molar ratio was **2**:**3**=1:3 and the catalyst 10% mol. Product **4j** was also isolated along with **4k** (54% yield).
[h] GC-MS analyses of the reaction mixture showed a complex mixture of products among which expected product MS (EI): m/z 228 (M^+) in traces and 4-nitroacetophenone dimethylacetal (**5**) MS (EI): m/z 196 (M^+) were detected.

The scope of the reaction was then evaluated by reacting **2a** and **2d** with 1,2-dimethylindole (**3b**); products **4e** and **4f** were isolated in yields that are comparable with those of **4a** and **4d** (entries 5–6). The steric effect was investigated by reacting *ortho*-substituted ketone **2e** with **3a**; **4g** was obtained, although after prolonged heating and in a lower yield than the *para*-substituted product (entry 7). Highly unactivated ketone **2h** did not even give traces of the expected product (entry 10).

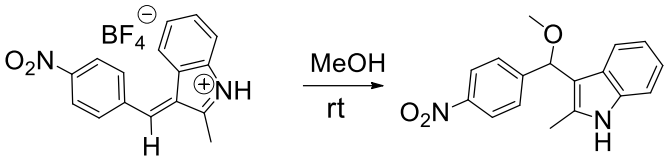
1,4-Diacetylbenzene (**2i**), a ketone that is potentially interesting for dehydrative coupling, was then reacted under the optimised reaction conditions. The presence of two carbonyl groups meant that the number of nucleophile equivalents was changed in order to give the monovinyl (**4j**) and the divinyl (**4k**) adducts (molar ratio **2i**:**3a**=2:1 or 1:3, respectively, catalyst loading was 10 mol% in

the latter case). Unfortunately, the concomitant formation of both compounds was observed in both reactions. After chromatographic purification, **4j** was isolated as the predominant product at the first molar ratio (65% yield, accompanied by only traces of **4k**), whilst a mixture of **4j** and **4k** was obtained at the second molar ratio (54% and 34% yields, respectively; entries 11–12).

Finally, a cyclic ketone was tested. Bulky 1-tetralone (**2j**) was reacted with 2-methylindole (**3a**); the corresponding product **4l** was obtained in quite good yield (entry 13).

We attempted to extend the scope of the reaction by including nucleophiles that are not indoles. Several trial reactions were carried out using ketone **2a** with 1-methylpyrrole (**3e**), 1,2,4-trimethoxybenzene (**3f**) and 3-methoxyphenol (**3g)** as the nucleophiles, while reaction temperature and time were varied (entries 14–18). Unfortunately, only 4-nitroacetophenone dimethylacetal (**5**) was detected by GC-MS analyses.

Intrigued by the finding of entry 9, where a nucleophilic solvent attack on the catalyst **1b** was observed, we decided to analyse the respective stabilities of salts **1a** and **1b** in our reaction conditions and a significant difference in stability was observed. Whilst salt **1a** seemed to remain unaltered in the unsuccessful reactions, salt **1b** quickly disappeared, even at room temperature. TLC analyses of the reaction mixture showed a spot that we believe to be a product of the solvent's nucleophilic attack on catalyst **1b** (more electrophilic than **1a**). This product's formation was confirmed, first by monitoring the stability of salts **1a** and **1b** in CD_3OD in NMR tubes, and then by stirring **1a** and **1b** in methanol at room temperature (see details in the experimental section). After 6 h, the first of the salts was almost completely recovered unaltered, whereas in the latter case, the reaction was stopped after 20 min (disappearance of the salt); reaction work-up and chromatographic purification furnished adduct **6** in a 76% yield (Scheme 4). This finding could open up new synthetic opportunities for our salts with other nucleophilic partners.



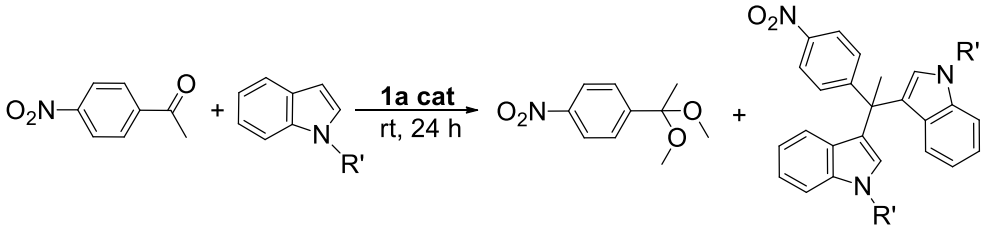
1b **6**

Scheme 4: Formation of product 6

The stability of **1a** was further tested by running reaction between **2a** and **3a** four months after its preparation; product **4a** was obtained in the same reaction conditions with the same yield, clearly showing no loss of catalytic efficiency. Furthermore, the scalability of the proposed synthetic method was tested in the same reaction on a 10 mmol scale; the reaction was complete after 6 h at rt, product **4a** was obtained in 77% yield.

After the screening of the above nucleophiles, several trials were performed on unsubstituted indole (**3c**) and 1-methylindole (**3d**). Reaction with ketone **2a** did not give the expected dehydrative coupling products under the usual reaction conditions. The only isolated products were the dimethylacetal of **2a** (namely **5**) and adducts **7a** and **7b**, which were produced by the reaction of **2a** with two equivalents of indole. Under these non-optimised conditions, the isolated yields were 76% and 86% for **7a** and **7b**, respectively (Scheme 5; for details, see experimental section).

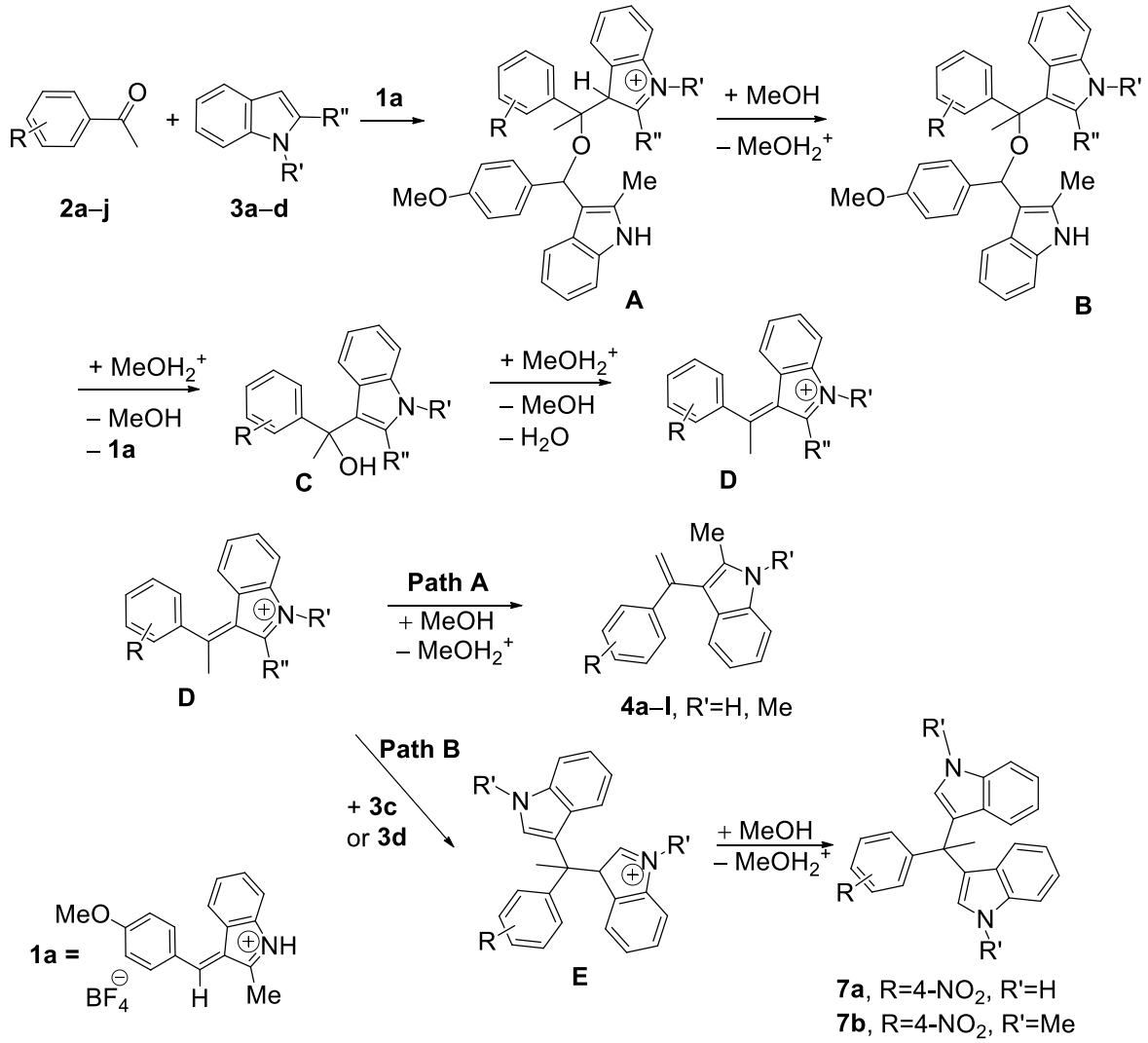
Scheme 5: Reactions of 2a with indoles 3c and 3d.



2a **3c, R'=H; 3d, R'=Me** **5** **7a**, R'=H; 76% yield. **7b**, R'=Me; 86% yield

A comparison with the literature[59-62] suggests that these findings can be explained by a lack of steric hindrance at C-2, which favours a second reaction with the nucleophile, after the first

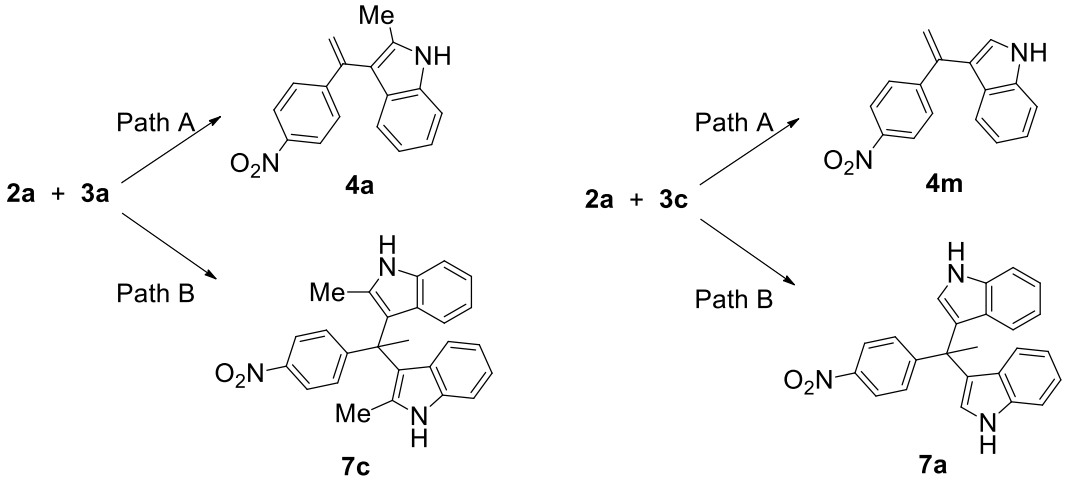
hydroxyalkylation step, rather than the dehydration step. A competing reaction mechanism can therefore be proposed when indole (or 1-methylindole) is the nucleophile; the reaction pathway relies on the absence of either steric hindrance[59-62] or the stabilising effect of a substituent,[63] in the C-2 position of the indole, as illustrated in Scheme 3 (Scheme 6; Path B).



Scheme 6: Competitive mechanisms in the dehydrative coupling of ketones 2 with indoles 3.

The reaction follows a well-known Lewis-acid-catalysed Friedel–Crafts type hydroxyalkylation reaction. In order to better rationalise the experimental findings, a computational method was used to study the reaction mechanism, as reported in Scheme 6, for the reactions of **2a** with **3a** (the energy profiles are shown in Figure 1a, and the reaction mechanism in Scheme 1a in the

Supplementary Data) and with **3c** (Figure 1b, and Scheme 1b in the Supplementary Data) in the presence of **1a**, used as the catalyst. The predictable products of paths A and B are shown in Scheme 7. All energy values and pictures of the structures are reported in the Supplementary Data.



Scheme 7: Predictable products of the reaction of 2a with 3a (4a and 7c) and with 3c (4m and 7a) using 1a as the catalyst.

In both cases, the rate-determining step is the Friedel–Crafts electrophilic attack of the ketone, activated by the catalyst, on the indole to form intermediates **A**. Throughout a proton transfer mediated by the solvent ($MeOH/MeOH_2^+$), intermediates **B** break into catalyst **1a** forming intermediates **C**. The alternative breakings from **B** (reported only in Figures 1a and 1b) to **D** plus the hydroxylated catalyst (**1a–OH**) are thermodynamically unfavoured. The generation of cations **D** requires the protonation of intermediates **C** by the solvent. $MeOH_2^+$ is generated by the following, almost isoergic, equilibrium (eq. 1):

$$\mathbf{1a} + 2\ MeOH \rightleftharpoons \mathbf{1a}\text{-}OMe + MeOH_2^+ \qquad \text{eq.1}$$

Two pathways open up once carbeniums **D** have been irreversibly generated. Path A sees prompt deprotonation generate alkenes **4a**, when the indole is **3a**, and **4m**, when the indole is **3c**. Path B sees the electrophilic attack on a second indole molecule generate intermediates **E** whose deprotonation finally generates adducts **7c**, when the indole is **3a**, and **7a**, when the indole is **3c**.

All the kinetic rate constants for all the reactions in paths A and B are in the order of min^{-1} or higher. This means that, due to the long reaction times (hours), the reactions that generate alkenes **4** and adducts **7** are subjected to thermodynamic control.

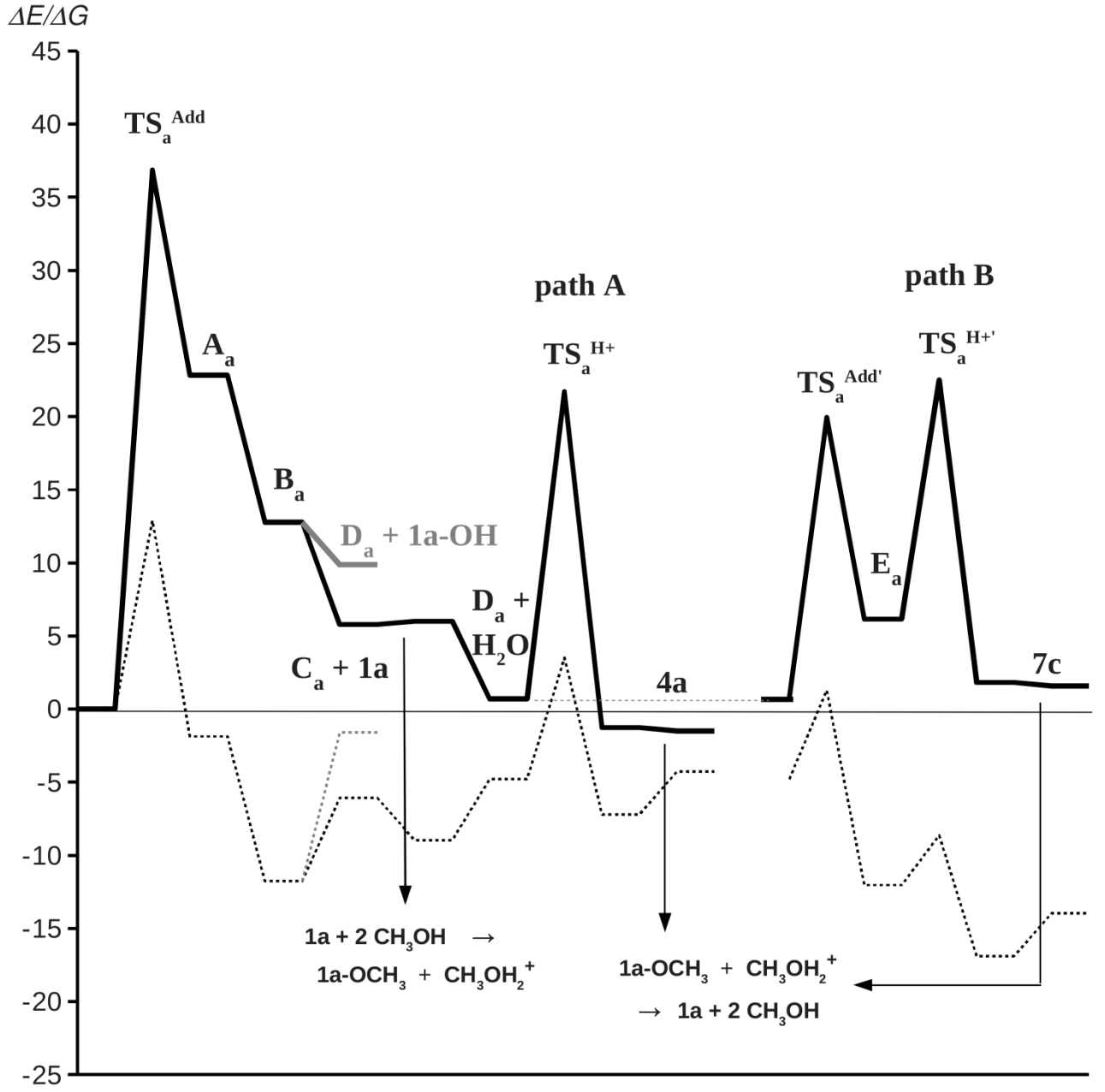
In the reaction of **2a** with indole **3a**, alkene **4a** is 4.3 kcal mol^{-1} more stable than the reactants in terms of energy and 1.5 kcal mol^{-1} in terms of free energy, while adduct **7c** is 14.0 kcal mol^{-1} more stable than the reactants in terms of energy but 1.6 kcal mol^{-1} less stable than the reactants in terms of free energy. This means that the alkene **4a** is thermodynamically favoured, as was observed experimentally. The rate of the estimated equilibrium constants, $K_{\mathbf{4a}}/K_{\mathbf{6c}}$, is 184; only traces of **7c** are expected to be formed.

When the indole is **3c**, alkene **4m** is 3.8 kcal mol^{-1} more stable than the reactants in terms of energy and 1.7 kcal mol^{-1} in terms of free energy while the adduct **7a** is 20.1 kcal mol^{-1} more stable than the reactants in term of energy and 5.1 kcal mol^{-1} in term of free energy. This means that, although both products are thermodynamically possible, adduct **7a** is favoured, as is coherent with experimental findings. The rate of the estimated equilibrium constants, $K_{\mathbf{6a}}/K_{\mathbf{4m}}$, is 295; now it is **4m** that is only estimated to be formed in traces.

The protonated solvent generated in the deprotonations of **D** or **E** reacts with **1a**–OMe regenerating the catalyst.

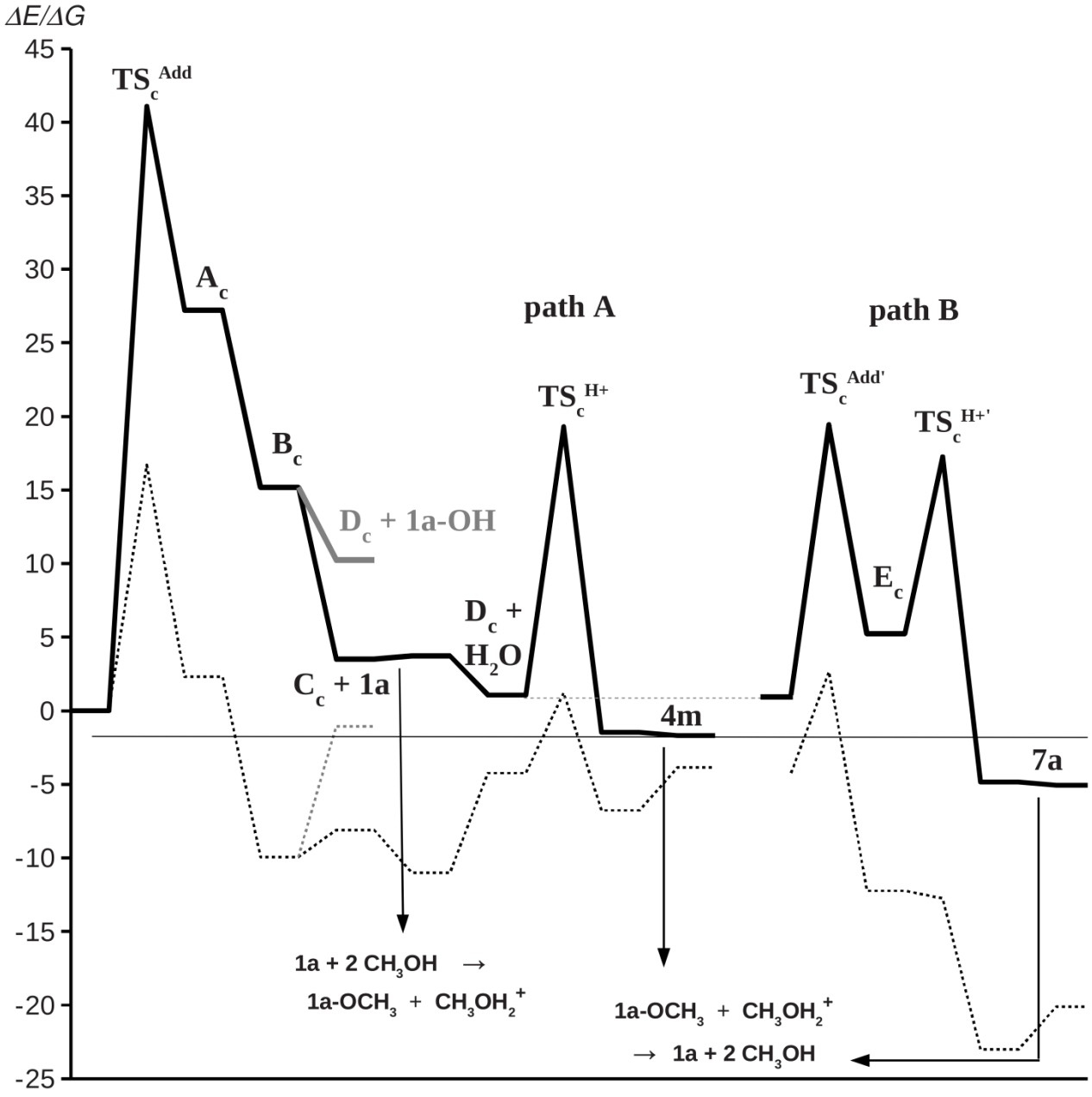
We provide a detailed comparison and discussion of the two energy profiles in the Supplementary Data. On the basis of the data, we propose an explanation of the different energies of the final products and, therefore, of the different outcomes shown by the reactions of **2a** with **3a** and **3c**. Herein, we only report that both the steric and the stabilising electronic effects shown by the methyl group, which is present in position 2 of indole **3a** and absent in **3c**, must be taken into account, and that the electronic effect plays a predominant role.

Figure 1a: Energy ($\Delta E = \Delta E_{el}+\Delta$ZPE)[a] and free energy (ΔG at room temperature)[b] profiles[c] for the reaction of 2a with 3a, with 1a as the catalyst.[d]



[a] Dashed lines. [b] Thick solid lines. [c] All energies are referred to that of the reactants. [d] See Scheme 3 or Scheme 1a in the Supplementary Data for the labels.

Figure 1b: Energy ($\Delta E = \Delta E_{el}+\Delta ZPE$)[a] and free energy ($\Delta G$ at room temperature)[b] profiles[c] for the reaction of 2a with 3c, with 1a as the catalyst.[d]



[a] Dashed lines. [b] Thick solid lines. [c] All energies are referred to that of the reactants. [d] See Scheme 3 or Scheme 1b in the Supplementary Data for the labels.

3. Conclusions

In this paper, we have reported the first application of highly stable, non-nucleophilic aryl(indol-3-yl)methylium salts for use as Lewis acid catalysts in a clean dehydrative coupling reaction between

selected ketones and indoles to give 3-vinylindoles. The advantages of this reaction are the use of equimolar amounts of inexpensive and easily available reagents, the low amounts of the stable and efficient catalyst used, the high atom efficiency, the production of only one molecule of water as a by-product and the mild reaction conditions. This simple and mild procedure has produced a library of largely new 3-(α-aryl)vinylindoles in modest to good yields. The formation of unexpected products has been explained. The explanation for the different outcomes that are observed in the reactions of **2a** with **3a** (and presumably **3b**) and with **3c** (and presumably **3d**) is based on the fact that the methyl group, which is present in position 2 of indole **3a** and absent from **3c**, acts both with steric effect in all intermediates and with stabilizing electronic effect on carbeniums only. The presence (or lack) and the relative relevance of these two factors are responsible for the formation of alkene **4a**, when **2a** reacts with **3a**, and that of adduct **7a**, when **2a** reacts with **3c**. Further detailed research into the synthetic applicability of these salts, both as Lewis acid catalysts and as electrophilic reagents, is currently underway.

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 spectrometer at 200 MHz and 50 MHz, respectively. 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. 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. Catalysts **1a** and **1b** were prepared as reported in literature.[40] 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. 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.

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

Catalyst **1** (5 mol%) was added to a solution of ketone **2** (2.0 mmol) and aromatic compound **3** (2.0 mmol) in anhydrous methanol (5 mL) under stirring. The reaction mixture was then stirred in an air atmosphere, at either room temperature or reflux (65 °C), as reported in Table 4. Upon completion, the reaction mixture was treated with H_2O/ DCM (1:1, 30 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-(4-nitrophenyl)ethenyl]-1H-indole (**4a**).*

Chromatographic purification (PE/Acetone 85:15) gave **4a** as a yellow solid; 0.42 g, (76% yield); mp 106.5–107.5 °C (DCM/PE); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.25 (s, 3H), 5.47 (d, *J* = 1.4 Hz, 1H), 5.82 (d, *J* = 1.0 Hz, 1H), 6.91–7.16 (m, 3H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 11.0 Hz, 2H), 8.10 (d, *J* = 11.2 Hz, 2H) overlapped with 8.08 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.6 (CH3), 110.2 (CH), 112.6 (C), 118.2 (CH2), 119.0 (CH), 119.8 (CH), 121.4 (CH), 123.4 (2 x CH), 127.7 (C), 127.9 (2 x CH), 133.3 (C), 135.0 (C), 140.8 (C), 146.9 (C), 148.3 (C); IR ν (cm^{-1}) 3381,

1587, 1510, 1343, 858, 748; MS *m/z* (%) 278 [M^+](100), 231 (65), 217(90); Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found C, 73.32; H, 5.10; N,10.11.

*4.2.2. 3-[1-(4-Cyanophenyl)ethenyl]-2-methyl-1H-indole (**4b**).*

Chromatographic purification (PE/Acetone 90:10) gave **4b** as a pale grey solid; 0.44 g (85% yield): mp 185–186 °C (DCM/PE); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3H), 5.42 (d, *J* = 1.4 Hz, 1H), 5.77 (d, *J* = 1.4 Hz, 1H), 6.94–7.12 (m, 3H), 7.24–7.29 (m, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 9.8 Hz, 2H), 8.03 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.6 (CH3), 110.2 (CH), 112.6 (C), 112.6 (C), 117.5 (CH2), 118.9 (C), 119.1 (CH), 119.7 (CH), 121.4 (CH), 127.7 (2 x CH), 131.9 (2 x CH), 133.3 (C), 135.0 (C), 141.0 (C), 141.4 (C) , 146.3 (C); IR ν (cm^{-1}) 3327, 2238, 1502, 1457, 899, 846, 738, 572; MS *m/z* (%) 258 [M^+](85), 243 (100); Anal. Calcd for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found C, 83.60; H, 5.40; N, 10.87.

*4.2.3. 3-[1-(4-Trifluoromethylphenyl)ethenyl]-2-methyl-1H-indole (**4c**).*[29]

Chromatographic purification (PE/Acetone 90:10) gave **4c** as a white solid; 0.47 g (78% yield): mp 83.5–84.5 °C (DCM/PE); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H), 5.42 (d, *J* = 1.6 Hz, 1H), 5.78 (d, *J* = 1.6 Hz, 1H), 6.95–7.20 (m, 3H), 7.24–7.29 (m, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.89 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.6 (CH3), 110.2 (CH), 113.1 (C), 116.7 (CH2), 119.3 (CH), 119.7 (CH), 121.3 (CH), 124.2 (C, q, J_1 = 270 Hz), 125.0 (CH, q, J_3 =3.8 Hz), 127.4 (CH), 127.9 (C), 129.6 (C, q, J_2= 33.0 Hz), 133.2 (C), 135.0 (C), 141.3 (C), 145.3 (C); MS *m/z* (%) 301 [M^+](100), 286 (75), 217 (50).

*4.2.4. 3-[1-(4-Chlorophenyl)ethenyl]-2-methyl-1H-indole (**4d**).*[29]

Chromatographic purification (PE/Acetone 85:15) gave **4d** as a white solid; 0.37 g (70% yield): mp 127.5–128.5 °C (DCM/PE); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H), 5.30 (d, *J* = 1.9 Hz, 1H),

5.68 (d, *J* = 1.9 Hz, 1H), 6.97–7.09 (m, 1H), 7.13–7.32 (m, 3 H) overlapped with 7.22 (d, *J* = 8.4, 2H) and 7.29 (d, *J* = 8.6 Hz, 2H), 7.87 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.7 (CH3), 110.1 (CH), 113.4 (C), 115.2 (CH2), 119.4 (CH), 119.6 (CH), 121.2 (CH), 128.0 (C), 128.2 (2 x CH), 128.5 (2 x CH), 133.1 (2 x C), 134.9 (C), 140.2 (C), 141.2 (C); MS *m/z* (%) 267 [M^+](75), 231 (55), 217 (100).

*4.2.5. 1,2-Dimethyl-3-[1-(4-nitrophenyl)ethenyl]indole (**4e**).*

The product separated from the reaction mixture, it was collected under vacuum and washed thoroughly with PE to give virtually pure **4e** as a pale yellow solid; 0.50 g (85% yield): mp 144.0–144.8 °C (DCM/PE); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.68 (s, 3H), 5.44 (br s, 1H), 5.83 (br s, 1H), 6.91–6.98 (m, 1H), 7.05–7.16 (m, 2H), 7.24–7.28 (m, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 8.09 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.3 (CH3), 29.6 (CH3), 108.7 (CH), 112.0 (CH2), 118.2 (C), 119.0 (CH), 119.5 (CH), 121.0 (CH), 123.4 (2 x CH), 126.9 (C), 127.8 (2 x CH), 135.1 (C), 136.5 (C), 141.1 (C), 146.9 (C), 148.5 (C); IR ν (cm^{-1}) 1593, 1507, 1343, 864, 736; MS *m/z* (%) 292 [M^+](100), 245 (70), 231 (78); Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found C, 73.89; H, 5.49; N, 9.51.

*4.2.6. 3-[1-(4-Chlorophenyl)ethenyl]-1,2-dimethylindole (**4f**).*[64]

The product separated from the reaction mixture, it was collected under vacuum and washed thoroughly with PE to give virtually pure **4f** as a white solid; 0.36 g (65% yield): mp 102.0–102.5 °C (DCM/PE); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.67 (s, 3H), 5.27 (br s, 1H), 5.69 (br s, 1H), 6.92–6.99 (m, 1H), 7.13–7.31 (m, 3 H) overlapped with 7.20 (d, *J* = 8.6, 2H) and 7.29 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.3 (CH3), 29.5 (CH3), 108.5 (CH), 112.8 (C), 115.1 (CH2), 119.3 (CH), 120.8 (CH), 127.2 (C), 128.1 (2 x CH), 128.4 (2 x CH), 128.7 (CH), 133.0 (C),

134.9 (C), 136.5 (C), 140.4 (C), 141.6 (C); MS *m/z* (%) 281 [M^+](100), 266 (40), 245 (90), 231 (100).

*4.2.7. 2-Methyl-3-[1-(2-nitrophenyl)ethenyl]-1H-indole (**4g**).*

Chromatographic purification (PE/Acetone 85:15) gave **4g** as a yellow solid; 0.36 g (65% yield) : mp 177.0–177.9 °C (DCM/PE); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H), 5.45 (s, 1H), 5.48 (s, 1H), 6.86–7.06 (m, 3H), 7.14–7.20 (m, 1H), 7.34–7.42 (m, 1H), 7.50–7.55 (m, 2H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.91 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5 (CH3), 110.2 (CH), 112.1 (CH2), 116.4 (C), 118.7 (CH), 119.8 (CH), 121.2 (CH), 123.7 (CH), 127.4 (C), 128.1 (CH), 131.4 (CH), 132.1 (CH), 133.6 (C), 134.8 (C), 138.1 (C), 139.5 (C), 149.3 (C); IR ν (cm^{-1}) 3422, 1522, 1456, 1353, 890, 742, 498; MS *m/z* (%) 278 [M^+](65), 219 (100); Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found C, 73.30; H, 5.02; N,10.12**.**

*4.2.8. 2-Methyl-3-(1-phenyl)ethenyl)-1H-indole (**4h**).*[23,30,29,22]

Chromatographic purification (PE/Acetone 90:10) gave **4h** as an oil; 0.27 g (59% yield); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.23 (s, 3H), 5.28 (d, *J* = 2.0 Hz, 1H), 5.68 (d, *J* = 1.8 Hz, 1H), 6.93–6.97 (m, 1H), 7.02–7.12 (m, 1H), 7.12–7.18 (m, 1H), 7.22–7.27 (m, 4H), 7.33–7.37 (m, 2H), 7.88 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.6 (CH3), 110.0 (CH), 113.8 (C), 114.8 (CH2), 119.4 (CH), 119.5 (CH), 121.0 (CH), 127.2 (2 x CH), 127.4 (CH), 128.0 (2 x CH), 128.2 (C), 132.9 (C), 135.0 (C), 141.7 (C), 142.3 (C); MS *m/z* (%) 233 [M^+](95), 218 (100), 217 (100).

*4.2.9. 2-Methyl-3-[(p-tolyl)ethenyl)-1H-indole (**4i**).*[23,29]

Chromatographic purification (PE/Acetone 80:20) gave **4i** as an oil; 0.27 g (54% yield); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.34 (s, 3H), 5.27 (d, *J* = 1.8 Hz, 1H), 5.71 (d, *J* = 1.8 Hz, 1H), 6.95–7.02 (m, 1H), 7.07–7.14 (m, 3H), 7.22–7.31 (m, 4H), 7.80 (br s, 1H); ^{13}C NMR (50 MHz,

$CDCl_3$) δ 12.6 (CH3), 21.0 (CH3), 110.0 (CH), 113.0 (C), 114.0 (CH2), 119.4 (CH), 119.6 (CH), 121.0 (CH), 127.0 (2 x CH), 128.3 (C), 128.8 (2 x CH), 133.0 (C), 135.0 (C), 137.1 (C), 138.8 (C), 142.1 (C); MS *m/z* (%) 247 [M^+](90), 232 (100), 217 (75).

*4.2.10. 3-[1-(4-Acetylphenyl)ethenyl]-2-methyl-1H-indole (**4j**).*

The compound was synthesised as described in general procedure, from 1,4-diacetylbenzene (**2i**, 4.0 mmol, 0.65 g) and 2-methylindole (**3a**, 2.0 mmol, 0.26 g) in the presence of **1a** (5 mol%, 0.068 g). Chromatographic purification (PE/Acetone 80:20) gave **4j** (oil); 0.36 g (65% yield); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.56 (s, 3H), 5.40 (d, *J* = 1.6 Hz, 1H), 5.78 (d, J = 1.6 Hz, 1H), 6.91–6.98 (m, 1H), 7.04–7.14 (m, 2H), 7.20–7.27 (m, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.15 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.6 (CH3), 26.5 (CH3), 110.2 (CH), 113.0 (C), 116.8 (CH2), 119.2 (CH), 119.6 (CH), 121.2 (CH), 127.3 (2 x CH), 127.9 (C), 128.2 (2 x CH), 133.2 (C), 135.0 (C), 135.9 (C), 141.6 (C), 146.6 (C), 197.9 (CO); IR ν (cm^{-1}) 3393, 3334, 1667, 1593, 1462, 1260, 739; MS *m/z* (%) 275 [M^+](100), 232 (65), 217 (80); Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found C, 82.80; H, 6.24; N, 5.02.

*4.2.11. 1,4-Bis[1-(indol-3-yl)ethenyl)]lbenzene (**4k**).*

The compound was synthesised as described in general procedure, from 1,4-diacetylbenzene (**2i,** 2.0 mmol, 0.32 g) and 2-methylindole (**3a**, 6.0 mmol, 0.79 g) in the presence of **1a** (10 mol%, 0.068 g). Chromatographic purification (PE/Acetone 80:20) gave **4j** (oil); 0.30 g (54% yield) and **4k** (solid); 0.26 g (34% yield); mp 184–185.5 °C (DCM/PE); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.23 (s, 6H), 5.28 (d, *J* = 1.8 Hz, 2H), 5.71 (d, *J* = 2.0 Hz, 2H), 6.90–7.12 (m, 4H), 7.20–7.26 (m, 4H), 7.29 (s, 4H), 7.84 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.7 (CH3), 110.0 (CH), 113.8 (C), 114.4 (CH2), 119.4 (CH), 119.5 (CH), 121.0 (CH), 127.0 (CH), 128.2 (C), 132.9 (C), 135.0 (C), 140.8 (C), 142.0

(C); IR ν (cm^{-1}) 3381, 1605, 1459, 1215, 846, 748; Anal. Calcd for $C_{28}H_{24}N_2$: C, 86.56; H, 6.23; N, 7.21. Found C, 86.60; H, 6.19; N, 7.18.

4.2.12. 4-(2-Methylindol-3-yl)-1,2-dihydronaphthalene (**4l**).[29]

Chromatographic purification (PE/Acetone 90:10) gave **4l** (oil); 0.35 g (68% yield); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.40–2.50 (m, 2H), 2.84–2.94 (m, 2H), 6.07 (t, *J* = 4.6 Hz, 1H), 6.89–7.15 (m, 6H), 7.22–7.25 (m, 2H), 7.84 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.4 (CH3), 23.5 (CH2), 28.3 (CH2), 110.2 (CH), 112.5 (C), 119.3 (CH), 119.4 (CH), 121.0 (CH), 125.5 (CH), 126.2 (CH), 126.6 (CH), 127.4 (CH), 128.7 (C), 129.2 (CH), 131.8 (C), 132.4 (C), 135.1 (C), 135.3 (C), 136.2 (C); MS *m/z* (%) 259 [M^+](100), 244 (65).

*4.3. Reaction of **1b** with methanol:*

1-Methoxy-1-(2-methylindol-3-yl)-1-(4-nitrophenyl)methane **(6)**.

Salt **1b** (1 mmol, 0.35 g**)** was suspended in methanol (5 mL) at rt; the reaction was stopped after 20 minutes (disappearance of the coloured salt). Usual work-up of the reaction and chromatographic purification (PE/acetone, 9:1) gave **6** as a pale yellow solid; 0.22 g (76% yield): mp 154.1–154.8 °C (DCM/PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.34 (s, 3H), 5.63 (s, 1H), 6.92–7.10 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 9.0 Hz, 2H), 8.01 (br s, 1H), 8.08 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0 (CH3), 56.3 (OCH3), 77.0 (CH), 109.9 (C), 110.3 (CH), 118.8 (CH), 119.7 (CH), 121.4 (CH), 123.2 (2 x CH), 126.7 (C), 126.9 (2 x CH), 133.5 (C), 135.2 (C), 146.5 (C), 150.1 (C); IR ν (cm^{-1}) 3375, 2940, 1599, 1512, 1456, 1346, 1087, 840, 748, 727; Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found C, 68.85; H, 5.40; N, 9.40.

*4.4. Dehydrative Coupling: gram-scale procedure for the synthesis of product **4a**.*

Catalyst **1** (5 mol%, 0.167 g) was added to a solution of ketone **2a** (10.0 mmol, 1.65 g) and 2-methylindole **3a** (10.0 mmol, 1.31 g) in anhydrous methanol (5 mL) under stirring. The reaction mixture was then stirred in an air atmosphere at room temperature for 6 hours. Then the reaction mixture was treated with H_2O/ DCM (1:1, 100 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 (PE/acetone 85/15) to give pure **4a** (2.15 g, 77% yield).

*4.5. Reactions of ketone **2a** with indoles **3c** and **3d**. Representative procedure.*

The reactions were performed as reported in the general procedure by reacting 4-nitroacetophenone (**2a,** 2.0 mmol, 0.33 g) and either indole (**3c**, 2.0 mmol, 0.23 g) or 1-methylindole (**3d**, 2.0 mmol, 0.26 g) in the presence of **1a** (5 mol%, 0.034 g) at room temperature. The reaction were monitored by TLC an GC analyses, and no traces of the expected products were detected. The reactions were stopped after running at rt for 24 hours, although no completion was observed. Yellow solid **7b** separated from the reaction mixture, was isolated by filtration and purified by gentle washings with cold methanol. Chromatographic purification (PE/Acetone 85:15) led to the recovery of acetal **5** and products **7a** and **7b**, which were quantified and characterised as reported below.

4.5.1. 1,1-Dimethoxy-1-(4-nitrophenyl)ethane **(5)**:[65]

Oil; 0.08 g, 20%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 3H), 3.12 (s, 6H), 7.60 (d, *J* = 9.0 Hz, 2H), 8.13 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.6 (CH3), 48.9 (OCH3), 101.0 (C), 123.2 (2 x CH), 127.2 (2 x CH), 147.2 (C), 150.0 (C); MS *m/z* (%) 196 [M^+-15](30), 180 [M^+-31]((100).

*4.5.2. 1,1-Bis(indol-3-yl)-1-(4-nitrophenyl)ethane **(7a)**:*[66,67]

Yellow solid; 0.29 g (76% yield) : mp 246.8–248 °C (DCM); ^{1}H NMR (200 MHz, CD_3COCD_3) δ 2.32 (s, 3H), 6.74–6.81 (m, 4H), 6.94–7.03 (m, 2H), 7.11–7.16 (m, 2H), 7.33–7.39 (m, 2H), 7.61 (d, *J* = 9.2 Hz, 2H), 8.07 (d, *J* = 9.0 Hz, 2H), 10.06 (br s, 2H); ^{13}C NMR (50 MHz, CD_3COCD_3) δ 43.9 (C), 111.4 (2 x CH), 118.3 (2 x CH), 120.9 (4 x CH), 122.1 (2 x C), 122.5 (2 x CH), 123.5 2 (2 x C), 126.0 (2 x CH), 129.1 (2 x CH), 137.5 (2 x C), 145.9 (C), 156.3 (C); the product is much less soluble in chloform, but ^{13}C NMR (50 MHz, $CDCl_3$) evidenced signal of the methyl group on the quaternary carbon at 28.6 ppm.

4.5.3. 1,1-Bis(1-methylindol-3-yl)-1-(4-nitrophenyl)ethane (**7b)**:

Pale yellow solid; 0.35 g (86% yield): mp 214.0–215.5 °C (DCM/PE); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.64(s, 6H), 6.48 (s, 2H), 6.89 (t, *J* = Hz, 7.8 Hz, 2H), 7.10–7.20 (m, 6H), 7.22-7.28 (m, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 8.03 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.0 (CH3), 32.5 (*N*-CH3), 43.9 (C), 109.3 (2 x CH), 118.6 (2 x CH), 121.2 (2 x CH), 121.5 (2 x CH), 122.9 (2 x CH), 126.2 (2 x C), 127.8 (2 x C), 127.9 (2 x CH), 128.9 (2 x CH), 137.6 (2 x C), 145.9 (C), 156.0 (C); IR ν (cm^{-1}) 2926, 1590, 1509, 1465, 1343, 733, 705; Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found C, 76.20; H, 5.62; N, 10.22.

5. Computational Method

The structures of reactants, intermediate adducts and transition states were optimized using the density functional method (DFT),[68] with the functional M06-2X[69,70] with the cc-pVDZ basis set.[71] The nature of the critical points was characterized by using vibrational analysis[72,73] which also furnished the Zero Point Energyes (ZPE) and entropies for the calculations of the Free Energies. These have been converted from the gas phase to the 1M standard state at 1 atm and 298.15 K.[74] The geometries have been refined by optimizing them with the larger basis set cc-pVTZ[71] and their energy calculated with even large basis set aug-cc-pVTZ.[71] The latter have been combined with the thermodinamic corrections calculated with the smallest basis set to get the final *E*+ZPE and Free energies. These are used to calculate the rate constant with the Eyring equation.[75] Solvent effects

were introduced in all using the polarized continuum method (IEF-PCM)[76-80] within the universal solvation model density (SMD).[81,82]

Calculations were performed by the quantum package Gaussian 09-A.02.[83] Figures in the Supplementary Information were obtained using the graphical program Molden.[84]

Supporting Data

Supplementary data to this article can be found online at …….

Supplementary data for this article include copies of the ^{1}H and ^{13}C NMR spectra, 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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