

1 Article

2 **Highly efficient tetranuclear Zn^{II}₂Ln^{III}₂ catalysts for**
 3 **the Friedel – Crafts alkylation of indoles and**
 4 **nitrostyrenes**

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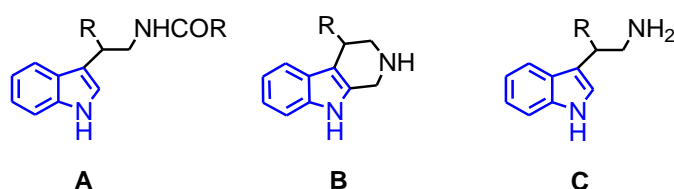
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11 **Abstract:** We demonstrate for the first time the high efficacy of tetranuclear Zn^{II}₂Ln^{III}₂ coordination
 12 clusters (CCs) as catalysts for Friedel-Crafts (FC) alkylation of indoles with a range of *trans*-β-
 13 nitrostyrenes. The reaction proceeds in good to excellent yields (76-99%) at room temperature with
 14 catalyst loadings as low as 1.0 mol%.

15 **Keywords:** Friedel-Crafts alkylation, Zn/4f, coordination clusters

16 **1. Introduction**

17 The Friedel-Crafts (FC) reaction of aromatic compounds with electron-deficient alkenes is used
 18 widely in synthetic organic chemistry.[1,2] The reaction between indole and β-nitrostyrene is
 19 important as it gives access to indole-based alkaloids such as melatonin analogues **A**, 1,2,3,4-
 20 tetrahydro-β-carbolines (THBCs, **B**), and “triptans” **C** (Scheme 1).[3,4]
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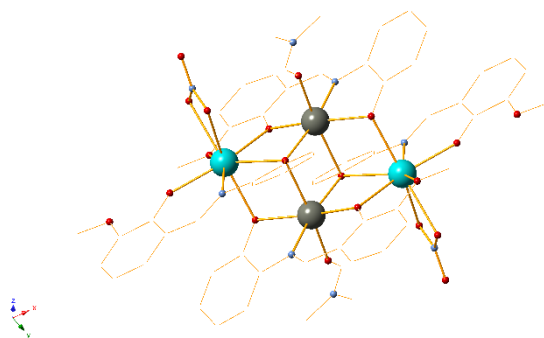
22

23 **Scheme 1.** Versatile intermediates in organic synthesis derived from Indolylnitroalkanes

24 Nitroalkenes have received considerable attention as active Michael acceptors[5] because the
 25 nitro derivatives can be transformed into amino compounds with a variety of different
 26 functionalities.[6–10] For the reaction between indole and β-nitrostyrene various catalytic systems
 27 have been proposed. These include hydrogen-bond-based compounds[11–16] such as
 28 thiourea,[11,14,15,17–20] phosphoric acid,[16] silanediols,[21,22] sulfamic acid[23] and 2,6-
 29 bis(amido)benzoic acid,[24] metal based compounds[25–41] such as Al^{III},[25,39] Cu^{II},[26–30,41]
 30 Zn^{II},[31–35,40,42] Fe^{III},[36] Pd^{II},[37], Rh^{III}[43,44] and Sm^{III},[38] and heterogeneous systems including
 31 metal organic frameworks,[45,46] nano *n*-propylsulfonated γ-Fe₂O₃ (NPS-γ-Fe₂O₃) [47] and zeolite
 32 HY.[48] However efficient metal catalytic systems for this transformation are very rare. Du [49–53]
 33 developed an efficient catalyst containing bisoxazolines and bisimidazolines-Zn(OTf)₂. Wang
 34 reported the involvement of a dimeric Cu^{II} coordination cluster (CC) and piperidine as catalyst for
 35 reactions between aromatic nitroalkenes and ortho-substituted indoles.[41] However, some of the
 36 reported protocols have drawbacks such as high catalyst loading, long reaction time, the need for

37 additives, low temperature (0 to -20°C) and multi-step designed ligands, thus limiting their practical
38 applications.

39 In 3d/4f chemistry, only few polynuclear CCs have been successfully used as homogenous
40 catalysts.^[54–56] We recently initiated a project on the synthesis of 3d/4f CCs stabilized by the Schiff
41 base organic ligand H₂L [(E)-(2-hydroxy-3-methoxybenzylidene-amino)phenol], that would display
42 catalytic properties.^[57–59] We also reported the synthesis and characterisation of a series of
43 isoskeletal^[60] tetranuclear Zn^{II}Ln^{III} CCs formulated as [Zn^{II}Ln^{III}₂L₄(NO₃)₂(DMF)₂] (**1Ln**) where Ln is
44 Y (**1Y**), Sm (**1Sm**), Eu (**1Eu**), Gd (**1Gd**), Dy (**1Dy**), Tb (**1Tb**) and Yb (**1Yb**) possessing a defect dicubane
45 topology. These compounds can be synthesized quantitatively in two steps, up to multigram scale
46 and are air stable for few months. We showed that these bimetallic species remain intact in organic
47 and aqueous solutions, by ESI-MS studies, EPR studies for **1Gd** and NMR studies for **1Y** analogues.
48 This precise topology shows that the Zn and the Ln centres are very close (approximately 3.3 Å),
49 permitting both metals to coordinate to the substrates and promote the coupling reaction.
50 Compounds **1Y** and **1Dy** showed high efficiency as catalysts, at room temperature, with low catalytic
51 loadings in FC alkylation of indole with aldehydes leading to bis-indolylmethane derivatives.^[59] A
52 study of the suitability of **1Ln** as catalysts in FC alkylation of indole with nitrostyrene is presented
53 herein.



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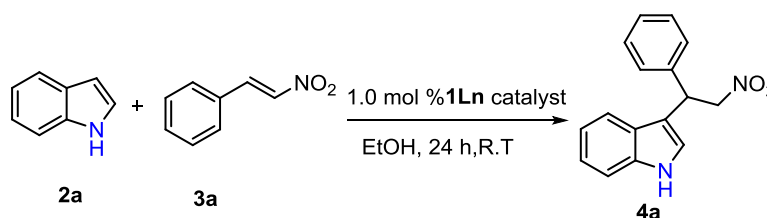
55 **Figure 1.** Molecular structure of **1Ln**. Colour code: Zn^{II}: grey; Ln^{III}: light blue; O: red; N:
56 blue. C and H atoms are omitted for clarity.

57 2. Results

58 The first step was to optimize the reaction conditions for the alkylation of indole. We screened
59 several reaction parameters, such as the use of different catalysts (Table 1, entries 1-9), solvents (Table
60 1, entries 10-14), temperature (Table 1, entries 15-17) and catalyst loading (Table 1, entries 18-20). We
61 studied the reaction between indole (0.50 mmol) **2** and nitroalkene (0.50 mmol) **3** in EtOH at room
62 temperature and a catalyst loading of 1.0 mol % (Table 1 entries 1-9). A blank experiment in the
63 absence of the 3d/4f CCs catalyst showed no conversion (Table 1, entry 1) and very low conversions
64 were obtained in the presence of Dy or Zn salts (Table 1, entries 2-3). The reactions with **1Dy** and **1Y**
65 after 24 h show very high yields, 99% and 94 %, respectively. (Table 1, entries 4-5). Other catalyst such
66 as **1Eu**, **1Gd**, **1Nd** and **1Tb** showed lower yields (Table 1, entries 1-6). Therefore, **1Dy** was the best
67 choice for this FC reaction. We then decided to identify the influence of the solvent on the catalytic
68 performance. Our catalyst showed high activity in ethanol with 99% yield of the desired product **4a**
69 (Table 1, entry 4). Solvents such as THF, water, acetonitrile and DMF had a negative influence on the
70 catalytic activity; therefore, ethanol was the best choice for further studies. At room temperature, the
71 yield of **4a** was 99%, but only 5% at 0 °C. Lower yields were obtained at 60°C (Table 1, entry 18), so
72 the following reactions were made at temperature. As shown in Table 1, it was sufficient to use a
73 catalyst loading of 1.0 mol% to obtain a yield up to 99% (Table 1, entry 4). An increase of the catalyst
74 loading from 1.0 mol% to 5 mol% led to remarkable decrease in the yield of the desired product **4a**
75 (Table 1, entries 19-20). This finding can be explained due to the low solubility of the catalyst. Further,
76 a decrease in the catalyst loading to 0.5 mol% also showed lower yield of desired product **4a** (Table

77 1, entry 18). Therefore, we used 1.0 mol % **1Dy** in ethanol at room temperature for further
 78 experiments.

79 **Table 1.** Optimization of the Friedel-Crafts Alkylation of Indole **2a** with *trans*- β -Nitrostyrene **3a**
 80 Catalyzed by **1Ln** Complexes^a



Entry	catalyst	Yield (%) ^b
1	none	0
2	Dy(OTf) ₃	8
3	Zn(OTf) ₂	20
4	1Dy	99
5	1Y	94
6	1Eu	55
7	1Gd	30
8	1Nd	12
9	1Tb	24
10	1Dy (Toluene)	30
11	1Dy (Water)	0
12	1Dy (THF)	0
13	1Dy (Acetonitrile)	0
14	1Dy (DMF)	5
15	1Dy (-30°C)	0
16	1Dy (0°C)	5
17	1Dy (60°C)	30
18	1Dy (0.5%)	26
19	1Dy (2.5%)	62
20	1Dy (5.0%)	17

81 ^aReaction conditions: indole **2a** (0.50 mmol), *trans*- β -nitrostyrene **3a** (0.50 mmol) in 3 mL of EtOH under 1.0 mol
 82 % **1Ln** complexes. ^bIsolated yield by column chromatography.

83
 84 To explore the scope of the reaction, various nitroalkenes were treated with indole (Table 2). In
 85 the first experiments R' was aromatic (Table 2, entries 1-8). Several catalytic systems gave slightly
 86 lower yields due to electronic effect of *para* substitution of the phenyl group of aromatic nitroalkenes.
 87 In all these cases, very good yields were obtained, ranging from 92% for the 4-fluoro substrate **4d** to
 88 98% for the tolyl substituted compound **4b**. A slight improvement of the yield up to 99% was
 89 observed by use of a heteroaromatic nitroalkene bearing a furan substituent (entry 8). The effect of
 90 substitution of the indole is also shown in Table 2 (entries 9-15). The substituent at the 5-position of
 91 indole had little effect on yield except for the electron-drawing group (-NO₂) (Table 2, entry 12).

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Table 2. Scope of the FC alkylation of Indoles with various nitro-styrenes catalysed by **1Dy**^a

Entry	R ¹	R ²	Yield (%) ^b
1	H	Ph	99(4a)
2	H	4-Me-Ph	98(4b)
3	H	4-MeO-Ph	96(4c)
4	H	4-F-Ph	92(4d)
5	H	4-Br-Ph	94(4e)
6	H	2-furan	99(4f)
7	OMe	Ph	97(4g)
8	Br	Ph	95(4h)
9	I	Ph	94(4i)
10	NO ₂	Ph	76(4j)
11	OCH ₂ C ₆ H ₅	Ph	96(4k)
12	OMe	2-furan	98(4l)
13	Br	2-furan	95(4m)
14	OCH ₂ C ₆ H ₅	2-furan	96(4n)
15	I	2-furan	95(4o)

^aReaction conditions: indole **2** (0.50 mmol) with trans- β -nitrostyrene **3** (0.50 mmol) in 3 mL of EtOH under 1.0 mol % **1Dy** complex. ^bIsolated yield by column chromatography.

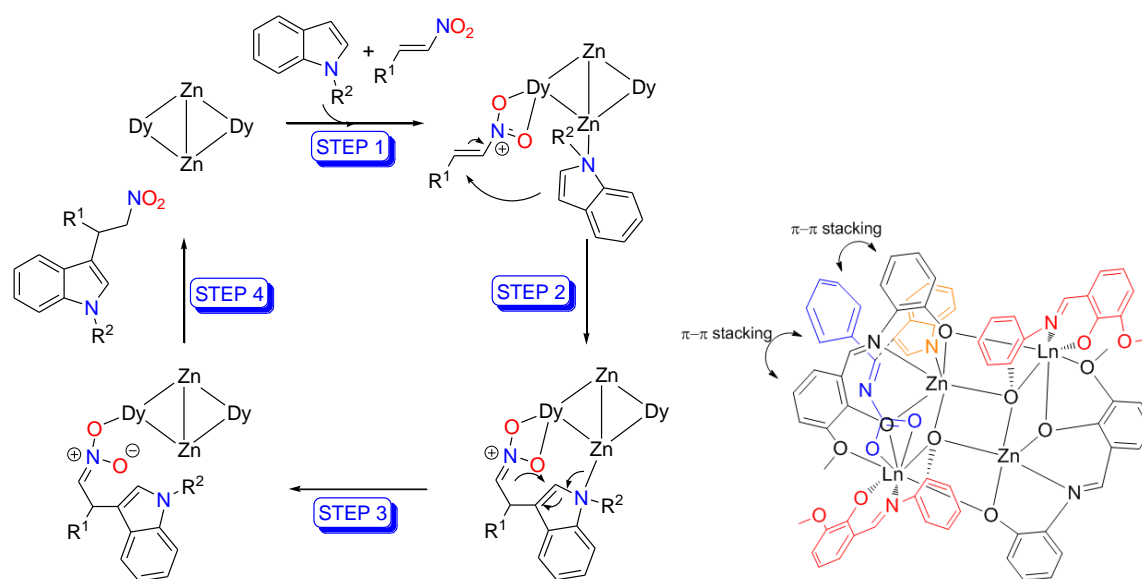
99 Further, we investigated the reaction of N-alkylated and 2-methyl indole with various
 100 nitrostyrene. The results are summarized in Table 3. The products were isolated in good to excellent
 101 yields (Table 3, entries 1-10). A change of the substituent at the nitrogen atom in **5**, and at the 2-
 102 position of indole did not show any profound effect on the yield of the desired product (99%, Table
 103 3, entries 1 and 6). Compound **6h** was characterized via single crystal X-Ray crystallography (see
 104 Figure S1).
 105

Table 3. Friedel-Crafts Alkylation of N-alkylated and 2-methyl Indoles with Various Nitroalkenes^a

Entry	R ¹	R ³	R ²	Yield (%) ^b
1	CH ₃	H	Ph	99(6a)
2	CH ₃	H	4-MeO-Ph	99(6b)
3	CH ₃	H	4-F-Ph	93(6c)
4	CH ₃	H	4-Br-Ph	95(6d)
5	CH ₃	H	2-furanyl	99(6e)
6	H	CH ₃	Ph	99(6f)
7	H	CH ₃	4-F-Ph	94(6g)
8	H	CH ₃	4-Br-Ph	96(6h)
9	H	CH ₃	2-furanyl	99(6i)
10	H	CH ₃	4-Me-Ph	98(6j)

^aReaction conditions: indole **5** (0.3 mmol), trans- β -nitrostyrene **3** (0.3 mmol), 3 mL of EtOH, 1.0 mol % **1Dy** complex. ^bIsolated yield by column chromatography.

106 The substrate binding of *trans*- β -nitrostyrene **3a** by **1Dy** was investigated by UV-Vis
 107 spectroscopy in a water/ethanol solution. A 0.1 mM solution *trans*- β -nitrostyrene **3a** exhibited a
 108 strong absorption at 320 nm. **1Dy** was added to the solution and absorption was recorded over 3 h
 109 with 5 minute intervals between measurements. It was observed (Figure S2) that the intensities of the
 110 peak at 320 nm gradually decreased. The quenching of band may be attributed to the bonding of
 111 nitrostyrene with **1Dy** through weak Van der Waals interactions. Similar quenching was observed
 112 with the indole substrate (Figure S3), indicating the binding behaviour of both substrates to **1Dy**.
 113 Thus both substrates can be activated after coordination with the two metal centres in **1Dy** which
 114 favours the conjugate addition of the nucleophiles. Similar studies were conducted with Zn(OTf)₂
 115 and Dy(OTf)₃ to determine the preference of each substrate for the Ln^{III} or Zn^{II} metal centres. **3a** shows
 116 a greater rate of quenching with Dy(OTf)₃ than Zn(OTf)₂, whereas with **2a** the rates are similar. This
 117 may suggest that **3a** preferentially binds to the Dy^{III} centre. The **1Dy** catalyst for both substrates
 118 demonstrates a greater rate of quenching than either Zn(OTf)₂ and Dy(OTf)₂, perhaps indicating a
 119 stronger interaction with the metal centres in tandem. Based on the above results and the crystal
 120 structure of **1Dy**⁵⁹ in which a nitrate group chelates to Dy (*trans*- β -nitrostyrene can be considered as
 121 alternative of nitrate), then a plausible mechanism and transition state can be proposed shown in
 122 Scheme 2. We envision that the nitroalkenes are activated by chelation to Dy^{III}⁴⁴ and π - π stacking
 123 between the phenyl group of the coordinating ligand L and the phenyl group of nitroalkenes. In
 124 addition, the indole substrate will bond to the Zn^{II} through the nitrogen atom and bring the two
 125 organic moieties efficiently close to favour the formation of alkylated product.



126

127 **Scheme 2.** (left) A plausible mechanism for the FC alkylation. (right) Proposed transition state model
 128 of catalyst

129 3. Discussion

130 We report herein, for the first time, a highly efficient, tetranuclear 3d/4f catalytic system for the
 131 FC alkylation of indoles with nitroalkenes. The reaction performs very well over a range of
 132 nitroalkenes and indoles, especially those with substituents in the para position. Products are
 133 obtained with up to 98% yield, at room temperature and with only 1% catalyst loading, showcasing
 134 the efficacy of these catalytic species. Further exploration of the mechanism of this specific reaction
 135 and involvement of chiral ligands for the synthesis of 3d/4f CCs and their employment in other
 136 asymmetric reactions is currently under way in our laboratory.

137 4. Materials and Methods

138 All chemicals and solvents were purchased from Sigma Aldrich, S. D. Fine Chemicals, and
139 commercial suppliers. The progress of the reaction was monitored by thin layer chromatography
140 (TLC) using Merck silica gel 60 F254 plates. Products were purified by column chromatography on
141 silica gel (60–120 mesh). NMR spectra were collected using a Bruker Advance III HD 500 MHz
142 Spectrometer. The ^1H and ^{13}C NMR spectroscopic data were analysed with a 500 MHz spectrometer
143 in either CDCl_3 . Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as
144 internal standard. The coupling constants (J) are reported in Hz, and the splitting patterns of the
145 proton signals are described as s (singlet), d (doublet), t (triplet), and m (multiplet).

146 **Synthesis of catalysts.** All CCs were synthesised according to the literature.^[59]

147 **General Procedure for the Friedel- Craft Reaction.** All experiments were carried out in the open
148 atmosphere and on a mmol scale. A 10 ml round bottom flask was charged with catalyst **1Dy** (1.0
149 mol%), nitrostyrene (0.5 – 0.3 mmol), indole (0.5 – 0.3 mmol). Solvent (3 mL) was added and the
150 reaction mixture was stirred for 24 h at room temperature. The product was purified by silica gel
151 column chromatography.

152 **Single crystal X-ray structure determinations.** Crystals suitable for single crystal X-ray
153 diffraction analyses were obtained for compound **6h**. Preliminary data on the space group and unit
154 cell dimensions as well as intensity data were collected on an Agilent Xcalibur Eos Gemini Ultra
155 diffractometer with CCD plate detector under a flow of nitrogen gas at 173(2) K using Mo $K\alpha$
156 radiation ($\lambda = 0.71073 \text{ \AA}$). CRYCALIS CCD and RED software. Reflection intensities were corrected
157 for absorption by the multi-scan method. Structure solution and refinement were accomplished using
158 Olex2,^[61] solved using either Superflip^[62] and refined with SHELXL.^[63] The non-hydrogen atoms
159 were refined with anisotropic thermal parameters. Hydrogen atoms were geometrically fixed and
160 allowed to refine using riding model. Geometric/crystallographic calculations were performed using
161 Olex2,^[61] package; graphics were prepared with Crystal Maker.^[64] CCDC 1482790.

162 **Supplementary Materials:** The following are available online at www.mdpi.com/link, Figure S1 The crystal
163 structure of compound **6h**. **Figure S2.** UV-Vis binding studies of $\text{Dy}(\text{OTf})_3$ (upper), $\text{Zn}(\text{OTf})_2$ (middle) and **1Dy**
164 (lower) with trans- β -nitro-styrene. **Figure S3.** UV-Vis binding studies of $\text{Dy}(\text{OTf})_3$ (upper), $\text{Zn}(\text{OTf})_2$ (middle)
165 and **1Dy** (lower) with indole

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