

Dy(OTf)₃ in ionic liquid: an efficient catalytic system for reactions of indole with aldehydes/ketones or imines

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Abstract—Dy(OTf)₃ immobilized in ionic liquids was found to be an efficient catalytic system for the reactions of indole with aldehydes/ketones or imines. Enhanced activity was observed. The use of ionic liquids as the reaction media allows facile separation and recycling of the catalyst.

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In recent years, considerable attention has been paid on the synthetic methods leading to indole derivatives because of their biological activities.¹ Various indole derivatives, such as 3-substituted indoles, are common components of drugs and are generally found to be of pharmaceutical interest in a variety of therapeutic areas.² In addition, 3-substituted indole derivatives are also versatile intermediates in organic synthesis,³ due to the feasibility of their 3-position for electrophilic substitution. Acyl chlorides and acid anhydrides are often used as the electrophilic reagents in such substitution with indoles.⁴ The reaction of indoles with aldehydes/ketones or imines as electrophiles is, however, only sparsely reported. Kamal and Qureshi⁵ reported the reactions of indole and 2-methylindole with aldehydes under controlled pH with reaction time as long as 10 days. Bergman et al.⁶ and Jackson et al.⁷ carried out the similar reactions under acidic conditions in moderate yields with the formation of cyclooligomeric compounds. Recently, Penieres-Carrillo et al.⁸ showed a significant improvement of the reaction by employing infrared irradiation as the energy source and a bentonitic clay as the catalyst under solvent-free conditions, though the reaction is applied only to aromatic aldehydes by far and the product yield still needs further improvement. Other catalysts, including LiClO₄,^{9a} In(OTf)₃,^{9b} and I₂,^{9c} were also found to promote the reaction, but with various limitations such as long

reaction time, complicated manipulations along with the involving of environmentally toxic media. Wang's group,¹⁰ on the other hand, has demonstrated that a 'green' process of the reactions of indole with carbonyl compounds can also be achieved by using lanthanide triflate as the efficient and mild catalyst in aqueous media.

To expend our effort toward environmentally benign synthesis,¹¹ we have recently conducted a research on room temperature reactions in ionic liquids, that is, a salt with a melting point below ambient temperature. Air- and moisture-stable room temperature ionic liquids as novel solvent system for organic reactions have attracted growing interest in recent years.¹² In ionic liquids, polar or ionic catalysts, such as lanthanide triflates, can be immobilized so as to allow an easy separation of the catalyst from the reagents and products. In favorable cases, reactivity enhancement can also be observed.¹³

In the present work, we firstly screened the reactions of indole with aldehydes and ketones in room temperature ionic liquids using dysprosium triflate as the catalyst.¹⁵ The reaction of indole with hexanal was chosen as the model reaction. Upon mixing of indole and hexanal in 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF₄) containing 10 mol% immobilized Dy(OTf)₃, sudden color change to dark red was observed in a few minutes, indicating a very fast catalytic reaction. We then reduced the amount of catalyst to 2 mol%. The reaction went to completion within 1 h

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at room temperature in 95% of yield. In comparison, the same reaction conducted in aqueous ethanol with 10 mol % Dy(OTf)₃ afforded the desired bisindolyl product in 84% yield after 24 h.^{10a} In the absence of Dy(OTf)₃, the reaction did not occur in ionic liquid (Table 1, entry 3). Among the ionic liquids tested, the reaction in [BMIM]BF₄ afforded the highest yield (95%, Table 1, entry 2). We next tested the reaction of acetone and obtained similar result (Table 1, entry 10).

The reaction was then applied to a variety of aromatic and aliphatic aldehydes and ketones, the results are all collected in Table 1. As it reveals, both the reaction time and yield are improved considerably in ionic liquids compared to those of the same reactions in aqueous media.

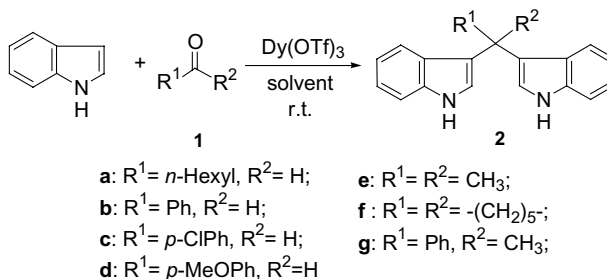
It is well known that imines can undergo electrophilic reactions in a similar way as carbonyl compounds. We next examined the reaction of indole with a variety of imines in ionic liquids. In a preliminary experiment, the reaction of indole with *N*-benzylidene aniline was carried out in the presence of Dy(OTf)₃ (5 mol %) using [BMIM]BF₄ as solvent. The reaction proceeded smoothly at room temperature to completion after 10 h, affording a secondary amine, 3-(phenylamino benzylidene) indole **3h** as the desired product, and phenyl bisindolyl methane **2b** as the by-product (Table 2, entry 2). Compared with the same reaction in aqueous media (Table 2, entry 1),^{10b} the reaction in ionic liquid showed an enhanced reactivity, but with the formation of a by-product, bis-

indolyl methane. The subsequent screening indicated that different ionic liquids may influence the distribution of the products (Table 2, entries 2–4). The reaction in [bupy]BF₄ gave the best result in terms of the yield of the secondary indolyl amine. In a control experiment, no reaction took place in the absence of Dy(OTf)₃ (Table 2, entry 5).

Other imines were also examined in the present work using Dy(OTf)₃ as catalyst in [bupy]BF₄. In all the cases as shown in Table 2, the reaction afforded secondary indolyl amines with moderate yields, along with significant amount of bisindolyl methanes.

The by-product bisindolyl methane was initially thought to result from decomposition of the corresponding imine in ionic liquid. However, a separate experiment in the absence of indole showed no imine decomposition after 24 h. In another experiment, benzoylhydrazone, a more stable imine against decomposition, was tested under the same conditions. The reaction afforded phenyl bisindolyl methane as the sole decomposed product. Therefore, it is most likely that the byproduct bisindolyl methane was derived from the indole–imine adduct; that is, the secondary amine underwent elimination to generate a benzylidene–indole intermediate **4**, which then reacted with a second indole to yield **2b** (Scheme 1). The weak association of Dy(OTf)₃ with the indole–hydrazone adduct may further facilitate the elimination, and thus only decomposition product was obtained in this case (Scheme 1).

Table 1. Reactions of indole with aldehydes/ketones catalyzed by Dy(OTf)₃^a



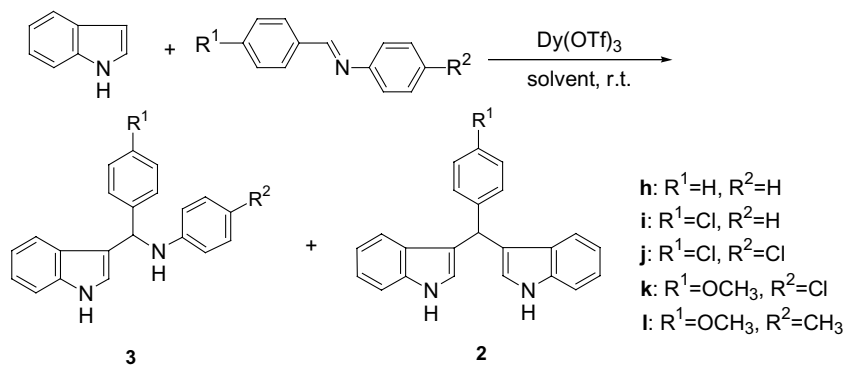
Entry	Aldehyde/ketone	Dy(OTf) ₃ (mol %)	Solvent	Time (h)	Product	Yield ^b (%)
1	1a	10	EtOH/H ₂ O (2:1)	24	2a	84
2	1a	2	[BMIM]BF ₄	1	2a	95
3	1a	—	[BMIM]BF ₄	1	No reaction	
4	1a	2	[BMIM]PF ₆ ^c	1	2a	88
5	1a	2	[bupy]BF ₄ ^d	1	2a	89
6	1b	2	[BMIM]BF ₄	1	2b	98
7	1c	2	[BMIM]BF ₄	1	2c	96
8	1d	2	[BMIM]BF ₄	1	2d	99
9	1e	10	EtOH/H ₂ O (2:1)	24	2e	76
10	1e	5	[BMIM]BF ₄	24	2e	96
11	1e	5	[BMIM]PF ₆	24	2e	94
12	1e	5	[bupy]BF ₄	24	2e	98
13	1f	5	[BMIM]BF ₄	24	2f	96
14	1g	10	[BMIM]BF ₄	24	2g	88

^aThe reactions were carried out on 1 mmol scale in 2 mL solvent. Molar ratio of indole:aldehyde/ketone = 2:1.

^bIsolated yield of pure product.

^c[BMIM]PF₆: 1-butyl-3-methylimidazolium hexafluorophosphate.

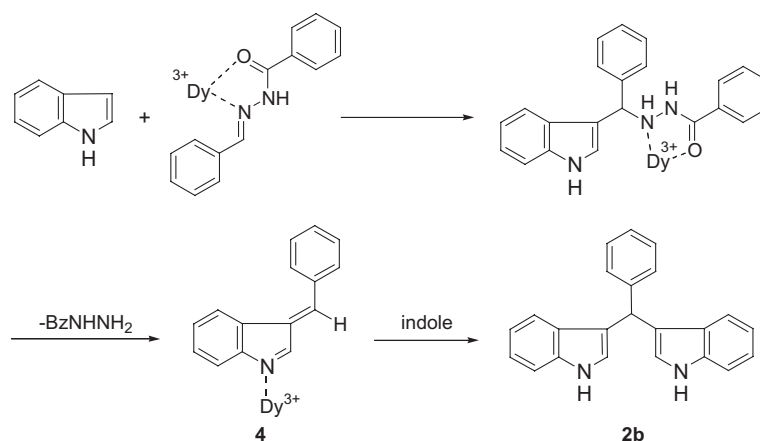
^d[bupy]BF₄: 1-butylpyridinium tetrafluoroborate.

Table 2. Dy(OTf)₃ catalyzed reactions of indole with imines in [bupy]BF₄^a

Entry	R ¹	R ²	Dy(OTf) ₃ (mol%)	Solvent	Time (h)	Product/yield (%) ^b
1	H	H	10	EtOH/H ₂ O (4:1)	24	3h 57 2b 12
2	H	H	5	[BMIM]BF ₄	10	3h 30 2b 45
3	H	H	5	[BMIM]PF ₆	10	3h 30 2b 55
4	H	H	5	[bupy]BF ₄	10	3h 47 2b 45
5	H	H	—	[bupy]BF ₄	10	No reaction
6	Cl	H	5	[bupy]BF ₄	10	3i 43 2c 42
7	Cl	Cl	5	[bupy]BF ₄	10	3j 53 2c 37
8	CH ₃	Cl	5	[bupy]BF ₄	10	3k 48 2d 52
9	CH ₃	OCH ₃	5	[bupy]BF ₄	10	3l 37 2d 45
10			5	CH ₂ Cl ₂ /[bupy]BF ₄ (10:1)	24	— 2h 61

^aThe reactions were carried out on 1 mmol scale in 2 mL solvent. Molar ratio of indole/imine = 1:1.

^bIsolated yield of pure product.

**Scheme 1.** Proposed mechanism of reaction of indole with benzoylhydrazone.

Recycling of Dy(OTf)₃ was then tested using hexanal and acetone as examples (Table 3).¹⁵ After each run, the reaction mixture was readily extracted with diethyl ether to separate the products. The ionic liquid phase contains Dy(OTf)₃, which was then reused directly for the next runs. It was found that the Dy(OTf)₃ catalyst can be recycled for at least six times with no significant loss of activity (Table 3).

In summary, lanthanide triflate immobilized in ionic liquid has been demonstrated to be a mild and efficient

catalytic system for the electrophilic substitution reactions of indole with a variety of carbonyl compounds and imines.¹⁴ Although ionic liquid itself cannot catalyze the reaction, enhanced activity was observed in ionic liquid using Dy(OTf)₃ as catalyst. Furthermore, the use of ionic liquid as solvent permits the product to be easily separated from the catalyst. The recovered catalyst could then be reused for several times with little loss of catalytic activity, thus the current immobilization strategy provides an efficient way toward the recovery and reuse of this expensive catalyst. The simple

Table 3. Recycling studies for the reaction of indole with hexanal and acetone^a

Number of cycles	1	2	3	4	5	6
Hexanal (2 mol%) ^b	95% ^c	94%	92%	91%	91%	90%
Acetone (5 mol%) ^b	96%	94%	94%	93%	93%	92%

^a Isolated yield of pure products.^b The numbers in the parentheses reference to the amount of catalyst.

procedure as well as easy recovery and reuse of this new catalytic system merit further investigation for developing other electrophilic substitutions of indoles and the like heterocyclic compounds, which are underway at this laboratory.

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- General procedure: To a 0.02 mmol dysprosium triflate solution of [BMIM]BF₄ (2 mL) was added indole (2 mmol) and aldehyde (1 mmol). The reaction mixture was sealed in a vial and stirred for 1 h. After complete conversion, as indicated by TLC, the product was extracted with diethyl ether and purified by flash chromatography on silica gel. Catalyst recycling study was conducted similarly. After extraction with diethyl ether to separate the products, the residue solvent was removed in vacuum and the resulting ionic liquid layer was reused for the next run.