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Lewis Acid-Catalyzed Reactions in Protic Media. Lanthanide-Catalyzed Reactions of Indoles with Aldehydes or Ketones

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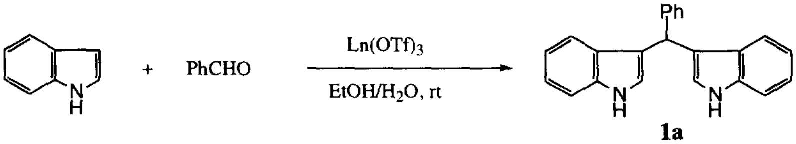
Abstract *Lanthanide triflates were found to be effective catalysts for reactions of indoles with aldehydes or ketones in aqueous solution.* Copyright © 1996 Elsevier Science Ltd

The acid catalyzed reactions of electron-rich heterocyclic compounds with *p*-dimethylamino benzaldehyde have been known as the Ehrlich test[1] for π-electron-excessive heterocycles such as pyrroles and indoles. The analogous reaction of indoles with other aromatic and aliphatic aldehydes and ketones produces azafulvenium salts which account for the color developed. The azafulvenium salts can undergo further addition with the second molecule of indoles to form bisindolyl-methanes.[2] The acids utilized in this type of reactions are protic acids[3] as well as Lewis acids,[4] for instance, aluminum chloride.

Recently, we reported[5] that lanthanide triflates[6] as stable Lewis acids in aqueous solution catalyze aqueous aza Diels-Alder reaction of aldehydes, amine hydrochlorides and dienes. We also found that lanthanide triflates effectively catalyze an aqueous condensation reaction of amine hydrochlorides and aldehydes to generate pyridinium derivatives.[7] In our further effort to explore the application of stable Lewis acids in protic solvents for organic synthesis, here we report lanthanide-catalyzed reactions of indoles with aldehydes or ketones in aqueous solution.

Scheme 1 Lanthanide-Catalyzed Reactions of Indole with Benzaldehyde



1a

We found that lanthanide triflates acted as reusable Lewis acids in chloroform or methanol/water or ethanol/water solvent systems to catalyze the reactions of indoles with aldehydes or ketones. In contrast, these reactions did not take place in the absence of lanthanides. The ethanol/water system was found the best for the catalytic reactions in terms of yield and product isolation, while use of chloroform as solvent normally resulted in side reactions such as oxidations. A typical experimental procedure is described here for the reaction of indole with benzaldehyde (**Scheme 1**): to a 0.10 M lanthanide triflate solution of ethanol and water (2/1, v/v) was added indole (2 mmol) and benzaldehyde (1 mmol). The reaction mixture was sealed in a vial and shaken overnight. The product precipitated out and the solid was collected and purified by flash chromatography. The recovered reaction solution was used as reaction medium for the second run and displayed comparable catalytic effect to the first one. When the ratio of indole to benzaldehyde was 5/1, 4/1, 3/1 or 2/1, the reaction gave exclusively the bisindolyl-methane adduct **1a**. Moreover, the main product was still **1a** with some minor by-products even if the ratio of indole to benzaldehyde was adjusted to 1/5.

Table 1 Effects of Different Lanthanide Triflates on the Reaction of Indole with Benzaldehyde

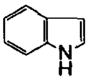
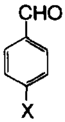
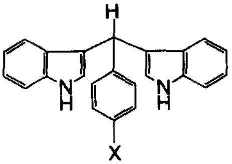
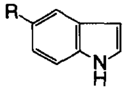
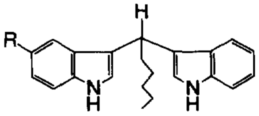
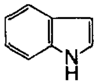
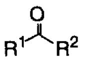
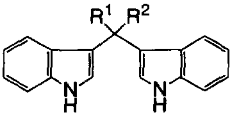
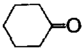
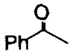
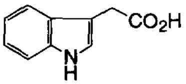
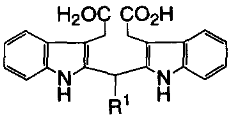
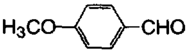
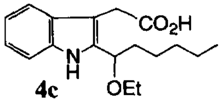
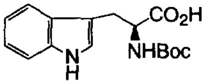
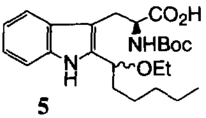
$Ln(OTf)_3$	La	Pr	Nd	Gd	Dy	Er	Yb
Yield (%)	87	87	66	64	93	78	86

Next, we examined seven lanthanide triflates in the model reaction of indole with benzaldehyde (**Scheme 1**). Data of the yields *vs* different lanthanides were summarized in **Table 1**. The reaction was catalyzed by all the lanthanides with moderate to excellent yields. Dysprosium triflate gave the best result so that it was chosen as the catalyst for the reactions listed in **Table 2**.

The lanthanide-catalyzed reaction was extended to substituted indoles and a number of other aromatic and aliphatic aldehydes or ketones (**Table 2**). All the reactions except entry 4 were carried out in a mixture of ethanol and water. Firstly, benzaldehyde with an electron-donating or an electron-withdrawing substituent was employed. Both anisaldehyde and *p*-chloro-benzaldehyde gave excellent yields of products **1b** (98%) and **1c** (99%) (entry 1). Secondly, hexanal reacted with indole or 5-methoxy-indole and gave good yields of products **2a** (84%) and **2b** (81%), respectively (entry 2). The reaction of hexanal with indole was carried out at different time intervals (4, 8, 24 and 40 h). The yield of these runs was 29, 56, 84 and 88%, respectively. No catalytic effect was observed when dysprosium triflate was replaced with sodium triflate or magnesium triflate. Thirdly, the reactions of three ketones with indole took longer time. Nevertheless, cyclohexanone afforded 90% yield of product **3a**, while acetone and acetophenone gave moderate yields of product **3b** (76%) and **3c** (77%), respectively (entry 3). In comparison, trifluoroboron etherate or aluminum chloride catalyzed reactions of acetone with indole were reported to generate several unexpected products.[4] Finally, 3-substituted indoles[8] such as indole-3-acetic acid and N-Boc-tryptophan were examined for the reactions with aldehydes or ketones (entry 4 and 5). Since the C-3 as the most active site was blocked in these cases, ketones did not react. However, aldehydes reacted but the products were different from above examples. The reaction of indole-3-acetic acid with anisaldehyde did not work in a mixture of ethanol and water; however, it took place in chloroform to produce **4a** in a 93% yield. The reaction of indole-3-acetic acid with hexanal generated different products in different solvents. With chloroform as solvent, it gave normal 2+1 adduct **4b** (84%); With ethanol/water system, it gave 1+1 ethanolysis product **4c** in 47% yield. Similarly, N-Boc-tryptophan reacted with hexanal in aqueous ethanol to afford 1+1 adduct **5** in 54% yield.

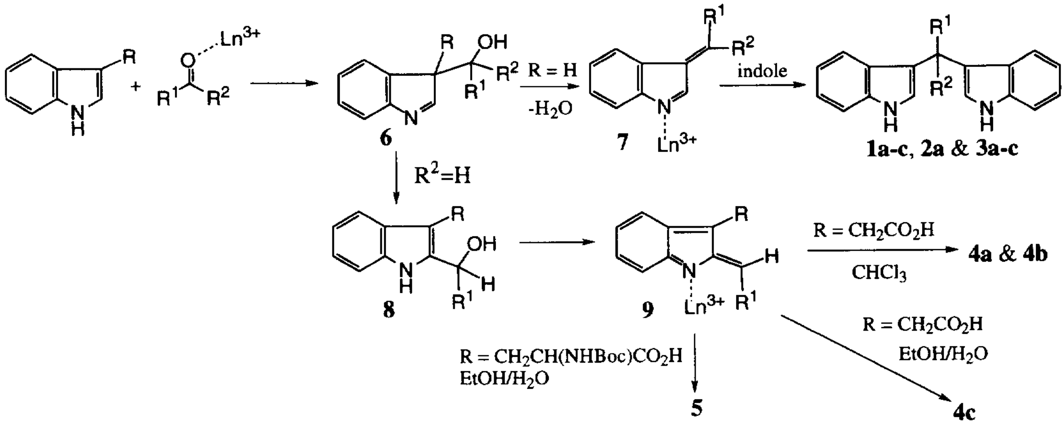
We propose the following mechanism to account for the lanthanide-catalyzed reaction (**Scheme 2**).[1, 2] An aldehyde or ketone was first activated by lanthanides and carried out an electrophilic substitution reaction at C-3 of an indole. After loss of water, an intermediate **7** was generated. The intermediate was further activated by lanthanides and served as an electrophile to attack a second molecule of indole to form 2+1 adduct **1a-c**, **2a** and **3a-c**. The fact that different ratios of reactants in the reaction of indole and benzaldehyde gave mainly the bisindolyl-methane product suggests that the intermediate **7** is more reactive than the activated aldehyde or ketone. For the reactions of 3-substituted indoles, products of 2-substitution were formed by initial attack of the electrophile at C-3, followed by 1, 2-shift to form intermediate **8**. The intermediate was dehydrated to form an

Table 2 The Reactions of Indoles with Aldehydes or Ketones Catalyzed by Dysprosium Triflate

Entry	Starting Material		Solvents and Reaction Time	Product	Yield
1					
		X = H	EtOH/H$_2$O (3/1), 12 h	**1a** X = H	95%
		X = OCH$_3$	EtOH/H$_2$O (3/1), 12 h	**1b** X = OCH$_3$	98%
		X = Cl	EtOH/H$_2$O (3/1), 12 h	**1c** X = Cl	99%
2					
	R = H		EtOH/H$_2$O (2/1), 24 h	**2a** R = H	84%
	R = OMe		EtOH/H$_2$O (2/1), 24 h	**2b** R = OMe	81%
3					
			EtOH/H$_2$O (2/1), 24 h	**3a** R^1 = R^2 = (CH$_2$)$_5$	90%
			EtOH/H$_2$O (2/1), 24 h	**3b** R^1 = R^2 = CH$_3$	76%
			EtOH/H$_2$O (3/1), 36 h	**3c** R^1 = CH$_3$, R^2 = Ph	77%
4		R^{1}CHO			
			CHCl$_3$, 24 h	**4a** R^1 = *p*-methoxy-phenyl	93%
			CHCl$_3$, 24 h	**4b** R^2 = n-hexyl	84%
			EtOH/H$_2$O (2/1), 36 h	 **4c**	47%
5			EtOH/H$_2$O (2/1), 36 h	 **5**	54%

intermediate **9**. In chloroform, the electrophilic substitution of intermediate **9** on a second molecule of 3-substituted indole afforded 2+1 adduct **4a** or **4b**; while in aqueous ethanol, ethanol as a nucleophile trapped **9** to provide product **4b** or **5**.

Scheme 2 Mechanism of the Lanthanide-Catalyzed Reactions of Indoles with Aldehydes or Ketones.



In summary, lanthanide triflates have been demonstrated to be mild and effective catalysts for the reactions of indoles with aldehydes or ketones in aqueous solution. The catalyzed reaction produced bisindolyl-methane adducts in high yields. The 3-substituted indoles gave mainly 2-substituted indole products in particular solvent systems.

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