Friedel–Crafts-Type Conjugate Addition of Indoles Using a Lewis Acid–Surfactant-Combined Catalyst in Water

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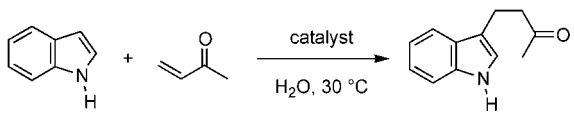
Organic reactions in aqueous media have attracted much attention,[1] firstly because water induces unique reactivities and selectivities which are not observed for reactions in organic media, and secondly because the use of water as a solvent reduces the use of harmful organic solvents and leads to the development of environmentally friendly chemical processes. Since the discovery of water-tolerant Lewis acids, Lewis acid-catalyzed reactions have become feasible in aqueous media.[2] However, in spite of the fact that various types of Lewis acid-catalyzed reactions in aqueous media have been developed so far, Friedel–Crafts reactions of aromatic compounds in such media have not yet been reported. Since Friedel–Crafts reactions are one of the most important Lewis acid-mediated reactions,[3] the development of catalytic Friedel–Crafts reactions in aqueous media should greatly contribute to the realization of "green" chemical processes.

In the course of our research on Lewis acid catalysis, we have found that Lewis acid–surfactant-combined catalysts (LASCs) were effective catalysts in water without using any organic co-solvents.[4] LASCs are composed of Lewis acidic metal cations and anionic surfactants, both of which are essential for efficient catalysis in water. Quite recently, we realized LASC-catalyzed Michael reactions of β-ketoesters to enones in water.[4d] These results prompted us to apply LASCs to the Friedel–Crafts-type conjugate addition of aromatic compounds in water. Among the aromatic compounds, we selected indoles as substrates because of their biological importance and high reactivity. Herein, we report that scandium tris(dodecyl sulfate), $Sc(DS)_3$, a representative LASC, can be used for conjugate addition of indoles to electron-deficient olefins in water.

The reaction of indole with methyl vinyl ketone was carried out as a model (Scheme 1).[5] Indeed, $Sc(DS)_3$ was found to be an efficient catalyst in water. The reaction was completed in 1 h to give the desired product in 98% yield (Table 1, entry 1). It should be mentioned that this reaction time is shorter than that reported for $Yb(OTf)_3$[5c,5d] and clay[5a,5e] catalyzed reactions in organic solvents.[6] It is also noted that only 2.5 mol % of the catalyst was sufficient, and that low temperature to control the reaction was not necessary, in contrast to the $BF_3 \cdot Et_2O$-catalyzed reaction for the same substrates.[5b,6]



Scheme 1.

When scandium triflate, $Sc(OTf)_3$, was used as a catalyst in water, the reaction was slow, and the product was obtained in only 28% yield (Table 1, entry 2). An anionic surfactant (sodium dodecyl sulfate, SDS) alone also gave the product in a low yield (entry 3). These results indicate that both the Lewis acidic scandium cation and the anionic surfactant moiety in $Sc(DS)_3$ are indispensable for efficient catalysis in water, suggesting that the formation of colloidal particles by a LASC with organic substrates is a key to the catalysis in other LASC-catalyzed reactions.[4f]

Table 1. Reaction of indole with methyl vinyl ketone in water (Scheme 1)

Entry	Catalyst (mol %)	Time (h)	Yield (%)
1	$Sc(DS)_3$ (2.5)	1	98
2	$Sc(OTf)_3$ (2.5)	5	28
3	SDS (7.5)	5	9

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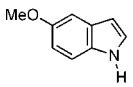
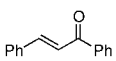
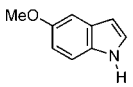
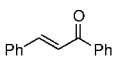
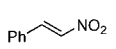
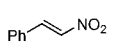
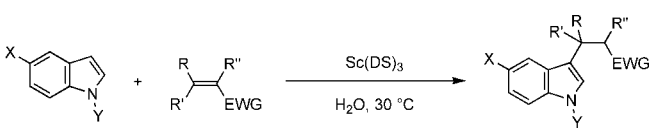
Table 2. $Sc(DS)_3$-catalyzed reactions of indoles with electron-deficient olefins in water[a]

Indole	Olefin	$Sc(DS)_3$ (mol %)	Time (h)	Yield (%)
		2.5	1	98
		2.5	4	95
		10	48	65
		10	48	47
		10	42	66
		2.5	36	55
		2.5	42	59
		2.5	10	87
		2.5	10	77

[a] All new products were properly characterized by ^{1}H- and ^{13}C-NMR, IR, and HRMS. For the reactions with electron-deficient olefins other than methyl vinyl ketone, optimization of the yields has not yet been made.

The LASC could be applied to other substrates as shown in Scheme 2 and Table 2. Not only enones but also β-nitrostyrene was successfully used as an electron-deficient olefin. It is noteworthy that solid substrates such as indole, 5-methoxyindole, and β-nitrostyrene as well as liquid ones such as *N*-methylindole, methyl vinyl ketone, and cyclopentenone reacted smoothly.



Scheme 2.

In the work-up procedure of the reactions, addition of ethyl acetate to the reaction mixture leads to facile phase separation of the organic phase, which includes the organic products, from the aqueous phase. Although this work-up procedure is convenient, a procedure without using any organic solvents is desirable in some cases. Therefore, it is noteworthy that centrifugation of the reaction mixture (3500 rpm, 20 min) afforded three separated phases, which were composed of water (upper phase), $Sc(DS)_3$ (middle, solid phase), and organic substances (lower phase).[4f] In principle, therefore, this centrifugation procedure enables the separation of organic substances and recovery of the catalyst without using organic solvents.

In summary, Lewis acid-catalyzed Friedel–Crafts-type conjugate addition of indoles to electron-deficient olefins in water was realized for the first time. The key to our success is the use of a surfactant-type catalyst, $Sc(DS)_3$. In the light of the increased demand for reduction of organic solvents in industry, the results described here will eventually lead to the development of environmentally benign processes.

Experimental Section

Preparation of $Sc(DS)_3$ from $ScCl_3$ and Sodium Dodecyl Sulfate

To a solution of SDS (3.4 g, 11.6 mmol) in water (100 mL) was added a solution of $ScCl_3 \cdot 6H_2O$ (1.0 g, 3.85 mmol) in water (20 mL) at rt. [4a] White precipitates appeared immediately, and the mixture was stirred for 10 min. The white solid was filtered, washed with water (50 mL × 5), and dried under vacuum (0.1 torr, 20 h) to afford $Sc(DS)_3$; yield: 2.3 g (71%); mp 240 °C; IR (KBr): ν = 1165, 1300 cm^{-1}; ^{1}H-NMR (CD_3OD): δ = 0.89 (9H, t, J = 6.7 Hz), 1.20–1.44 (54 H, m), 1.63–1.71 (6 H, m), 4.11 (6 H, t, J = 6.6 Hz); ^{13}C-NMR (CD_3OD): δ = 14.4, 23.7, 26.8, 30.3, 30.4, 30.5, 30.7, 30.7, 30.8, 30.8, 33.1, 70.6; ^{45}Sc-NMR (CD_3OD): δ = –109.3 [$ScCl_3$ (δ = 0) as an external standard for ^{45}Sc-NMR]. Anal.: calcd. for $C_{36}H_{75}O_{12}S_3Sc \cdot 3H_2O$: C, 48.30; H, 9.12; S, 10.74; found: C, 48.15; H, 9.02; S, 10.53.

Typical Procedure for $Sc(DS)_3$-Catalyzed Reactions

To a suspension of $Sc(DS)_3$ (0.00625 mmol) in water (1.5 mL) was added indole (0.25 mmol) and methyl vinyl ketone (0.75 mmol) at 30 °C. The reaction mixture was stirred for 1 h. After addition of aqueous $NaHCO_3$ and brine, the mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography gave the desired adduct in 98% yield.

References and Notes

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[6] $Yb(OTf)_3$-catalyzed reaction: $Yb(OTf)_3$ (2 mol %), 22 h at rt in acetonitrile (72% yield),[5c,d] Montmorillonite clay-catalyzed reactions: 2 h at 40 °C in methylene chloride (75% yield)[5a] or 2 h at 40 °C in nitromethane (83% yield),[5e] $BF_3 \cdot Et_2O$-catalyzed reaction: $BF_3 \cdot Et_2O$ (20 mol %), 2 h at –20 °C in nitromethane (86% yield).[5b]