

## Lewis Acid Catalysis in Aqueous Media: Copper(II)-Catalyzed Aldol and Allylation Reactions in a Water-Ethanol-Toluene Solution

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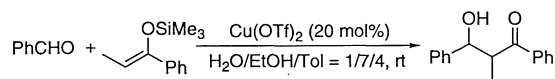
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Cu(OTf)<sub>2</sub> was found to be a stable Lewis acid in aqueous media and to activate carbonyl compounds effectively. Aldol reactions of silyl enol ethers with aldehydes and allylation reactions of tetraallyltin with carbonyl compounds proceeded smoothly in aqueous media, to afford the corresponding adducts in high yields. In addition, the catalyst could be easily recovered quantitatively after the reaction was completed and could be reused.

Lewis acid-catalyzed reactions are of current great interest because of their unique reactivities and selectivities, and for the mild conditions used.<sup>1</sup> While many Lewis acid-catalyzed reactions have been developed, strict anhydrous conditions are needed when typical Lewis acids such as AlCl<sub>3</sub>, TiCl<sub>4</sub>, SnCl<sub>4</sub>, etc. are used. Recently, we have found that rare earth triflates (Ln(OTf)<sub>3</sub>, Sc(OTf)<sub>3</sub>) are stable Lewis acids in water<sup>2</sup> and that aldol reactions,<sup>3</sup> allylation reactions,<sup>4</sup> Mannich reactions,<sup>5</sup> Diels-Alder reactions,<sup>6</sup> etc. proceed smoothly in aqueous media in the presence of a catalytic amount of a rare earth triflate.

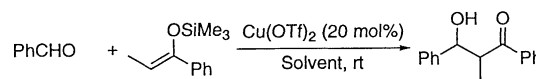
In the course of our investigations on Lewis acid catalysis in water, we have found several unique properties of Cu(II) in aldol and allylation reactions in aqueous media.<sup>7</sup> We first investigated the use of Cu(II) salts in the aldol reaction of the silyl enol ether of propiophenone with benzaldehyde. The effect of Cu(II) salts is summarized in Table 1. While Cu(OTf)<sub>2</sub>, Cu(ClO<sub>4</sub>)<sub>2</sub>, and Cu(NO<sub>3</sub>)<sub>2</sub> were effective in the aldol reaction in water-ethanol-toluene (1:7:4) and Cu(OTf)<sub>2</sub> gave the best yield, only moderate to low yields of the product were obtained when CuSiF<sub>6</sub>, CuF<sub>2</sub>, CuCl<sub>2</sub>, Cu(OCOCH<sub>3</sub>)<sub>2</sub>, or CuSO<sub>4</sub> was employed. It was indicated that copper salts with less nucleophilic counter anions such as OTf<sup>-</sup> and ClO<sub>4</sub><sup>-</sup> effectively catalyzed the reaction, while low yields were observed when copper salts with more nucleophilic counter anions such as F<sup>-</sup>, Cl<sup>-</sup>, CH<sub>3</sub>COO<sup>-</sup>, and SO<sub>4</sub><sup>2-</sup> were used.<sup>8</sup> Copper salts with less nucleophilic counter anions are more cationic and thus the high Lewis acidity makes it possible to promote the desired reaction.



**Table 1.** Effect of Cu(II) Salts

Catalyst	Yield/%	Catalyst	Yield/%
Cu(ClO <sub>4</sub> ) <sub>2</sub>	81	Cu(NO <sub>3</sub> ) <sub>2</sub>	72
Cu(OTf) <sub>2</sub>	84	Cu(OCOCH <sub>3</sub> ) <sub>2</sub>	7
CuF <sub>2</sub>	48	CuSO <sub>4</sub>	26
CuCl <sub>2</sub>	4	CuSiF <sub>6</sub>	32

We also found interesting solvent effects (Table 2). While the reactions were successfully carried out in THF-water or water-ethanol-toluene,<sup>9</sup> lower yields were obtained in pure water. As for organic solvents, good yields were obtained when dichloromethane, acetonitrile, or dimethylsulfoxide was used. It



**Table 2.** Effect of Solvents

Solvent	Yield/%	Solvent	Yield/%
THF/H <sub>2</sub> O = 9/1	64	DMF	14
H <sub>2</sub> O/EtOH/Tol = 1/7/4	84	DMSO	63
THF	28	Toluene	11
CH <sub>2</sub> Cl <sub>2</sub>	65	Benzene	5
EtOH	18	H <sub>2</sub> O	trace
CH <sub>3</sub> CN	61	Et <sub>2</sub> O	6

should be noted that good *syn* selectivity was observed when the reaction was carried out in toluene-ethanol-water.

Several examples of the Cu(OTf)<sub>2</sub>-catalyzed aqueous aldol reactions of silyl enol ethers with aldehydes are summarized in Table 3 (entries 1-8). Aromatic and aliphatic as well as heterocyclic aldehydes worked well under these conditions, and commercial formaldehyde solution also reacted with a silyl enol ether directly in the presence of a catalytic amount of Cu(OTf)<sub>2</sub>. Moderate to good *syn* selectivities were obtained, while lower diastereoselectivities were observed in other aqueous aldol reactions reported previously.<sup>3,8-10</sup> The catalyst was recovered quantitatively after the reaction was completed, and could be reused (see the experimental procedure). In addition, it was found that allylation reactions of aldehydes with tetraallyltin<sup>11</sup> proceeded smoothly in the presence of a catalytic amount of Cu(OTf)<sub>2</sub> in toluene-ethanol-water, to afford the homoallylic alcohols in high yields (Table 3, entries 9-18). The reactions were successfully carried out in aqueous media even in the presence of 5 mol% Cu(OTf)<sub>2</sub>, and a ketone, a ketoester, and a non-protected sugar reacted smoothly to afford the corresponding allylated adducts in high yields. Stoichiometry of an aldehyde and tetraallyltin was investigated in water-ethanol-toluene = 1:7:4; benzaldehyde:tetraallyltin = 1:1, 90% yield; 2:1, 89% yield; 4:1, 90% yield. These results indicate that four allyl groups of tetraallyltin can be transferred.

A typical experimental procedure is described for the aqueous aldol reaction of the silyl enol ether of propiophenone with benzaldehyde: To a Cu(OTf)<sub>2</sub><sup>12</sup> (0.1 mmol, 20 mol%) solution (water-ethanol-toluene = 1:7:4, 1.5 ml) was added a mixture of the silyl enol ether of propiophenone (0.75 mmol) and benzaldehyde (0.5 mmol) in water-ethanol-toluene (1:7:4, 1.5 ml) at rt. The mixture was stirred for 5 h at this temperature. Toluene (1.5 ml) and water (1.0 ml) were then added and the organic layer was separated. The product was extracted with ethyl acetate (1.5 ml x 2), and the combined organic layers were dried. After a usual work up, the crude product was chromatographed on silica gel to yield the pure aldol adduct (84%, *syn/anti* = 85/15). The catalyst was recovered from the

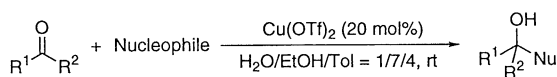






Table 3. Copper(II)-Catalyzed Reactions

Entry	R <sup>1</sup>	R <sup>2</sup>	Nucleophile	Yield /%
1	Ph	H	 1	84 <sup>a</sup>
2	(p-Cl)Ph	H	1	90 <sup>b</sup>
3	(o-MeO)Ph	H	1	95 <sup>c</sup>
4	H	H	1	50 <sup>d</sup>
5	2-furyl	H	1	82 <sup>e</sup>
6	2-pyridine	H	1	59 <sup>f</sup>
7	Ph(CH <sub>2</sub> ) <sub>2</sub>	H	1	57 <sup>g,h</sup>
8	Ph	H	 2	68 <sup>i</sup>
9	Ph	H	 2	94 <sup>j</sup>
10	(p-Cl)Ph	H	2	quant.
11	(o-MeO)Ph	H	2	70
12	2-pyridine	H	2	72
13	Ph(CH <sub>2</sub> ) <sub>2</sub>	H	2	88
14		H	2	89
15	PhCOCHO•H <sub>2</sub> O	H	2	87 <sup>k</sup>
16	Ph(CH <sub>2</sub> ) <sub>2</sub>	Me	2	67 <sup>d</sup>
17	Ph	CO <sub>2</sub> Et	2	94
18	2-deoxy-D-ribose		2	75 <sup>d,l</sup>

<sup>a</sup>Syn/anti = 85/15. <sup>b</sup>Syn/anti = 79/21. <sup>c</sup>Syn/anti = 83/17. <sup>d</sup>The reaction was carried out at 70 °C. <sup>e</sup>Syn/anti = 72/28. <sup>f</sup>Syn/anti = 70/30. <sup>g</sup>Syn/anti = 75/25. <sup>h</sup>Cu(ClO<sub>4</sub>)<sub>2</sub> was used. <sup>i</sup>Syn/anti = 81/19. <sup>j</sup>Cu(OTf)<sub>2</sub> 10 mol%, 89%; 5 mol%, 85%. <sup>k</sup>Diallylated product was obtained. <sup>l</sup>Diastereomer ratio = 59/41.

aqueous layer quantitatively after removal of water (100 °C/0.5 mmHg, 48 h) and could be reused. 2nd run: 82% yield (syn/anti = 82/18); 3rd run: 81% yield (syn/anti = 82/18).

We have now found that rare earth triflates and Cu(OTf)<sub>2</sub> are efficient Lewis acids in some aqueous reactions. Finally, the catalytic activity of Cu(OTf)<sub>2</sub> was estimated in the aldol reaction of the silyl enol ether of propiophenone with benzaldehyde, and the result is summarized in Figure 1. It was found that the reaction rate was fastest when Sc(OTf)<sub>3</sub> was used, and that Cu(OTf)<sub>2</sub> gave the second fastest rate. It should be noted that Cu(OTf)<sub>2</sub> promoted the reaction faster than lanthanide triflates

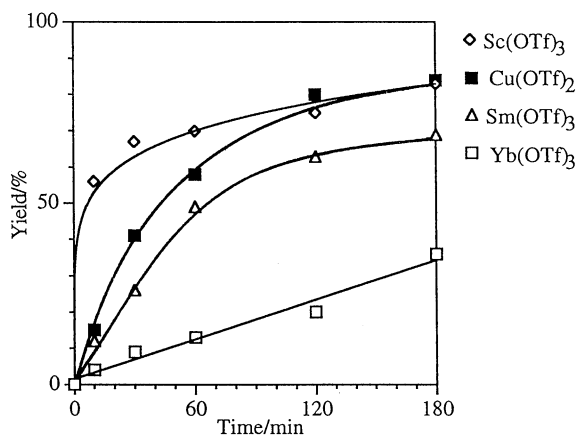


Fig. 1. Effect of Catalysts.

such as Sm(OTf)<sub>3</sub> and Yb(OTf)<sub>3</sub> did.

In summary, we have found that Cu(OTf)<sub>2</sub> is an excellent catalyst for aldol and allylation reactions in aqueous media. While most Lewis acids decompose or are deactivated in water, Cu(OTf)<sub>2</sub> was found to be stable in aqueous media and to activate carbonyl compounds as a Lewis acid effectively. Moreover, the catalyst could be easily recovered quantitatively after the reaction was completed and could be reused. Further investigations to search for other stable Lewis acids in water as well as to develop useful synthetic reactions using Cu(OTf)<sub>2</sub> as a Lewis acid catalyst are in progress.

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