Iron(III) Chloride as a Water-Compatible Lewis Acid for Diastereoselective Aldol Reactions in Water in the Presence of a Surfactant

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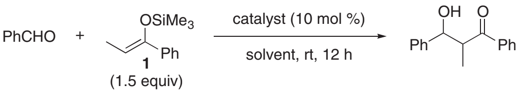
(Received December 1, 2003; CL-031169)

Diastereoselective aldol reactions of various aldehydes with silicon enolates in water have been successfully carried out using iron(III) chloride and a surfactant. Contrary to previous understanding, iron(III) chloride has been shown to be a water-compatible Lewis acid. In this catalytic system, epimerization of the product was not observed, and this result indicates that the diastereoselectivity was controlled kinetically.

Organic reactions in water without using harmful organic solvents are of significant current interest, especially in relation to today's environmental concerns.[1] In the course of our investigations to develop water-compatible Lewis acids, we have demonstrated that rare earth metal cations (Sc^{3+}, Yb^{3+}, etc.) combined with anionic surfactants can be used as Lewis acids in water.[2] These Lewis acid–surfactant-combined catalysts such as $Sc(DS)_3$ and $Yb(DS)_3$ (DS: dodecyl sulfate) have been applied to various organic reactions including aldol,[2] allylation,[3] and Michael reactions[4] in water. On the other hand, in order to elucidate and expand the Lewis acid catalysis and also other catalysis in water, more precise investigations on the behavior of other metals with various ligands are necessary. We then reexamined water-compatible Lewis acids[5] using aldol reactions of benzaldehyde with silicon enolates as model reactions.[6] As a result, iron(III) chloride ($FeCl_3$), which had been regarded as a water-incompatible Lewis acid,[7] was found to catalyze aldol reactions diastereoselectively in water in the presence of a surfactant.[8] Herein, we report that $FeCl_3$ catalyzed aldol reactions in water.

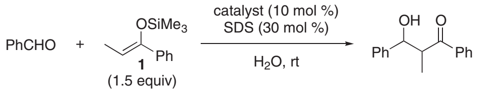
Table 1. Aldol reactions in aqueous media



Entry	Catalyst/mol %	Solvent	Yield/%	*syn*/*anti*
1	$Sc(OTf)_3$ (10) + SDS (30)	H_2O	95	50/50
2	$FeCl_3$ (10) + SDS (30)	H_2O	53	85/15
3	$FeCl_3$ (10)	H_2O/THF = 1/9	45	71/29

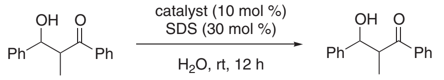
Initially, we screened various metal salts for the aldol reaction of benzaldehyde with silicon enolate **1** in water in the presence of SDS (sodium dodecyl sulfate). Among Lewis acids tested, $FeCl_3$ was found to give the product in moderate yield with relatively good *syn*/*anti* selectivity compared with $Sc(OTf)_3$ (Table 1, Entries 1 and 2). It is noted that $FeCl_3$ was a water-compatible Lewis acid here, contrary to previous understanding.[7] Furthermore, $FeCl_3$ is an inexpensive, environmentally benign, and relatively strong Lewis acid.[9] Although silicon enolate **1** was rapidly hydrolyzed under the reaction conditions because of strong acidity, the reaction proceeded in moderate yield. Interestingly, the yield and selectivity of the reaction in water were superior to that of the reaction in an H_2O/THF mixed solvent (Entry 3). The higher yield in water is ascribed to heterogeneity of the water/surfactant system which suppressed H^+-promoted hydrolysis of silicon enolate **1**, while hydrophobic interaction between the substrates worked to promote the aldol reaction.

Table 2. Reaction profiles for aldol reactions in water



Time/min	Catalyst: $Sc(OTf)_3$		Catalyst: $FeCl_3$	
	Yield/%	*syn*/*anti*	Yield/%	*syn*/*anti*
10	23	51/49	46	86/14
60	74	50/50	57	86/14
720	95	50/50	53	85/15

Table 3. Treatment of the product with the catalytic systems

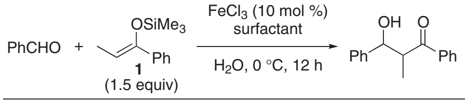


Entry	Catalyst	*syn*/*anti*	
		before reaction	after reaction
1	$Sc(OTf)_3$	84/16	82/18
2	$FeCl_3$	84/16	82/18

Next, we were interested in the differences in diastereoselectivities between the $FeCl_3$- and $Sc(OTf)_3$-catalyzed reactions. Quite recently, Juaristi et al. have reported that epimerization of the product was observed in a $CeCl_3$-catalyzed aldol reaction in aqueous media (H_2O/*i*-PrOH = 1/19).[10] However, in each case of the $FeCl_3$- and $Sc(OTf)_3$-catalyzed reaction, the diastereomeric ratio of the product remained unchanged in the course of the reaction (Table 2). In addition, the diastereomeric ratio was retained when the diastereomerically enriched, isolated product was directly treated with each catalyst (Table 3). Therefore, it was concluded that an epimerization process did not occur in either catalytic system. These results indicate that the diastereoselectivities of these reactions are kinetically controlled, and thus reflect the characteristics of the catalysts.

To optimize the conditions of the $FeCl_3$-catalyzed aldol reactions, we examined the effect of surfactants (Table 4). Interestingly, decreasing the amounts of SDS improved the yield significantly, and 10 mol % of SDS was found to give a good result (Entry 3). When 30 or 20 mol % of SDS was used, the hydrolysis of silicon enolate **1** occurred rapidly (Entries 1 and 2). On the other hand, when 5 mol % of SDS was used, both the hydrolysis and the aldol reaction became slower (Entry 4). The aldol reaction as well as the hydrolysis of the silicon enolate hardly occurred in the absence of the surfactant (Entry 5). As for surfactants, both CTAB and Triton® X-100 resulted in poor yields (Entries 6

Table 4. Effect of surfactants



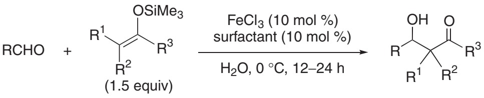
Entry	Surfactant/mol %	Yield/%	*syn*/*anti*
1	SDS (30)	71	84/16
2	SDS (20)	81	86/14
3	SDS (10)	83	87/13
4	SDS (5)	71	87/13
5	–	trace	87/13
6	CTAB[a]	21	92/8
7	Triton® X-100	20	80/20
8	$C_8H_{17}C_6H_4SO_3Na$ (10)	92	90/10
9	$C_{12}H_{25}C_6H_4SO_3Na$ (10)	89	91/9

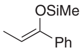
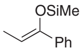
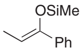
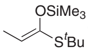
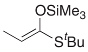
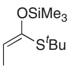
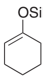
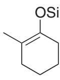
[a] Cetyltrimethylammonium bromide.

and 7). Among anionic surfactants, benzenesulfonates with long alkyl chains gave higher yields and selectivities compared with SDS (Entries 8 and 9).

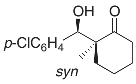
Several examples of $FeCl_3$-catalyzed aldol reactions in water are summarized in Table 5. In the case of silicon enolate **1**, the reactions with aromatic, α,β-unsaturated, and aliphatic aldehydes afforded the corresponding products in moderate to good yields with high diastereoselectivities (Entries 1 to 3). When silicon enolate (*E*)-**2** derived from *S-tert*-butylthiopropionate was applied to this catalytic system, high diastereoselectivity was attained although the rapid hydrolysis of (*E*)-**2** resulted in lower yield (Entry 4). To prevent the rapid hydrolysis of silicon enolates, we tried addition of a base. Among the bases tested, NaOH improved the yield up to 61% without losing the diastereoselectivity (Entry 5). Disappointingly, silicon enolate (*Z*)-**2** or **3** afforded each product with lower diastereoselectivity (Entries 6 and 7). However, this catalytic system worked well for diastereoselective construction of a quaternary center by using silicon enolate **4** (Entry 8).[11] These results indicate that the substituent at the same side of the trimethylsiloxy group is important for inducing high diastereoselectivity.

Table 5. $FeCl_3$-catalyzed aldol reactions in water

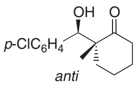


Entry	Aldehyde	Silicon Enolate	Surfactant	Yield/%	*syn*/*anti*
1	*p*-$MeOC_6H_4CHO$	 **1**	$C_{12}H_{25}C_6H_4SO_3Na$	86	91/9
2	$CH_2{=}CHCHO$		$C_{12}H_{25}C_6H_4SO_3Na$	66	87/13
3	$Ph(CH_2)_2CHO$		$C_{12}H_{25}C_6H_4SO_3Na$	76	89/11
4	PhCHO	 (*E*)-**2**[a]	SDS	37	94/6
5[b]	PhCHO	 (*E*)-**2**[a]	SDS	61	95/5
6[b]	PhCHO	 (*Z*)-**2**[c]	SDS	24	67/33
7[b]	PhCHO	 **3**	SDS	73	53/47
8[b]	*p*-ClC_6H_4CHO	 **4**[d]	SDS	48	6/94[e]

[a] *E*/*Z* = 95/5. [b] NaOH (10 mol %) was added. [c] *E*/*Z* = 2/98. [d] Mixture of regio isomers = 88/12.
[e] The stereochemistry was assigned by analogy from the benzaldehyde adduct as follows.



syn



anti

In conclusion, $FeCl_3$ was found to catalyze highly diastereoselective aldol reactions in water in the presence of a surfactant. The fact that epimerization of the product was not observed indicates that the diastereoselectivity is controlled kinetically in this catalytic system. When rapid hydrolysis of silicon enolates resulted in lower yields, the addition of NaOH was effective for improving the yields. Although the transition state structure and the real catalytic species have not been clear yet, the use of strong Lewis acids such as $FeCl_3$ in water will add a new aspect to organic reactions in water/surfactant systems.

This work was partially supported by CREST, SORST, and ERATO, Japan Science and Technology Agency (JST), and a Grant-in-Aid for Scientific Research from Japan Society of the Promotion of Science. N. A. thanks the JSPS fellowship for Japanese Junior Scientists.

References and Notes

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4 Y. Mori, K. Kakumoto, K. Manabe, and S. Kobayashi, *Tetrahedron Lett.*, **41**, 3107 (2000).
5 We have already found that Fe^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+} salts are water-compatible Lewis acids. S. Kobayashi, S. Nagayama, and T. Busujima, *J. Am. Chem. Soc.*, **120**, 8287 (1998).
6 We like to use this system to evaluate Lewis acid catalysis in water because decomposition (hydrolysis) of silicon enolates is competitive to the desired aldol reactions.
7 When the effects of metal salts in the aldol reaction were studied in $H_2O/THF = 1/9$ at rt, $FeCl_3$ (20 mol %) gave only 21% yield. See Ref. 5.
8 For our recent examples of diastereoselective aldol reactions in water, see: Y. Mori, K. Manabe, and S. Kobayashi, *Angew. Chem., Int. Ed.*, **40**, 2816 (2001); Y. Mori, J. Kobayashi, K. Manabe, and S. Kobayashi, *Tetrahedron*, **58**, 8263 (2002).
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10 O. Muñoz-Muñiz, M. Quintanar-Audelo, and E. Juaristi, *J. Org. Chem.*, **68**, 1622 (2003).
11 For an example, see: S. Yamago, D. Machii, and E. Nakamura, *J. Org. Chem.*, **56**, 2098 (1991).