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Iron(II)-Derived Lewis Acid/Surfactant Combined Catalysis for the Enantioselective Mukaiyama Aldol Reaction in Pure Water

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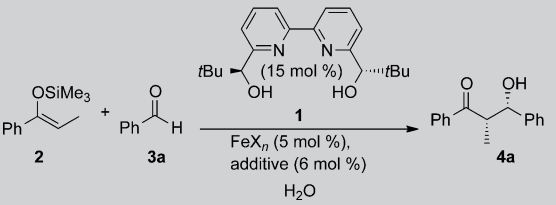
The catalytic asymmetric Mukaiyama aldol reaction in pure water was performed by using a combination of iron(II) dodecyl sulfate, a chiral bipyridine ligand, and benzoic acid. By using the obtained iron(II)-derived Lewis acid/surfactant combined catalyst, the desired products were afforded in good yields with high diastereo- and enantioselectivities.

Since its discovery in 1973, the Mukaiyama aldol reaction has been studied extensively, and many efforts have been invested for better stereocontrol of the process.[1] Since the first reports with the use of a chiral tin(II)-derived Lewis acid,[1c,d] many developments have been made to get greener and more efficient catalysts and to use environmentally benign solvents. A few studies, initiated by Kobayashi's pioneering work,[2] reported conditions for the catalytic asymmetric Mukaiyama aldol reaction under aqueous conditions, but all of them either afforded moderate enantioselectivities[2a–e] or lacked substrate generality.[2f–i] Recently, a very efficient system involving iron(II) and Bolm's ligand[3] showed large generality and wide scope but still needed dimethoxyethane as an organic cosolvent.[4] In addition to these results usually requiring an organic cosolvent (EtOH or 1,2-dimethoxyethane), the use of surfactants and Lewis acid surfactant combined (LASC) catalysts have emerged as promising systems for the asymmetric Mukaiyama aldol reaction in pure water.[2c,5] However, only moderate enantioselectivities (< 70 % *ee*) have been reported.[5a] Thus, there is clearly place for improvements towards the development of the Mukaiyama aldol reaction in water without using any organic solvent.

Water has many advantages as a solvent for organic reactions regarding cost, safety, and environmental concerns, but it is also known for its exceptional reactivity and selectivity enhancements.[6] As most chiral Lewis acids decompose rapidly in an aqueous environment, their development is a real challenge.[7] LASC catalysts have the unique particularity of acting both as Lewis acids and as surfactants to form hydrophobic colloidal particles in water.[8] In the context of our ongoing research on enantioselective Mukaiyama aldol reactions in aqueous media,[4] we herein disclose a new Lewis acid surfactant combined catalyst for this reaction by using environmentally benign iron(II) dodecyl sulfate [$Fe(OSO_3C_{12}H_{25})_2$, $Fe(DS)_2$] and a chiral bipyridine ligand, that is, Bolm's ligand.[3] To the best of our knowledge, this is the first example of the use of $Fe(DS)_2$ as a Lewis acid in organic synthesis.[9] Iron is one of the most abundant metals on Earth; it is inexpensive, environmentally benign, and relatively nontoxic in comparison with other metals.[10] The iron catalyst is easily prepared and generates chiral metallomicelles that are stable in pure water. The results suggest that the LASC catalyst acts both as a chiral catalyst to activate the substrate and as a surfactant to form colloidal particles.

First, we screened various iron-derived Lewis acids with Bolm's ligand **1** (Table 1). It was found that $Fe(DS)_2$ was an effective catalyst for the reaction of silyl enol ether **2** with benzaldehyde (**3a**); corresponding aldol **4a** was afforded in low yield with moderate stereoselectivities (Table 1, entry 1). The role of benzoic acid as an additive (1.2 equiv. relative to the iron salt) has already been highlighted in previous work.[2k,4] By using this additive, the yield and enantioselectivities were sig-

Table 1. Determination of the optimal catalytic micellar system.[a]



Entry	FeX_n	Additive (mol %)	Yield **4a** [%]	*dr*[b]	*er*[c]
1	$Fe(DS)_2$	–	33	81:19	83:17
2	$Fe(DS)_2$	$PhCO_2H$	80	91:9	96:4
3	$Fe(DS)_2$	HCl	24[d]	–	–
4	$Fe(DS)_2$	CH_3CO_2H	44	85:15	89:11
5	$Fe(DS)_2$	$C_{11}H_{25}CO_2H$	84	80:20	95:5
6	$Fe(DS)_2$	$PhCO_2H$ + NaDS (15)	70	90:10	95:5
7	$Fe(DS)_2$	$PhCO_2H$ + *n*-hexyl alcohol (10)	90	91:9	94:6
8	$Fe(DS)_3$	$PhCO_2H$	77	82:18	89:11
9	$Fe(OSO_3C_8H_{17})_2$	$PhCO_2H$	71	90:10	95:5
10	$Fe(OSO_3C_{18}H_{37})_2$	$PhCO_2H$	75	90:10	88:12
11	$Fe(ClO_4)_2 \cdot 6\,H_2O$	$PhCO_2H$	27[d]	–	–

[a] Reaction conditions: silyl enol ether (1.2 equiv.), aldehyde (1.0 equiv.), 25 °C, 24 h. [b] The *syn/anti* diastereoisomeric ratio was determined by ^1H NMR spectroscopy. [c] The enantiomeric ratio (*syn*) was determined by HPLC analysis on a chiral stationary phase. [d] Conversion calculated by ^1H NMR spectroscopy.

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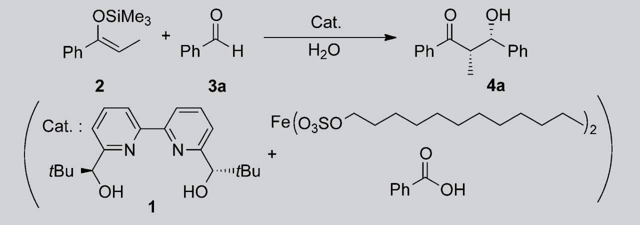
nificantly increased (Table 1, entry 2). Replacing benzoic acid with hydrochloric or acetic acid led to a decrease in the yield, diastereoselectivity, and enantioselectivity (Table 1, entries 3 and 4). Lauric acid,[11] which may act both as a surfactant and as an acid additive, afforded the desired product with slightly better conversion but with decreased stereoselectivities (Table 1, entry 5). The effect of the addition of sodium dodecylsulfate (NaDS) was then investigated (Table 1, entry 6). A slight erosion of the stereoselectivity occurred in parallel to a decrease in the yield in **4a**, presumably owing to a reduction in the local concentration of Fe^{II}. As the addition of alkyl-chain alcohols can sometimes increase the solubilizing properties of micelles for reagents,[12] we tested *n*-hexyl alcohol as an additive for the reaction. Effectively, the micelles appeared to be much more stable during the reaction with the use of this additive. Although the conversion increased, the enantioselectivity eroded (94:6 *er* compared to 96:4 without the additive; Table 1, entry 7 vs. 2). A similar yield but with lower stereoselectivities were obtained by using $Fe(DS)_3$ instead of $Fe(DS)_2$ (Table 1, entry 8).

Given that alkyl chain length of surfactants is known to have an effect on both the critical micellar concentration and the maximum reactant concentration inside the micelle, we tested other long-chain aliphatic sulfates as iron(II) counterions. It was found that $Fe(DS)_2$ was the most appropriate catalyst for this reaction. Longer and shorter linear alkyl chains did not appear to be optimal for our model reaction (Table 1, entries 9 and 10). The reaction without a surfactant [using $Fe(ClO_4)_2·6H_2O$] in pure water showed that the LASC catalyst was essential to catalyze the reaction and to avoid the hydrolysis of the silyl enol ether (Table 1, entry 11). All these results suggest that substrates are concentrated into the hydrophobic phase of the micelles, which greatly accelerates the addition of the silyl enol ether to the carbonyl partner. Presumably, water is kept out of the organic phase, and this leads to reduced hydrolysis rate for the silyl enol ether, and also, the aqueous environment helps the rapid hydrolysis of the iron–aldolate to ensure better catalytic turnover.[6i] We assume that the Fe^{+2} cation, bound to the tetradentate bipyridine ligand and surrounded by the two sulfates, keeps an ideal hydrolysis constant and water exchange rate constant to ensure good catalytic activity in water.[7]

Table 2. Optimization of the reaction conditions.[a]



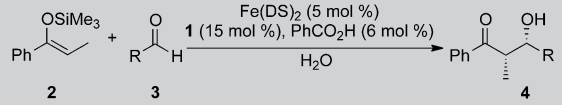
Entry	Fe/**1** [mol %]	*T* [°C]	Conc.[b] [mmol L^{-1}]	Yield [%]	*dr*[c]	*er*[d]
1	5:15	25	15	80	91:9	96:4
2	5:6	25	15	74	90:10	89:11
3	1:3	25	15	56	89:11	86:14
4	5:15	25	7.5	80	90:10	95:5
5	5:15	25	25	72	90:10	95:5
6	5:15	0	15	16	93:7	92:8
7	5:15	40	15	40	58:42	80:20
8[e]	5:15	25	15	85	89:11	92:8

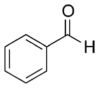
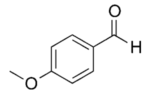
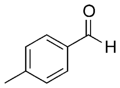
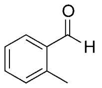
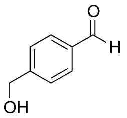
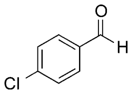
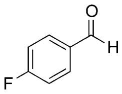
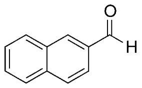
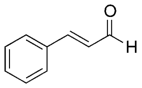
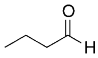
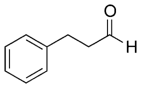
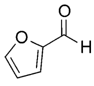
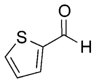
[a] Reaction conditions: silyl enol ether (1.2 equiv.), benzaldehyde (1.0 equiv.), benzoic acid [1.2 equiv. relative to $Fe(DS)_2$], 24 h. [b] Concentration of $Fe(DS)_2$. [c] The *syn/anti* diastereoisomeric ratio was determined by ^1H NMR spectroscopy. [d] The enantiomeric ratio (*syn*) was determined by HPLC analysis on a chiral stationary phase. [e] With 2 equiv. of benzaldehyde.

Further optimization of the conditions regarding catalyst concentration showed that the optimal concentration was 5 mol % Fe^{+2} with a Fe/ligand ratio of 1:3 (Table 2, entry 1). By using a smaller ratio of 1:1.2 (Table 2, entry 2), the reaction proceeded more slowly, which occurred together with an erosion in the enantioselectivity, presumably because a part of the metallomicelle was not coordinated to the chiral ligand. Increasing the ratio up to 1:4 did not give better results.[13] The use of a catalytic charge of 1 mol % of Fe^{+2} resulted in a decrease in both the conversion and the enantioselectivity (Table 2, entry 3). Concentration, relative to $Fe(DS)_2$, was then studied. Slightly lower selectivities were obtained under more diluted (Table 2, Entry 4) and more concentrated (Table 2, Entry 5) conditions. A concentration of 15 mM relative to $Fe(DS)_2$ appeared to be optimal for the reaction. Decreasing the temperature did not improve the enantioselectivity and this also led to a very poor yield (Table 2, entry 6). A higher temperature dramatically affected the stereoselectivities and did not improve the conversion, as decomposition of the silyl enol ether was observed (Table 2, entry 7). We observed that $Fe(DS)_2$ was insoluble in both pure water and benzaldehyde. As mentioned in an earlier work, the LASC catalyst presumably forms a monolayer around the substrates, and thus it is necessary for the appearance of colloidal particles in water.[8] Accordingly, we tested the addition of an excess amount of benzaldehyde to the reaction. In this case, a better yield was observed, but the enantioselectivity dropped (Table 2, entry 8).

Subsequently, various aldehydes were tested under the optimized conditions (Table 2, entry 1) by using the new LASC chiral catalyst. In all cases, the aldol products were reproducibly formed in moderate to very good yields with high stereoselectivities. Various benzaldehydes substituted with electron-donating and electron-withdrawing groups were examined (Table 3, entries 1 to 7). An aldehyde bearing an unprotected alcohol was even used (Table 3, entry 5). Despite a lower yield, a high enantioselectivity was obtained. Naphthaldehyde was less reactive than benzaldehyde but afforded a very good enantioselectivity (Table 3, entry 8). A conjugated aldehyde such as cinnamaldehyde was a good substrate (Table 3, entry 9). High enantioselectivities were obtained with aliphatic *n*-butanal and 3-phenylpropanal (Table 3, entries 10 and 11). Our conditions were finally applied to heteroaromatic aldehydes, which provided the aldol products in good yields with excellent enantioselectivities (95:5 *er*; Table 3, entries 12 and 13). We studied the reactivity of the silyl enol ether derived from acetophenone under our conditions to verify the intrinsic enantiocontrol of the reaction. In this case, the substrate was

Table 3. Catalytic Mukaiyama aldol reaction with the use of $Fe(DS)_2$ as LASC catalyst: Substrate scope.[a]



Entry	Aldehyde	Yield [%]	*dr*[b]	*er*[c]
1		80	91:9	96:4
2		63	92:8	94:6
3		63	84:16	93:7
4		82	89:11	93:7
5		39	89:11	91:9
6		78	85:15	93:7
7		88	89:11	96:4
8		65	84:16	95:5
9		75	78:22	88:12
10		64	86:14	98:2
11		85	91:9	97:3
12		75	90:10	95:5
13		78	85:15	95:5

[a] Reaction conditions: silyl enol ether (1.2 equiv.), aldehyde (1.0 equiv.), 25 °C, 48 h. [b] The *syn/anti* diastereoisomeric ratio was determined by ^{1}H NMR spectroscopy. [c] The enantiomeric ratio (*syn*) was determined by HPLC analysis on a chiral stationary phase.

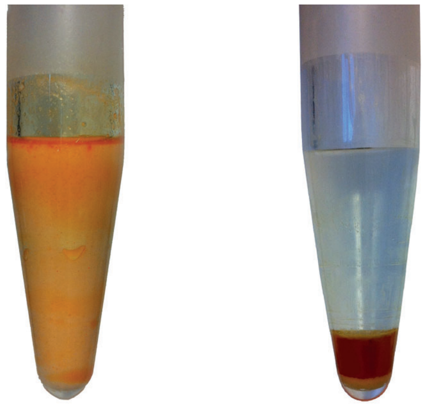


Figure 1. Appearance of the reaction mixture before and after centrifugation.

hydrolyzed faster, which led to a low yield of the aldol product and a very low enantioselectivity (11 % yield, 52:48 *er*).

With the objective of making our methodology more environmentally benign, we used centrifugation to separate the products from the aqueous layer.[8] Rotation of the reaction medium for 20 min at 3500 rpm allowed us to separate the organic products from the aqueous phase without the need for any organic solvents for extraction (see Figure 1). Compared to the ethyl acetate workup procedure, the yield of the isolated product was identical and no erosion of the enantioselectivity was detected. We then scaled up our reaction 50-fold (3.65 g of silyl enol ether and 1.56 g of benzaldehyde) and obtained exactly the same enantioselectivity and a slightly decreased yield of the desired product (71 vs. 80 % on a 0.5 mmol scale). Centrifugation was used as the only workup procedure, which was followed by silica gel column chromatography, and this afforded the aldol product along with the recycled ligand.

In conclusion, we were able to develop an efficient catalytic system that proceeds in pure water and affords good yields and high enantioselectivities (up to 98:2 *er*). Compared with other methods that employ chiral Cu^{II} or Sc^{III}, our system is advantageous in that it is the most efficient in the Mukaiyama aldol reaction in pure water with the use of a chiral LASC catalyst. To the best of our knowledge, this is the first report of the use of $Fe(DS)_2$ as a Lewis acid in organic synthesis. Both $Fe(DS)_2$ and the chiral ligand could be easily prepared, and they formed a very efficient catalyst under aqueous conditions. The generality of our system was highlighted by the wide range of aldehydes that could be used in this process (aromatic, conjugated, heteroaromatic, and aliphatic). Centrifugation makes the isolation process easier and allows solvent and time economy. A scale up of the reaction showed that the enantioselectivity was maintained at the same level. Our methodology could be therefore applied on a multigram scale for the asymmetric Mukaiyama aldol reaction in the synthesis of drugs or pharmaceutical products as nontoxic metals are involved and no organic solvents are used in the reaction process. These results pave the way for new developments in asymmetric catalysis by using iron(II) dodecylsulfate as a Lewis acid in pure water.

Experimental Section

Preparation of $Fe(DS)_2$

A 0.1 M aqueous solution of $FeCl_2$ (28.8 mg mL^{-1} water) was added to an equal proportion of a 0.1 M aqueous solution of sodium dodecyl sulfate (12.7 mg mL^{-1} water) at room temperature. The solution was mixed until complete dissolution and placed at 2 °C. The precipitate was washed several times with 0.1 M $FeCl_2$. The solid was recrystallized in water and dried under high vacuum to afford $Fe(DS)_2$ as white crystals.[9a]

Mukaiyama aldol reaction of silyl enol ethers with various aldehydes

General procedure: In a glass tube, the iron salt and the ligand were added to distilled water (1 mL). The mixture was stirred for 1 h at 25 °C to ensure complexation. Aldehyde **3 a**–**l** (0.30 mmol), benzoic acid (2.2 mg, 0.018 mmol), and silyl enol ether (0.36 mmol) were subsequently added to the mixture. The mixture was stirred at 25 °C for the desired time. The resulting mixture was either centrifuged for 20 min at 3500 rpm or extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was dried with anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure, and the residue was purified by column chromatography (hexane/ethyl acetate) to give the aldol product. The enantiomeric excess of the product was determined by HPLC analysis on a chiral stationary phase.

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Keywords: aldol reaction · enantioselectivity · iron · Lewis acids · surfactants

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[11] Lauric acid has already proved to enhance yield and enantioselectivities in a Cu^{II}/bis-oxazoline-catalyzed asymmetric Mukaiyama aldol reaction (*ee* < 69 %); see: K. Manabe, Y. Mori, S. Nagayama, K. Odashima, S. Kobayashi, *Inorg. Chim. Acta* **1999**, *296*, 158 and ref. [5a].

[12] T. Dwars, E. Paetzold, G. Oehme, *Angew. Chem. Int. Ed.* **2005**, *44*, 7174; *Angew. Chem.* **2005**, *117*, 7338.

[13] 71 % yield and 92 % *ee* were obtained for the reaction with benzaldehyde using 5 mol % $Fe(DS)_2$ and 20 mol % of ligand.

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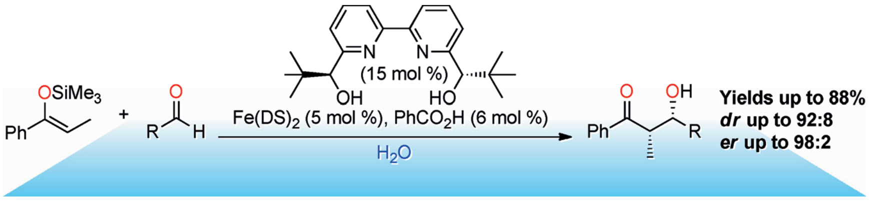

On a slippery slope: The catalytic asymmetric Mukaiyama aldol reaction in pure water is performed by using a combination of iron(II) dodecyl sulfate [Fe(DS)$_2$], a chiral bipyridine ligand, and benzoic acid. By using the obtained iron(II)-derived Lewis acid/surfactant combined catalyst, the desired products are afforded in good yields with high diastereo- and enantioselectivities.

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Iron(II)-Derived Lewis Acid/Surfactant Combined Catalysis for the Enantioselective Mukaiyama Aldol Reaction in Pure Water