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Sc(III)-Catalyzed Enantioselective Addition of Thiols to α,β-Unsaturated Ketones in Neutral Water

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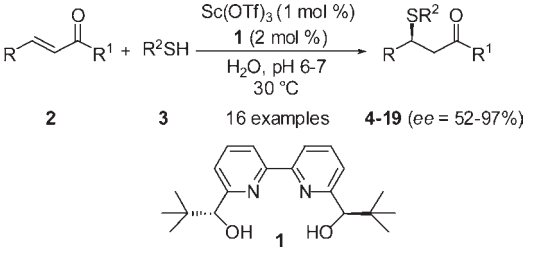
ABSTRACT



This report concerns Lewis acid catalyzed enantioselective sulfa-Michael addition in neutral water by using a very efficient $Sc(OTf)_3$/bipyridine 1 catalytic system. It is noteworthy that the protocol presented employs water as a reaction medium and allows us to obtain very high stereoselectivity and satisfactory yields for β-keto sulphides deriving from aliphatic thiols. The recovery and reuse of both the aqueous medium and the catalytic system is also reported.

Enantioselective sulfa-Michael addition (SMA) is one of the most important reactions for the construction of the C−S bond and for the synthesis of chiral sulfur compounds.[1] Accordingly, considerable efforts have been devoted to the development of enantioselective protocols employing both metal and organocatalysts.[1]

Our group has been focusing its attention on the study and development of new methodologies to realize organic reactions in water and under solvent-free conditions.[2,3]

Surprisingly, we found that just one paper has been reported on the use of water in the asymmetric Michael addition of thiols to chalcones using *per*-6-amino-β-cyclodextrin (*per*-6-ABCD) as a catalyst and achieving an enantiomeric excess up to 61%.[4] On the other hand, quite a few asymmetric Michael reactions in water using carbon nucleophiles have been recently reported.[5,6] Most of them were devoted to the use of organocatalysts,[5] while the metal-catalyzed process has been scarcely investigated.[6]

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In the past few years, Kobayashi et al. have been using bipyridine **1**[7] as a chiral ligand in water in the presence of a Lewis acid surfactant catalyst (LASC), to promote the stereoselective ring-opening of epoxides with different nucleophiles,[8] and also the asymmetric aldol reaction.[9] We have contributed to this study by using a $Zn(OTf)_2$–SDS–bipyridine **1** system as a catalyst in the stereoselective ring-opening of epoxides with amines in water.[2a] To our knowledge, the LASC–bipyridine **1** combination has never been used for the asymmetric Michael reaction in water.[10]

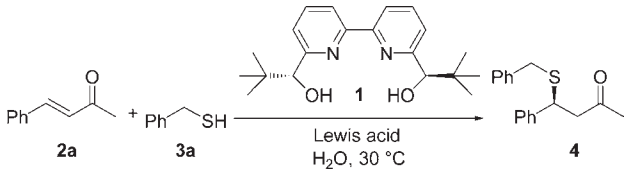
Herein, we report the first Lewis acid catalyzed enantioselective sulfa-Michael addition in water.

Our preliminary investigations revealed that the $Zn(OTf)_2$–SDS–bipyridine **1** system was not able to catalyze this transformation in an enantioselective fashion, probably due to the high affinity of the Zn(II) ion for the sulfur atom. Therefore, we searched for alternative Lewis acids that proved to efficiently work with the bipyridine ligand **1**.[8,9]

We first investigated the ability of $Sc(OTf)_3$ and (*R*,*R*)-bipyridine **1** in the reaction of *trans*-4-phenyl-3-buten-2-one (**2a**) with benzylmercaptan (**3a**) in water (Table 1).

To date, a limited number of asymmetric SMAs involving simple alkyl thiols and acyclic α,β-unsaturated ketones have been reported. Definition of the protocol for realizing this transformation efficiently is still a challenge.[1b,h,4,11] Preliminary experiments were conducted by simply mixing, at 30 °C, reagents and catalyst with no pH control, and the conversion to Michael adduct **4** was low while the enantioselectivity of the process was satisfactory (Table 1, entry 1).

Table 1. Screening Results for the Asymmetric SMA of **3a** to **2a**[a]



2a **3a** **4**

entry	Lewis acid (mol %)	**1** (mol %)	*t* (h)	conversion[b] (%)	ee[c] (%)
1[d]	$Sc(OTf)_3$ (2)	5	47	46	57
2[d,e]	$Sc(OTf)_3$ (2)	5	47	90	73
3[e]	$Sc(OTf)_3$ (2)	5	24	99	74
4[d,f]	$Sc(OTf)_3$ (2)	5	2	100	0
5	$Sc(OTf)_3$ (2)	5	24	97	91
6[g]	$Sc(OTf)_3$ (2)	5	24	97	88
7	$Sc(OTf)_3$ (1)	2	24	95 (85)[h]	91
8	$Yb(OTf)_3$ (1)	2	144	96	64
9	$In(OTf)_3$ (1)	2	144	87	−2
10	$Bi(NO_3)_3$ (1)	2	144	10	n.d.
11	$Sc(OTf)_3$ (1)	2	24	<5[i]	49

[a] Reaction conditions: **2a** (0.5 mmol), **3a** (0.5 mmol), H_2O (1.0 mL), catalyst (as indicated in the table), NaOH (3–6 mol %, depending on Lewis acid), 30 °C. [b] Determined by GC analysis. [c] The ee value was determined by HPLC analysis using a CHIRALCEL AD-H column. [d] Reaction conducted without NaOH. [e] 2 mol % of SDS were used. [f] 5 mol % of CTAOH were used. [g] Reaction carried out at 5 °C. [h] Yield of purified product **4** reported in parentheses. [i] Reaction performed in dichloromethane.

Shorter reaction times were achieved by imparting a higher homogeneity with SDS (2 mol %); this also resulted in an enhancement of enantioselectivity (Table 1, entry 2).

We also noticed that the pH of the aqueous mixture resulting from the mixing of the reagents was acidic (Table 1, entries 1, 2, 4), and therefore we decided to raise the pH to neutrality adding a catalytic amount of NaOH (Table 1, entry 3). In this case a complete conversion was obtained after 24 h, but with no improvement of enantioselectivity (Table 1, entry 3 vs 2). CTAOH was used as a cationic surfactant alternative to SDS, but the product was obtained as a racemate (Table 1, entry 4). The best result was achieved by performing the reaction under neutral conditions with no surfactant where the conversion of **2a** to **4** was complete in 24 h with a 91% ee (Table 1, entry 5). No improvements were observed by performing the reaction at 5 °C (Table 1, entry 6), while reducing the amount of the catalytic complex had no effect on the rate and enantioselectivity (Table 1, entry 7). We used other Lewis acids, but only $Yb(OTf)_3$ reached a sufficient level of enantioselectivity (Table 1, entries 8–10). The use of an organic solvent such as dichloromethane as a medium led to poorer results (Table 1, entry 11).

Finally, we investigated the recycling of the aqueous medium and the Sc(III) catalyst. After workup of a 10 mmol

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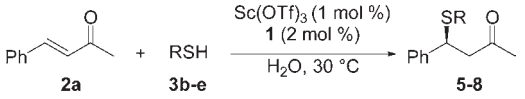
scale reaction of **2a** with **3a** (extraction with ethyl acetate; see Supporting Information), the mother liquors containing a Sc(III) catalyst and NaOH were recovered and directly reused without any pH adjustment. No decrease in the efficiency of the process in terms of yields and enantiomeric excesses was observed after three subsequent runs (see Supporting Information).

The scope of the reaction was investigated by using different thiols under the optimized conditions (Table 2).

All aliphatic thiols gave the corresponding Michael adducts in generally high yields and with high enantioselectivities (Table 2, entries 1–6). Compared to benzyl mercaptan (**3a**), thiols **3b**–**d** are less reactive and reaction times increased particularly with the bulkier *tert*-butyl thiol (**3c**), which however led to a very good 96% ee (Table 2, entry 3). A higher concentration[12] (2.0 M instead of 0.5 M) resulted in faster reactions and also in an improvement of the enantioselectivity in the case of *n*-BuSH **3b** (Table 2, entry 2 vs 1). In the case of the scarcely reactive *t*-BuSH **3c**, 5 mol % of $Sc(OTf)_3$ and 6 mol % of **1** were used, but no effect on the rate of reaction was observed (Table 2, entry 5 vs 4). The same level of enantioselectivity was observed with cyclopentylthiol (**3d**) (Table 2, entry 6).

Table 2. Asymmetric SMA of Thiols **3b**–**e** to **2a** under Neutral Conditions[a]



2a **3b-e** **5-8**

3b: R = *n*-C_4H_9
3c: R = *t*-C_4H_9
3d: R = *c*-C_5H_9
3e: R = C_6H_5

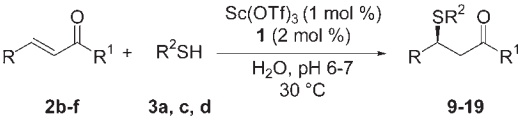
entry	thiol	*t* (h)	product	conversion[b] (%)	ee[c] (%)
1	**3b**	70	**5**	64	83
2[d]	**3b**	46	**5**	93 (83)	94
3	**3c**	139	**6**	63	96
4[d]	**3c**	216	**6**	90 (78)	97
5[d,e]	**3c**	216	**6**	93 (78)	97
6[d]	**3d**	46	**7**	83 (76)	97
7[f]	**3e**	4	**8**	81 (72)	52
8[f,g]	**3e**	1	**8**	100	46

[a] Reaction conditions: **2a** (0.5 mmol), **3b**–**e** (0.5 mmol), H_2O (1.0 mL), $Sc(OTf)_3$ (1 mol %), **1** (2 mol %), NaOH (3–20 mol %, the minimum quantity to reach pH = 7), 30 °C. [b] Determined by GC analyses; for the optimized reactions isolated yields are indicated in parentheses. [c] The ee value was determined by HPLC analysis on chiral support. [d] 2 M. [e] $Sc(OTf)_3$ (5 mol %) and **1** (6 mol %) were used. [f] $Sc(OTf)_3$ (2 mol %), **1** (5 mol %), −5 °C. [g] 2 mol % NaOH, reaction mixture pH = 4.

In contrast satisfactory results were not obtained with thiophenol (**3e**). This is probably ascribable to its high acidity (Table 2, entry 7–8).

To extend the reaction scope the additions of three selected thiols **3a**, **3c**, **3d** to various α,β-unsaturated ketones **2b**–**f** were considered (Table 3).

Table 3. Asymmetric SMA of Thiols (**3a**,**3c**,**3d**) to Enones (**2b**–**f**)[a]



2b-f **3a, c, d** **9-19**

2b: R = *p*-ClC_6H_4, R^1 = Me
2c: R = *p*-$NO_2C_6H_4$, R^1 = Me
2d: R = C_3H_7, R^1 = Me
2e: R = C_5H_{11}, R^1 = Me
2f: R = Ph, R^1 = Ph

entry	enone	thiol	*t* (h)	product	yield[b] (%)	ee[c] (%)
1	**2b**	**3a**	24	**9**	87	90
2	**2c**	**3a**	23	**10**	88	89
3	**2d**	**3a**	4	**11**	80	84
4	**2e**	**3a**	6	**12**	82	94
5	**2f**	**3a**	4	**13**	73	92 (>99)
6[d]	**2b**	**3c**	139	**14**	79	97
7[d]	**2d**	**3c**	242	**15**	65	92
8[d]	**2f**	**3c**	23	**16**	60	97
9[d]	**2b**	**3d**	120	**17**	75	95
10[d]	**2d**	**3d**	168	**18**	71	76
11[d]	**2f**	**3d**	21	**19**	84	96 (>99)

[a] Reaction conditions: see Table 2. [b] Yield of the isolated product. [c] The ee value was determined by HPLC analysis on chiral support; the ee after recrystallization is indicated in parentheses. [d] 2.0 M.

Highly enantioenriched products **9**–**19** were obtained with both aryl- and alkyl-substituted enones. In particular, *trans*-chalcone **2f** reacted in the sulfa-Michael addition with very high levels of stereocontrol (92–97% ee).

In conclusion, we have realized the first Lewis acid catalyzed enantioselective sulfa-Michael addition in water by using a very efficient $Sc(OTf)_3$/bipyridine **1** catalytic system under neutral conditions. The protocol presented here allowed the β-keto sulphides **4**–**19** to be obtained with high stereoselectivity and satisfactory yields. Moreover, both the aqueous medium and catalytic system can be recovered and recycled with no loss in enantioselectivity.

Further studies are focusing on extending these results to the stereoselective Michael additions in water of other acceptors and nucleophiles.

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Supporting Information Available. Experimental procedures, characterization data, copies of the ^1H and ^{13}C NMR and HPLC charts for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) The reaction mixture was heterogeneous, and the term concentration referred to a formal concentration calculated by considering the reactants to be completely soluble in water.