

Heterogeneous Catalytic Sulfimidation using Immobilized Cu(acac)₂

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Abstract: The heterogeneous sulfimidation of various sulfides by microencapsulated copper(II) acetylacetonate, [MC-Cu(acac)₂], and Cu(acac)₂ immobilized in ionic liquids using [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (PhI=NTs) as nitrene donor has been developed to afford the corresponding sulfimides in good to excellent yields. In the presence of a chiral bis(oxazoline) as ligand, asymmetric induction occurs to afford the chiral sulfimides (up to 50% ee). The ionic liquid containing the immobilized bis(oxazoline)-copper catalyst can be reused for several cycles with consistent activity and enantioselectivity.

Keywords: asymmetric sulfimidation; bis(oxazoline); copper acetylacetonate; ionic liquids; microencapsulation; [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane

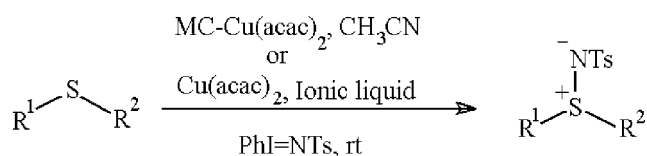
Chiral sulfoxides have emerged as versatile building blocks in the synthesis of pharmaceutical products and as chiral ligands in asymmetric catalysis.^[1] Sulfimides are the nitrogen equivalents of sulfoxides and their use in organic synthesis is rather limited due to the lack of convenient synthetic methods for optically active sulfimides. Sodium salts of chiral sulfimides are useful asymmetric methylidene transfer reagents to prochiral carbonyl groups leading to optically active epoxides.^[2] Sulfimidation is a nitrene transfer reaction and various reagents have been employed to achieve this transformation. Chiral sulfimides were first prepared from enantiomerically pure sulfoxides^[3] or by kinetic resolution of racemic sulfimides using an optically active base.^[4] Evans et al.^[5] have reported PhI=NTs to be an effective asymmetric nitrene transfer reagent to alkenes in the presence of a catalytic amount of Cu(I) salt together with a chiral 4,4'-disubstituted bis(oxazoline) ligand. Uemura et al.^[6–8] described catalytic asymmetric sulfimidation using a chiral Cu(I) bis(oxazoline) complex

as catalyst and PhI=NTs as nitrene donor, albeit at longer reaction times with moderate enantioselectivity. Mn(salen)^[9] and Ru(salen)^[10] complexes were also used as efficient catalysts for enantioselective sulfimidation showing good enantioselectivity. However, the scope of the reaction is limited using these catalysts as they require longer reaction times and are not reusable. Recently, the amidation of thioanisole has been reported by Latour et al.^[11] using a non-heme iron complex. The development of more efficacious protocol is thus most timely.

Immobilized catalysts have been of great interest due to several advantages, such as the ease of product work-up, separation, isolation and reuse of the catalyst.^[12] Microencapsulation is a rather new method for immobilizing catalysts onto polymers accomplished by physical envelopment by the polymers. A variety of reactions has been reported using this technique.^[13] Kobayashi et al.^[14,15] have pioneered the use of microencapsulation as a technique for immobilizing metal complexes.

Yet another approach for easy catalyst separation, recycling and separation of products is the use of room temperature ionic liquids.^[16] They offer an alternative and ecologically favorable medium compared to conventional organic liquids, as they are non-volatile, recyclable and non-explosive. Catalysts having polar or ionic character can be immobilized without additional structural modification and thus ionic solutions containing the catalyst can be easily separated from reagents and products. Ionic liquids have proven to be excellent solvents for many organic reactions^[17] and they are also used in enantioselective catalysis.^[18–21] Mayoral et al.^[22–24] reported enantioselective reactions using chiral bis(oxazoline)-metal complexes immobilized onto organic and anionic supports and also in ionic liquids.

We have recently reported the aziridination of olefins using PhI=NTs as a nitrene donor by MC-Cu(acac)₂^[25] and Cu(acac)₂ immobilized in ionic liquids.^[26] In the present investigation, we have explored the synthesis of sulfimides catalyzed by MC-Cu(acac)₂ and separately by Cu(acac)₂ immobilized in ionic liquids in the pres-

**Scheme 1.**

ence of PhI=NTs (Scheme 1). We have further explored the asymmetric sulfimidation using 4,4'-disubstituted bis(oxazolines) as chiral ligands and the results are reported herein.

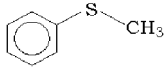
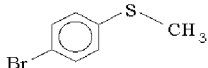
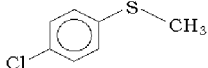
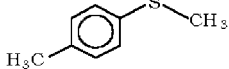
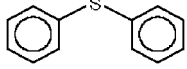

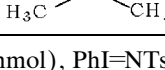
The preparation of the MC-Cu(acac)₂ is rather simple and was accomplished following the Kobayashi protocol^[14] using 1 g of polystyrene and 120 mg of Cu(acac)₂. Measurement of the mass increase of the resultant MC-Cu(acac)₂ indicates that 100 mg of Cu(acac)₂ are encapsulated, and the copper content is 0.38 mmol/g.

A variety of sulfides were subjected to the sulfimidation reaction in the presence of 5.6 mol % of MC-Cu(acac)₂ in MeCN, one equivalent PhI=NTs and 1 mmol of sulfide at 25 °C and good yields of sulfimides were obtained. The results are summarized in Table 1. Aliphatic sulfides gave higher yields than aromatic sulfides (entry 6, 7). Aromatic sulfides bearing electron-releasing groups (entry 4) are found to be more reactive than

those bearing electron-withdrawing groups in the sulfimidation reaction. In separate experiments, the syntheses of sulfimides were carried out using Cu(acac)₂ immobilized in ionic liquids. The ionic liquids, bmimBF₄ and bmimPF₆ were synthesized according to the procedures reported in the literature.^[27] A variety of sulfides was subjected to the sulfimidation reaction in the presence of 4.6 mol % of Cu(acac)₂ in 1 mL of ionic liquid, 1 equivalent of PhI=NTs and 1 mmol of sulfide at 25 °C and the corresponding sulfimides were obtained in good yields with both aromatic and aliphatic sulfides. The results are summarized in Table 1. Both bmimBF₄ and bmimPF₆ showed almost similar activities in the sulfimidation reactions. Furthermore, it is evident from the results that the product yields are almost similar to those from the MC-Cu(acac)₂ reactions, however, the reaction was faster in the ionic liquid.

In order to confirm that this process is truly heterogeneous, the catalyst was removed after the reaction by filtration, fresh aliquots of reactants were added to the filtrate and the reaction was monitored by the dissolution of PhI=NTs. While complete conversion was observed in the reaction carried out with the recovered catalyst, there was absolutely no conversion in the reaction carried out with the filtrate. After the reaction, the filtrates of both the catalytic systems were analyzed for leaching

Table 1. Sulfimidation of sulfides with PhI=NTs using immobilized Cu(acac)₂.^[a]

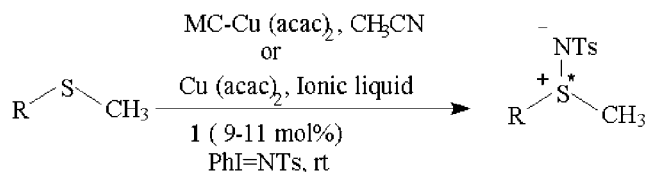
Entry	Substrate	MC-Cu(acac) ₂		bmimBF ₄	
		Time [h]	Yield [%] ^[b]	Time [min]	Yield[%] ^[b]
1		1	86 85 ^[c]	15	86 85 ^[c] 84 ^[d]
2		2	75	15	77
3		3	78	20	78
4		1	88	15	86
5		6	75	20	78
6		1	79	20	78
7		0.33	92	5	94

^[a] Sulfide (0.5 mmol), PhI=NTs (0.5 mmol), Cu(acac)₂ (4–6 mol %), ionic liquid (1 mL) and acetonitrile (3 mL) were used.

^[b] Isolated yields.

^[c] With used catalyst.

^[d] With bmimPF₆.

Table 2. Asymmetric sulfimidation of sulfides with PhI=NTs using immobilized Cu(acac)₂.^[a]

Entry	R	MC-Cu(acac) ₂			IL-Cu(acac) ₂		
		Ligand	Isolated Yield [%]	% ee ^[b]	Ligand	Isolated Yield [%]	% ee ^[b]
1	4-MeC ₆ H ₄	1a	84	12	1a	82	15
2	4-MeC ₆ H ₄	1b	86	23	1b	85	50
			86	22 ^[c]		85	50 ^[c]
			85	18 ^[d]		83	26 ^[d]
						80	16 ^[e]
3	C ₆ H ₅	1b	84	9	1b	85	30
4	4-BrC ₆ H ₄	1b	84	5 ^[d]	1b	84	11 ^[d]
			72	5		74	18

^[a] Sulfide (0.5 mmol), PhI=NTs (0.5 mmol), Cu(acac)₂ (4–6 mol %), bis(oxazoline)/Cu = 2, ionic liquid (1 mL) and acetonitrile (3 mL) were used.

^[b] The ee values were determined by HPLC using Daicel Chiralcel OJ column (hexane/2-propanol = 4:1, flow rate 0.5 mL/min).

^[c] With used catalyst.

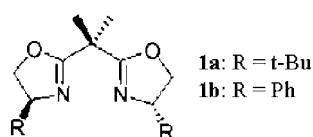
^[d] With bis(oxazoline)/Cu = 1.

^[e] With Cu(acac)₂ using acetonitrile as solvent for 1 h.

of copper metal using AAS. AAS results indicate leaching of 0.49% of Cu in MC-Cu(acac)₂ and 0.58% Cu in IL-Cu(acac)₂ during the reaction. Further, the recovered catalyst was reused for several cycles with consistent activity.

Sulfimidation is a bimolecular reaction. It is also a second order reaction as both reactants are used with the same initial concentration. Therefore, the rate constant K is given by: $1/t \ln x/a(a-x)$. The rate constant K is calculated for the sulfimidation of methyl *p*-tolyl sulfide with PhI=NTs using MC-Cu(acac)₂ and IL-Cu(acac)₂, and found to be 31.4 and 29.3, respectively. The amount of the catalyst used is almost the same in both cases, but the concentrations of the catalyst as well as the reactants were higher by a factor of 2.46 and 3, respectively, in the case of IL. So even if the rate constant is almost equal in both the cases, the reaction time is shorter in the case of IL by a factor of 7. All these factors explain the higher reaction rate in the case of IL-Cu(acac)₂.

The methodology was then applied to the asymmetric synthesis of sulfimides using 4,4'-disubstituted bis(oxazolines) **1a** and **1b** as chiral ligands. All experiments were performed using 4–6 mol% of the catalyst and 9–11 mol% of the chiral ligand. The reaction proceeded smoothly to give the expected sulfimides in good yields,



with moderate enantioselectivities (ees) (50%). The results are presented in Table 2.

When bis(oxazoline) **1a** is used as a ligand there is no difference in ee in the presence of MC-Cu(acac)₂ or an ionic liquid-Cu(acac)₂ (entry 1). However, the use of **1b** as the chiral ligand leads to a significant difference in the results obtained between the use of MC-Cu(acac)₂ and the reaction in ionic liquid-Cu(acac)₂. Comparatively higher ees were observed for Cu(acac)₂ immobilized in ionic liquid (Table 2). Also it is observed that the reaction was significantly faster in bmimBF₄ with enantiomeric enrichment than in acetonitrile. We have examined the effect of the L/Cu (ligand:copper) ratio on ees, and higher ees are obtained using the L/Cu ratio of 2 (Table 2).

Finally, upon completion of the reaction, the ionic liquid phase containing BmimBF₄, Cu(acac)₂ and the chiral ligand were almost quantitatively recovered by simple extraction of the product with 1:4 hexane/ethyl acetate. The recovered ionic liquid phase containing the catalyst and the chiral ligand was reused for several cycles with consistent activity (Table 2, entry 1). In the case of the MC-Cu(acac)₂ catalyzed enantioselective sulfimidation, the catalyst can be reused for several cycles with consistent activity and enantioselectivity with fresh addition of chiral ligand.

In conclusion, the heterogeneous sulfimidation of various sulfides by either microencapsulated copper(II) acetylacetonate [MC-Cu(acac)₂] or Cu(acac)₂ immobilized in ionic liquids using [N-(*p*-tolylsulfonyl)imino]-

phenyliodinane (PhI=NTs) as nitrene donor has been demonstrated to afford the corresponding sulfimides in good to excellent yields. In the presence of a chiral bis(oxazoline) as ligand, asymmetric induction occurs to afford the chiral sulfimides (up to 50% ee). The ionic liquid containing the immobilized bis(oxazoline)-copper catalyst can be reused for several cycles with consistent activity and enantioselectivity.

Experimental Section

Typical Procedure for Sulfimidation using MC-Cu(acac)₂

To acetonitrile (3 mL) were added MC-Cu(acac)₂ (0.075 g, 0.028 mmol), methyl phenyl sulfide (0.062 g, 0.5 mmol) and PhI=NTs (0.186 g, 0.5 mmol) and the reaction mixture was stirred at room temperature for the time shown in Table 1. The reaction was monitored by the disappearance of PhI=NTs from the reaction mixture. After completion of the reaction, the catalyst was filtered off and the filtrate concentrated and purified by column chromatography (hexane/ethyl acetate, 20/80, v/v) to afford the pure product as a white solid. Yield: 0.126 g (86%); mp 132 °C (lit^[28]: 131–132 °C). ¹H NMR (CDCl₃, 200 MHz): δ = 2.34 (s, 3H, CH₃) 2.81 (s, 3H, CH₃) 7.12–7.71 (m, 9H, Ar-H); IR (KBr): ν = 3030, 2928, 1597, 1447, 1279, 1142, 1090, 962, 756, 662, 575 cm⁻¹; anal. calcd. for C₁₄H₁₅NO₂S₂: C 57.31, H 5.15, N 4.77, S 21.84; found: C 57.28, H 5.16, N 4.67, S 21.55.

Typical Procedure for Sulfimidation using Cu(acac)₂ Immobilized in Ionic Liquid

To a solution of Cu(acac)₂ (0.006 g, 0.023 mmol) in ionic liquid (1 mL) were added methyl *p*-tolyl sulfide (0.069 g, 0.5 mmol) and PhI=NTs (0.186 g, 0.5 mmol) and the reaction mixture was stirred at room temperature. The reaction was monitored by the disappearance of PhI=NTs. After completion of the reaction, the product was extracted with 1:4 hexane/ethyl acetate by simple decantation and purified by column chromatography on silica gel (hexane/ethyl acetate, 20/80 v/v as eluent) to afford the pure product as a white solid. Yield: 0.131 g (86%); mp 125 °C (lit^[29]: 125–126 °C). ¹H NMR (CDCl₃, 200 MHz): δ = 2.35 (s, 3H, CH₃) 2.4 (s, 3H, CH₃) 2.81 (s, 3H, CH₃) 7.16 (d, 2H, *J* = 8.1 Hz, Ar-H) 7.29 (d, 2H, *J* = 8.1 Hz, Ar-H) 7.57 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.73 (d, 2H, *J* = 8.3 Hz, Ar-H); IR (KBr): ν = 3032, 2922, 1597, 1495, 1406, 1275, 1136, 1088, 997, 951, 814, 754, 664, 571 cm⁻¹; anal. calcd. for C₁₅H₁₇NO₂S₂: C 58.60, H 5.57, N 4.56, S 20.80; found: C 58.50, H 5.47, N 4.58, S 20.20.

Typical Procedure for Asymmetric Sulfimidation using MC-Cu(acac)₂

To acetonitrile (3 mL) were added MC-Cu(acac)₂ (0.075 g, 0.028 mmol), and 4,4'-disubstituted bis(oxazoline) **1b** (0.019 g, 0.056 mmol) and the mixture was stirred for 1 h. Then methyl phenyl sulfide (0.062 g, 0.5 mmol) and PhI=NTs

(0.186 g, 0.5 mmol) were added to this solution and the resulting mixture was stirred at room temperature for 1 h. After completion of the reaction, the catalyst was filtered off and the filtrate concentrated and purified by column chromatography (hexane/ethyl acetate, 20/80, v/v) to afford the pure product as a white solid. Yield: 0.123 g (86%). HPLC (Daicel Chiralcel OJ column, 20% *i*-PrOH in hexane, flow rate 0.5 mL/min): *t*_R = 31.4 (minor), *t*_R = 49.8 (major).

Typical Procedure for Asymmetric Sulfimidation using Cu(acac)₂ Immobilized in Ionic Liquid

To ionic liquid (1 mL) were added Cu(acac)₂ (0.006 g, 0.023 mmol) and 4,4'-disubstituted bis(oxazoline) **1b** (0.016 g, 0.047 mmol) and the mixture was stirred for 1 h. Methyl *p*-tolyl sulfide (0.069 g, 0.5 mmol) and PhI=NTs (0.186 g, 0.5 mmol) were then added to this solution and the resulting mixture was stirred at room temperature for 15 min. After completion of the reaction, the product was extracted with 1:4 hexane/ethyl acetate by simple decantation and purified by column chromatography on silica gel (hexane/ethyl acetate, 20/80 v/v as an eluent) to afford the pure product as a white solid. Yield: 0.13 g (85%). HPLC (Daicel Chiralcel OJ column, 20% *i*-PrOH in hexane, flow rate 0.5 mL/min): *t*_R = 30.5 (minor), *t*_R = 33.5 (major).

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