

Copper(I)-Fesulphos Lewis Acid Catalysts for Enantioselective Mannich-Type Reaction of *N*-Sulfonyl Imines

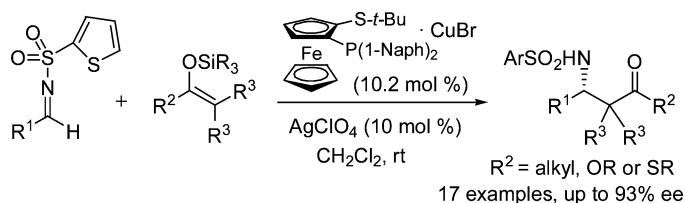
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ABSTRACT



Copper(I) complexes of Fesulphos ligands are efficient chiral Lewis acid catalysts in the Mannich-type addition of silyl enol ethers of ketones, esters, and thioesters to *N*-(2-thienyl)sulfonyl aldimines. The corresponding optically active β -amino carbonyl derivatives were obtained in good yields (58–91%) and with moderate to good enantioselectivity (61–93% ee). Removal of the *N*-activating group was achieved under mild conditions by simple treatment of the products with Mg in methanol.

The catalytic enantioselective Mannich-type addition of enolate anion equivalents to imines represents an extremely powerful strategy for the preparation of chiral nonracemic β -amino carbonyls, which are key structural units in biologically relevant compounds such as β -lactams and β -amino acids.¹ Consequently, the development of organocatalysts² and metal-based chiral catalysts^{3–7} to promote this reaction

has received a great deal of attention in recent years. Despite the impressive progress achieved in this reaction there is still room for improvement, especially toward developing novel procedures displaying a wide structural scope with regard to the substitution at the two reaction partners, imine and enolate. Thus, although there are some very efficient asymmetric metal-catalyzed protocols for the addition of enolate reagents to *N*-aryl imines,³ *N*-acyl imines,⁴ *N*-acyl hydrazones,⁵ and *N*-phosphinoyl imines,^{4d–e,6} the use of sulfonyl

(1) For reviews, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, 99, 1069. (b) Córdova, A. *Acc. Chem. Res.* **2004**, 37, 102. (c) Marques, M. B. *Angew. Chem., Int. Ed.* **2006**, 45, 348.

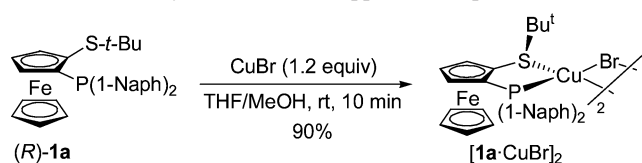
(2) For recent reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, 43, 5138. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, 3, 719. For selected references on asymmetric Mannich reactions using organocatalysts, see: (c) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, 128, 1040. (d) Ibrahim, I.; Zou, W.; Xu, Y.; Córdova, A. *Adv. Synth. Catal.* **2006**, 348, 211. (e) Rodríguez, B.; Bolm, C. *J. Org. Chem.* **2006**, 71, 2888. (f) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, 44, 6700. (g) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, 44, 4564. (h) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, 44, 2896. (i) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, 127, 11256. (j) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, 44, 4079.

(3) For recent examples with *N*-aryl imines of aromatic and aliphatic aldehydes, see: (a) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, 40, 2271. (b) Yamashita, Y.; Ueno, M.; Kuriyama, Y.; Kobayashi, S. *Adv. Synth. Catal.* **2002**, 344, 929. (c) Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, 4, 3395. (d) Kobayashi, S.; Kobayashi, J.; Ishitani, H.; Ueno, M. *Chem. Eur. J.* **2002**, 8, 4185. (e) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, 125, 338. (f) Jaber, N.; Carrée, F.; Fiaud, J.-C.; Collin, J. *Tetrahedron: Asymmetry* **2003**, 14, 2067. (g) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5476. (h) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, 126, 3734. (i) Josephsohn, N. S.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Org. Lett.* **2005**, 7, 2711. (j) Ithori, Y.; Yamashita, Y.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, 127, 15528. For a Reformatsky-type reaction, see: (k) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, 44, 3600.

imines as electrophiles is limited mainly to the case of the highly electronically activated α -tosyliminoesters.⁷ However, as a result of their great synthetic availability, stability, and structural variety, aryl, alkenyl, and alkyl *N*-sulfonyl imines are very appealing *N*-protected electrophiles in Mannich-type reactions.⁸ To the best of our knowledge, there are only two precedents concerning the use of nonactivated *N*-sulfonyl imines, in particular tosylimines, both involving the participation of a particular type of nucleophile partner: enolates of glycine Schiff bases⁹ and *N*-(2-hydroxyacetyl)pyrrole.¹⁰

We recently described that the readily available and air-stable copper(I) complexes of sulfenylphosphino-ferrocenes (Fesulphos ligands),¹¹ particularly the bulky bis(1-naphthyl)-phosphine derivative [**1a**·CuBr]₂ (Scheme 1), in combination

Scheme 1. Synthesis of the Copper(I) Complex [**1a**·CuBr]₂



with AgClO₄, behave as highly efficient chiral Lewis acid catalysts for the formal aza Diels–Alder reaction of *N*-sulfonyl imines with Danishefsky diene under very mild reaction conditions.¹² Extending the interest of this novel P,S-copper complex in asymmetric catalysis,¹³ we report herein its efficiency as general catalyst in the enantioselective Mannich-type reaction of a broad structural variety of *N*-sulfonyl imines and silyl enolates.

(4) (a) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143. (b) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507. (c) Nakamura, Y.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2481. (d) Matsunaga, S.; Yoshida, T.; Naoya, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (e) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778.

(5) (a) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640. (b) Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2006**, *12*, 1205.

(6) (a) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (b) Yoshida, T.; Morimoto, H.; Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3470. (c) Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339.

(7) For *N*-tosyl α -iminoesters, see: (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. (c) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359.

(8) The deprotection of commonly used phenyl- and tolyl-sulfonamides are typically somewhat troublesome because of the required harsh reaction conditions (see, for instance: Sharma, A. K.; Hergenrother, J. P. *Org. Lett.* **2003**, *5*, 2107).

(9) Bernardi, L.; Gotherf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583.

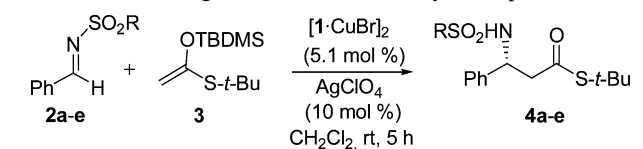
(10) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365.

(11) García Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679.

(12) García Mancheño, O.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456. The reaction of Danishefsky diene with *N*-tosylimines catalyzed by [**1**·CuBr]₂/AgClO₄ occurs mainly by a stepwise process: initial Mannich-type addition followed by in situ acid-catalyzed cyclization to the formal aza Diels–Alder adduct.

Tosylimines are by far the type of *N*-sulfonyl imines most used in organic synthesis. However, in recent years, we¹⁴ and others¹⁵ have shown that the substitution at sulfur, especially when heteroaryl groups are used, can dramatically affect the chemical behavior of *N*-sulfonyl imines, paving the way for the development of novel reactive patterns of great synthetic value. Thus, we first focussed on searching for the optimal *N*-sulfonyl protecting group. In this pursuit, several sulfonyl imines of benzaldehyde (**2a–e**) were readily prepared¹⁶ and subjected to the reaction with 1-*tert*-butyldimethylsilyloxy-1-*tert*-butylthioethene (**3**) under our optimized catalyst system,¹² a combination of [**1a**·CuBr]₂ (5.1 mol %) and AgClO₄ (10 mol %) in CH₂Cl₂¹⁷ at room temperature¹⁸ for 5 h. Table 1 highlights the important role of the nature

Table 1. Screening of Different *N*-Sulfonyl Groups



entry	R	imine	conv (%) ^a	yield (%) ^b	product	ee (%) ^c
1	NMe ₂	2a	0		4a	
2	<i>p</i> -NO ₂ C ₆ H ₄	2b	20		4b	
3	<i>p</i> -Tol	2c	50	39	4c	90
4	2-pyridyl	2d	90	65	4d	39
5	2-thienyl	2e	95	80	4e	91

^a Determined by ¹H NMR analysis of the crude reaction mixture (the remaining product is starting material). ^b Isolated yield after chromatographic purification. ^c Determined by HPLC using chiral stationary phases.

of the sulfonyl group on the reactivity and enantioselectivity of the process. While imines **2a** and **2b** led to the recovery of the starting material or were hardly reactive (entries 1 and 2), the *N*-tosyl imine **2c** reached 50% conversion under identical conditions, affording the addition product **4c** with 39% yield and 90% ee (entry 3). Heteroarylsulfonyl imines **2d**^{14b} and **2e** showed enhanced reactivity, the reaction being almost completed after 5 h (90–95% conversion, entries 4 and 5). However, whereas the *N*-(2-pyridyl)sulfonyl imine **2d** gave **4d** with low enantioselectivity (39% ee), the *N*-(2-thienyl)sulfonyl derivative **2e** produced **4e** with 91% ee.

At this point, we confirmed the superiority of the complex [**1a**·CuBr]₂ over the copper(I) bromide complexes of other

(13) For the application of Fesulphos ligands in other metal-promoted transformations, see: (a) García Mancheño, O.; Gómez Arrayás, R.; Carretero, J. C. *Organometallics* **2005**, *24*, 557. (b) Cabrera, S.; Gómez Arrayás, R.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 17938. (c) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. See also ref 11.

(14) (a) Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *J. Org. Chem.* **2005**, *70*, 7451. (b) Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629.

(15) Sugimoto, H.; Nakamura, S.; Hattori, M.; Ozeki, S.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2005**, *46*, 8941.

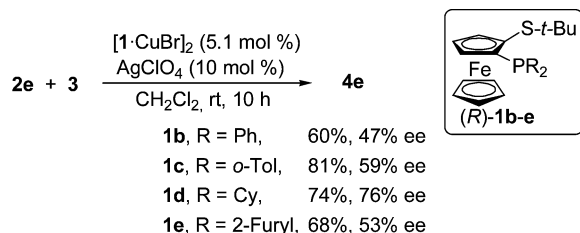
(16) See Supporting Information for details.

(17) DCE provided similar results, whereas toluene led to lower yields and enantioselectivities. The use of coordinating solvents such as THF or DMF resulted in no reaction.

(18) Lower temperature (0 °C) led to unpractical conversions.

members of the Fesulphos family of ligands (**1b–e**). The diphenylphosphine (**1b**, 60%, 47% ee), the bis(*o*-tolyl)-phosphine (**1c**, 81%, 59% ee), the dicyclohexylphosphine (**1d**, 74%, 76% ee), and the difurylphosphine (**1e**, 68%, 53% ee) ligands provided poorer results in the reaction of imine **2e** with **3** (Scheme 2). On the other hand, the chloride

Scheme 2. Copper(I) Bromide Complexes of Other FeSulphOs Ligands [(**1b–e**)·CuBr]₂ in the Mannich-Type Reaction of **2e** with **3**

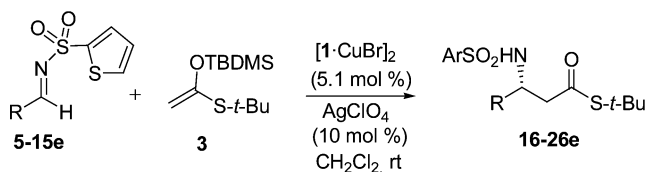


complex [**1a**·CuCl]₂ led to similar results (79%, 90% ee) as [**1a**·CuBr]₂ in this model reaction, albeit it was less reactive.

From a practical point of view, it is important to note that these sulfonamide products are stable crystalline solids, enabling thereby an enhancement of their enantiomeric purity by recrystallization. For instance, a single recrystallization from hexane/CH₂Cl₂ of a 91% ee sample of **4e** resulted in enantiomerically pure **4e** (ee > 99%).¹⁹ In addition, crystals of this product suitable for X-ray crystallographic analysis allowed its absolute configuration (*R*) to be unequivocally established.¹⁶

Having established the optimal sulfonyl protecting group²⁰ and the catalyst system, we next evaluated the scope of the reaction of **3** with differently substituted *N*-(2-thienyl)sulfonyl imines. As shown in Table 2, a number of representative aryl imines underwent addition with consistently high enantioselectivity, regardless of their steric or electronic nature (81–93% ee, entries 1–6). Both electron-withdrawing (F, Cl) and electron-donating (Me, OMe) substituents, as well as *ortho*-, *meta*-, and *para*-substitution, were well tolerated. In contrast, the *N*-(2-thienyl)sulfonyl imine of 2-furyldehyde (**12e**) resulted in a significant decrease of the enantioselectivity (49% ee, entry 9). Besides the aromatic aldimines, we next evaluated alkenyl- and alkyl-substituted imines, a kind of substrate much less studied in catalytic asymmetric Mannich-type reactions. Cinnamyl aldimine **13e** showed decreased reactivity, affording the addition product in moderate 40% yield and 71% ee (entry 10), whereas the substrate **14e**, vinylogous of 2-furyl derivative **12e**, showed higher reactivity (83% yield) but modest asymmetric induction (60% ee, entry 11). The aliphatic enolizable imine of cyclohexanecarbaldehyde (**15e**) did also participate in the

Table 2. Mannich-Type Reaction of Imines **5e–15e** with **3**



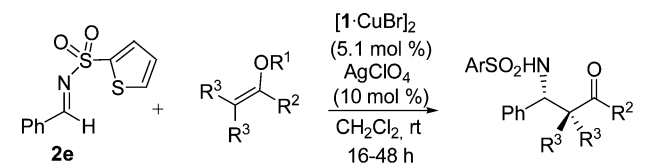
entry	R	imine	time (h)	product	yield (%) ^a	ee (%) ^b
1	Ph	2e	19	4e	80	91 (>99) ^c
2	(<i>p</i> -F)C ₆ H ₄	5e	22	16e	60	82
3	(<i>p</i> -OMe)C ₆ H ₄	6e	72	17e	58	81
4	<i>o</i> -Tol	7e	14	18e	77	93
5	(<i>m</i> -OMe)C ₆ H ₄	8e	12	19e	91	83 (94) ^c
6	(<i>m</i> -Cl)C ₆ H ₄	9e	12	20e	80	88 (98) ^c
7	1-naphth	10e	13	21e	86	88
8	2-naphth	11e	19	22e	71	91
9	2-furyl	12e	28	23e	87	49
10	PhCH=CH	13e	43	24e	40	71
11	(2-furyl)CH=CH	14e	12	25e	83	60
12	Cy	15e	17	26e	70	76 (88) ^c

^a Isolated yield after chromatographic purification. ^b Determined by HPLC using chiral stationary phases. ^c In parentheses is % ee after one recrystallization

asymmetric Mannich reaction of **3** in the presence of [**1a**·CuBr]₂/AgClO₄, affording the addition product **26e** in 70% yield and 76% ee (entry 12). As shown in four cases the enantiopurity of the Mannich products can be significantly increased after a single recrystallization¹⁹ (entries 1, 5, 6, and 12; 88–99% ee).

The generality of the process with regard to the silyl enol ether nucleophile is summarized in Table 3. Gratifyingly,

Table 3. Mannich-Type Addition of Silyl Enol Ethers of Esters and Ketones to Imine **2e**



entry	R ¹	R ²	R ³	product	yield (%) ^a	ee (%) ^b
1	TBDMS	OMe	H	27e	75	80
2	TBDMS	OMe	Me	28e	77	86
3	TMS	Ph	H	29e	71	93
4	TMS	(<i>p</i> -OMe)C ₆ H ₄	H	30e	80	85
5	TMS	2-Naph	H	31e	90	86

^a Isolated yield after chromatographic purification. ^b Determined by HPLC using chiral stationary phases.

not only thioester-derived nucleophiles but also silyl enol ethers of esters (entries 1 and 2) and silyl enol ethers of ketones (entries 3–5) underwent smooth addition reaction to imine **2e**, leading to the corresponding β-amino derivatives in good yields (71–90%) and high enantioselectivities (80–93% ee).

(19) The recrystallization yields were typically in the range of 70–90%.

(20) Further confirmation of the superiority of *N*-(2-thienyl)sulfonyl imines over the *N*-tosyl derivatives resulted from the comparative reaction of **3** with the naphthyl imine **11e** and its *N*-tosyl derivative **11c**. Thus, while imine **11e** led to the addition product **22e** with 71% yield and 91% ee (Table 2, entry 8), **11c** afforded **22c** in 36% yield and 81% ee.

From a synthetic applicability point of view, it is important to note that the resulting 2-thienylsulfonyl-protected amino ester and thioester derivatives²¹ can be readily deprotected in high yields under mild reaction conditions by treatment with magnesium in methanol (Table 4).²² Under these

Table 4. Deprotection of the (2-Thienyl)sulfonamide Group

entry	substrate, ee (%) ^a	R ¹	R ²	X	yield (%) ^b	product ee (%) ^a
1	4e , >99	Ph	H	S- <i>t</i> -Bu	83	32 , >99
2	20e , 98	<i>m</i> -ClC ₆ H ₄	H	S- <i>t</i> -Bu	84	33 , 98
3	28e , 86	Ph	Me	OMe	87	34 , 86

^a Determined by HPLC using chiral stationary phases. ^b Isolated yield after chromatographic purification.

reaction conditions recrystallized samples of thioesters **4e** and **20e** (>99% and 98% ee, respectively) underwent the cleavage of the sulfonamide moiety and methanolysis of the thioester group to give the methyl β -aminoesters **32**²³ and **33** in good yields (83–84%, entries 1 and 2) without erosion

(21) Unfortunately, this *N*-deprotection method is not suitable for ketone derivatives. For example, complete disappearance of starting material was observed upon treatment of compounds **30e** and **31e** with Mg in MeOH for 4 h, but only decomposition products were detected in the reaction mixture.

(22) These reductive reaction conditions had been reported for the cleavage of 2-pyridylsulfonyl-protected amines: Pak, C. S.; Lim, D. S. *Synth. Commun.* **2001**, 2209.

(23) Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.-i.; Tomioka, K. *Org. Lett.* **2004**, 6, 1721.

of the enantiomeric purity (>99% and 98% ee, respectively). Similarly, deprotection of the ester **28e** (86% ee) afforded the β -aminoester **34**^{3a} in 83% yield with the same enantiomeric excess (86% ee, entry 3). In the case of the known compounds **32**²³ and **34**,^{3a} comparison of their optical rotation value with that reported in the literature allowed us to confirm the absolute configuration of the Mannich products previously established by X-ray diffraction analysis of **4e**.

In summary, we have shown that the combination of Cu^I-Fesulphos as catalyst and 2-thienylsulfonyl imines as substrates provides a highly enantioselective and broad structural procedure for the Mannich-type reactions of silyl enolates. This novel methodology displays a wide tolerance with respect to both the substitution at the imine substrate (aryl, alkenyl, and alkyl imines) and the nucleophile (silyl enolates of thioesters, esters, and ketones). Further investigation to clarify the exact role of the 2-thienylsulfonyl group and application of this strategy to the vinylogous Mannich-type reaction and other enantioselective reactions of *N*-sulfonylimines are currently in progress in our lab.

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Supporting Information Available: Full experimental details, copies of ¹H NMR and ¹³C NMR of all new compounds, and X-ray crystallography data of (*R*)-**4e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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