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

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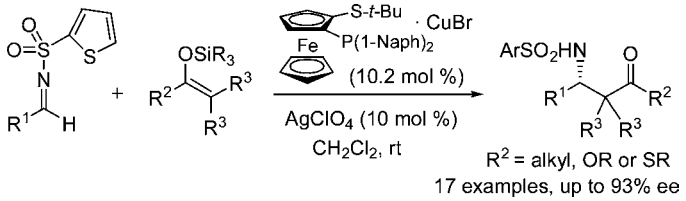
ABSTRACT



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 organocatalysts[2] 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

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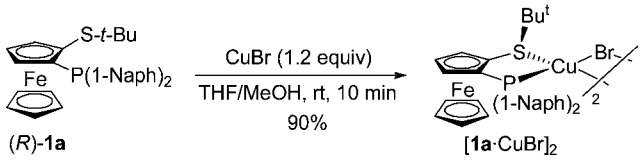
imines as electrophiles is limited mainly to the case of the highly electronically activated α-tosyliminoesters.[7] However, as a result of their great synthetic availability, stability, and structural variety, aryl, alkenyl, and alkyl *N*-sulfonyl imines are very appealing *N*-protected electrophiles 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 bases[9] 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 $AgClO_4$, 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.

Tosylimines are by far the type of *N*-sulfonyl imines most used in organic synthesis. However, in recent years, we[14] and others[15] 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 prepared[16] 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 $AgClO_4$ (10 mol %) in CH_2Cl_2[17] at room temperature[18] 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	*p*-$NO_2C_6H_4$	**2b**	20		**4b**	
3	*p*-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 ^{1}H 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

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(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.; Gothelf, 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]$_2$/$AgClO_4$ occurs mainly by a stepwise process: initial Mannich-type addition followed by in situ acid-catalyzed cyclization to the formal aza Diels−Alder adduct.

(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.

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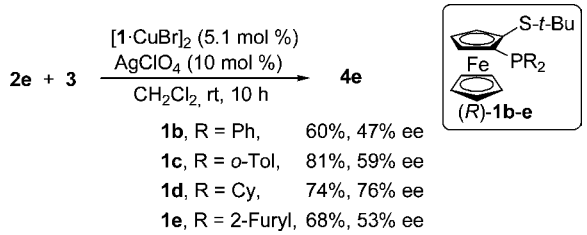
(16) See Supporting Information for details.

(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 FeSulfOs 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.

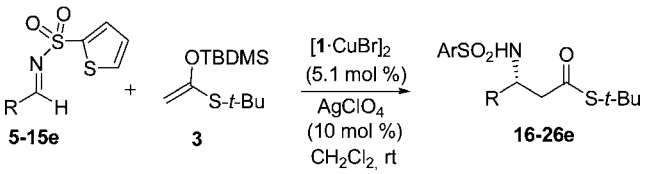
From a practical point of view, it is important to note that these sulfonamide products are stable crystalline solids, enabling thereby an enhancement of their enantiomeric purity by recrystallization. For instance, a single recrystallization from hexane/CH_2Cl_2 of a 91% ee sample of **4e** resulted 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 group[20] 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-furyladehyde (**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

(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.

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



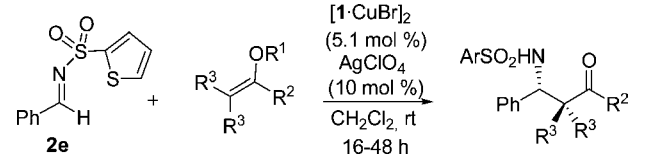
entry	R	imine	time (h)	product	yield (%)[a]	ee (%)[b]
1	Ph	**2e**	19	**4e**	80	91 (>99)[c]
2	(*p*-F)C_6H_4	**5e**	22	**16e**	60	82
3	(*p*-OMe)C_6H_4	**6e**	72	**17e**	58	81
4	*o*-Tol	**7e**	14	**18e**	77	93
5	(*m*-OMe)C_6H_4	**8e**	12	**19e**	91	83 (94)[c]
6	(*m*-Cl)C_6H_4	**9e**	12	**20e**	80	88 (98)[c]
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**·$CuBr]_2$/$AgClO_4$, 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 recrystallization[19] (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**



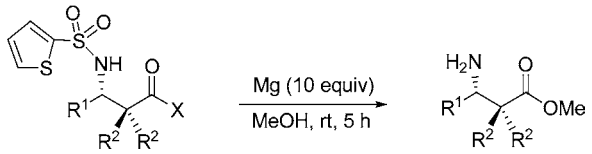
entry	R^1	R^2	R^3	product	yield (%)[a]	ee (%)[b]
1	TBDMS	OMe	H	**27e**	75	80
2	TBDMS	OMe	Me	**28e**	77	86
3	TMS	Ph	H	**29e**	71	93
4	TMS	(*p*-OMe)C_6H_4	H	**30e**	80	85
5	TMS	2-Naph	H	**31e**	90	86

[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).

From a synthetic applicability point of view, it is important to note that the resulting 2-thienylsulfonyl-protected amino ester and thioester derivatives[21] 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-*t*-Bu	83	**32**, >99
2	**20e**, 98	*m*-ClC_6H_4	H	S-*t*-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 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 ^{13}C 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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(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.

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