Catalytic Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides with Vinyl Sulfones
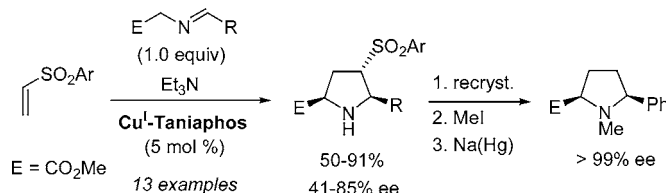
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Received February 6, 2006

ABSTRACT

A general protocol for the enantioselective catalytic 1,3-dipolar cycloaddition of azomethine ylides with aryl vinyl sulfones is described. Nearly complete exo selectivity and enantioselectivities up to 85% ee are attained with Cu(CH$_3$CN)$_4$ClO$_4$/Taniaphos as the catalyst system. The resulting enantioenriched 3-sulfonyl cycloadducts are versatile intermediates in the synthesis of 2,5-disubstituted pyrrolidines.

The 1,3-dipolar cycloaddition of azomethine ylides with alkenes is an extremely powerful and convergent strategy for the stereoselective synthesis of substituted pyrrolidines, a structural motif found in many alkaloids as well as an important building blocks for natural product synthesis.[1] Toward the goal of developing enantioselective variants of this reaction with maximum chemical efficiency, the metal-assisted catalytic asymmetric cycloaddition of azomethine ylides with electron-deficient alkenes is receiving increasing attention.[2] Since the first protocol reported by Jørgensen et al. in 2002,[3] some efficient enantioselective procedures have been described with Zn(II),[3] Ag(I),[4] Cu(I),[5] and Cu(II)[6] complexes of a variety of chiral N,N-, P,P- P,N-, and P,S-bidentate ligands as catalysts. Despite the high levels of asymmetric induction achieved, a drawback of these proce-

dures is that they have been generally applied to a narrow range of activated alkenes, typically commercially available conjugated carbonyl dipolarophiles such as acrylates, maleates, fumarates, and maleimides.

In this context, it is surprising that the catalytic enantioselective 1,3-dipolar cycloaddition of vinyl sulfones has been scarcely studied, especially considering the high electron-deficient character of the C=C bond of α,β-unsaturated sulfones,[7] their high regiocontrol shown in this reaction,[7a,8] and the great chemical versatility of the sulfonyl group.[7c,9] To the best of our knowledge, the reaction of phenyl vinyl

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(2) For a review, see: Nájera, C.; Sansano, J. M. *Angew. Chem.*, *Int. Ed.* **2005**, *44*, 6272.

(3) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem.*, *Int. Ed.* **2002**, *41*, 4236.

(4) (a) Zeng, W.; Zhou, Y.-G. *Org. Lett.* **2005**, *7*, 5055. (b) Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431. (c) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem.*, *Int. Ed.* **2004**, *43*, 5971. (d) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (e) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.

(5) (a) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (b) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241.

(6) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043.

(7) (a) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, UK, 1993. (b) Tanaka, K.; Kaji, A. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C., Eds.; Wiley: New York, 1988; Chapter 15, p 759. (c) Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903.

sulfone with (±)-alanine methyl ester 2-naphthaldehyde Schiff base in the presence of stoichiometric amounts of AgOTf and a chiral P,P-ligand, reported by Grigg et al.,[10] constitutes the only scattered example on the participation of a vinyl sulfone in chiral Lewis acid-promoted 1,3-dipolar cycloadditon of azomethine ylides, the pyrrolidine cycloadduct being obtained in 70% ee.
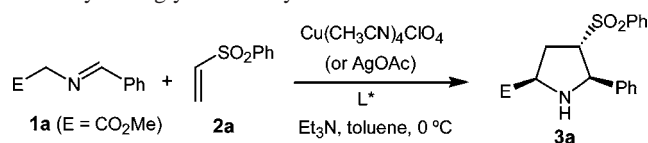
We describe herein a systematic study on metal-catalyzed asymmetric 1,3-dipolar cycloaddition of vinyl sulfones with azomethine ylides, reaching ee values up to 85% ee in the presence of the catalyst system Cu(I)-Taniaphos.

Taking into account our recent results in enantioselective Cu(I)-catalyzed 1,3-dipolar cycloadditions,[5a] we chose as the model reaction the cycloaddition of N-benzylideneglycine methyl ester (1a) with phenyl vinyl sulfone (2a) in the presence of catalytic amounts of Cu(CH$_3$CN)$_4$ClO$_4$ (10 mol %), a chiral ligand (10 mol %), and Et$_3$N[11] as base (18 mol %). Interestingly, most of the ligands used led to complete conversion within 6−24 h in toluene[12] at 0 °C, providing with complete regioselectivity and very high exo-selectivity[13] the cycloadduct 3a. The enantioselectivity exerted by a representative set of chiral ligands is shown in Table 1.

Low to moderate enantiocontrol was attained from well-established commercially available P,P-ligands, such as Binap, Chiraphos, Norphos, and Phanephos (19−42% ee; entries 1−4), while very low reactivity and enantioselectivity were observed in the case of N,N-bisoxazoline (BOX) ligands (entries 5 and 6). On the other hand, the monodentate phosphoramidite described by Feringa et al.[14] provided 3a almost in racemic form (entry 7).
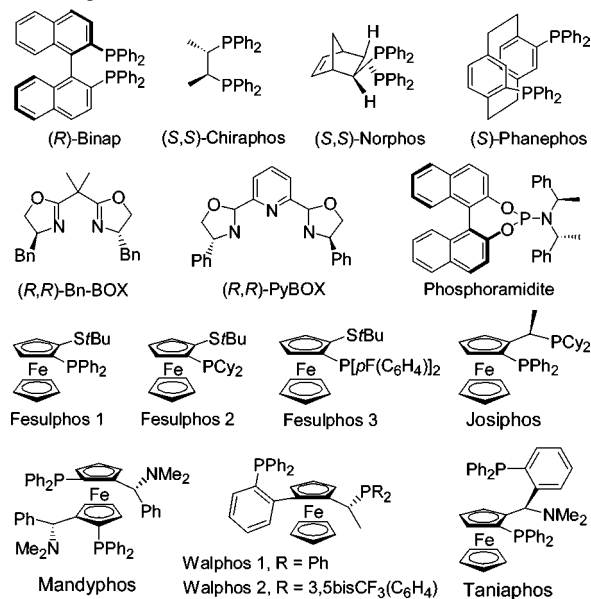
In contrast, the ferrocene P,S-ligands developed by our group (Fesulphos ligands)[15] provided moderate enantioselectivities, within the range 50−60% ee (entries 8−10). Speculating that chiral 1,2-disubstituted ferrocene structures could be appropriate ligands for this reaction, we finally surveyed several commercially available P,N- and P,P-

(8) For examples on the participation of vinyl sulfones in 1,3-dipolar cycloaddition with azomethine ylides, see: (a) Wittland, C.; Risch, N. J. Prakt. Chem. 2000, 342, 311. (b) Laduron, F.; Viehe, H. G. Tetrahedron Lett. 2002, 58, 3543. (c) Clark, R. B.; Pearson, W. H. Org. Lett. 1999, 1, 349. (d) Plancquaert, M.-A.; Redon, M.; Janousek, Z.; Viehe, H. G. Tetrahedron 1996, 52, 4383.

(9) For a review on desulfonylation/functionalization strategies, see: Nájera, C.; Yus, M. Tetrahedron 1999, 55, 10547.

(10) Grigg, R. Tetrahedron: Asymmetry 1995, 6, 2475.

(11) Other bases such as DPA, DBU, and K$_2$CO$_3$ provided similar or somewhat lower enantioselectivity in the model reaction.

(12) The Cu^I-Taniaphos catalyzed reaction of 1a with 2a was studied in five different solvents (toluene, THF, CH$_2$Cl$_2$, Et$_2$O, and DMF). Toluene and THF provided the best enantioselectivities (83% ee in both cases), whereas CH$_2$Cl$_2$ led to the lowest asymmetric induction (62% ee).

(13) In all cases only the exo adduct 3a was detected in the ¹H NMR spectra of the crude reaction mixture. This stereochemical result sharply contrasts with the supposedly endo-selectivity described in the previous example of silver−azomethine ylide cycloaddition of phenyl vinyl sulfone (see ref 10).

(14) For a review, see: Feringa, B. L. Acc. Chem. Res. 2000, 33, 346.

(15) (a) García Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. J. Org. Chem. 2003, 68, 3679. For recent applications of Fesulphos in asymmetric catalysis, see: (b) Cabrera, S.; Gómez Arrayás, R.; Alonso, I.; Carretero, J. C. J. Am. Chem. Soc. 2005, 127, 17938. (c) García Mancheño, O.; Gómez Arrayás, R.; Carretero, J. C. Organometallics 2005, 24, 557. (d) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. Angew. Chem., Int. Ed. 2004, 43, 3944. (e) García Mancheño, O.; Gómez Arrayás, R.; Carretero, J. C. J. Am. Chem. Soc. 2004, 126, 456. See also ref 5a.

Table 1. Cu^I- and Ag^I-Catalyzed Enantioselective Cycloaddition of Phenyl Vinyl Sulfone with N-Benzylideneglycine Methyl Ester

entry[a]	ligand (L*)	yield[b] (%)	ee (%)[c]
1	(R)-Binap	63	−26 (−13)[d]
2	(S,S)-Chiraphos	21	−19
3	(S,S)-Norphos	29	−42
4	(S)-Phanephos	71	−37
5	(R,R)-Bn-BOX	19	5
6	(R,R)-PyBOX	2	9
7[e]	phosphoramidite	65	3
8	Fesulphos 1	83	51 (62)[d]
9	Fesulphos 2	71	59 (51)[d]
10	Fesulphos 3	79	53 (52)[d]
11	Josiphos	69	−4
12	Mandyphos	77	16
13	Walphos 1	62	58 (−6)[d]
14	Walphos 2	78	62 (−40)[d]
15	Taniaphos	87	83 (63)[d]

[a] Reaction conditions: 1a (1.0 equiv), 2a (1.0 equiv), Cu(CH$_3$CN)$_4$ClO$_4$ or AgOAc (10 mol %), L* (10 mol %), Et$_3$N (18 mol %), toluene, 0 °C, 6−24 h. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC (Chiralpak AS). [d] In parentheses ee in the presence of AgOAc (10 mol %) instead of Cu(CH$_3$CN)$_4$ClO$_4$. [e] Reaction performed in CH$_2$Cl$_2$ at room temperature.

ferrocene ligands (entries 11−15). Gratifyingly, we found an excellent reactivity and a significant enhancement of the enantioselectivity in the presence of Taniaphos[16] (entry 15), which provided 3a in 87% yield and 83% ee.[17] Recrystallization of this sample (CH$_2$Cl$_2$-hexane, −20 °C) afforded 3a in enantiomerically pure form. Interestingly, a reduction of the catalyst loading from 10 to 5 mol % did not affect

(16) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. Angew. Chem. Int. Ed. 1999, 38, 3212.
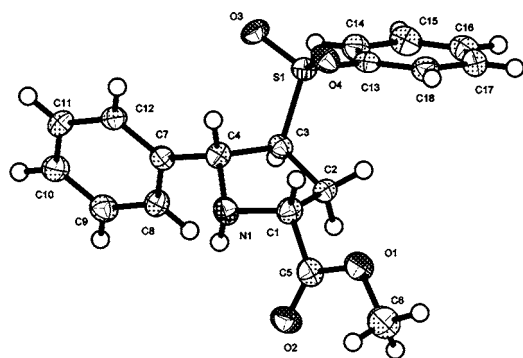
Figure 1. Crystal structure of **3a**.

the enantioselectivity of the reaction between **1a** and **2a** (83% ee in both cases), although a slight decrease of the reactivity (24 h instead of 6 h at 0 °C) was observed.[18] The relative and absolute (2R,3S,5R) configuration of **3a** was unequivocally established by X-ray diffraction analysis (Figure 1).

Considering that AgOAc has been the most used precatalyst in enantioselective 1,3-dipolar cycloadditions of azomethine ylides, we briefly studied the silver-mediated reaction between **1a** and **2a** using AgOAc instead of Cu-$(CH_3CN)_4ClO_4$. Except for the case of Fesulphos 1 (Table 1, entry 8, value in parentheses), all tested ligands induced lower asymmetric induction than that of the copper-catalyzed process. It is worth noting that in the Ag-promoted reaction Taniaphos proved also to be the best ligand.

Having found the Cu(I)-Taniaphos combination as the optimal catalytic system, we studied the effect of the substitution at the aryl vinyl sulfone. In this regard substrates **2b−d**,[19] of varied electronic properties at the aryl moiety, were surveyed in the Cu(I)-Taniaphos-catalyzed reaction of **1a** (Table 2).

Similarly to the model substrate **2a**, vinyl sulfones **2b−d** led to a single diasteromer *exo*-**3**, whose configuration was assigned by chemical analogy with **3a** and the similarity of their ^{1}H NMR data. Pyrrolidines **3** were isolated in all cases with good yields (71−87%), except for the case of the electronically richer *o*-(N,N-dimethylamino)phenyl sulfone
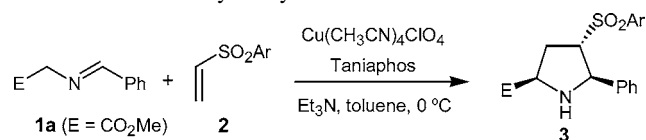
Table 2. Cu(I)-Taniaphos-Catalyzed Reaction of Azomethine Precursor **1a** with Aryl Vinyl Sulfones **2a−d**

entry[a]	sulfone	time (h)	product	yield (%)[b]	ee (%)[c]
1	**2a**	4	**3a**	87	83
2	**2b**	24	**3b**	71	75[d]
3	**2c**	3	**3c**	87	83
4	**2d**	3	**3d**	72	50
5	**2e**	24	**3e**	nr	nr

[a] Reaction conditions: **1a** (1.0 equiv), **2** (1.0 equiv), $Cu(CH_3CN)_4ClO_4$ (10 mol %), Taniaphos (10 mol %), Et_3N (18 mol %), toluene, 0 °C. [b] In pure product after silica gel chromatography. [c] Determined by HPLC (Chiralpak AS). [d] Determined by HPLC from its *N*-methyl derivative (see the Supporting Information for details).
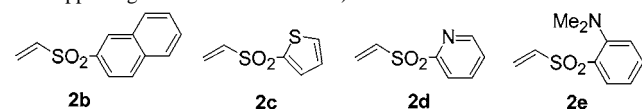
2e,[20] which led to the recovery of the starting material unaltered. Disappointingly, in comparison with **2a**, none of the new vinyl sulfones **2b−e** produced an enhancement of the enantioselectivity. As the best result, the thiophenyl vinyl sulfone **2b** provided the same asymmetric induction (83% ee), while the potentially coordinating 2-pyridyl derivative **2d**[21] gave the lowest enantiocontrol (50% ee).

Next, to establish the scope of this 1,3-dipolar cycloaddition with regard to the dipole component, a variety of substituted azomethine ylide precursors were studied with use of 5 mol % of Cu(I)-Taniaphos. The results are collected in Table 3.

The cycloaddition is widely general regardless of the substitution at the aromatic ring of the aryl imine. Both electronically rich and electronically poor arenes, as well as substitution at para, meta, and ortho position, are well tolerated (entries 1−7). The reaction was highly exo-stereoselective for all these 1,3-dipoles, providing in good yields (71−92%) a single pyrrolidine (**4−10**) with enantioselectivities depending on the particular aryl group. Para- and meta-substituted aromatic rings led to enantioselectivities very similar to that of the model reaction (82−85% ee), whereas the reaction with bulkier imines, such as the 2-naphthyl imine **1g** (entry 6) and the *o*-tolyl imine **1h** (entry 7), was significantly less enantioselective (65% and 41% ee, respectively). Aliphatic imines (entry 8) and the α-substituted 1,3-dipole precursor **1j** (entry 9) were also suitable substrates, the latter giving rise to the pyrrolidine **12** with a stereogenic quaternary center at C-5 (80% ee). However, in this case the chemical yield was much lower, likely due to the

(17) Typical experimental procedure: A mixture of Taniaphos (6.9 mg, 0.01 mmol) and $Cu(CH_3CN)_4ClO_4$ (3.2 mg, 0.01 mmol) in toluene (1 mL) was stirred at room temperature for 30 min. Then, a solution of **1a** (35.6 mg, 0.20 mmol) in toluene (0.5 mL) and Et_3N (5 μL, 0.036 mmol) were added. The mixture was cooled to 0 °C, treated with a solution of **2a** (33.6 mg, 0.20 mmol) in toluene (0.5 mL), and stirred at 0 °C for 24 h. The reaction mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography (hexanes−EtOAc 3:1) to afford **3a** as a white solid; yield 60 mg (87%).

(18) By contrast, an unpractical very slow reaction was observed by decreasing the catalyst loading to 2 mol %.

(19) Sulfones **2b−d** were readily available by reaction of the corresponding aryl disulfide with vinylmagnesium bromide and subsequent oxidation of the resulting thioether to sulfone with $Na_2W_7O_4·2H_2O/H_2O_2$. The preparation of **2e** required the condensation of methyl *o*-(N,N-dimethylamino)phenyl sulfone with formaldehyde as the key step. See the Supporting Information for details.

(20) For the use of *o*-(N,N-dimethylamino)phenyl vinyl sulfones in the Heck reaction, see: (a) Mauleón, P.; Núñez, A. A.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2003**, *9*, 1511. (b) Mauleón, P.; Alonso, I.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1291.

(21) For the use of 2-pyridyl sulfones in transition metal-catalyzed processes, see: (a) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961. (b) Mauleón P.; Carretero, J. C. *Org. Lett.* **2004**, *6*, 3195. (c) Llamas, T.; Gómez Arrayás, R. *Adv. Synth. Catal.* **2004**, *346*, 1651.

Table 3. Cu(I)-Taniaphos-Catalyzed Reaction of a Variety of Azomethine Precursors with Phenyl Vinyl Sulfone
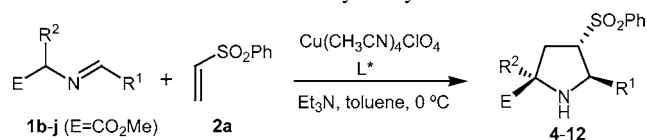

entry[a]	1	R[1]	R[2]	product	yield (%)[b]	ee (%)[c]
1	1b	p-F(C$_6$H$_4$)	H	4	91	82
2	1c	p-OMe(C$_6$H$_4$)	H	5	71	84
3	1d	m-F(C$_6$H$_4$)	H	6	83	85[d]
4	1e	m-OMe(C$_6$H$_4$)	H	7	71	85
5	1f	m-Tol	H	8	74	79[d]
6	1g	2-Naph	H	9	71	65
7	1h	o-Tol	H	10	92	41
8	1i	Cy	H	11	50	69
9	1j	Ph	Me	12	38[e]	80

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.0 equiv), Cu(CH$_3$CN)$_4$ClO$_4$ (5 mol %), Taniaphos (5 mol %), Et$_3$N (18 mol %), toluene, 0 °C, 24 h. [b] In pure product after silica gel chromatography. [c] Determined by HPLC (Chiralpak AD). [d] Determined by HPLC from its N-methyl derivative (see the Supporting Information). [e] The other isomer was isolated in 4% yield.

sensitivity of the process to steric effects at the azomethine component.

Finally, to illustrate some synthetic possibilities of the enantioenriched 3-sulfonylated pyrrolidine products, we explored some desulfonylation reactions (Scheme 1).[9] After N-methylation of a recrystallyzed sample of **3a** (ee >99%) with MeI (NaH, DMF, rt) to give **13** (92% yield) and further reductive desulfonylation with Na(Hg), the enantiomerically

(22) The acyclic γ,δ-unsaturated α-aminoester **15** was also isolated as a byproduct with a 29% yield in the desulfonylation step, as a result of a Julia-like reaction involving the cleavage of the C−N bond. For related Julia-like reactions, see: Iradier, F.; Gómez Arrayás, R.; Carretero, J. C. *Org. Lett.* **2001**, *3*, 2957 and references therein.
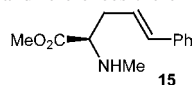
Scheme 1. Desulfonylation Reactions on the Cycloadduct **3a**
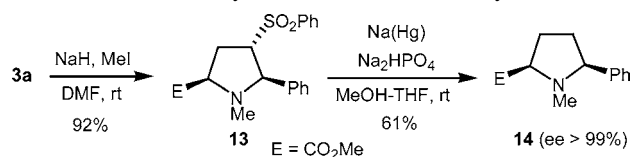
pure cis-1,5-disubstituted pyrrolidine **14** was isolated in 61% yield.[22] It must be noted that in the sequence 1,3-dipolar cycloaddition + desulfonylation the phenyl vinyl sulfone acts as a synthetic equivalent of ethylene, a type of unactivated olefin unsuitable for the reaction with azomethine ylides.

In conclusion, a general protocol for the catalytic enantioselective 1,3-dipolar cycloaddition of vinyl sulfones with azomethine ylides has been developed. The Cu^I-Taniaphos catalyst system (5−10 mol %) showed the best performance, providing 3-sulfonyl pyrrolidines with very high exo selectivity and enantioselectivities in the range 41−85% ee. Transformation of the reaction products into enantiopure 2,5-disubstituted pyrrolidines highlighted their synthetic potential. Mechanistic studies, as well as the extension to other types of 1,3-dipoles are under current investigation.

Supporting Information Available: Full experimental details, copies of ^{1}H NMR and ^{13}C NMR of all new compounds, and X-ray crystallography data for (−)-exo-**3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060314C