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Catalytic Enantioselective Reduction of β,β-Disubstituted Vinyl Phenyl Sulfones by Using Bisphosphine Monoxide Ligands**

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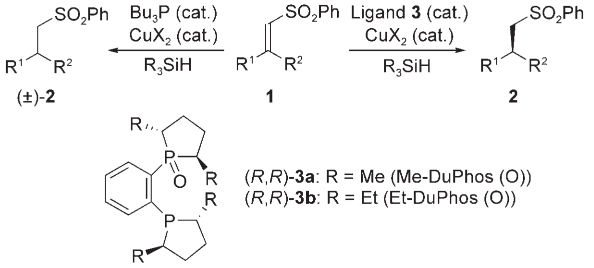
Sulfones with β stereocenters are important compounds in organic chemistry that provide valuable intermediates in the synthesis of biologically active compounds and natural products.[1] These versatile synthons can be converted into several functionalities by alkylation, halogenation, oxidation, and desulfonylation reactions and by Julia olefinations.[2,3] One attractive approach to generate this moiety is the reduction of the carbon–carbon double bond of vinyl sulfones.

Optically active alkyl phenyl sulfones have been synthesized by hydrogenation of β,β-disubstituted vinyl phenyl sulfones with rhodium as a catalyst, but high hydrogen pressure is required.[4] Misun and Pfaltz have also performed a conjugate reduction of vinyl phenyl sulfones with sodium borohydride and a catalytic amount of a chiral semicorrin cobalt complex but the enantioselectivities were modest (≤40% *ee*).[5] During the preparation of this manuscript, Carretero and co-workers published an efficient methodology to perform the asymmetric conjugate reduction of β,β-disubstituted vinyl 2-pyridyl sulfones.[6] This method could be applied to a wide variety of substrates with excellent yields and enantioselectivities. However, when the 2-pyridyl substituent on sulfones was replaced by a phenyl group, the resulting vinyl sulfones were inert under the developed reaction conditions. Thus, the conjugate asymmetric reduction of vinyl phenyl sulfones has not been accomplished by a convenient and general procedure. Herein, we report the enantioselective reduction of vinyl phenyl sulfones catalyzed by a copper–phosphine complex (Scheme 1).

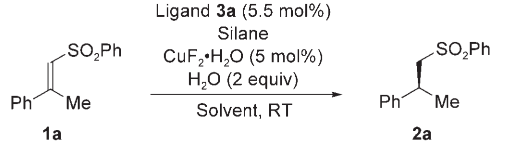
Over the last few years, the copper-catalyzed hydrosilylation of prochiral unsaturated compounds bearing electron-withdrawing substituents has been successfully employed to reduce β,β-disubstituted unsaturated carbonyls,[7] nitroalkenes,[8] imines,[9] ketones,[10] and nitriles.[11] This approach can usually be accomplished at ambient pressure and temperature with readily available reagents. Given the efficiency of stoichiometric achiral copper hydride reagents to reduce β,β-disubstituted vinyl sulfones,[12] we felt that a copper–phosphine-catalyzed hydrosilylation, with silanes as a safe source of hydride that tolerates sensitive functional groups,[13] could be applicable to the conjugate reduction of vinyl phenyl sulfones **1**.



Scheme 1. Reduction of vinyl phenyl sulfones **1**.

Our initial efforts focused on identifying the best chiral phosphine and the optimal reaction conditions for the reduction to enantioenriched **2** in high yields (Table 1). As a first screening, we treated substrate **1a** under reaction

Table 1: Enantioselective reduction of vinyl phenyl sulfones **1a**.[a]



Entry	Solvent	Silane ([equiv])	Yield[b] [%]	*ee*[c] [%]
1[d]	toluene	PMHS (4)	22	92
2	DME	$PhSiH_3$ (1.5)	19	99
3	THF	$PhSiH_3$ (1.5)	31	99
4	MTBE	$PhSiH_3$ (1.5)	50	99
5	toluene	$PhSiH_3$ (1.5)	66	99
6	benzene	$PhMeSiH_2$ (2.0)	19	99
7	benzene	PMHS (2.0)	28	99
8	benzene	$PhSiH_3$ (1.5)	39–78	99
9	benzene	$PhSiH_3$ (2.3)	51	99
10	benzene	$PhSiH_3$ (3.8)	36	99
11[e]	benzene	$PhSiH_3$ (1.5)	92	97
12[f]	benzene	$PhSiH_3$ (1.5)	95	98
13[g]	benzene	$PhSiH_3$ (1.5)	85	99

[a] Reactions were carried out overnight under argon at room temperature. DME: 1,2-dimethoxyethane; THF: tetrahydrofuran; MTBE: *tert*-butyl methyl ether; PMHS: polymethylhydrosiloxane; Tol-Binap: 2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl. [b] Determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c] Enantiomeric excess determined by chiral SFC. [d] Conditions: Tol-Binap (10 mol%) instead of **3a**, CuCl (5 mol%), no H_2O, NaO*t*Bu (5 mol%) as an additive. [e] With 20 mol% solid NaOH. [f] With 20 mol% aq. KOH. [g] With 20 mol% aq. NaOH.

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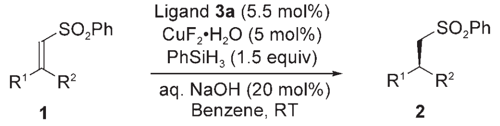
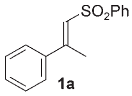
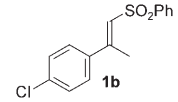
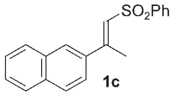
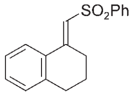
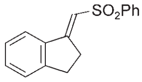
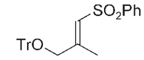
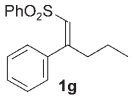
conditions developed by Buchwald and co-workers[7a] for the reduction of β,β-disubstituted unsaturated esters. This approach resulted in good enantioselectivities, but the products were obtained in poor yields (Table 1, entry 1). Recently, we have shown that the hemilabile bidentate ligand Me-DuPhos monoxide is particularly effective in copper-catalyzed nucleophilic addition reactions with sp^2 centers. In the presence of this ligand, the copper-catalyzed addition of diorganozinc reagents to phosphinoylimines and nitroalkenes proceeded with a high level of enantiocontrol.[14,15]

Our initial attempt at reducing substrate **1a** by using ligand **3a** and $CuF_2{\cdot}H_2O$, as a cheap source of copper, generated sulfone **2a** with high enantioselectivity (99% *ee*). However, the yield was mediocre in DME (Table 1, entry 2). At that point, we focused on increasing the conversion without affecting the enantiocontrol. Various solvents were tested and it was found that ethers (Table 1, entries 3 and 4) gave lower conversions than less polar aromatic solvents such as toluene and benzene (Table 1, entries 5 and 8). Phenylsilane was superior to phenylmethylsilane and PMHS (Table 1, entries 6 and 7); however, the yield of the reduction product significantly decreased when more than 1.5 equivalents were used (Table 1, entries 9 and 10).

Good conversion could be achieved in benzene with 1.5 equivalents of phenylsilane, but the results were not constant and the yield varied from 39–78% (Table 1, entry 8). Finally, we discovered that the addition of a basic additive was necessary to obtain reproducible conversions. We believe that the presence of NaOH or KOH is crucial in order to eliminate the detrimental competitive silylation of water by $PhSiH_3$ and, consequently, to reach full conversion.[7b,16,17] When a catalytic amount of solid NaOH or aqueous KOH was introduced into the reaction mixture, a slight decrease in the enantioselectivity was observed (Table 1, entries 11 and 12), whereas 20 mol% of 5.5 M aqueous NaOH afforded 85% yield and 99% *ee* (Table 1, entry 13).[18,19] It is important to mention that the use of a hemilabile bidentate ligand is essential for the efficient reduction of vinyl phenyl sulfones since Me-DuPhos gave sulfone **2a** with only 7% yield and JosiPhos[22] led to 32% yield and 93% *ee* under these optimal conditions.

Table 2: Synthesis of enantioenriched alkyl sulfones **2a–g**.



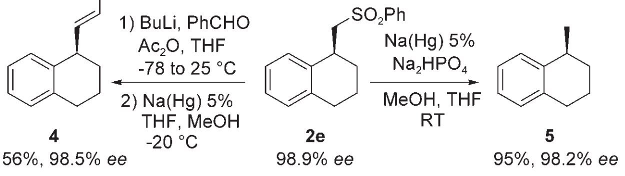
Entry	Vinyl sulfone	Yield[a] [%]	*ee*[b] [%]
1	 **1a**	85 (83)	99
2	 **1b**	93 (85)	98
3	 **1c**	85 (98)	98
4	 **1d**	97 (81)	99
5	 **1e**	90 (88)	99
6[c]	 **1f**	89 (77)	70
7		94[d]	90[d]
8	 **1g**	61 (33)	97[e]

[a] Yields of isolated product; values in brackets are yields of isolated product with 10 mol% of Bu_3P instead of **3a**. [b] Enantiomeric excess determined by chiral SFC. [c] Tr: triphenylmethyl. [d] Ligand **3b** was used instead of **3a**. [e] The absolute configuration could not be correlated.

A variety of vinyl phenyl sulfones were submitted to these optimized conditions, and the results are summarized in Table 2. All of the reactions proceeded smoothly and were complete after being stirred at room temperature for 12 h. Substrates bearing the α-methyl styryl subunit (Table 2, entries 1–3) underwent the conjugate reduction with high yields and excellent *ee* values. Excellent stereocontrol was also observed in the case of cyclic substrates such as the indenyl, **1d**, and the tetrahydronaphthyl, **1e**, derivatives, with 99% *ee* in both cases (Table 2, entries 4 and 5). For the acyclic aliphatic sulfone **1f**, Me-DuPhos(O) gave moderate enantioselectivities (Table 2, entry 6). However, when the bulkier Et-DuPhos(O) (**3b**) was used instead of **3a**, the reaction afforded **2f** in 94% yield and 90% *ee* (Table 2, entry 7). When a substrate with a longer lateral β-propyl chain was reduced (Table 2, entry 8), the yield dropped to 61% but the enantioselectivity remained very high (97% *ee*).

During the course of this study on the reduction of vinyl phenyl sulfones, racemic mixtures were synthesized by replacing Me-DuPhos(O) with an achiral ligand. More σ-donating phosphines (such as Bu_3P) led to higher conversions than triarylphosphines (>98% with Bu_3P versus 74% with Ph_3P).[20] All aromatic vinyl sulfones reacted with good to excellent yields. The γ-oxygenated sulfone **2f** was isolated with 77% yield and substrate **2g**, flanked with a phenyl group and an *n*-propyl chain at the β position, afforded the desired product in 33% yield (Table 2).

Chiral sulfones **2** provide a convenient handle for further transformations (Scheme 2). For example, sulfone **2e** could be treated under the Julia olefination conditions[3] to provide the *E* alkene **4** as the major isomer (85:15) in 56% yield and



Scheme 2. Useful transformations of enantioenriched sulfones.

without erosion of the enantiomeric excess. Moreover, sulfone **2e** could be desulfonylated[2b] to an unfunctionalized tertiary chiral center by using Na(Hg). This approach is an interesting alternative to the Ir-catalyzed hydrogenation of alkenes by Pfaltz and co-workers.[21]

In conclusion, we have developed a hydrosilylation of β,β-disubstituted vinyl sulfones that provides racemic and optically active alkyl sulfones efficiently. Excellent enantiomeric excesses and high yields were obtained at room temperature by using the hemilabile bidentate ligands **3a** or **3b**. We have demonstrated that these substrates have great potential in total synthesis by performing various useful transformations such as olefination and desulfonylation.

Experimental Section

General procedure: A flame-dried 10-mL round-bottomed flask equipped with an egg-shaped magnetic stirring bar was charged with $CuF_2 \cdot H_2O$ (3 mg, 0.025 mmol, 5 mol%) and ligand **3a** (8.8 mg, 0.027 mmol, 5.5 mol%) in a glove box. Benzene (1.5 mL) was added to the mixture and the resulting suspension was stirred under argon at room temperature for 1 h. After that, $PhSiH_3$ (92 μL, 0.75 mmol, 1.5 equiv) was added and the resulting mixture was stirred for exactly 1 min. A 5.5 M aqueous solution of NaOH (18 μL, 0.10 mmoles, 20 mol% of NaOH and equal to 2 equivalents of water) was then added and, immediately afterwards, a solution of the vinyl sulfone **1** (0.5 mmoles, 1 equiv) dissolved in a minimum amount of benzene (1.5 to 4 mL) was added through a syringe under argon. The heterogeneous mixture was stirred for 12 h at room temperature. The mixture was filtered over celite and the reaction flask was washed twice with benzene (2 × 2 mL). The filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (10–20% EtOAc/hexane) to afford the desired enantioenriched sulfone **2** as a white powder.

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[17] Various amounts of H_2O and several alcohols (MeOH, EtOH, *i*PrOH) were tested, but lower conversions were observed.

[18] The catalyst loading can be decreased to 2.5 mol% (85%, 98% *ee*) or even to 1 mol% (63%, 97% *ee*).

[19] In the final optimized conditions, the benzene used as the reaction media and washing solvent during the work-up procedure can be replaced by toluene, with similar results (84%, 99% *ee*).

[20] The use of 5 mol% of Bu_3P was equally effective.

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[22] Me-DuPhos = 1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene; JosiPhos = [(diphenylphosphanyl)ferrocenyl]ethyldicyclohexylphosphine.