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Catalytic Enantioselective Addition of Diorganozinc Reagents to Vinyl Sulfones

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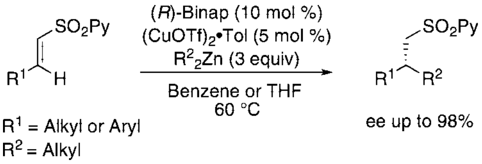
ABSTRACT

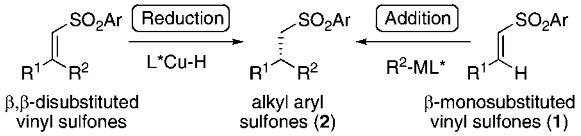


An efficient method for the catalytic asymmetric conjugate addition of diorganozinc reagents to vinyl sulfones is reported. Using a Binap•Cu complex, enantioselectivities up to 98% ee and high yields can be attained for a variety of substrates. Several dialkylzinc reagents are also compatible with this procedure.

Sulfones bearing β stereocenters are powerful tools for synthesizing complex natural or biologically active molecules.[1] The value of these subunits stems from the ease with which they can be derivatized to provide a variety of building blocks, such as aldehydes or ketones, alkynes, alkenes, alkanes, and haloalkanes.[2] Indeed, their versatility has been exploited by different research groups for the total synthesis of the immunosuppressive agent rapamycin.[3,4]

Optically active sulfones **2** may be accessed by the catalytic enantioselective reduction of β,β-disubstituted vinyl sulfones (Scheme 1).[5] Our group[6] and Carretero et al.[7] have simultaneously developed conditions which lead to enantioenriched alkyl aryl sulfones in excellent yields and enantiomeric excesses using a hydrosilylation approach.

Scheme 1. Approaches to Enantioenriched Alkyl Aryl Sulfones



A complementary convergent approach to chiral sulfones **2** is the 1,4-addition of organometallic reagents to β-monosubstituted vinyl sulfones (Scheme 1). Nonasymmetric and diastereoselective conjugate nucleophilic additions to vinyl sulfones, to produce β chiral centers, have been known for years and are still present in today's literature.[8] The first

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(4) (a) Linde, R. G., II; Egbertson, M.; Coleman, R. S.; Jones, A. B.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2771. (b) Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5060. (c) Ley, S. V.; Norman, J.; Pinel, C. *Tetrahedron Lett.* **1994**, *35*, 2095. (d) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285. (e) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleckza, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947.

(5) For hydrogenation systems leading to β-chiral sulfones substituted with carboxylic acids and β-hydroxy sulfones, see: (a) Paul, J. M.; Palmer, C. U.S. Patent 6,274,758, August 14, 2001. (b) Wan, X.; Meng, Q.; Zhang, H.; Sun, Y.; Fan, W.; Zhang, Z. *Org. Lett.* **2007**, *9*, 5613.

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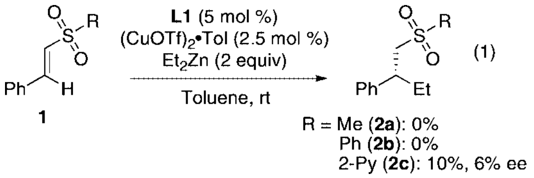
catalytic enantioselective addition to vinyl sulfones was reported by Hayashi and consisted of the rhodium-catalyzed 1,4-addition of an aryltitanium species followed by a *cine*-substitution leading to the elimination of the sulfonyl group.[9] Later, Carretero published a catalytic enantioselective conjugate addition of aromatic boronic acids onto β-mono- and β,β-disubstituted vinyl sulfones with high to excellent yields and good enantioselectivities.[10]

We recently developed copper-catalyzed additions of diorganozinc reagents to sp^2 centers, such as phosphinoylimines[11] and nitroalkenes,[12] using the hemilabile Me-DuPHOS(O) (**L1**) as a chiral ligand. We envisioned extending this system to vinyl sulfones which could circumvent the problem of synthesizing enantioenriched β,β-dialkylsubstituted sulfones with sterically similar substituents. Herein, we describe the asymmetric copper-catalyzed addition of diorganozinc reagents to β-monosubstituted vinyl sulfones.

Initially, we tested our optimized conditions for the addition of diorganozinc reagents to phosphinoylimines. However, treating Me and Ph vinyl sulfones **1a** and **1b** with diethylzinc and a catalytic amount of copper(I) triflate and Me-DuPHOS(O) in toluene (eq 1) gave none of the addition product.



It has been shown, in several copper-catalyzed systems, that reactivity may be enabled or accelerated by the presence of a proximal Lewis basic group such as a pyridine moiety by complexation to the catalyst.[13] Furthermore, Carretero discovered that such a substituent promoted the rhodium-catalyzed 1,4-addition of boronic acid to vinyl sulfones. Previously, in our research group, we found that 2-pyridyl sulfones were optimal to generate *E*,*Z*-dienes using the Julia−Kocienski olefination.[14] This information, combined with our background expertise on heteroaryl-substituted sulfones, led us to study the effect of having a 2-pyridylsulfone as the electron-withdrawing substituent on the efficiency of the addition. Interestingly, the 2-pyridyl group allowed the formation of the desired adduct in 10% yield and 6% ee with Me-DuPHOS(O).

In order to enhance both the reactivity and the enantioselectivity of the system, we screened several chiral phosphines (Figure 1).[15] We first tested the bisphosphine Me-DuPHOS (**L2**, Table 1, entry 1), and an improvement in the enantioselectivity was observed compared to its hemilabile equivalent Me-DuPHOS(O). We then turned our attention to ferrocenyl-type ligands. Josiphos (**L3**) gave comparable results to those obtained with Me-DuPHOS(O), whereas Mandyphos (**L4**) offered 17% yield and 64% ee (entries 2 and 3). Seeing that P,N-ligands offered promising results, we studied the impact of ligands **L5** and **L6** of the same family. While *i*Pr-PHOX provided very low activity, the binaphthyl Quinap increased conversions and enantioselectivities (entries 4 and 5). In general, the C_2 symmetric bisphosphine ligands with a binaphthyl scaffold (**L7**−**10**) seemed to afford better yields and enantiomeric excesses. Best results were achieved with Binap which gave 50% yield and 89% ee (entry 6).[16] The bulkier Tol-Binap ligand (**L8**) led to the addition product with similar enantiocontrol but with a much lower reactivity (entry 7).

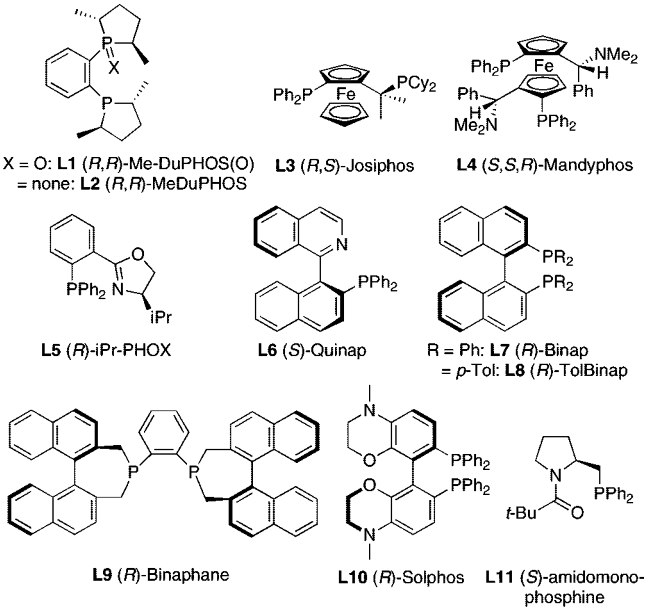


Figure 1. Various chiral phosphines tested.

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(10) (a) Mauleón, P.; Carretero, J. C. *Org. Lett.* **2004**, *6*, 3195. (b) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961. (c) Mauleón, P.; Alonso, I.; Rivero, M. R.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 9924.

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(14) Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett.* **2001**, *42*, 5149.

(15) Carbophos, BDPP, Phanephos, Segphos, Diop, and Chiraphos ligands all gave ≤10% conversion.

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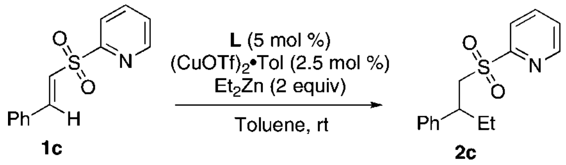
Table 1. Ligand Screening for the Addition of Et_2Zn on Vinyl Sulfone **1c**

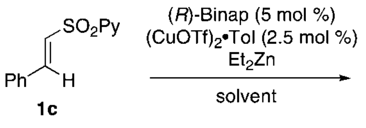


entry	ligand	yield (%)[a]	ee (%)[b]	configuration[c]
1	**L2**	4	32	*R*
2	**L3**	15	10	*R*
3	**L4**	17	64	*R*
4	**L5**	7	4	*R*
5	**L6**	42	65	*S*
6	**L7**	50	89	*R*
7	**L8**	23	78	*S*
8	**L9**	43	34	*R*
9	**L10**	9	49	*R*
10	**L11**	21	53	*S*

[a] Determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard. [b] Enantiomeric excesses determined by SFC using a chiral stationary phase. [c] Determined by comparison with literature data of the sign of optical rotation.

A systematic optimization of the enantioselective addition of Et_2Zn to vinyl sulfone **1c** (Table 2) showed that the less polar aromatic benzene afforded better yields and enantioselectivities than toluene (Table 2, entry 2). Lower conversions to the desired product **2** were observed when etheral solvents were tested (entries 3−5). Conversely, THF gave a significant increase in enantioselectivities with 98% (entry 5).[17] The concentration of the reaction media was another factor that dramatically influenced the conversions. Concentrating the reaction down to 0.2 M provided an improvement of 18% yield (entry 6). Also, by adding an excess of diorganozinc reagent and warming the reaction mixture to 60 °C, 81% yield and 97% ee were obtained (entry 10). Finally, increasing the catalyst loading to 10 mol % gave 87% yield and 98% ee. Having two sets of conditions in hand, one in benzene that provides high yields (entry 12) and another in THF that generates excellent enantioselectivities (entry 11), we explored the scope of the reaction.

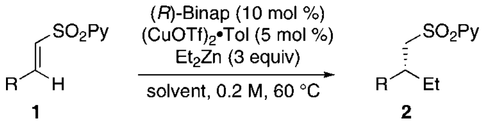
Table 2. Optimization of the Addition of Et_2Zn on Vinyl Sulfone **1c**



entry	solvent (concentration)	Et_2Zn (equiv)	temperature (°C)	yield[a] (%)	ee[b] (%)
1	toluene (0.1)	2	25	50	89
2	benzene (0.1)	2	25	62	94
3	DME (0.1)	2	25	18	93
4	Et_2O (0.1)	2	25	36	90
5	THF (0.1)	2	25	41	98
6	THF (0.2)	2	25	59	98
7	THF (0.2)	3	25	66	98
8	THF (0.2)	3	40	70	97
9	THF (0.2)	3	60	76	95
10[c]	THF (0.2)	3	60	81	97
11[d]	THF (0.2)	3	60	87 (72)[e]	98
12[d]	benzene (0.2)	3	60	99 (93)[e]	92

[a] Determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard. [b] Enantiomeric excesses determined by chiral SFC using a chiral stationary phase. [c] Binap (7 mol %) and $(CuOTf)_2$·Tol (3.5 mol %) were used. [d] Binap (10 mol %) and $(CuOTf)_2$·Tol (5 mol %) were used. [e] Isolated yield in parentheses.

Table 3. Copper-Catalyzed Asymmetric Diorganozinc Addition to Vinyl Sulfones under Optimal Conditions



entry	R	solvent[a]	yield (%)[b]	ee (%)[c]
1	Ph (**1c**)	A	72	98
2	Ph (**1c**)	B	93	92
3	4-$MeOC_6H_4$ (**1d**)	A	61	98
4	4-$MeOC_6H_4$ (**1d**)	B	80	91
5	4-$CF_3C_6H_4$ (**1e**)	A	57	94
6	4-$CF_3C_6H_4$ (**1e**)	B	83	84
7	2-naphthyl (**1f**)	A	63	97
8	2-naphthyl (**1f**)	B	77	88
9	*i*Pr (**1g**)	A	55	96
10	*i*Pr (**1g**)	B	67	93
11	Me (**1h**)	A	93	88
12	Me (**1h**)	B	92	93

[a] Solvent A = THF, solvent B = benzene. [b] Isolated yields. [c] Enantiomeric excesses determined by SFC using a chiral stationary phase.

We submitted a variety of vinyl sulfones **1** to the optimized conditions in benzene and in THF (Table 3). Vinyl sulfones with aromatic substituents at the β position **1c**−**f** (entries 1−8) underwent the catalytic conjugate addition with excellent enantioselectivities (94−98%) and moderate to good yields (57−72%) in THF. The same reactions carried out in benzene afforded very high yields (80−93%) and good enantioselectivities (84−92%) of the sulfones **2**. Vinyl sulfones bearing electron-donating groups (**1d**) provided the desired products with slightly better enantioselectivities than those bearing electron-withdrawing groups (**1e**), but with similar yields. The more hindered 2-naphthyl sulfone **2f** was generated in high yields and enantioselectivities.

Notably, α,β-unsaturated sulfones with a propensity to isomerize to the γ,β position under basic conditions[18] were compatible with this system and led to addition products in good to excellent yields and enantioselectivities (entries

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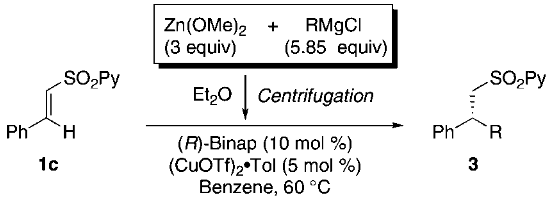
(17) $Cu(OTf)_2$, $Cu(PF_6)_2$•4MeCN, CuBr, CuOAc, $Cu(OMe)_2$, and CuCl all gave lower yields and/or enantioselectivities.

(18) Sataty, I.; Meyers, C. Y. *Tetrahedron Lett.* **1974**, *47*, 4161.

Table 4. Several Diorganozinc Reagents Added to Vinyl Sulfone **1c**



entry	R	product	yield (%)[a]	ee (%)[b]
1[c,d]	Me	**3a**	81	98
2	*n*-Pr	**3b**	52	89
3	*n*-Bu	**3c**	53	90
4[d]	$PhCH_2CH_2$	**3d**	72	90
5	*c*-Hex	**3e**	14	17

[a] Isolated yields. [b] Enantiomeric excesses determined by SFC using a chiral stationary phase. [c] Neat R_2Zn was used. [d] Six equiv of R_2Zn was used.

9−12).[19] *The formation of these enantioenriched sulfones (**2g** and **2h**), which are β,β-dialkylsubstituted with sterically unbiased groups, clearly demonstrates the efficiency of this new process.* Compounds with such substituents cannot be accessed with good enantiodifferentiation by the reduction of *β*,*β*-disubstituted vinyl sulfones due to the lack of facial selectivity induced by the copper hydride. Moreover, these *β*,*β*-dialkylsubstituted sulfones are not accessible using the rhodium-catalyzed boronic acid addition since these additions require aromatic or alkenyl nucleophiles.[10]

We recently reported a straightforward procedure to generate salt-free diorganozinc reagents in Et_2O from Grignard reagents and $Zn(OMe)_2$.[20] Using this method, we synthesized various diorganozinc reagents and submitted them to our system (Table 4). Similar results to those of obtained with neat dialkylzinc reagents could be achieved. Due to the lower reactivity of Me_2Zn,[21] an excess of this reagent was used to reach 81% yield and 98% ee (entry 1). Dipropyl- and dibutylzinc gave the same level of enantiocontrol as the addition of Et_2Zn performed in THF (entries 2 and 3). Finally, organometallic reagents bearing long aromatic functionalized chains are tolerated as well (entry 4). As shown in entry 5, the system is limited to primary diorganozinc reagents since the α-branched dicyclohexylzinc afforded only 14% yield of the addition product **3e** (17% ee), traces of reduction, and mainly the starting material **1c**.

In summary, we developed a novel copper-catalyzed enantioselective addition of diorganozinc reagents to vinyl sulfones. This approach allows the formation of optically active alkyl sulfones with good to excellent yields and enantiomeric excesses and is complementary to already known procedures. Additionally, we have shown that several dialkylzinc reagents are compatible with this methodology.

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Supporting Information Available: Experimental procedures for the preparation of compounds and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) We submitted the cyclic vinyl sulfones (cyclohexa-1,5-dien-1-ylsulfonyl)benzene and 2-(cyclohex-1-en-1-ylsulfonyl)pyridine to our optimized conditions in benzene, but none of the addition product was observed in both cases.

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