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# Catalytic asymmetric conjugate addition of dialkylzinc reagents to $\alpha,\beta$ -unsaturated sulfones†

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An efficient method is reported for the highly enantioselective copper-catalyzed conjugate addition of dialkylzinc reagents to  $\alpha,\beta$ -unsaturated sulfones using a monodentate phosphoramidite ligand.

The conjugate addition of organometallic reagents to  $\alpha,\beta$ -unsaturated compounds is one of the most versatile and widely used synthetic methods for carbon–carbon bond formation.<sup>1</sup> Enantioselective metal-catalyzed versions of this transformation are used as key-steps in the synthesis of numerous natural products and biologically active compounds and have been studied extensively over the past decade.<sup>2</sup>

An important goal in extending the current methodology is the development of an enantioselective catalytic method for the addition of organometallic reagents to  $\alpha,\beta$ -unsaturated sulfones. Optically active sulfones with a stereocenter at the  $\beta$ -position are valuable intermediates in organic chemistry due to their ease of derivatization yielding a variety of building blocks, including aldehydes or ketones, alkenes, alkynes, alkanes and haloalkanes.<sup>3</sup> In 2007, Carretero *et al.*<sup>4</sup> and Charette and Desrosiers<sup>5</sup> both reported methodology for the catalytic asymmetric conjugate reduction of  $\beta,\beta$ -disubstituted  $\alpha,\beta$ -unsaturated sulfones leading to alkyl aryl sulfones. Using a hydrosilylation approach excellent yields and enantiomeric excesses were obtained.

A complementary approach to sulfones bearing  $\beta$  stereocenters is the asymmetric conjugate addition of organometallic reagents to  $\alpha,\beta$ -unsaturated sulfones. In 2004, Mauleón and Carretero reported a rhodium-catalyzed asymmetric conjugate addition of organoboronic acids to  $\alpha,\beta$ -unsaturated sulfones giving high to excellent yields and enantioselectivities.<sup>6</sup>

Recently, Charette *et al.* reported a method for the catalytic asymmetric conjugate addition of diorganozinc reagents to  $\beta$ -substituted vinyl sulfones using a bidentate phosphorus based ligand (Binap) and elevated temperatures (60 °C) with good results.<sup>7</sup> Performing the reaction in benzene gave high yields and lower enantioselectivities while using THF gave an increase in ee, but lower yields. Our group recently developed a copper-catalyzed asymmetric conjugate addition of Grignard reagents to  $\alpha,\beta$ -unsaturated sulfones giving excellent results using a bidentate phosphorus based ligand (Tol-Binap) and aliphatic substrates.<sup>8</sup>

In this paper we describe the first asymmetric conjugate addition of diorganozinc reagents to  $\alpha,\beta$ -unsaturated sulfones using a

Table 1 Optimization of solvent and temperature<sup>a</sup>

	Solvent	Temperature (°C)	Conversion <sup>b</sup> (%)	ee <sup>c,d</sup> (%)
1 <sup>e</sup>	Toluene	−40	100 (72 h)	94 (S)
2 <sup>e</sup>	Toluene	−25	100 (48 h)	95 (S)
3 <sup>e</sup>	Toluene	−10	100 (24 h)	95 (S)
4 <sup>e</sup>	Toluene	0	100 (24 h)	92 (S)
5	Toluene	0	100 (24 h)	88 (S)
6	THF	0	0 (24 h)	nd
7	Et <sub>2</sub> O	0	25 (24 h)	nd
8	<i>t</i> -BuOMe	0	30 (24 h)	nd
9	DCM	0	12 (24 h)	nd

<sup>a</sup> Conditions: **1** (1 equiv., 0.1 mmol), Et<sub>2</sub>Zn (3.2 equiv.), Cu(OTf)<sub>2</sub> (5 mol%), (S,R,R)-**L1** (10 mol%). <sup>b</sup> Conversion determined by GC-MS. <sup>c</sup> Enantiomeric excess determined by chiral HPLC (See the ESI†). <sup>d</sup> Determined by comparison with literature data based on the sign of optical rotation. <sup>e</sup> Slow addition of the substrate **1a** over 5 h.

monodentate phosphoramidite ligand (**L1**). Among all the ligands used so far in the field of copper-catalyzed conjugate addition of organometallic reagents, phosphoramidites stand out as readily accessible, inexpensive and easily modified.<sup>9</sup> The excellent enantioselectivities that phosphoramidites give in the conjugate addition of dialkylzinc reagents to a variety of substrates<sup>10</sup> encouraged us to use them as ligands in the conjugate addition of diorganozinc reagents to  $\alpha,\beta$ -unsaturated sulfones.

Initially, we studied the addition of diethylzinc to  $\alpha,\beta$ -unsaturated sulfone **1a** using phosphoramidite **L1** (Fig. 1) at various temperatures and in different solvents (Table 1).

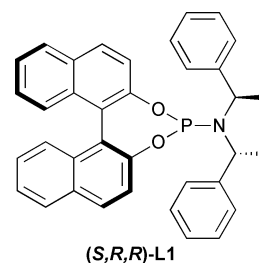


Fig. 1 Structure of ligand (S,R,R)-**L1**.

At −40 °C in toluene, full conversion was obtained after 3 days giving the product with excellent ee (entry 1). Upon increasing the reaction temperature full conversion was obtained in 24 h while the enantioselectivity remained excellent (entries 2–4). Upon direct addition of the substrate to the reaction mixture the enantiomeric

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† Electronic supplementary information (ESI) available: General procedures for the synthesis of substrates and products; <sup>1</sup>H and <sup>13</sup>C NMR spectral data of all products. See DOI: 10.1039/b917269f

**Table 2** Influence of copper source<sup>a</sup>

	[Cu] source	Conversion <sup>b</sup> (%)	ee <sup>c,d</sup> (%)
1	Cu(OTf) <sub>2</sub>	100	88 (S)
2	CuI	0	nd
3	CuTC	0	nd
4	CuBr <sub>2</sub>	5	nd
5	CuOTf-benzene	40	83 (S)

<sup>a</sup> Conditions: **1** (1 equiv., 0.1 mmol), Et<sub>2</sub>Zn (3.2 equiv.), Cu salt (5 mol%), (S,R,R)-L1 (10 mol%) in toluene at 0 °C. <sup>b</sup> Conversion determined by GC-MS after 24 h. <sup>c</sup> Enantiomeric excess determined by chiral HPLC (See the ESI†). <sup>d</sup> Determined by comparison with literature data based on the sign of optical rotation.

excess dropped only slightly (entry 5). Use of either ethereal solvents or DCM resulted in a large decrease in conversion (entries 6–9).

After optimization of reaction temperature and solvent the influence of the copper source was examined (Table 2).

The catalyst based on copper(II) triflate gave full conversion after 24 h and high enantiomeric excess. Changing the counterion of the copper source had a dramatic effect on the conversion of substrate **1a**. This effect was observed for both copper(I) and copper(II) salts and almost no conversion was obtained after 24 h (entries 2–4). When copper(I) triflate was used the conversion increased again, but both the conversion and the enantiomeric excess were lower than the result obtained with copper(II) triflate (entry 5). The nature of the counterion is of extreme importance and it seems that the triflate counterion is necessary in order to give good results.<sup>11</sup>

Changing the metal to ligand ratio did not have any effect on the enantioselectivity, but upon using a ratio of 1:1.5 of copper to ligand the conversion after 24 h increased slightly (Table 3).

After establishing the optimal conditions for the addition of diethylzinc, several other diorganozinc reagents were examined (Table 4). With the less reactive dimethylzinc no conversion was

**Table 3** Influence of copper to ligand ratio<sup>a</sup>

Reaction scheme showing the conversion of **1a** to **2a** using  $\text{Cu}(\text{OTf})_2$ ,  $(S,R,R)\text{-L1}$ ,  $\text{Et}_2\text{Zn}$  (3.2 eq) in toluene at  $0^\circ\text{C}$  for 16 h.

	$\text{Cu}(\text{OTf})_2$ (mol%)	<b>L1</b> (mol%)	$[\text{Cu}]/\text{L1}$	Conversion <sup>b</sup> (%)	ee <sup>c,d</sup> (%)
1	5	11	1:2.2	82	88 ( <i>S</i> )
2	11	11	1:1	82	88 ( <i>S</i> )
3	7.5	11	1:1.5	85	88 ( <i>S</i> )

<sup>a</sup> Conditions: **1** (1 equiv., 0.1 mmol),  $\text{Et}_2\text{Zn}$  (3.2 equiv.),  $\text{Cu}(\text{OTf})_2$ ,  $(S,R,R)\text{-L1}$  in toluene at  $0^\circ\text{C}$ . <sup>b</sup> Conversion determined by GC-MS after 16 h. <sup>c</sup> Enantiomeric excess determined by chiral HPLC (See the ESI†). <sup>d</sup> Determined by comparison with literature data based on the sign of optical rotation.

**Table 4** Addition of various diorganozinc reagents to sulfone **1**<sup>a</sup>

$\text{Cu(OTf)}_2$  (7.5 mol %)  
 $(S,R,R)\text{-L1}$  (11 mol %)  
 $\text{R}_2\text{Zn}$  (3.2 eq)  
 toluene, 24 h  
 $0^\circ\text{C}$

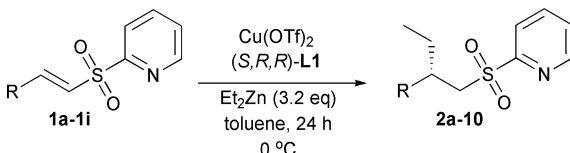
	R	Product	Conversion <sup>b</sup> (%)	ee <sup>c,d</sup> (%)
1	Et	<b>2a</b>	100 (70)	92(S) <sup>e</sup>
2	Me	<b>2b</b>	0	nd
3	<i>n</i> -Bu	<b>2c</b>	84 (73) <sup>f</sup>	66(+)
4	<i>i</i> -Pr	<b>2d</b>	100 (61)	85(S)
5	Ph <sup>g</sup>	<b>2e</b>	0	nd

<sup>a</sup> Conditions: **1** (1 equiv., 0.25 mmol),  $\text{R}_2\text{Zn}$  (3.2 equiv.),  $\text{Cu(OTf)}_2$  (7.5 mol%),  $(S,R,R)\text{-L1}$  (11 mol%) in toluene at  $0^\circ\text{C}$ . <sup>b</sup> Conversion determined by GC-MS after 24 h. Isolated yields in parentheses. <sup>c</sup> Enantiomeric excess determined by chiral HPLC (See the ESI†). <sup>d</sup> Determined by comparison with literature data based on the sign of optical rotation. <sup>e</sup> Slow addition of the substrate over 5 h. <sup>f</sup> Conversion determined by GC-MS after 5 days. <sup>g</sup> In this case 2-naphthyl substituted sulfone **1i** was used.

obtained after 24 h (entry 2). Di *n*-butylzinc gave less than 10% conversion after 24 h. Even after 5 days the conversion was not complete, nevertheless the product could be isolated in good yield and with moderate enantiomeric excess (entry 3). The more reactive diisopropylzinc gave full conversion after 24 h and both the isolated yield and enantiomeric excess dropped slightly compared with diethylzinc (entry 4). Unfortunately, the use of diphenylzinc did not give any reaction (entry 5).

Using optimized conditions we then studied the influence of the substitution pattern of the substrate on the conjugate addition of diethylzinc (Table 5). Because excellent results have been obtained using Grignard reagents on aliphatic substrates,<sup>8</sup> we focused our efforts on a range of aromatic substrates for which excellent ee's were found. Introduction of a chloride at the *ortho* position gave a drop in ee (entry 2). Moving the chloride further away from the

**Table 5** Asymmetric conjugate addition of Et<sub>2</sub>Zn to  $\alpha,\beta$ -unsaturated sulfones<sup>a</sup>

				
	R	Product	Yield <sup>b,c</sup> (%)	ee <sup>d,e</sup> (%)
1	Ph	<b>2a</b>	70	92 ( <i>S</i> ) <sup>f</sup>
2	<i>o</i> -Cl Phenyl	<b>3</b>	85	70 (+)
3	<i>m</i> -Cl Phenyl	<b>4</b>	66	84 (+)
4	<i>p</i> -Cl Phenyl	<b>5</b>	68	89 (+)
5	<i>p</i> -Me Phenyl	<b>6</b>	46 <sup>g</sup>	92 (+)
6	<i>p</i> -CF <sub>3</sub> Phenyl	<b>7</b>	84	96 ( <i>S</i> )
7	<i>p</i> - <i>i</i> -Pr Phenyl	<b>8</b>	52 <sup>g</sup>	90 (+)
8	<i>p</i> -Br Phenyl	<b>9</b>	86	96 (+)
9	2-Naphthyl	<b>10</b>	83	93 ( <i>S</i> )

reaction centre increased the enantiomeric excess (entries 2–4). We attribute this effect to steric hindrance.

In the instance of electron donating substituents such as the *para* methyl and *para* isopropyl substituted substrates full conversion was not achieved after 24 h giving lower isolated yields. Fortunately, the lower reaction rate did not negatively influence the enantiomeric excess and excellent ee's were obtained (entries 5 and 7). Furthermore, *para* trifluoromethyl-, *p*-bromo- and 2-naphthyl-substituted substrates gave good yields and excellent enantiomeric excesses (entries 6, 8 and 9).

In summary, we have developed a highly enantioselective copper-catalyzed conjugate addition of dialkylzinc reagents to a range of aromatic  $\alpha,\beta$ -unsaturated sulfones using a monodentate phosphoramidite ligand. This procedure provided  $\beta$ -substituted 2-pyridyl sulfones in moderate to good yields (46–86%) and good to excellent enantiomeric excess (70–96%) and is complementary to our recent publication on the addition of Grignard reagents to aliphatic substrates.<sup>8</sup> These enantioenriched sulfones are potentially useful intermediates in the preparation of a wide variety of functionalized chiral building blocks.

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