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Catalytic Asymmetric Conjugate Addition of Grignard Reagents to α,β-Unsaturated Sulfones

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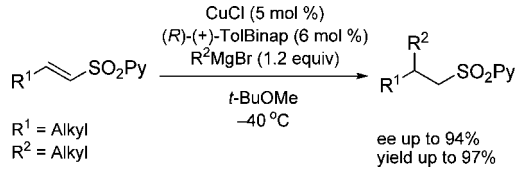
ABSTRACT



A highly efficient method is reported for the asymmetric conjugate addition of Grignard reagents to α,β-unsaturated 2-pyridylsulfones. Using a Cu/TolBinap complex, excellent enantioselectivities and high yields are obtained for a wide variety of aliphatic substrates.

The conjugate addition of organometallic reagents to α,β-unsaturated compounds is one of the most versatile of methods for the formation of C−C bonds.[1] This transformation is used as a key step in the synthesis of numerous natural products and biologically active compounds and has been the subject of intensive research over the past decade.[2]

The development of a catalytic method for the enantioselective conjugate addition reaction of organometallic reagents to α,β-unsaturated sulfones is an important goal in extending the current methodology. Sulfones with a stereocenter at the β-position are highly versatile synthons in organic chemistry due to the ease of derivatization and access to a wide range of building blocks, including aldehydes and ketones, alkynes, alkenes, alkanes, and haloalkanes.[3]

Recently, Carretero et al.[4] and Charette et al.[5] both reported a methodology for the catalytic asymmetric conjugate reduction of β,β-disubstituted α,β-unsaturated sulfones leading to alkyl aryl sulfones in excellent yields and enantiomeric excesses. A complementary approach to sulfones bearing β stereocenters is the asymmetric conjugate addition of organometallic reagents to α,β-unsaturated sulfones. In 2004, Mauleón and Carretero reported a rhodium-catalyzed asymmetric conjugate addition of organoboronic acids to α,β-unsaturated sulfones with high to excellent yields and good enantioselectivities.[6] The very recent report by Charette et al. on a catalytic asymmetric conjugate addition of diorganozinc reagents to β-substituted vinyl sulfones prompted us to disclose our results on the enantioselective conjugate addition of Grignard reagents to sulfones.[7]

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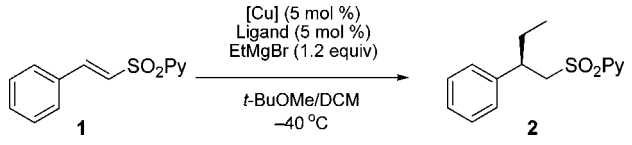
Catalytic methods for the addition of Grignard reagents to α,β-unsaturated ketones, esters, and thioesters developed in our group[8] stimulated us to explore the extension of the Cu-catalyzed Grignard addition to α,β-unsaturated sulfones. Common Grignard reagents are complementary to diorganozinc reagents and have in some cases distinct advantages such as their ready availability and the transfer of all the alkyl groups of the organometallic reagent.

In this paper, we describe the first asymmetric copper-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated sulfones. The reaction shows a broad scope and high yield and enantioselectivity.

Initially, we studied the addition of ethylmagnesium bromide to α,β-unsaturated sulfone **1** using bidentate phosphine ligands (**L1**−**L4**, Table 1). All reactions gave full conversion overnight, but the best results were obtained using binaphthyl-type phosphine ligands **L1** and **L4**, whereas ferrocenyl-type ligands **L2** and **L3** gave negligible enantioselectivity. Tol-Binap **L1** provided a slightly higher enantiomeric excess compared to Binap (**L4**) and was used for further screening.

Table 1. Copper/Ligand Catalyzed Addition of EtMgBr to αβ-Unsaturated Sulfone **1**[a,b]

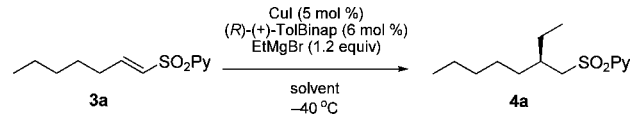


entry	ligand	ee[c,d] (%)
1	(*R*)-Tol-Binap (**L1**)	47 (*R*)
2	(S,R_{Fc})-Josiphos (**L2**)	6 (*S*)
3	(R,R_{Fc})-Taniaphos (**L3**)[9]	3 (*S*)
4	(*R*)-Binap (**L4**)	46 (*R*)

[a] Conditions: **1** (1 equiv, 0.1 mmol in DCM), EtMgBr (1.2 equiv), CuI (with **L1**/**L4**) or CuBr·Me_2S (with **L2**/**L3**) (5 mol %), **L1**−**L4** (5 mol %) in *t*-BuOMe at −40 °C, 16 h. [b] Full conversion after 16 h, determined by GC-MS. [c] Enantiomeric excess determined by chiral HPLC (see the Supporting Information). [d] Determined by comparison with literature data based on the sign of the optical rotation.

Next we switched to aliphatic substrates, and by applying the Cu-TolBinap system, the addition to α,β-unsaturated sulfone **3a** in several solvents was examined (Table 2). In all cases, full conversion was obtained overnight at −40 °C.

Table 2. Solvent Dependence in the Addition of EtMgBr to Sulfone **3a**[a,b]



entry	solvent	ee[c,d] (%)
1	DCM	87 (+)
2	toluene	80 (+)
3	*t*-BuOMe	88 (+)
4	*t*-BuOMe[e]	92 (+)
5	THF	8 (−)
6	Et_2O	76 (+)
7	CPME[f]	68 (+)

[a] Conditions: **3a** (1 equiv, 0.1 mmol), EtMgBr (1.2 equiv), CuI (5 mol %), **L1** (6 mol %) in solvent at −40 °C, 16 h. [b] Full conversion after 16 h, determined by GC−MS. [c] Determined by chiral HPLC (see the Supporting Information). [d] The absolute stereochemistry of the product is not known. [e] Slow addition of substrate over 5 h. [f] CPME = cyclopentyl methyl ether.

Running the reaction in DCM or *t*-BuOMe resulted in similar enantioselectivities (Table 2, entries 1 and 3).

Using toluene, Et_2O, or CPME as a solvent provided a slightly lower ee. However, slow addition of the substrate over 5 h to the reaction mixture in *t*-BuOMe increased the enantiomeric excess significantly (entry 4). Notably, the use of THF resulted in a very low enantiomeric excess.[10]

The influence of the 2-pyridyl group was examined by applying the asymmetric conjugate addition to the corresponding *p*-tolyl-substituted α,β-unsaturated sulfone instead of a 2-pyridyl-substituted sulfone **3a**. This decreased the reaction rate and enantiomeric excess (35% conversion after 3 d, 31% ee) dramatically. This effect of the 2-pyridyl group has also been noted also by Carretero[4,6] and Charette and co-workers[7] for related systems. The 2-pyridyl group seems to be necessary both in terms of enantioselectivity and reactivity.

With the exception of copper(I) cyanide, which gave a lower enantiomeric excess, all copper(I) and copper(II) salts tested provided similar results in the conjugate addition reaction of EtMgBr to sulfone **3a** (Table 3). In all cases, a quantitative conversion was obtained and no significant effect of the change in counterion (except for CN^-) was observed. Slow addition of the substrate to the reaction mixture increased the enantioselectivity in some cases (Table 3, entries 4 and 5), and copper(I) chloride was found to be the

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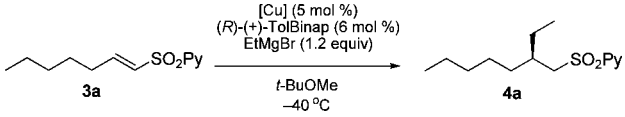
(9) The correct stereochemistry of (+)-Taniaphos **L3** is (+)-(R,R_{Fc}). Based on information in the literature, previous articles have erroneously depicted the ligand as its (R,S_{Fc}) diastereomer. See also: (a) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 3666. (b) Fukuzawa, S.-i.; Yamamoto, M.; Hosaka, M.; Kikuchi, S. *Eur. J. Org. Chem.* **2007**, 5540–5545. (c) Fukuzawa, S.-i.; Yamamoto, M.; Kikuchi, S. *J. Org. Chem.* **2007**, *72*, 1514–1517.

(10) This dependence is in contrast to that reported by Charette and co-workers for organozinc reagents in which an increase in enantioselectivity was observed with THF as solvent; see ref 7.

(11) Other sulfones with a substituted phenyl group at the γ-position gave equally moderate results (*p*-CF_3-**1**: 65% yield, 51% ee and *p*-Br-**1**: 76% yield, 70% ee) under the optimized conditions.

Table 3. Influence of Copper Source on the Addition of EtMgBr to Sulfone **3a**[a,b]



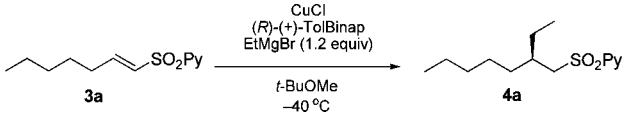
entry	[Cu] source	ee[c,d] (%)
1	CuCN	69 (+)
2	CuBr·Me_2S	89 (+)
3	$Cu(OTf)_2$	87 (+)
4	CuI	88 (+)
5	CuI[e]	92 (+)
6	CuCl	93 (+)
7	CuCl[e]	93 (+)

[a] Conditions: **3a** (1 equiv, 0.1 mmol), EtMgBr (1.2 equiv), Cu salt (5 mol %), **L1** (6 mol %) in *t*-BuOMe at −40 °C, 16 h. [b] Full conversion after 16 h, determined by GC−MS. [c] Enantiomeric excesses determined by chiral HPLC (see the Supporting Information). [d] The absolute stereochemistry of the product is not known. [e] Slow addition of substrate over 5 h.

most suitable copper source for this reaction giving quantitative conversion and 93% ee (Table 3, entries 6 and 7).

Increasing the metal to ligand ratio to 2:1 results in a decrease in enantioselectivity (Table 4). We attribute this to

Table 4. Influence of Copper to Ligand Ratio on the Addition of EtMgBr to Sulfone **3a**[a,b]



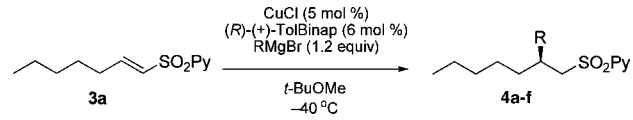
entry	CuCl (mol %)	L1 (mol %)	[Cu]/**L1**	ee[c,d] (%)
1	5	5	1:1	83 (+)
2	10	5	2:1	62 (+)
3	5	10	1:2	85 (+)
4	5	6	1:1.2	93 (+)

[a] Conditions: **3a** (1 equiv), EtMgBr (1.2 equiv), CuCl, and **L1** in *t*-BuOMe at −40 °C, 16 h. [b] Full conversion after 16 h, determined by GC−MS. [c] Enantiomeric excesses determined by chiral HPLC (see the Supporting Information). [d] The absolute stereochemistry of the product is not known.

the fact that not all of the copper is bound to the ligand, giving rise to a significant amount of ligand-free copper-mediated reaction. It was found that a small excess of ligand with respect to the copper gave the best result. Increasing the ligand to metal ratio further (entry 3) did not improve the enantioselectivity.

Several Grignard reagents were examined using the conditions optimized for EtMgBr (Table 5). In all cases, full conversion was observed after 16 h, and high isolated yields and ee's (except for entry 6) were obtained. With MeMgBr a slightly lower enantiomeric excess and yield were attained. Both *n*-BuMgBr and $C_6H_5C_2H_4MgBr$ gave similar enanti-

Table 5. Asymmetric Conjugate Addition of Various Grignard Reagents to Sulfone **3a**[a,b]



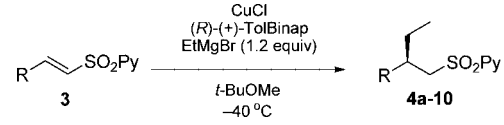
entry	R	product	yield[c] (%)	ee[d,e] (%)
1	Et	**4a**	97	93 (+)
2	Me	**4b**	80	89 (−)
3	*n*-Bu	**4c**	88	93 (+)
4	$C_6H_5C_2H_4$	**4d**	87	87 (−)
5	But-3-enyl	**4e**	95	94 (+)
6	Ph	**4f**	80	0

[a] Conditions: **3a** (1 equiv), RMgBr (1.2 equiv), CuCl (5 mol %), **L1** (6 mol %) in *t*-BuOMe at −40 °C, 16 h. [b] Full conversion after 16 h, determined by GC-MS. [c] Isolated yields. [d] Enantiomeric excesses determined by chiral HPLC (see Supporting Information). [e] The absolute stereochemistry of the products is not known.

oselectivities and a slightly lower yield (Table 5, entries 3 and 4). Furthermore, the use of but-3-enylmagnesium bromide also resulted in excellent yield and enantioselectivity (Table 5, entry 5). Notably, the reaction using PhMgBr did not proceed in an enantioselective manner (Table 5, entry 6).

The synthetic applicability of this highly enantioselective procedure was extended using a set of α,β-unsaturated substrates under the optimized conditions (Table 6). All

Table 6. Asymmetric Conjugate Addition of EtMgBr to α,β-Unsaturated Sulfones[a,b]



entry	**3**	R	product	yield (%)[c]	ee[d,e] (%)
1	**3a**	*n*-Pent	**4a**	97	93 (+)
2	**3b**	*n*-Oct	**5**	90	92 (+)
3	**3c**	*i*-Bu	**6**	88	94 (−)
4	**3d**	*i*-Pr	**7**	93	88 (−)
5	**3e**	*c*-Hex	**8**	94	94 (−)
6	**3f**	$TBDPSOC_2H_4$	**9**	91	92 (+)
7	**3g**	$C_6H_5C_2H_4$	**10**	91	93 (+)

[a] Conditions: **3** (1 equiv, 0.2 mmol), EtMgBr (1.2 equiv), CuCl (5 mol %), **L1** (6 mol %) in *t*-BuOMe at −40 °C, 16 h. [b] Full conversion after 16 h, determined by GC−MS. [c] Isolated yields. [d] Enantiomeric excesses determined by chiral HPLC (see the Supporting Information). [e] The absolute stereochemistry of the products is not known.

sulfones provided the desired products in excellent yields (88−97%) and excellent enantioselectivities (88−94%).

Substitution of the α,β-unsaturated sulfone at the γ- or δ-position did not influence the enantioselectivities or yields (Table 6, entries 1−5), and the reactions proceed with both excellent yields and enantiomeric excesses. The presence of

a protected alcohol group or phenyl group at the δ-position in the substrate did not affect this enantioselective transformation either and the reactions resulted in high isolated yields of optically active β-substituted sulfones with excellent ee's. This is in sharp contrast with the results obtained for sulfone **1** substituted with a phenyl group at the γ-position (Table 1, 47% ee) which gave only moderate results under the optimized conditions (75% yield, 50% ee).[11]

In summary, we have developed a novel copper-catalyzed asymmetric conjugate addition of Grignard reagents to a range of aliphatic α,β-unsaturated sulfones. This procedure has a broad scope for aliphatic substrates and provides β-substituted 2-pyridyl sulfones in both excellent yields (88−97%) and enantioselectivities (88−94%). These enantioenriched sulfones are versatile intermediates in the preparation of a wide variety of functionalized chiral building blocks.

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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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