

Highly Versatile Enantioselective Conjugate Addition of Grignard Reagents to α,β -Unsaturated Thioesters

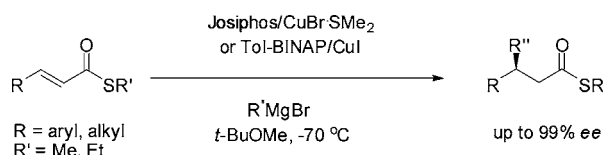
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Received October 4, 2007

ABSTRACT



Herein, we report efficient catalysts for the asymmetric copper-catalyzed conjugate addition of Grignard reagents to α,β -unsaturated thioesters. MeMgBr adds to aromatic α,β -unsaturated thioesters with excellent enantioselectivities and moderate to good yields using Josiphos/CuBr and Tol-BINAP/CuI complexes. The use of bulky Grignard reagents leads to unprecedented enantioselectivities in the 1,4-addition to a broad range of aromatic and aliphatic α,β -unsaturated thioesters using Tol-BINAP/CuI. The highest enantioselectivities reported so far for the addition of Grignard reagents to crowded β -substituted aliphatic substrates are achieved with Tol-BINAP/CuI.

The conjugate addition (CA) of organometallic reagents to α,β -unsaturated compounds is one of the most versatile methodologies for the formation of C–C bonds.¹ This transformation has been used as a key step in the synthesis of numerous natural products and biologically active compounds. The introduction of monodentate phosphoramidite ligands led to the first highly enantioselective catalytic conjugate addition of dialkylzinc reagents.² Nowadays, due to intensive research over the past decade, CA can be performed in a catalytic asymmetric fashion using a broad range of donor and acceptor compounds with a variety of chiral ligands.³

In 2004, a breakthrough in the catalytic enantioselective CA of Grignard reagents was reported from our laboratories⁴ using a catalyst based on Josiphos⁵ (**L1** or **L2**, Figure 1)

and CuBr·SMe₂. This catalytic system proved to be extremely efficient in the CA of Grignard reagents to α,β -

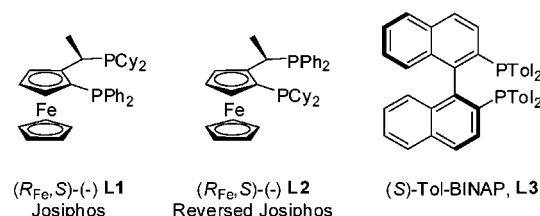


Figure 1. Diposphine ligands used in CA.

unsaturated enones^{4,6} and esters.⁷ More recently, Loh and co-workers reported an alternative catalyst based on Tol-BINAP and CuI for the enantioselective CA of Grignard reagents to α,β -unsaturated esters.⁸ Using this catalyst, Grignard reagents derived from secondary and bulky alkyl halides can be added with high enantioselectivities.

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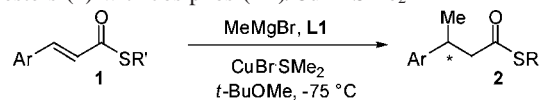
Despite this progress, an efficient catalyst for the addition of MeMgBr to α,β -unsaturated esters is still lacking. This impedes the introduction of one of the most common and valuable structural motifs in biologically relevant compounds like polydeoxypropionate chains.⁹

To address this issue, we recently developed the Josiphos/CuBr-catalyzed CA of Grignard reagents to α,β -unsaturated thioesters,¹⁰ which are more reactive and synthetically very versatile.¹¹ The application of this methodology in an iterative fashion has culminated in the construction of 1,3-oligomethyl (deoxypropionate) arrays used in the synthesis of mycosteric acid¹² and phthioceranic acid,¹³ both isolated from *Mycobacterium tuberculosis*. However, in spite of the wide applicability, this methodology presents two limitations: (1) addition of sterically hindered Grignard reagents proceeds with poor enantioselectivity and (2) aromatic substrates with substituents on the phenyl ring display low reactivity toward the addition of MeMgBr.

Herein, we report an extension of the catalytic protocol for the copper-catalyzed conjugate addition of MeMgBr to aromatic α,β -unsaturated thioesters using Josiphos/CuBr·SMe₂. We also report the high enantioselective copper catalyzed conjugate addition of MeMgBr and sterically demanding Grignard reagents to aromatic and aliphatic α,β -unsaturated thioesters using a new catalytic system based on Tol-BINAP/CuI.

Our initial efforts in broadening the substrate scope of the CA of Grignard reagents were focused on the reactivity and selectivity of the Josiphos/CuBr complex toward aromatic α,β -unsaturated thioesters (Table 1). In general, aryl-substituted substrates are less reactive toward the CA of Grignard reagents (see, for example, entry 1, 90% conversion

Table 1. CA of MeMgBr to Aromatic α,β -Unsaturated Thioesters (**1**) with Josiphos (**L1**)/CuBr·SMe₂^a



entry	1	Ar	R'	convn ^b (%)	yield ^c (%)	ee ^d (%)
1	1a	Ph	Me	90	65 (2a)	95 (S) ^e
2	1b	<i>p</i> -Cl-Ph	Me	95	60 (2d)	>99 (S) ^e
3	1d	<i>p</i> -Me-Ph	Et	75	33 (2f)	>99 (+)
4	1e	<i>p</i> -MeO-Ph	Et	35	24 (2g)	93 (+)

^a Conditions: **1** (1 equiv), MeMgBr (1.2 equiv), CuBr·SMe₂ (5 mol %), **L1** (6 mol %) in *t*-BuOMe at −75 °C, 12 h. ^b Determined by ¹H NMR. ^c Isolated yield. ^d Determined by chiral HPLC. ^e Absolute configuration determined by correlation with known compounds (see Supporting Information).

overnight) compared to aliphatic substrates, which give full conversion typically in 2–5 h.¹⁰ In order to increase the reactivity of the substrate, the substituent at the *para* position of the phenyl ring was varied. Reactions were typically carried out with 6 mol % of Josiphos ligand (**L1**), 5 mol % of CuBr·SMe₂, and 1.1 equiv of MeMgBr in *t*-BuOMe at −75 °C. The reactivity of **1b**, containing an electron-withdrawing substituent at the *para* position of the aromatic ring, did not increase significantly compared to unsubstituted cinnamic thioester **1a** (90% conversion, overnight). Surprisingly, the enantioselectivity increased to >99% (entry 2). Thioesters **1d** and **1e**, bearing electron-donating groups at the *para* position of the aromatic ring, proved to be even less reactive (75 and 35% conversion overnight) although the ee's remained at excellent levels.¹⁴

Since Josiphos/copper complexes are not active enough in the addition of MeMgBr to aromatic α,β -unsaturated thioesters, we screened several monodentate and bidentate phosphorus-containing chiral ligands and copper sources. Most catalysts employed gave low enantioselectivities, but the *in situ* prepared complex from CuI (1 mol %) and (*S*)-Tol-BINAP (1.1 mol %) catalyzed the 1,4-addition of MeMgBr to **1a** to reach, in 16 h at −70 °C in *t*-BuOMe,¹⁵ full conversion and excellent regio- and enantioselectivity (88% yield, >99:1, 1,4-addition versus 1,2-addition product, 94% ee; Table 2, entry 1). At higher temperature (−50 °C), full conversion was achieved in 8 h albeit with much lower enantioselectivity (40% ee). Increased ratios of ligand to metal (1.5:1 and 2:1) had no detectable effect on the ee of the reaction.¹⁶ As expected, this catalytic system also showed to be effective in the addition of EtMgBr to **1a**, affording **2b** in good yield and enantioselectivity (Table 2, entry 2). Remarkably, addition of bulky *i*-BuMgBr gave **2c** in good yield and enantioselectivity (Table 2, entry 3).

(14) It is worth noting that, in all cases, the isolated yields are rather low compared to the conversions; this may be due to partial decomposition of the starting material during the reaction.

(15) Reagent-grade *t*-BuOMe was used without further purification.

(16) These findings are in contrast with those of Loh and co-workers who reported an increase in ee when a 2:1 ratio of ligand/metal was used instead of a 1:1 ratio; see ref 8.

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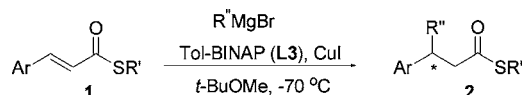
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Table 2. CA of Grignard Reagents ($R''\text{MgBr}$) to α,β -Unsaturated Thioesters **1**^a

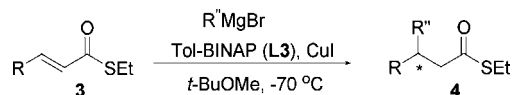
entry	1	Ar	R'	R''	convn ^b (%)	yield ^c (%)	ee ^d (%)
1	1a	Ph	Me	Me	>99	88 (2a)	94 (<i>R</i>) ^e
2	1a	Ph	Me	Et	>99	93 (2b)	92 (–) ^e
3	1a	Ph	Me	<i>i</i> -Bu	74	70 (2c)	80 (–)
4	1c	<i>p</i> -Cl-Ph	Et	Me	>99	93 (2e)	99 (–)
5	1d	<i>p</i> -Me-Ph	Et	Me	39	34 (2f)	99 (–)
6	1e	<i>p</i> -MeO-Ph	Et	Me	22	15 (2g)	96 (–)

^a Conditions: **1** (1 equiv), $R''\text{MgBr}$ (4 equiv), CuI (1 mol %), **L3** (1.1 mol %) in *t*-BuOMe at $-70\text{ }^{\circ}\text{C}$, 16 h. ^b Determined by GC–MS. ^c Isolated yield. ^d Determined by chiral HPLC. ^e Absolute configuration determined by correlation with known compounds (see Supporting Information).

To determine the scope of the Tol-BINAP/copper-catalyzed reaction with respect to substituents on the aromatic ring of the cinnamic thioester, we tested the addition of MeMgBr to **1c–e**. The reaction with activated substrate **1c** proceeded with excellent enantioselectivity and full conversion (Table 2, entry 4). Substrates **1d** and **1e**, bearing an electron-donating group, displayed high enantioselectivity but, unfortunately, low reactivity toward the addition of MeMgBr (39% and 22% conversion, respectively), which is no improvement compared to the use of Josiphos.

In view of these promising results with aromatic substrates, we turned our attention to the Tol-BINAP/copper catalyzed addition of Grignard reagents to aliphatic α,β -unsaturated thioesters. A variety of Grignard reagents could be added to substrate **3a** in good yields and enantioselectivities using the optimal conditions that were established for the aromatic substrates (Table 3). Gratifyingly, when linear alkyl Grignard reagents ($R = \text{Et}$ and *n*-Bu; entries 1 and 3) were used as nucleophiles, **4a** and **4c** were obtained with 80 and 74% ee, respectively. Moreover, for bulky Grignard reagents like *i*-PrMgBr and *i*-BuMgBr, enantioselectivities were found to be higher (65–94%; entries 2, 4, 8 and 9) than those obtained with the Josiphos/CuBr complex.¹⁰ Addition of sp^2 -hybridized Grignard reagent PhMgBr proceeded in good yield, but no enantioselectivity was observed (Table 3 entry 5).

The highly desirable addition of MeMgBr to aliphatic α,β -unsaturated thioesters was achieved with good yields and high enantioselectivities. Linear substrate **3c** underwent stereoselective addition of MeMgBr in 90% yield and 93% ee (Table 3, entry 7). For branched substrate **3b**, with $R = i\text{-Pr}$, the reaction proceeded with full conversion and excellent enantioselectivity (99% ee, Table 3, entry 6). Furthermore, this copper-catalyzed CA is also effective in the addition of MeMgBr to functionalized substrate **3d**, bearing a protected alcohol at the γ -position (95% yield and 83% ee; Table 3, entry 10).

Table 3. Tol-BINAP/CuI-Catalyzed CA of Grignard Reagents to α,β -Unsaturated Thioesters^{a,b}

entry	3	R	R''	yield ^c (%)	ee ^d (%)
1	3a	Me	Et	53 (4a) ^e	80 ^f (<i>S</i>) ^g
2	3a	Me	<i>i</i> -Pr	70 (4b)	66 ^f (–)
3	3a	Me	<i>n</i> -Bu	94 (4c)	74 ^f (<i>R</i>) ^g [90] ^h
4	3a	Me	<i>i</i> -Bu	88 (4d)	82 (+)
5	3a	Me	Ph	85 (4e)	0
6	3b	<i>i</i> -Pr	Me	82 (4b)	99 (–)
7	3c	<i>n</i> -Pent	Me	90 (4f)	93 ^f (–) [96] ^h
8	3c	<i>n</i> -Pent	<i>i</i> -Pr	89 (4g)	65 (–) [25] ^h
9	3c	<i>n</i> -Pent	<i>i</i> -Bu	95 (4h)	94 ⁱ (–) [15] ^h
10	3d	CH_2OTBDPS	Me	95 (4i)	83 (–) [98] ^h

^a Conditions: **1** (1 equiv), $R''\text{MgBr}$ (4 equiv), CuI (1 mol %), **L3** (1.1 mol %) in *t*-BuOMe at $-70\text{ }^{\circ}\text{C}$, 8 h. ^b All conversions >99% (GC–MS). ^c Isolated yield. ^d Determined by chiral GC or HPLC. ^e Volatile product. ^f Ee determined on the corresponding methyl ester. ^g Absolute configuration determined by correlation with known compounds (see Supporting Information). ^h Ee reported for the CA of Grignard reagents using Josiphos (6 mol %) and $\text{CuBr}\cdot\text{SMe}_2$ (5 mol %) in *t*-BuOMe at $-75\text{ }^{\circ}\text{C}$ (see ref 10). ⁱ Ee determined on the corresponding alcohol (see Supporting Information).

By way of comparison, we present in square brackets in Table 3 the enantioselectivities reported for the CA of Grignard reagents to α,β -unsaturated thioesters using Josiphos (**L1**, 6 mol %) and $\text{CuBr}\cdot\text{SMe}_2$ (5 mol %) in *t*-BuOMe at $-75\text{ }^{\circ}\text{C}$.¹⁰ From these results, we can point out that both catalytic systems are complementary. While slightly higher enantioselectivities are achieved with Josiphos ligand for the addition of primary linear Grignard reagents, Tol-BINAP turns out as the right choice for secondary or bulky organomagnesium compounds (see entries 3 and 7–10). γ -Functionalized substrate **3d** gives higher enantioselectivity when Josiphos is used as a ligand (see entry 10), whereas the crowded β -substituted aliphatic substrate **3b** only undergoes 1,4-addition with high enantioselectivity when the complex Tol-BINAP/CuI is used as catalyst (see entry 6).

In conclusion, this study shows that Tol-BINAP/CuI is a more active catalyst than Josiphos/CuBr in the conjugate addition of MeMgBr to cinnamic acid thioesters, giving excellent enantioselectivities for these reactions.

Moreover, Tol-BINAP/CuI allows the enantioselective addition of a wide variety of Grignard reagents, including relatively unreactive MeMgBr and bulky Grignard reagents, to aliphatic α,β -unsaturated thioesters. Catalyst loadings as low as 1.1 mol % are tolerated providing products in good yields and enantioselectivities up to 99%.

Acknowledgment. Financial support from the Dutch Ministry of Economics Affairs (ETT scheme; Grant Nos. EEKT-97107 and -99104). M.A.F.-I. thanks the Spanish Ministry of Education and Science for a postdoctoral

fellowship. We thank T. D. Tiemersma-Wegman (GC and HPLC, Stratingh Institute for Chemistry, University of Groningen) and A. Kiewiet (MS, Stratingh Institute for Chemistry, University of Groningen) for technical assistance. A generous gift of Josiphos from Solvias is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectroscopic data of the reaction products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL702425A