

# Copper(I) Thiolate Catalysts in Asymmetric Conjugate Addition Reactions

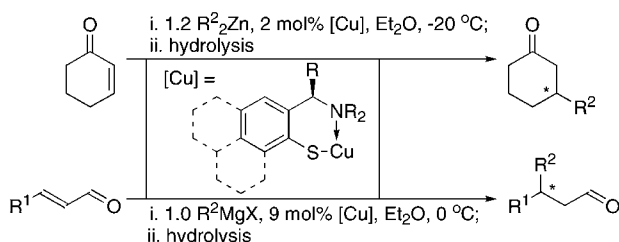
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Received March 23, 2004

## ABSTRACT



Full conversion and enantioselectivities up to 83% have been obtained in the conjugate addition reactions of diethyl zinc to Michael acceptors catalyzed by well-defined (chiral) copper(I) aminoarenethiolates. Interesting differences between organozinc or Grignard reagents have been found: for cyclic enones  $R_2Zn$  reagents afford better results, whereas earlier work showed that  $RMgX$  reagents react more selectively with acyclic enones.

Enantioselective copper-catalyzed 1,4-additions have been extensively studied.<sup>1</sup> Most of these studies involved the use of chiral ligands in the presence of copper(II) salts<sup>2</sup> or copper(I) complexes formed in situ, leaving salts (e.g., LiI) present during catalysis.<sup>3</sup> So far, only a few reports described the use of salt-free, well-defined, and fully characterized chiral copper(I) complexes as catalysts.<sup>4,5</sup> Salt-free prepared copper-

(I) aminoarenethiolates<sup>4</sup> **1a** and enantiopure **1b** (Figure 1) have been tested as catalysts in several types of C–C coupling reactions, e.g., 1,4-additions,<sup>6</sup> 1,6-additions,<sup>7</sup> cross-couplings,<sup>8</sup> and allylic substitutions.<sup>9</sup> In these initial studies we found that, in the 1,4-addition of Grignard reagents to  $\alpha,\beta$ -unsaturated enones, enantioselectivities up to 76% were

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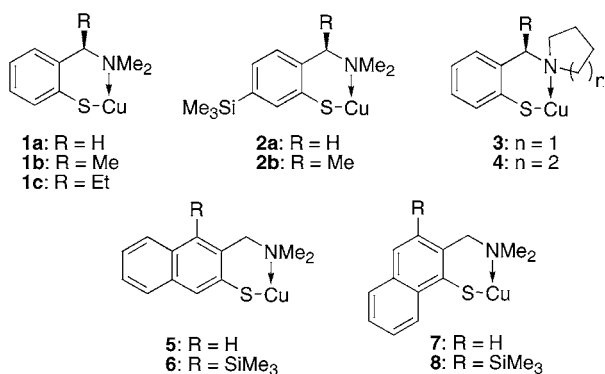
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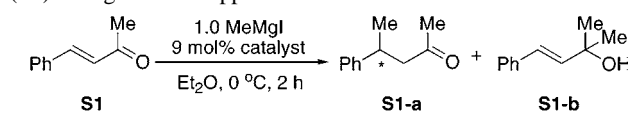
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**Figure 1.** Modified copper(I) aminoarenethiolates **1–8**.

achieved by using the enantiopure copper(I) aminoarenethiolate **1b** in catalytic amounts (Table 1).<sup>4,6</sup> These results

**Table 1.** Addition of MeMgI to *trans*-4-Phenylbuten-2-one (**S1**) Using Chiral Copper Aminoarenethiolates



entry	catalyst <sup>a</sup>	regioselectivity <sup>b</sup>	
		<b>S1-a</b> : <b>S1-b</b>	ee %, config
1	<b>1b</b>	>99:<1	76, <i>S</i>
2	<b>1c</b>	>99:<1	63, <i>S</i>
3	<b>2b</b>	>99:<1	72, <i>S</i>
4	<b>3</b>	94:6	70, <i>S</i>
5	<b>4</b>	95:5	50, <i>S</i>

<sup>a</sup> All catalysts have (*R*)-configuration. <sup>b</sup> Conversion was quantitative.

were obtained for acyclic enones, whereas for cyclic enones poor ee's and low selectivities were found. For example, for the addition of *n*-BuMgI to cyclohexenone, an ee of 23% was obtained with a selectivity (1,4- vs 1,2-addition) of 64%.<sup>8</sup> Interestingly, when RLi reagents were tested instead of RMgX, no ee was found for both acyclic and cyclic enones.<sup>10</sup> As recently high selectivities in Michael additions with R<sub>2</sub>-Zn reagents have been achieved,<sup>2</sup> we decided to test our chiral catalysts also in zinc-mediated 1,4-additions.

In the present study we report on the addition of diethylzinc to a variety of Michael acceptors in the presence of catalytic amounts of well-defined, salt-free copper(I) aminoarenethiolates **1–8** (Figure 1).

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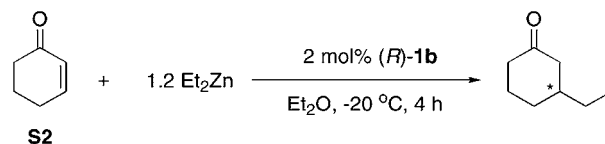
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A new set of modified complexes was tested with ligand variations at the benzylic position (**1c**) and the amine functionality; dimethylamine was replaced for either a pyrrolidinyll (**3**) or a piperidyl ring (**4**). Furthermore, trimethylsilyl groups were introduced *meta* to the thiocopper moiety (**2a**, **2b**, **6**, and **8**). Another modification was the use of a naphthalene instead of a benzene backbone (**5–8**).<sup>11</sup>

First, chiral catalysts **1c**, **2b**, **3**, and **4** were tested in the Michael addition of MeMgI to *trans*-4-phenylbuten-2-one (**S1**) (Table 1).<sup>6</sup> Complex **1b** proved to be the best catalyst under these conditions. Catalysts **3** and **4** gave slightly lower regioselectivity and showed partial 1,2-product formation.

For the diethylzinc addition to Michael acceptors, frequently applied conditions, i.e., 2 mol % Cu complex for 4 h at –20 °C, were used.<sup>1,2</sup> For 2-cyclohexen-1-one (**S2**) full conversion and an enantiomeric excess of 83% were achieved with catalyst **1b** (Table 2).

**Table 2.** Addition of Et<sub>2</sub>Zn to 2-Cyclohexen-1-one (**S2**) Using Catalyst (*R*)-**1b**



entry	solvent	additive	conversion (%)	ee %, config
1	Et <sub>2</sub> O		>99	83, <i>R</i>
2	Et <sub>2</sub> O	LiI	85	15, <i>R</i>
3	Et <sub>2</sub> O <sup>b</sup>		3	13, <i>R</i>
4	toluene		90	70, <i>R</i>
5	THF		23	10, <i>R</i>

<sup>a</sup> Selective to 1,4-product. <sup>b</sup> Me<sub>2</sub>Zn instead of Et<sub>2</sub>Zn

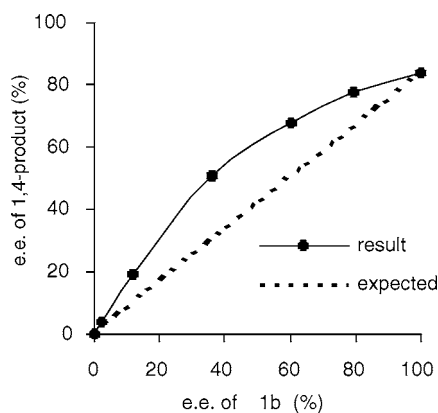
In contrast to the formation of the (*S*)-enantiomer of the 1,4-product when reacting MeMgI with **S1** catalyzed by (*R*)-**1b**, addition of MeMgI or Et<sub>2</sub>Zn to enone **S2** resulted in the preferential formation of the (*R*)-enantiomer. An additive such as LiI (1 equiv) resulted in slower reaction rates and a drastic drop in ee (entry 2). The addition of Me<sub>2</sub>Zn to **S2** instead of Et<sub>2</sub>Zn was extremely slow.<sup>12</sup> Variations in solvent indicated that diethyl ether was the best solvent under these conditions; the reaction rate in THF was much slower, while the ee was lower too. However, for entries 2–5 the reaction is still selective to the 1,4-product.

The influence of the ee of the catalyst on the ee of the 1,4-product was studied for the **1b**-catalyzed addition of Et<sub>2</sub>Zn to cyclohexenone (**S2**) in diethyl ether (Figure 2).

A positive correlation ((+)-NLE) was observed between the ee of catalyst **1b** and the ee of the 1,4-product (Figure 2). Both positive and negative NLE (= nonlinear effect) relationships have been observed for Cu-catalyzed additions

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**Figure 2.** Nonlinear relation between the ee of catalyst **1b** and the ee of the 1,4-product in the Et<sub>2</sub>Zn addition to cyclohexenone.

of organozinc or Grignard reagents to enones.<sup>3b,4,13,14</sup> Especially the **1b**-catalyzed addition of MeMgI to **S1** was very complex.<sup>13a</sup>

Subsequently, complexes **2–8** were tested using the same protocol as applied for **1b** in diethyl ether (cf. Table 3).

**Table 3.** Reaction of Et<sub>2</sub>Zn with Substrates **S1–S4**, with 2 mol % of Cu(SAr) Catalyst (**1–8**)

entry	catalyst )		1,4-addition product (yield (%), <sup>a</sup> ee (%), <sup>b</sup> configuration)			
	achiral	( <i>R</i> )-enantiomer	<b>S1</b> <sup>a</sup>	<b>S2</b> <sup>a</sup>	<b>S3</b> <sup>a</sup>	<b>S4</b> <sup>a</sup>
1		<b>1b</b>	48, 59, <i>S</i>	>99, 83, <i>R</i>	86, 35, (+)	99, 22, <i>S</i>
2		<b>1c</b>	39, 3, <i>S</i>	>99, 40, <i>R</i>	71, 16, (–)	96, 10, <i>S</i>
3		<b>2b</b>	67, 62, <i>S</i>	>99, 81, <i>R</i>	87, 37, (+)	97, 15, <i>S</i>
4		<b>3</b>	10, 28, <i>S</i>	52, 6, <i>R</i>	48, 8, (–)	93, 5, <i>S</i>
5		<b>4</b>	17, 15, <i>S</i>	98, 63, <i>R</i>	35, 12, (–)	79, 0, -
6	<b>1a</b>		60	99	89	95
7	<b>2a</b>		84	>99	96	96
8	<b>5</b>		9	72	50	90
9	<b>6</b>		44	99	84	96
10	<b>7</b>		41	93	93	96
11	<b>8</b>		39	93	88	98

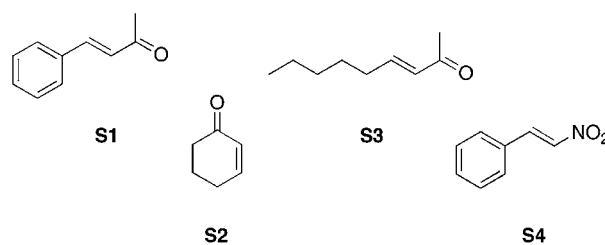
<sup>a</sup> The yield of 1,4-product was determined by GC–MS. <sup>b</sup> The ee was determined by chiral GC on a LipodexE (25 m × 0.25 mm) capillary column.

Besides acyclic enone **S1** and cyclic enone **S2**, *trans*-3-nonen-2-one (**S3**), and *trans*-β-nitrostyrene (**S4**) were also tested (Figure 3).

The results of the both chiral and achiral complexes in catalysis are listed in Table 3 (entries 1–11). For 2-cyclohexen-1-one (**S2**) and *trans*-β-nitrostyrene (**S4**) (almost) full conversion was obtained. In nearly all cases, the catalysts showed a slower reaction rate for *trans*-4-phenylbuten-2-one (**S1**) and *trans*-3-nonen-2-one (**S3**). Irrespective of this slow reaction rate, the selectivity toward the 1,4-product is

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**Figure 3.** Substrates **S1–S4** used in this work.

always very high. For **S2** the selectivity was 100%. For substrates **S1**, **S3**, and **S4** the selectivity is larger than 95%. **S1** and **S3** afford 1–5% of side products that were identified as the Michael adduct of the resulting enolate to the starting enone. For **S4** the formation of two side products (1–5%) is observed. One of the side products could be identified as arising from an ipso-type substitution (vinyl substitution).<sup>15</sup>

Since all reactions were quenched after the same period (4 h) the reaction rates can be compared. The reaction rates for these conditions increase for the substrates in the order **S1** < **S3** < **S4** ≈ **S2**. The best results are obtained for catalysts **1a,b** and **2a,b**. The worse performance of catalysts **3**, **4**, and **5** can be explained by low solubility of these complexes and the intermediates in diethyl ether. Complexes **1b**, **2a,b**, and **6–8** are very soluble in diethyl ether, whereas **1a** is moderately soluble.

Differences in reaction rate and enantioselectivity can also be explained by the differences in the CH(R)NZ<sub>2</sub> substituent. For instance, the conversion and enantioselectivity of all substrates with **1b** and **2b** are higher than for **1c**, where R = Et instead of Me. Catalysts **3** and **4**, where Z<sub>2</sub> = (CH<sub>2</sub>)<sub>4</sub> and (CH<sub>2</sub>)<sub>5</sub>, respectively, have more steric bulk around the catalytic center than **1b**. Especially for the acyclic substrates **S1** and **S3** this has a negative effect on both the reaction rate and enantioselectivity.

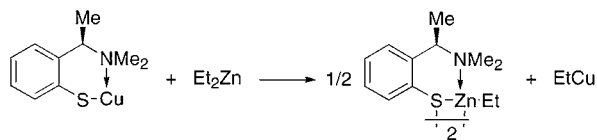
For substrates **S1**, **S2**, and **S4** the respective enantiomers formed in excess have the same configuration. However, the configuration of the product resulting from **S3** is dependent on the catalyst.

Whereas **1b** and **2b** afford the (+)-enantiomer of substrate **S3** in excess, **1c**, **3**, and **4**, each having more bulky amino substituents than **1b** and **2b**, afford the (–)-enantiomer of substrate **S3**. Of the achiral catalysts, **2a** gives the best yields for all substrates.

The observation of a positive NLE indicates that aggregate formation influences the rate-determining step in the 1,4-addition reaction. Several preliminary experiments were carried out to get information about the nature of possible intermediates. Stoichiometric mixing of **1b** with diethylzinc in diethyl ether resulted in the formation of a soluble complex, which at room temperature decomposed, leaving a Cu<sup>0</sup> mirror and a black precipitate. Analysis of the supernatant revealed that [Zn(SAr)Et]<sub>2</sub> had been formed

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quantitatively. These observations can be explained by a transmetalation reaction, which results in the formation of known  $[\text{Zn}(\text{SAr})\text{Et}]_2$  and  $\text{EtCu}$  (Figure 4). The latter is



**Figure 4.** Stoichiometric mixing of **1b** with  $\text{Et}_2\text{Zn}$ .

thermally unstable and decomposes to yield metallic copper.

The NLE behavior of the addition of diethylzinc to benzaldehyde in the presence of zinc bis(aminoarenethiolate) is comparable to that of the **1b**-catalyzed addition of diethylzinc to **S2**.<sup>16</sup> A mechanism involving dimeric resting states of the type  $[\text{Zn}(\text{SAr})\text{Et}]_2$  could explain the positive NLE in the latter reaction.

Complex  $(R)\text{-}[\text{Zn}(\text{SAr})\text{Et}]_2$  was prepared<sup>16</sup> and tested as catalyst (2 mol %) in the addition reaction of  $\text{Et}_2\text{Zn}$  to **S2**. In the standard reaction time (4 h) used in this study, a conversion of only 8% was achieved to a racemic 1,4-addition product. This result shows that the zinc thiolate as

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such cannot catalyze this reaction and indicates that a mixed copper–zinc thiolate complex is the active intermediate. Interestingly, the use of a combination of  $(R)\text{-}[\text{Zn}(\text{SAr})\text{Et}]_2$  (2 mol %) with  $(R)\text{-1b}$  (2 mol %) led to full conversion to the 1,4-product, but with a somewhat lower ee (65% ee (*R*) vs 83% ee (*R*)). The same experiment, but now using  $(R)\text{-}[\text{Zn}(\text{SAr})\text{Et}]_2$  and  $(S)\text{-1b}$  (both 2 mol %) as a mixed catalyst, again gave full conversion to the 1,4-product, now with 15% ee (*S*). The addition of  $(R)\text{-}[\text{Zn}(\text{SAr})\text{Et}]_2$  to the **1b**-catalyzed reaction seemed to slow the reaction and made it less selective.

It was shown that there are significant differences between the reactivity of Grignard and diorganozinc reagents to enones catalyzed by copper(I) aminoarenethiolates. For a cyclic enone, such as **S2**, the use of diethylzinc in the presence of copper(I) aminoarenethiolates is preferred, in contrast to acyclic enones (**S1**) where Grignard reagents give the best result. For the Grignard addition to acyclic enones a multishaped NLE has been reported, whereas the present study shows a positive NLE for the diethylzinc addition to cyclic enones. The latter observation could be explained by a mechanism involving dimeric resting states of the type  $[\text{Zn}(\text{SAr})\text{Et}]_2$ .

**Acknowledgment.** Financial support from NWO/CW and COST D12 is gratefully acknowledged.

**Supporting Information Available:** Experimental details and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL049457U