

Copper(I) Thiolate Catalysts in Asymmetric Conjugate Addition Reactions

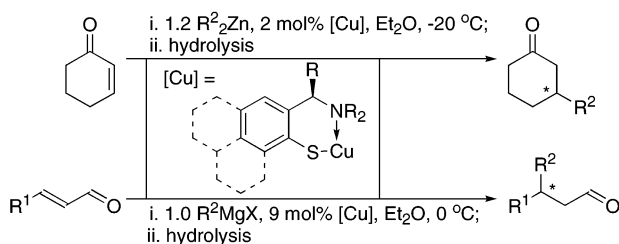
Anne M. Arink,[†] Thijs W. Braam,[†] Roy Keeris,[†] Johann T. B. H. Jastrzebski,[†]
Cyril Benhaim,[‡] Stéphane Rosset,[‡] Alexandre Alexakis,^{*,‡} and
Gerard van Koten^{*,†}

Debye Institute, Department of Metal-Mediated Synthesis, Utrecht University,
Padualaan 8, 3584 CH Utrecht, The Netherlands, and Department of Organic
Chemistry, University of Geneva, 30, Quai Ernest Ansermet,
1211 Geneva 4, Switzerland

g.vankoten@chem.uu.nl; alexandre.alexakis@chiorg.unige.ch

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 R₂Zn 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.¹ Most of these studies involved the use of chiral ligands in the presence of copper(II) salts² or copper(I) complexes formed in situ, leaving salts (e.g., LiI) present during catalysis.³ So far, only a few reports described the use of salt-free, well-defined, and fully characterized chiral copper(I) complexes as catalysts.^{4,5} Salt-free prepared copper-

(I) aminoarenethiolates⁴ **1a** and enantiopure **1b** (Figure 1) have been tested as catalysts in several types of C–C coupling reactions, e.g., 1,4-additions,⁶ 1,6-additions,⁷ cross-couplings,⁸ and allylic substitutions.⁹ In these initial studies we found that, in the 1,4-addition of Grignard reagents to α,β -unsaturated enones, enantioselectivities up to 76% were

[†] Utrecht University.

[‡] University of Geneva.

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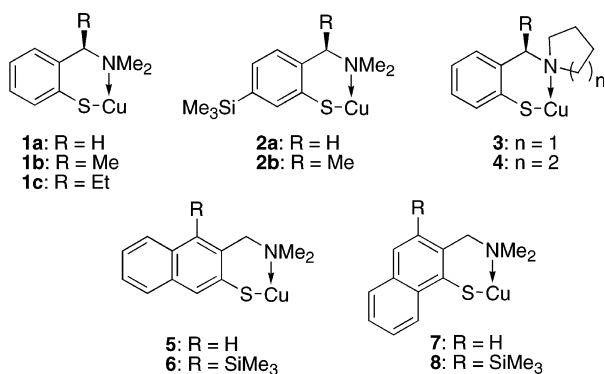
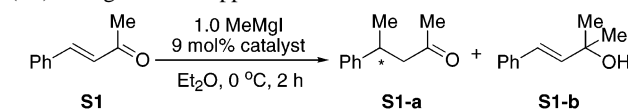


Figure 1. Modified copper(I) aminoarenethiolates **1–8**.

achieved by using the enantiopure copper(I) aminoarenethiolate **1b** in catalytic amounts (Table 1).^{4,6} These results

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



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

^a All catalysts have (*R*)-configuration. ^b 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%.⁸ Interestingly, when RLi reagents were tested instead of RMgX, no ee was found for both acyclic and cyclic enones.¹⁰ As recently high selectivities in Michael additions with R₂-Zn reagents have been achieved,² 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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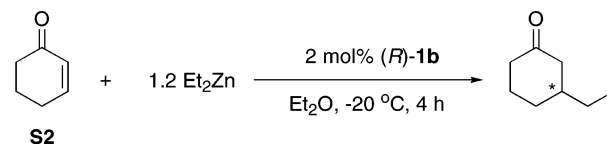
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A new set of modified complexes was tested with ligand variations at the benzylic position (**1c**) and the amine functionality; dimethylamine was replaced for either a pyrrolidinyll (**3**) or a piperidyl ring (**4**). Furthermore, trimethylsilyl 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**).¹¹

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).⁶ 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 $-20^\circ C$, were used.^{1,2} 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 Et₂Zn to 2-Cyclohexen-1-one (**S2**) Using Catalyst (*R*)-**1b**



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

^a Selective to 1,4-product. ^b Me₂Zn instead of Et₂Zn

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 Et₂Zn 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 Me₂Zn to **S2** instead of Et₂Zn was extremely slow.¹² 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 Et₂Zn 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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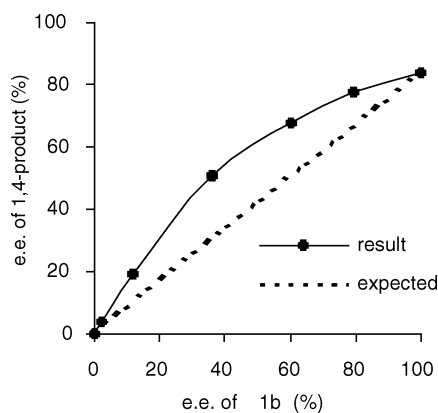


Figure 2. Nonlinear relation between the ee of catalyst **1b** and the ee of the 1,4-product in the Et₂Zn addition to cyclohexenone.

of organozinc or Grignard reagents to enones.^{3b,4,13,14} Especially the **1b**-catalyzed addition of MeMgI to **S1** was very complex.^{13a}

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

Table 3. Reaction of Et₂Zn with Substrates **S1–S4**, with 2 mol % of Cu(SAr) Catalyst (**1–8**)

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

^a The yield of 1,4-product was determined by GC–MS. ^b 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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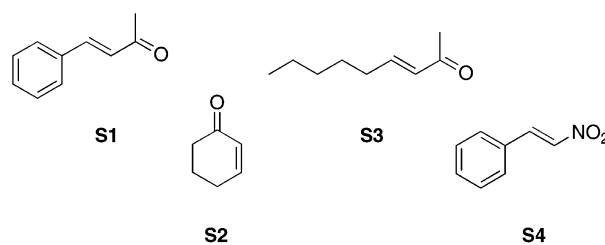


Figure 3. Substrates **S1–S4** used in this work.

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 (vinylic substitution).¹⁵

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)NZ₂ 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 Z₂ = (CH₂)₄ and (CH₂)₅, 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 Cu⁰ mirror and a black precipitate. Analysis of the supernatant revealed that [Zn(SAr)Et]₂ 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 EtCu (Figure 4). The latter is

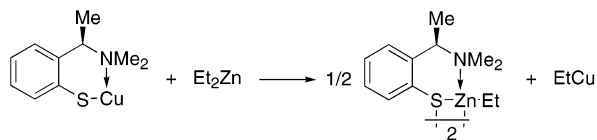


Figure 4. Stoichiometric mixing of **1b** with Et_2Zn .

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**.¹⁶ 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 prepared¹⁶ and tested as catalyst (2 mol %) in the addition reaction of Et_2Zn 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(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