

# Asymmetric Induction in the Arenethiolatocopper(I)-Catalyzed Substitution Reaction of Grignard Reagents with Allylic Substrates

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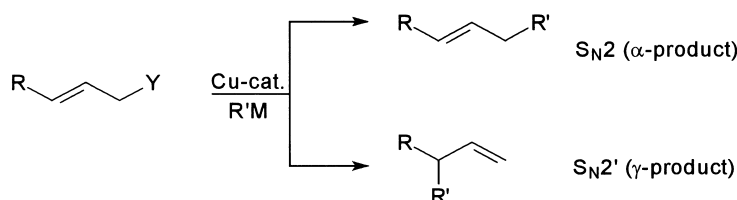
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Received 13 December 1999; accepted 10 January 2000

**Abstract**—The influence of some experimental parameters on the regio- and enantioselectivity in the  $\gamma$ -selective substitution reaction of Grignard reagents RMgX with acyclic allylic acetates catalyzed by the arenethiolatocopper(I) complex (*S*)-**1** was studied. When more bulky arenethiolatocopper(I) complexes than (*S*)-**1** were employed in a reaction of allylic acetate **3** with *n*-BuMgI, the enantioselectivities observed for the  $\gamma$ -product were lower. With an arenethiolatocopper(I) catalyst prepared in situ, several Grignard reagents were studied in a substitution reaction with acetate **2**. Compared to *n*-BuMgI, more bulky Grignard reagents gave no improvement of the enantioselectivity in the formation of the  $\gamma$ -product. © 2000 Elsevier Science Ltd. All rights reserved.

Metal-mediated carbon–carbon bond formation has become a versatile synthetic methodology in contemporary organic chemistry.<sup>1</sup> Copper-catalyzed reactions constitute an important class, and well-known examples include Michael addition reactions and cross-coupling reactions of organometallic reagents with organic halides or allylic substrates.<sup>2</sup> The allylic substitution reaction has attracted much attention and several methods have been developed for control of the regio- and stereochemistry in this type of reactions.<sup>3–6</sup> The leaving group can be displaced either in an  $\alpha$ (S<sub>N</sub>2) or  $\gamma$ (S<sub>N</sub>2') fashion by the organometallic reagent (Scheme 1).

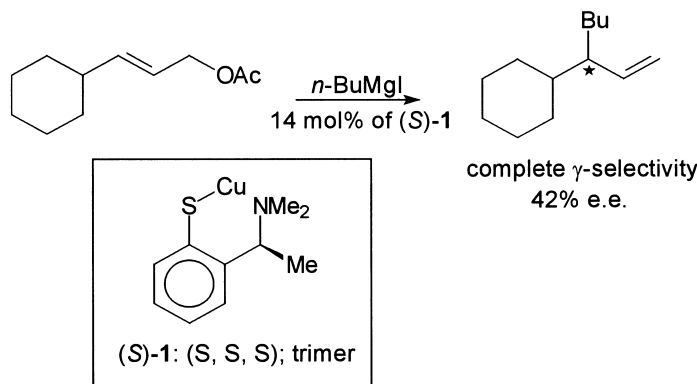
Although asymmetric induction in copper-promoted Michael additions to  $\alpha,\beta$ -unsaturated systems is quite well established,<sup>7–9</sup> the corresponding enantioselective versions of organocopper-based allylic substitution reactions are less developed. Asymmetric S<sub>N</sub>2' substitution of allylic substrates with a chiral leaving group by organocuprates has been reported<sup>10</sup> but catalytic procedures employing chiral ligands on copper are scarce.<sup>11,12</sup> In 1995, we described the first example on the use of a chiral copper(I) complex as a catalyst in the cross-coupling of Grignard reagents with allylic substrates.<sup>11</sup> E.e.'s up to 42% were



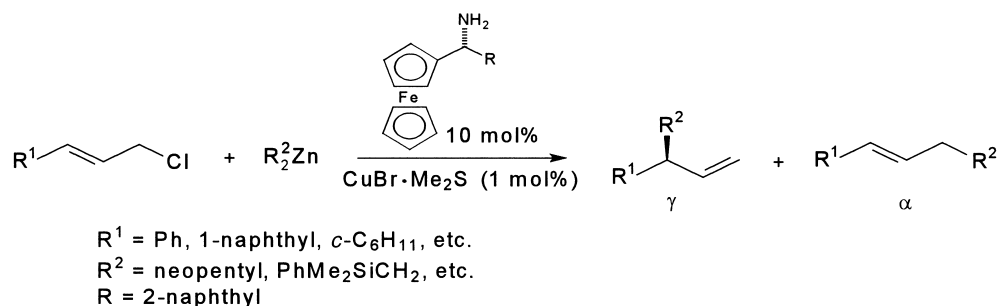
**Scheme 1.** Copper-catalyzed allylic substitution reactions.

**Keywords:** asymmetric induction; copper catalysis; allylic substitution; cross-coupling.

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**Scheme 2.** An asymmetric allylic substitution reaction catalyzed by a chiral arenethiolatocopper(I) complex.



**Scheme 3.** Copper(I)-catalyzed asymmetric allylic substitution reactions according to Dübner and Knochel.<sup>12</sup>

obtained in the reaction of allylic acetates with *n*-BuMgI catalyzed by chiral arenethiolatocopper(I) complex (*S*)-**1** (Scheme 2). Recently, chiral ferrocenyl amine ligands were employed in copper-catalyzed enantioselective substitution of allyl chlorides with diorganozinc compounds (Scheme 3).<sup>12</sup> The alkylated products were obtained in up to 87% e.e. with good  $S_N2'$  selectivity but the reaction is limited to sterically hindered dialkylzinc reagents.

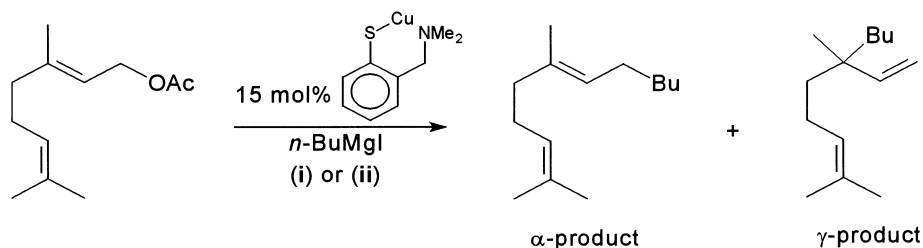
In addition to our earlier work with (*S*)-**1** as a catalyst,<sup>11</sup> we now wish to report on a more detailed study of the asymmetric cross-coupling reaction of Grignard reagents  $R'MgX$  with acyclic allylic substrates  $RCH=CHCH_2Y$ , catalyzed by this type of copper complexes. We have further investigated the experimental parameters for these reactions. Various Grignard reagents  $R'MgX$  have been investigated in the allylic substitution reactions as well as the influence of different arenethiolato ligands in the catalyst. We also include the results obtained with a catalyst

prepared in situ from an arenethiol and a copper salt under various conditions.

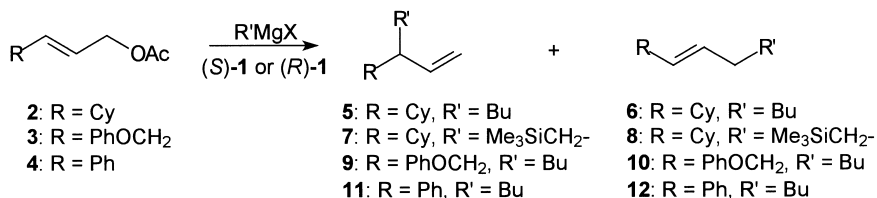
## Results and Discussion

### Reactions with preformed arenethiolatocopper(I) complexes

We started our investigations with arenethiolatocopper(I) complex (*S*)-**1** which was prepared from (–)-(*S*)- $\alpha$ -methylbenzylamine according to a literature procedure.<sup>13</sup> It was previously shown that the regioselectivity of the reaction between geranyl acetate and *n*-BuMgI catalyzed by an achiral arenethiolatocopper(I) complex can be tuned to either  $\alpha$  or  $\gamma$  substitution by variation of the reaction conditions (Scheme 4).<sup>14</sup> For the present study, using (*S*)-**1**, the  $\gamma$ -selective reaction conditions were chosen. Thus, the reactions were performed in diethyl ether at 0°C. The



**Scheme 4.** Selectivity for either the  $\alpha$ - or  $\gamma$ -product in an allylic substitution reaction of geranyl acetate by varying the reaction conditions: (i): Et<sub>2</sub>O, 0°C, 120 min addition time of *n*-BuMgI, 100%  $\gamma$ -product; (ii): THF, –30°C, 5 min addition time of *n*-BuMgI, 100%  $\alpha$ -product.

**Table 1.** Influence of the addition method and the Grignard reagent (n.det.=not detected)

Entry	Substrate	R'MgX	Mol% <b>1</b> <sup>a</sup>	AM <sup>b</sup>	Yield (%) <sup>c</sup>	$\alpha$ : $\gamma$ Ratio <sup>d</sup>	E.e. of $\gamma$ (%) <sup>e</sup>	$[\alpha]_D$ (°) <sup>e</sup>
1	<b>2</b>	<i>n</i> -BuMgI	15 ( <b>R</b> )	A	100 (88)	0:100	41 ( <b>5</b> )	-4.5
2	<b>2</b>	<i>n</i> -BuMgI	100 ( <b>S</b> )	A	100	0:100	45 ( <b>5</b> )	+4.8
3	<b>2</b>	<i>n</i> -BuMgBr	15 ( <b>R</b> )	A	(67) <sup>f</sup>	0:100	50 ( <b>5</b> ) <sup>g</sup>	-4.9
4	<b>2</b>	Me <sub>3</sub> SiCH <sub>2</sub> MgI	15 ( <b>R</b> )	A	(30) <sup>f</sup>	0:100	53 ( <b>7</b> )	n.det.
5	<b>2</b>	<i>n</i> -BuMgI	14 ( <b>S</b> )	C	100	0:100	42 ( <b>5</b> )	+4.4
6	<b>2</b>	<i>n</i> -BuMgI	20 ( <b>S</b> )	C	100	0:100	41 ( <b>5</b> )	+4.3
7	<b>3</b>	<i>n</i> -BuMgI	13 ( <b>S</b> )	A	100	0:100	34 ( <b>9</b> )	n.det.
8	<b>3</b>	<i>n</i> -BuMgI	15 ( <b>S</b> )	B	100	0:100	18 ( <b>9</b> )	n.det.
9	<b>3</b>	<i>n</i> -BuMgI	13 ( <b>S</b> )	C	100	0:100	30 ( <b>9</b> )	n.det.
10	<b>4</b>	<i>n</i> -BuMgI	15 ( <b>R</b> )	A	100	0:100	28 ( <b>11</b> )	-10.5

<sup>a</sup> Amount of **1** based on monomeric copper units.

<sup>b</sup> AM=addition method; Method A: The Grignard reagent (1.25 equiv.) was added to a solution of **1** and allylic substrate (1 equiv.) in diethyl ether at 0°C. Method B: The allylic acetate (1 equiv.) was added slowly to a solution of **1** and *n*-BuMgI (1.25 equiv.) in diethyl ether at 0°C. Method C: The allylic acetate and *n*-BuMgI were added separately within 120 min to a solution of **1** in diethyl ether at 0°C.

<sup>c</sup> Unless otherwise stated; substrate **2**: yield of **5** determined by GC and <sup>1</sup>H NMR. Substrate **3** or **4**: yield of **9** or **11** determined by GC. Isolated yields in parentheses.

<sup>d</sup>  $\alpha$ : $\gamma$  ratio determined by GC.

<sup>e</sup> E.e. of **5** determined by optical rotation ( $[\alpha]_D = -9.4$  corresponds to 88% e.e. of *R*-enantiomer<sup>10a</sup>). E.e. of **9** determined by HPLC. E.e. of **7** and **11** determined by GC.

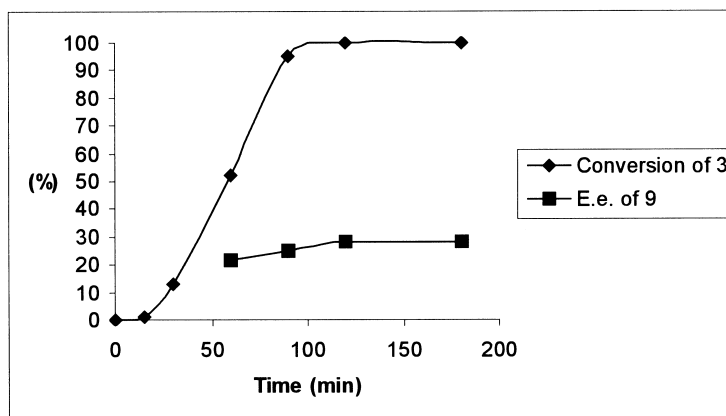
<sup>f</sup> Only isolated yield was determined.

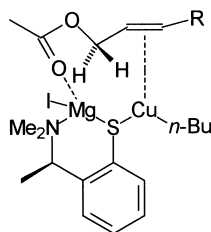
<sup>g</sup> The e.e. was determined by GC. The e.e. determined by optical rotation was 46%. In all cases GC analysis gave somewhat higher e.e. values than obtained by measuring the optical rotation.

influence of some reaction parameters on the yield and asymmetric induction of the  $\gamma$ -product was then studied with the use of allylic acetates **2**, **3** and **4** (Table 1).

The order of addition of the Grignard reagent and the allylic acetate has an influence on the outcome of the reaction (Table 1). Three different addition methods were studied. The Grignard reagent was added slowly (120 min) to a solution of the catalyst and the substrate (method A), or the substrate was added slowly to a solution of the catalyst and the Grignard reagent (method B). In a third addition method the substrate and the Grignard reagent were added

separately, at the same rate, to the reaction mixture (method C). Methods A and C investigated with (*E*)-3-cyclohexyl-2-propenylacetate (**2**)<sup>4d</sup> resulted in all cases in regioselective formation of the  $\gamma$ -product (Entries 1–6). Both methods afforded  $\gamma$ -product **5** with a significant e.e., 42% e.e. with method C and 41% e.e. with method A, respectively. The e.e. obtained with method A could be improved to 45% by using one equivalent of (*S*)-**1** (Entry 2). When *n*-BuMgBr was employed instead of *n*-BuMgI, the e.e. increased to 50% (Entry 3). The substitution reaction with the bulky Me<sub>3</sub>SiCH<sub>2</sub>MgI gave  $\gamma$ -product **7** with 53% e.e (Entry 4). However, the yield of **7** in the latter case was low due to

**Figure 1.** Reaction time vs. conversion of **3** and e.e. of **9**.



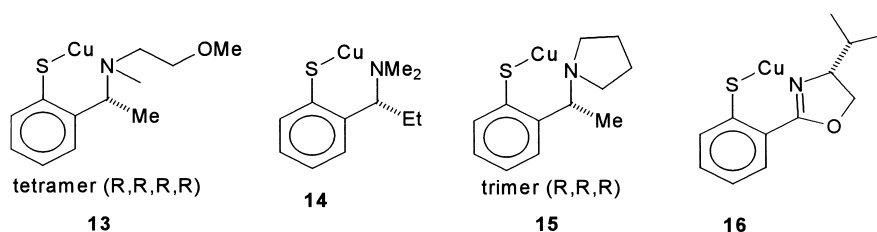
**Figure 2.** Proposed intermediate in arenethiolatocopper(I)-catalyzed substitution reactions of allylic acetates.

incomplete conversion of **2**. With (*E*)-1-acetoxy-4-phenoxy-2-butene (**3**)<sup>4b,15</sup> as substrate, all three methods afforded  $\gamma$ -product **9** with complete chemo- and regioselectivity (Entries 7–9). Methods A and C proved to be superior to method B which gave the same regioselectivity, but a lower enantioselectivity (Entry 8). Since the results obtained with methods A and C are almost equal, the experimentally easier addition method A was used exclusively in the further experiments.

Both substrates **2** and **3** gave the substitution product with complete  $\gamma$ -selectivity and a similar enantioselectivity. In order to study the influence of the substituent R in more detail, we employed *trans*-cinnamyl acetate (**4**) as substrate. Compounds of this type are of special interest since it is known that a conjugated double bond in the allylic substrate favors formation of the  $\alpha$ -product ( $S_N2$ -substitution).<sup>16</sup> However, the reaction between **4** and *n*-BuMgI using addition method A with 15 mol% of (*R*)-**1** as catalyst resulted in complete conversion to the  $\gamma$ -substitution product 3-phenyl-1-heptene (**11**) which was formed with 28% e.e.

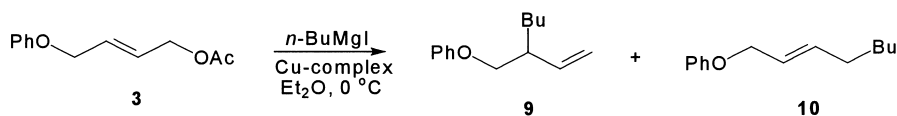
Using addition method A, we followed the progress of the reaction of **3** with *n*-BuMgI catalyzed by 15 mol% of complex (*S*)-**1**. Samples of the reaction mixture were collected at regular time intervals and the conversion of **3** and the e.e. of  $\gamma$ -product **9** were determined. The results are presented in Fig. 1. At the beginning the reaction is slow and only 1% conversion of **3** is obtained after 15 min. However, after about 20 min, the reaction becomes faster and the conversion then increases approximately linearly with time. The reaction reaches completion after 120 min. The e.e. of **9** increases from 22% after 60 min addition time, to 28% after 120 min addition time. The results indicate that catalysis does not really start until at least one equivalent (or may be even two equivalents) of the Grignard reagent is present relative to the amount of catalyst, i.e. the key-intermediate will at least have one molecule of Grignard reagent bound per copper center. The allylic acetate will then coordinate preferably with either the *re* or the *si*-face of the double bond to give the earlier proposed catalytic intermediate (Fig. 2).<sup>11</sup>

In order to investigate the influence of the chiral ligand in the copper-catalyzed allylic substitution reactions, different arenethiolatocopper(I) complexes (Fig. 3) were prepared and tested in the reaction of acetate **3** with *n*-BuMgI. Complex **13** (tetramer) was prepared starting from (+)-(*R*)- $\alpha$ -methylbenzylamine via monomethylation of the amine moiety followed by introducing the methoxy-arm according to a literature procedure.<sup>13c</sup> Complex **14** was prepared starting from (+)-(*R*)- $\alpha$ -ethylbenzylamine (e.e. 90%), obtained by the enantioselective addition of diethyl zinc to benzaldehyde followed by conversion of the hydroxyl group into an amine function by standard methods.<sup>17</sup> The synthesis of complex **15** was performed in an analogous way



**Figure 3.** Chiral arenethiolatocopper(I) complexes applied in asymmetric substitution reactions of **3**.

**Table 2.** Substitution reactions of **3** catalyzed by different types of chiral arenethiolatocopper(I) complexes (method A: *n*-BuMgI (1.25 equiv.) added within 120 min to a solution of **3** (1 equiv.) and 15 mol% of copper(I) complex (based on monomeric copper units) in Et<sub>2</sub>O at 0°C)



Entry	Cu-complex	Conversion (%) <sup>a</sup>	Yield of <b>9</b> + <b>10</b> (%) <sup>a</sup>	$\alpha$ : $\gamma$ ( <b>10</b> : <b>9</b> ) Ratio <sup>a</sup>	E.e. of <b>9</b> (%) <sup>b</sup>
1	( <i>S</i> )- <b>1</b>	100	100	0:100	34
2	<b>13</b>	100	95	5:95	4
3	<b>14</b>	100	100	0:100	12
4	<b>15</b>	100	86 <sup>c</sup>	0:100	13
5	<b>16</b>	95	95	2:98	0

<sup>a</sup> Conversion, yield and  $\alpha$ : $\gamma$  ratio determined by GC and <sup>1</sup>H NMR.

<sup>b</sup> E.e. determined by HPLC.

<sup>c</sup> Isolated yield after purification by column chromatography.

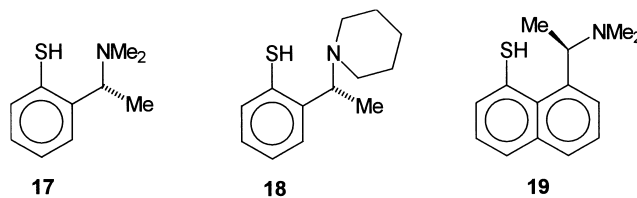


Figure 4. Structure of the ligands employed in the in situ preparation of arenethiolatocopper(I) catalysts.

as described for (*S*)-**1**.<sup>13c</sup> The intermediates were synthesized in accordance with a literature procedure.<sup>17b</sup> The structure of **15** was determined by X-ray crystallography and was found to consist of trimeric units.<sup>18</sup> The arenethiolatocopper(I) complex **16**, with a chiral isopropyl containing oxazoline moiety, was prepared according to a literature procedure starting from (–)-(*S*)-valinol.<sup>19</sup>

Table 2 shows the results obtained with these catalysts. Whereas complex (*S*)-**1** gave the  $\gamma$ -product with complete selectivity in 34% e.e. (Entry 1), complex **13** gave the substitution product in an  $\alpha$ : $\gamma$  ratio of 5:95 (**10**:**9**) with only 4% e.e. for the  $\gamma$ -product (Entry 2). Complex **14**, with an ethyl group at the chiral carbon center, gave a selective formation of the  $\gamma$ -product with an e.e. of 12% (Entry 3). Complex **15**, with a pyrrolidine ring, also gave a completely  $\gamma$ -selective reaction. However, the e.e. of the  $\gamma$ -product was low (13%). The oxazoline substituted arenethiolatocopper(I) catalyst **16** gave 95% conversion of the substrate and the substitution product was formed with an  $\alpha$ : $\gamma$  ratio of 2:98 (**10**:**9**). However, the  $\gamma$ -product was found to be racemic. The results clearly show that all investigated complexes give the substitution product with high  $\gamma$ -selectivity, but complexes **13**–**16** all give lower asymmetric inductions than (*S*)-**1** for the studied reaction.

### Reactions with arenethiolatocopper(I) complexes prepared in situ

The arenethiolatocopper(I) complexes described above are highly air-sensitive compounds and are therefore not easy to prepare, store and handle. We therefore turned to the possibility of performing the allylic substitution reactions with arenethiolatocopper(I) catalysts prepared in situ from the corresponding arenethiols and a copper(I) source. This approach has been reported earlier by Pfaltz and co-workers.<sup>19</sup> Thus, treatment of arenethiol **17**<sup>13b</sup> (Fig. 4) with *n*-BuLi yields the lithium arenethiolate. Subsequent reaction with a copper(I) source gives (*R*)-**1**. Addition of the allylic substrate and a Grignard reagent to this reaction mixture leads to the desired reaction. One difference to the preformed catalyst system is that the in situ prepared catalyst will contain one equivalent of lithium salt, which could have an effect on the reaction. We have performed various reactions of allylic substrates **2** and **4** using catalysts prepared in situ to study the influence of different experimental parameters such as the copper source and the Grignard reagent.

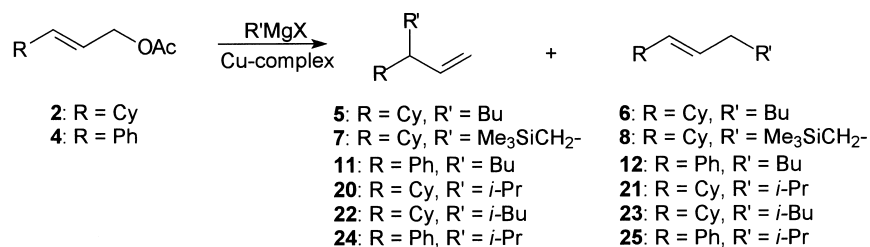
The reaction of **2** with *n*-BuMgI, using the catalyst generated from **17** and CuI, resulted in selective formation of the  $\gamma$ -product (Table 3, Entry 1). The e.e. was almost the same as that observed with the preformed catalyst (40 and

42% e.e., respectively). The presence of one equivalent of lithium iodide seems to have no influence on the outcome of the reaction. An increase of temperature from 0 to 20°C did not change the enantioselectivity (Entry 2). The same effect was observed with the preformed catalyst.<sup>11</sup> With two equivalents of ligand, no significant change of the e.e. was found (Entry 3), indicating that one ligand molecule is strongly bound to the copper atom in the catalytic intermediate. A control experiment with CuI as catalyst, in the absence of ligand, gave an incomplete conversion of **2** (Entry 4). The  $\gamma$ -selectivity was still high ( $\alpha$ : $\gamma$ =5:95), but beside the substitution products the alcohol 3-cyclohexyl-(2*E*)-propenol, formed by attack of the Grignard reagent on the ester carbonyl group, and other unidentified products were observed. This leads to the conclusion that the arenethiolate ligand is necessary for a fast and efficient  $\gamma$ -selective substitution reaction.

We also investigated the influence of the copper source on the outcome of the substitution reaction. With CuCl and Cu(OTf)<sub>2</sub> the conversion of **2** was complete and only the  $\gamma$ -substitution product was formed (Entries 5 and 6). The reaction with Cu(OTf)<sub>2</sub> as copper source showed a lower e.e. for the  $\gamma$ -product. From this copper salt the active copper(I) species is formed by in situ reduction by the Grignard reagent. The fact that CuI and CuCl both result in formation of the  $\gamma$ -product with the same e.e. supports the proposal that the lithium halide present in the reaction mixture has no influence on the outcome of the reaction. With CuBr·Me<sub>2</sub>S the conversion and the e.e. of the  $\gamma$ -product were much lower (Entry 7). This is probably caused by the coordinated dimethyl sulfide which hampers formation of the catalytic intermediate (Fig. 2). Replacement of the iodide in the Grignard reagent by bromide had a negative influence on the outcome of the substitution reaction. With *n*-BuMgBr the reaction was not completely  $\gamma$ -selective and the e.e. of the  $\gamma$ -product was lower (Entry 8). This is in contrast to the reaction with *n*-BuMgBr in the presence of the preformed copper complex which gave the  $\gamma$ -product with 50% e.e. (Table 1). Replacement of CuI by CuBr as copper source gave the  $\gamma$ -product with a slightly improved e.e. of 36% (Entry 9). We also investigated ligand **18**<sup>17b</sup> (Fig. 4) in the allylic substitution reaction of **2**. Preparation of a preformed copper(I) arenethiolate with this ligand proved to be cumbersome. The catalyst prepared from **18** and CuI gave complete conversion of **2** and the reaction was  $\gamma$ -selective. However, the e.e. observed for the  $\gamma$ -product was only 10% (Entry 10).

Ligand **19** (Fig. 4) was prepared from commercially available (+)-(*R*)-1-(1-naphthyl)ethylamine. The arenethiolatocopper catalyst prepared from **19** gave complete conversion of **2** in a reaction with *n*-BuMgI (Entry 11). The  $\alpha$ : $\gamma$  ratio

**Table 3.** Substitution reactions of **2** and **4** catalyzed by arenethiolatocopper(I) complexes prepared in situ (unless otherwise stated the reactions were carried out with a copper(I) complex prepared from arenethiol **17**. The Grignard reagent (1.25 equiv.) was added within 120 min to a solution of the allylic acetate (1 equiv.) and 15 mol% of the copper(I) complex (prepared in situ) in Et<sub>2</sub>O at 0°C)



Entry	Substrate	R'MgX	Copper salt	T (°C)	Conversion (%) <sup>a</sup>	α:γ Ratio <sup>a</sup>	E.e. of γ (%) <sup>b</sup>
1	<b>2</b>	<i>n</i> -BuMgI	CuI	0	100	0:100	40
2	<b>2</b>	<i>n</i> -BuMgI	CuI	20	100	0:100	40
3 <sup>c</sup>	<b>2</b>	<i>n</i> -BuMgI	CuI	0	100	0:100	39
4 <sup>d</sup>	<b>2</b>	<i>n</i> -BuMgI	CuI	0	65	5:95	–
5	<b>2</b>	<i>n</i> -BuMgI	CuCl	0	100	0:100	40
6	<b>2</b>	<i>n</i> -BuMgI	Cu(OTf) <sub>2</sub>	0	100	0:100	35
7	<b>2</b>	<i>n</i> -BuMgI	CuBr·Me <sub>2</sub> S	0	60	0:100	7
8	<b>2</b>	<i>n</i> -BuMgBr	CuI	0	100	8:92	30
9	<b>2</b>	<i>n</i> -BuMgBr	CuBr	0	100	8:92	36
10 <sup>c</sup>	<b>2</b>	<i>n</i> -BuMgI	CuI	0	100	0:100	10
11 <sup>f</sup>	<b>2</b>	<i>n</i> -BuMgI	CuI	0	100	3:97	35 <sup>g</sup>
12	<b>2</b>	<i>i</i> -PrMgI	CuI	0	100	0:100	34
13	<b>2</b>	<i>i</i> -PrMgI	CuI	–30	100	0:100	29
14	<b>2</b>	<i>i</i> -PrMgBr	CuI	0	100	0:100	14
15	<b>2</b>	Me <sub>3</sub> SiCH <sub>2</sub> MgI	CuI	20	100	0:100	37
16	<b>2</b>	<i>i</i> -BuMgBr	CuI	0	80	30:70	40
17	<b>2</b>	PhMgI	CuI	0 <sup>h</sup>	–	–	–
18	<b>4</b>	<i>n</i> -BuMgI	CuI	0	100	0:100	30
19	<b>4</b>	<i>i</i> -PrMgI	CuI	0	100	0:100	18
20	<b>4</b>	<i>i</i> -PrMgBr	CuI	0	100	0:100	25

<sup>a</sup> Conversion and α:γ ratio determined by GC. Isolated yields at 100% conversion: 50–95%.

<sup>b</sup> E.e. determined by GC.

<sup>c</sup> Ligand to copper ratio 2:1.

<sup>d</sup> No ligand added.

<sup>e</sup> Ligand **18** was employed.

<sup>f</sup> Ligand **19** was employed.

<sup>g</sup> The (*S*)-enantiomer was formed in excess (see text).

<sup>h</sup> No allylic substitution observed. A reaction performed at 20°C gave no improvement.

was 3:97 and the e.e. of the γ-product was 35%. Complex (*R*)-**1** and the complexes prepared from (*R*)-**17** or (*R*)-**18** always gave (*R*)-**5** in excess. However, the catalyst prepared from (*R*)-**19** gave (*S*)-**5** in excess. The reason for this change in enantioselectivity is at the moment not clear but further investigations are underway. In this case a seven-membered chelate would be formed instead of the six-membered chelate formed from (*R*)-**1** (cf. Fig. 2).

Since the substitution reactions with *n*-butylmagnesium halides gave the γ-product with only moderate enantioselectivities we have investigated other, more bulky Grignard reagents. Some results are included in Table 3. It is noteworthy that the secondary Grignard reagents *i*-PrMgI and *i*-PrMgBr can also be employed (Entries 12–14).<sup>18,19</sup> With all Grignard reagents the γ-selectivity was complete except for the reaction with *i*-BuMgBr (Entry 16). However, the enantioselectivities were always lower than found with the *n*-butyl Grignard reagents. The bulky Me<sub>3</sub>SiCH<sub>2</sub>MgI gave the γ-product with an e.e. not higher than 37% (Entry 15) which is substantially lower than the enantioselectivity obtained with the preformed catalyst. The reaction with this Grignard reagent had to be carried out at 20°C. At

0°C there was almost no conversion of **2**. The reaction of **2** with PhMgI resulted in recovery of **2** and formation of 3-cyclohexyl-(2*E*)-propenol (Entry 17). This shows that a copper(I) arenethiolato complex is not a suitable catalyst for reactions with aryl Grignard reagents.

Finally, we studied some reactions of **4** with Grignard reagents in the presence of the catalyst prepared in situ from ligand **17** and CuI (Table 3, Entries 18–20). In all cases the substitution reaction was completely γ-selective. Again the reaction with *n*-BuMgI gave the γ-product with a moderate e.e. (30%, Entry 18).

## Conclusions

We have shown that the outcome of the asymmetric substitution reaction of allylic acetates with Grignard reagents catalyzed by a chiral arenethiolatocopper(I) catalyst depends on the addition procedure of the reactants. Using the most convenient addition method we followed the progress of an allylic substitution reaction in time. At least one equivalent of Grignard reagent relative to the

amount of copper species is necessary to start the catalytic reaction, which provides further support for our earlier proposed structure of the catalytic intermediate. Varying the chiral ligand in the catalysts showed that any group larger than a methyl group on the amino function lowers the chiral induction in the formation of the  $\gamma$ -product. Performing the reactions with an arenethiolatocopper(I) catalyst prepared in situ was also possible. Different Grignard reagents were investigated and it was shown that reagents more bulky than *n*-BuMgI gave the  $\gamma$ -products with the same or with lower enantioselectivity. We are currently investigating various other chiral nitrogen- and sulfur-containing ligands in the copper-catalyzed asymmetric substitution reaction of allylic acetates.

## Experimental

**General:** Mass spectra were determined using a Thermoquest 2000A GC–MS with a Varian DB-5 column (15 m $\times$ 0.32 mm). <sup>1</sup>H (300 MHz) and <sup>13</sup>C (75 MHz) NMR spectra were recorded using a Varian Mercury 300 spectrometer with CDCl<sub>3</sub> as solvent using residual CHCl<sub>3</sub> (7.26 and 77.0 ppm, respectively) as internal standard. The infrared spectrum of **19** was recorded using a Perkin–Elmer Spectrum One spectrophotometer. The e.e. was determined either with analytical HPLC using a Chiralcel OD-H column (eluent: 99–99.5% hexane, 0.5–1% 2-propanol, compound **9**) or GC using a CP-Chirasil-Dex CB column (70°C isotherm). Optical rotations were measured using a Perkin–Elmer 241 polarimeter at the sodium D line ( $\lambda$ =589 nm). Merck silica gel (Silica 60, 230–400 mesh) was used for flash column chromatography. TLC was performed on deactivated silica (0.25 mm, Merck F<sub>254</sub>). All reactions were run under a dry argon or nitrogen atmosphere. Diethyl ether was dried over Na-benzophenone prior to use. Grignard reagents were made according to standard procedures and titrated before use.<sup>20</sup> *trans*-Cinnamyl acetate (**4**) was purchased from Lancaster and used without further purification. (+)-(*R*)- $\alpha$ -Methylbenzylamine (e.e. 99%) was purchased from Acros. (+)-(*R*)-Naphthylethylamine was purchased from Lancaster. (*E*)-3-Cyclohexyl-2-propenylacetate (**2**)<sup>4d</sup> and (*E*)-1-acetoxy-4-phenoxy-2-butene (**3**)<sup>4b,15</sup> were prepared according to literature procedures. The spectral data were consistent with those previously reported. The copper complexes **1**,<sup>13c</sup> **13**,<sup>13c</sup> **14**,<sup>17</sup> **15**,<sup>13c,17</sup> and **16**<sup>19</sup> and the arenethiols **17**<sup>13b</sup> and **18**<sup>17b</sup> were prepared according to literature procedures. The NMR data of **1**, **13**, **16**, **17** and **18** were consistent with those reported in the references.

## Synthesis of the arenethiol ligands

**(*R*)-(2-Piperidino)-2-ethyl-1-benzenethiol (18).** Compound **18** was prepared according to Ref.17b, but a modified work-up procedure was used. After addition of conc. HCl (aq.), all volatiles were evaporated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and filtrated through a short column of silica. The solvent was evaporated in vacuo and the crude product was crystallized from CH<sub>2</sub>Cl<sub>2</sub> by addition of Et<sub>2</sub>O. The resulting white needle-shaped crystals were washed with Et<sub>2</sub>O and dried in vacuo to yield 31% of **18**. The NMR data were in accordance with those reported except that all signals in the

<sup>1</sup>H NMR spectrum (CD<sub>3</sub>OD) should be shifted 1.45 ppm downfield.

**8-(1-Dimethylaminoethyl)-1-naphthalenethiol (19).** (+)-(*R*)-1-(1-Naphthyl)ethylamine (2 g, 11.7 mmol) was mixed with formic acid (5 ml) at 0°C. Formaldehyde (37% aq., 5 ml) was added dropwise to the stirred reaction mixture. The resulting solution was refluxed overnight (or until CO<sub>2</sub>-evolution had ceased). The reaction mixture was acidified with conc. HCl (aq.) and washed with Et<sub>2</sub>O (2 $\times$ 20 ml). The aqueous phase was made alkaline with sat. NaOH (aq). Extraction with Et<sub>2</sub>O (3 $\times$ 50 ml) followed by drying over Na<sub>2</sub>SO<sub>4</sub> and evaporation of the solvent in vacuo gave the crude (*R*)-1-(1-naphthyl)ethyl-*N*-dimethylamine which was purified by bulb-to-bulb distillation (150°C, 1.5 mm Hg) to yield 1.70 g (73%) of the pure product.  $[\alpha]_D^{19} = +67.3^\circ$  ( $c=1.1$  in CHCl<sub>3</sub>). Spectral data were in accordance with those reported earlier.<sup>21</sup> This amine (250 mg, 1.25 mmol) was dissolved in dry Et<sub>2</sub>O (5 ml) and *t*-BuLi (1.7 M in pentane, 0.8 ml) was added dropwise at room temperature. The clear red solution was stirred for 1 h and then added via canula to a suspension of sublimed S<sub>8</sub> (40 mg) in Et<sub>2</sub>O (2 ml). The reaction mixture was stirred overnight. Conc. HCl (aq., 105  $\mu$ l) was added. After 10 min all volatiles were removed in vacuo. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and filtered through a short silica column. Crystallization from CH<sub>2</sub>Cl<sub>2</sub> and Et<sub>2</sub>O yielded 97 mg (33%) of **19** as pale yellow needle-shaped crystals which were washed with Et<sub>2</sub>O and dried in vacuo.  $[\alpha]_D^{18} = -65.2^\circ$  ( $c=0.99$  in CHCl<sub>3</sub>). mp=125°C. <sup>1</sup>H NMR:  $\delta$  7.72 (dd,  $J=8.0$  Hz, 1.6 Hz, 1H), 7.62 (d,  $J=8.6$  Hz, 2H), 7.46 (d,  $J=8.6$  Hz, 1H), 7.40 (ddd,  $J=8.4, 6.8, 1.6$  Hz, 1H), 7.26 (ddd,  $J=7.9, 6.9, 1.0$  Hz, 1H), 4.77 (q,  $J=6.9$  Hz, 1H), 2.76 (s, 6H), 1.91 (d, 6.9 Hz, 3 H). <sup>13</sup>C NMR:  $\delta$  136.8, 131.4, 130.3, 129.0, 128.7, 126.8, 126.3, 125.1, 122.7, 118.4, 65.0, 40.5, 14.8. IR (CHCl<sub>3</sub>): 3018, 2952, 1614, 1589, 1476, 1220, 1210, 1080, 780 cm<sup>-1</sup>.

## General procedure for the arenethiolatocopper(I) catalyzed cross-coupling reactions with preformed copper catalysts

Slow additions were carried out using a dropping funnel or a syringe pump under an atmosphere of dry, oxygen-free nitrogen.

**Addition method A.** The required amount of (*R*)- or (*S*)-**1** was dissolved in toluene (15 ml). The allylic substrate (1 mmol), dissolved in Et<sub>2</sub>O (15 ml), was added and the reaction mixture cooled to 0°C. The Grignard reagent (1.25 mmol) in Et<sub>2</sub>O (100 ml) was added dropwise over 2 h. After complete addition, the reaction mixture was stirred for another 30 min. The reaction mixture was quenched with NH<sub>4</sub>Cl and the internal standard *n*-dodecane was added. A GC-sample was taken and the reaction mixture was then extracted with Et<sub>2</sub>O (6 $\times$ 25 ml) and the combined organic layers were dried (MgSO<sub>4</sub>). The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography with pentane as eluent.

**Addition method B.** The required amount of (*R*)- or (*S*)-**1** was dissolved in toluene (15 ml). The Grignard reagent (1.25 mmol) was added to the catalyst and the reaction

mixture was cooled to 0°C. The allylic substrate (1 mmol), dissolved in Et<sub>2</sub>O (100 ml), was added dropwise over 2 h. After complete addition, the reaction mixture was stirred for another 30 min. The work-up procedure was the same as described for method A.

**Addition method C.** The required amount of (*R*)- or (*S*)-**1** was dissolved in toluene (15 ml) and the reaction mixture was cooled to 0°C. The Grignard reagent (1.25 mmol), dissolved in Et<sub>2</sub>O (50 ml), and the allylic substrate (1 mmol), dissolved in Et<sub>2</sub>O (50 ml), were added separately at the same time to the catalyst solution in 2 h. After complete addition, the reaction mixture was stirred for another 30 min. The work-up procedure was the same as described for method A.

### General procedures for the arenethiolatocopper(I) catalyzed cross-coupling reactions with catalysts prepared in situ

Addition of the Grignard reagent was carried out using a syringe pump under an atmosphere of dry, oxygen-free argon.

The chiral arenethiol ligand (0.085 mmol) was dissolved in Et<sub>2</sub>O (45 ml) and the solution was cooled to –78°C. A solution of *n*-BuLi in hexanes (1.6 M, 75 μl) was added and the mixture was stirred for 10 min. The solution was warmed to 0°C and copper(I) iodide (0.085 mmol) was added. (In an alternative procedure, which gave equal results, the solution of the lithium arenethiolate was added to a suspension of CuI in Et<sub>2</sub>O.) The solution was stirred at 0°C for another 30 min and then the allylic substrate (0.549 mmol), dissolved in Et<sub>2</sub>O (5 ml), was added by syringe. The Grignard reagent (1.25 equiv. of a solution in Et<sub>2</sub>O) was added dropwise over 2 h. After complete addition, the reaction mixture was stirred for 1 h. The reaction was quenched by adding a 2 M solution of HCl (10 ml). The organic layer was separated and the aqueous layer was extracted three times with a 1:1 mixture of pentane and ether. The combined organic layers were washed with a saturated solution of NaCl and dried (MgSO<sub>4</sub>). The substitution products were purified by flash column chromatography with pentane as eluent.

### Characterization of the $\gamma$ -substitution products

**3-(Cyclohexyl)heptene (5).** The spectral data were in accordance with the literature.<sup>4d</sup>

**((3-Cyclohexyl)-1-buten-4-yl)trimethylsilane (7).** <sup>1</sup>H NMR:  $\delta$  5.57 (ddd, *J*=16.8, 10.3, 6.5 Hz, 1H), 4.90 (dd, *J*=4.1, 2.2 Hz, 1H), 4.86 (dd, *J*=10.6, 2.1 Hz, 1H), 1.98 (m, 1H), 1.75 (m, 5H), 1.10 (m, 6H), 0.69 (dd, *J*=14.6, 4.1 Hz, 1H), 0.56 (dd, *J*=14.7, 10.0 Hz, 1H), –0.03 (s, 9H). <sup>13</sup>C NMR:  $\delta$  143.22, 113.67, 46.07, 44.60, 30.97, 29.24, 26.86, 26.83, 19.58, –0.50. MS: 210 (M<sup>+</sup>, 0.2), 195 (34), 167 (15), 136 (10), 73 (100).

**3-(Phenyl)oxy)methyl-1-heptene (9).** The spectral data were in accordance with the literature.<sup>14b</sup>

**3-Phenyl-1-heptene (11).** The e.e. was determined by GC.

An e.e. of 30% corresponds to  $[\alpha]_D^{25} = -11.2^\circ$  (*c*=1.25 in CHCl<sub>3</sub>). The spectral data were in accordance with the literature.<sup>6c</sup>

**3-Cyclohexyl-4-methyl-1-pentene (20).** <sup>1</sup>H NMR:  $\delta$  5.51 (ddd, *J*=17.0, 10.2, 7.1 Hz, 1H), 5.02 (dd, *J*=10.3, 2.6 Hz, 1H), 4.87 (m, *J*=17.0, 2.5 Hz, 1H), 1.68 (m, 6H), 1.46 (m, 1H), 1.15 (m, 6H), 0.85 (d, 3H, *J*=6.9 Hz), 0.78 (d, 3H, *J*=6.6 Hz). <sup>13</sup>C NMR:  $\delta$  139.25, 116.26, 57.18, 38.54, 32.09, 30.19, 27.52, 27.14, 27.09, 27.02, 21.87, 21.40. MS: 166 (M<sup>+</sup>, 0.3), 138 (21), 123 (12), 95 (14), 81 (100), 67 (90), 55 (64).

**3-Cyclohexyl-5-methyl-1-hexene (22).** <sup>1</sup>H NMR:  $\delta$  5.53 (ddd, *J*=17.0, 10.0, 6.8 Hz, 1H), 4.96 (dd, *J*=10.2, 2.2 Hz, 1H), 4.90 (ddd, *J*=17.0, 2.5, 0.8 Hz, 1H), 1.86 (m, 1H), 1.60 (m, 6H), 1.10 (m, 8H), 0.87 (d, *J*=6.6 Hz, 6H). <sup>13</sup>C NMR:  $\delta$  141.65, 114.45, 47.76, 42.16, 41.17, 39.01, 33.36, 31.26, 29.68, 26.82, 26.35, 22.63, 21.55. MS: 180 (M<sup>+</sup>, 0.1), 152 (14), 124 (16), 96 (40), 81 (85), 67 (84), 55 (100).

**3-Phenyl-4-methyl-1-pentene (24).** The spectral data were in accordance with the literature.<sup>10d</sup> The e.e.'s obtained by GC were in agreement with the e.e.'s obtained after comparison of the optical rotation with the literature value ( $[\alpha]_D^{25} = -95.5^\circ$  (*c*=1.5 in CHCl<sub>3</sub>) corresponds to 78% e.e. for (*R*)-**24**).<sup>10d</sup>

### Acknowledgements

Financial support from the Netherlands Organization for Scientific Research (NWO), the Royal Swedish Academy of Sciences, The Swedish Foundation for Strategic Research and the Swedish Natural Science Research Council is gratefully acknowledged.

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