



# Highly enantioselective copper-catalyzed substitution of allylic chlorides with diorganozincs

Frank Dübner and Paul Knochel\*

*Ludwig-Maximilians-Universität München, Department Chemie, Butenandtstraße 5-13, Haus F, 81377 Munich, Germany*

Received 14 September 2000; accepted 22 September 2000

---

## Abstract

The new ferrocenyl ligand **1i** allows the performance of a highly enantioselective copper catalyzed  $S_N2'$ -allylic substitution of allylic chlorides with diorganozincs, providing substituted products with enantiomeric excesses of up to 98%. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* copper; enantioselective allylation; zinc; asymmetric synthesis; ferrocene.

---

The allylic substitution reaction of allylic electrophiles with organometallic reagents is an excellent method for forming new carbon–carbon bonds.<sup>1–3</sup> Palladium(0)-catalyzed allylic substitutions have proven to be excellent methods for the enantioselective substitution with stabilized organometallic reagents such as malonate anions or related species; however, enantioselective substitution with alkyl groups is more limited.<sup>4–9</sup>

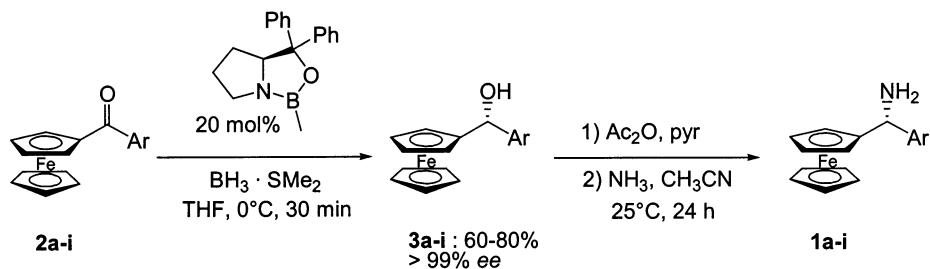
Alternatively, copper-catalyzed allylic substitutions with alkyl organometallics show more promise. Unfortunately, only moderate enantioselectivities have been obtained up to now.<sup>10–12</sup> Recently, we have reported that ferrocenyl amines such as **1c** are excellent ligands for the enantioselective substitution of allylic chlorides with diorganozincs. The enantiomeric excess with dineopentylzinc reaches 87%, but the reaction requires a temperature of  $-90^\circ\text{C}$  and is limited to very hindered diorganozincs.<sup>12</sup> Thus, under these conditions, the substitution of cinnamyl chloride with the less hindered dipentylzinc provides an enantiomeric excess of only 26%.

Herein, we wish to report the use of an improved ligand, which allows the reaction to be performed at  $-30^\circ\text{C}$  and leads to products with enantioselectivities of up to 98%. Thus, we have prepared a range of ferrocenyl amines of type **1**, starting from the readily prepared ferrocenyl ketones **2a–i**, followed by an enantioselective CBS reduction,<sup>13</sup> providing the corresponding

---

\* Corresponding author. Fax: 089/2180-7680; e-mail: paul.knochel@cup.uni-muenchen.de

alcohols **3a-i** in good yields (60–88%) and excellent enantioselectivities (>99% *ee*). The acylation of the alcohols **3a-i** with acetic anhydride in pyridine furnishes the corresponding acetates, which by treatment with aqueous ammonia in CH<sub>3</sub>CN provide the ferrocenyl amines **1a-i** in 40–60% yield (Scheme 1). These ligands were tested in the substitution of cinnamyl chloride with dineopentylzinc [THF, –50°C, CuBr·Me<sub>2</sub>S (1 mol%), ligand **1** (10 mol%)] leading to product **6a** (Table 2).



Scheme 1.

We observed that steric hindrance in the ligand is a key parameter for obtaining a high enantioselectivity. Thus, both the naphthyl (entry 3 of Table 1) and the 9-phenanthrenyl substituted ligands (entry 5) gave better results than the phenyl substituted system (Ar=Ph). However, best results were obtained by introducing sterically hindered substituents on the phenyl ring (entries 4, 6, 7, 8 and 9), leading finally to the ferrocenyl amine **1i** as the best ligand (92% *ee*).

Table 1

Optimization of the ferrocenyl amine ligand **1** for the copper catalyzed allylic substitution of cinnamyl chloride with dineopentylzinc

Entry	Ar	Catalyst	S <sub>N</sub> 2'/S <sub>N</sub> 2	<i>ee</i> (%)
1	Phenyl	<b>1a</b>	95:5	32
2	1-Naphthyl	<b>1b</b>	93:7	33
3	2-Naphthyl	<b>1c</b>	95:5	42
4	<i>p</i> -Biphenyl	<b>1d</b>	97:3	38
5	9-Phenanthrenyl	<b>1e</b>	98:2	61
6	<i>o</i> -Bromophenyl	<b>1f</b>	96:4	38
7	<i>p-tert</i> -Butylphenyl	<b>1g</b>	96:4	56
8	3,5-Dimethylphenyl	<b>1h</b>	97:3	66
9	3,5-Di- <i>tert</i> -Butylphenyl	<b>1i</b>	98:2	92 <sup>a</sup>

<sup>a</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +62 (*c* 1.5, CHCl<sub>3</sub>).

A further improvement in the reaction conditions, by the simultaneous addition of the diorganozinc **4** and the allylic chloride **5** in 3 h using a syringe pump, increased the enantioselectivity of product **6** and avoided the using of very low reaction temperatures (–30°C instead of –50°C or –90°C). The results are summarized in Table 2 and Scheme 2.<sup>14</sup>

Dineopentylzinc still gives the best results, with over 98% *ee* in the case of *p*-trifluoromethylcinnamyl chloride (entry 2 of Table 2). Remarkably, now *n*-dialkylzincs such as dipentylzinc (entry 7) and diethylzinc (entry 8) also give satisfactory results (44–65% *ee*).

Table 2  
 Enantioselective addition of diorganozincs to allylic chlorides catalyzed by CuBr·DMS (1 mol%) in the presence of the chiral ligand **1i** at  $-30^{\circ}\text{C}$  (simultaneous addition of the reagents)

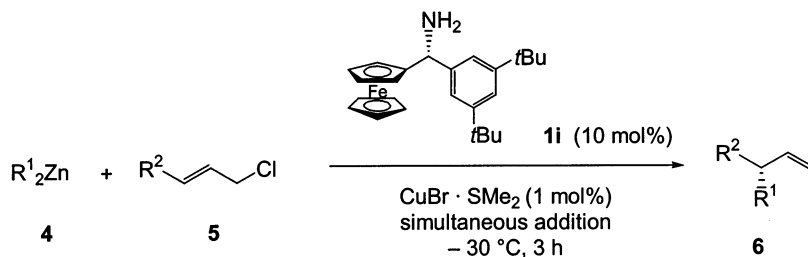
Entry	Diorganozinc ( $\text{R}^1$ )	Allylic Chloride ( $\text{R}^2$ )	Product	$\text{S}_{\text{N}}2'$ : $\text{S}_{\text{N}}2$	<i>ee</i> (%) <sup>a,d</sup>	Yield (%) <sup>b</sup>	
1	<i>neo</i> -Pentyl	Phenyl		<b>6a</b>	98 : 2	96 (82)	82
2	<i>neo</i> -Pentyl	4- $\text{CF}_3$ - $\text{C}_6\text{H}_4$		<b>6b</b>	98 : 2	98 (87)	85
3	<i>neo</i> -Pentyl	2-Thienyl		<b>6c</b>	97 : 3	77 (63)	80
4	<i>neo</i> -Pentyl	<i>c</i> -Hexyl		<b>6d</b>	99 : 1	90 (76)	84
5	<i>neo</i> -Pentyl	1-Naphthyl		<b>6e</b>	98 : 2	86 (71)	72
6	<i>iso</i> -Butyl	Phenyl		<b>6f</b>	98 : 2	72 (45)	86
7	Pentyl	Phenyl		<b>6g</b>	98 : 2	65 (26)	88
8	Ethyl	Phenyl		<b>6h</b>	98 : 2	44 (10); 52 <sup>c</sup>	89

<sup>a</sup> The enantiomeric excess was determined by gas chromatography using a CP-Chiralsil-Dex CB column. The enantiomeric excess in parentheses was obtained using the previous best ligand **1c** at  $-50^{\circ}\text{C}$  or  $-90^{\circ}\text{C}$ .

<sup>b</sup> Yield of analytically pure products.

<sup>c</sup> Using the mixed diorganozinc reagent *n*-ethyl-*neo*-pentylzinc.

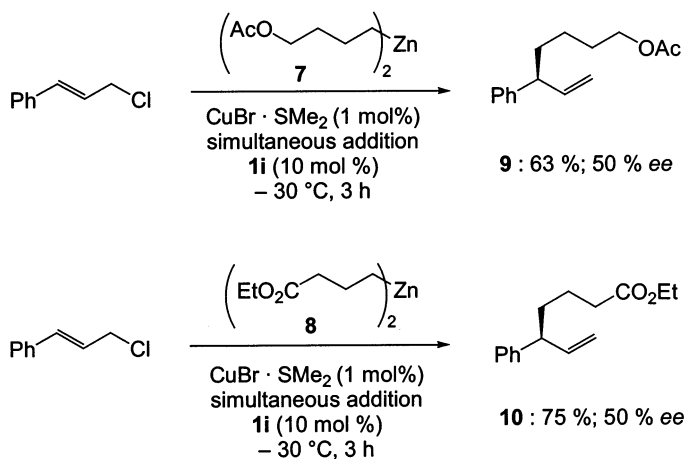
<sup>d</sup> The sign of the optical rotation was positive in all examples. The value of  $[\alpha]_{\text{D}}^{20}$  for **6a** was +65, for **6b** +57 ( $c = 1.5$ ,  $\text{CHCl}_3$ ).



Scheme 2.

By using mixed diorganozinc reagents,<sup>15</sup> specifically *n*-alkyl-*neo*-pentylzincs, it was further possible to increase the enantioselectivity of the reaction. In the case of ethyl as the *n*-alkyl group, compound **6h** is formed with 52% *ee* compared to 44% *ee* using diethylzinc (Table 2, entry 8). Interestingly, the formation of product **6a** was not observed; only the ethyl group is transferred, leading to **6h**.

As well as simple alkyl groups, functionalized diorganozincs, such as di(4-acetoxybutyl)zinc<sup>2-9</sup> **7** and di(4-carboethoxybutyl)zinc<sup>6,16</sup> **8** also add to cinnamyl chloride with 50% *ee*, providing the functionalized products **9** and **10** in 63–75% yield and with complete  $\text{S}_{\text{N}}2'$ -regiocontrol (Scheme 3).



Scheme 3.

In summary, we have found that the new ferrocenylamine **1i** allows enantioselective allylic substitution reactions to be performed for the first time with primary and secondary dialkylzincs as well as with functionalized diorganozincs with a good level of enantioselectivity. Further improvement of the reaction conditions and the investigation of intramolecular substitutions are currently underway in our laboratories.<sup>17</sup>

## Acknowledgements

We thank Zeneca Ltd for a fellowship to F.D. and the Fonds der Chemischen Industrie for generous support. We thank the BASF AG, Degussa AG and Chemetall GmbH for the generous gift of chemicals.

## References

1. Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.
2. Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547–550.
3. Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.
4. Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727–10737.
5. Trost, B. M.; Hildebrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416–10417.
6. Trost, B. M.; Heinemann, C.; Ariza, X.; Weigand, S. *J. Am. Chem. Soc.* **1999**, *121*, 8667–8668.
7. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554.
8. Pfaltz, A. *Synlett* **1999**, 835–842.
9. Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem.* **1997**, *69*, 513–518.
10. Van Klaveren, A.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J. E.; van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059–3062.
11. Meuzelaar, G. J.; Karlström, A. S. E.; van Klaveren, M.; Persson, E. S. M.; del Villar, A.; van Koten, G.; Bäckvall, J. E. *Tetrahedron* **2000**, *56*, 2895–2903.
12. Dübner, F.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 379–381.
13. Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950–968; for recent applications of related chiral ferrocenyl ligands in asymmetric reductions, see: Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212–3215.
14. The absolute configuration of products **6** were determined as cited in Ref. 12.
15. Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 1471–1474.
16. Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275–8319.
17. Typical procedure. Preparation of ethyl 5-phenyl-6-heptenoate (**10**). To a cooled (–30°C) solution of CuBr·SMe<sub>2</sub> (4.11 mg, 0.02 mmol) and ligand **1i** (68.2 mg, 0.20 mmol) in THF (5 mL) is added the diorganozinc **8** (2.40 mmol) in THF and cinnamyl chloride (0.31 g, 2.00 mmol) simultaneously over a period of 3 h. After usual work up, the crude residue is purified by chromatography (silica gel, pentane). Evaporation of the solvents furnishes product **10** (232 mg, 1.00 mmol, 50% yield, 50% *ee*) as a colorless oil.