Enantioselective Copper-Mediated Allylic Substitution with Grignard Reagents Employing a Chiral Reagent-Directing Leaving Group

Bernhard Breit,* Daniel Breuninger
Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg, Albertstr. 21, 79104 Freiburg, Germany
Fax +49(761)203 8715; E-mail: bernhard.breit@organik.chemie.uni-freiburg.de.
Received 31 March 2004

Abstract: Enantioselective copper-mediated allylic substitution with Grignard reagents was achieved employing the ortho-diphenylphosphanylferrocene carboxylate (o-DPPF) system as a planar chiral reagent-directing leaving group. Careful optimization of reaction parameters resulted in excellent regioselectivities and enantioselectivities of up to 95% ee.

Key words: asymmetric synthesis, synthetic methods, allylic substitution, organocopper reagents, Grignard reagents

Introduction

Allylic substitution employing carbon nucleophiles is a fundamental carbon–carbon bond forming reaction in organic synthesis.1 Particularly useful are copper-mediated and -catalyzed allylic substitutions since they allow the introduction of hard nucleophiles such as alkyl-, alkenyl- and aryl-type substituents.2

An interesting synthetic aspect of these reactions is the 1,3-chirality transfer starting from enantiomerically pure secondary allylic alcohol derivatives. Thus, stereochemistry of the allylic substitution with organocopper reagents generally proceeds with inversion, i.e. anti-attack of the nucleophile with respect to the leaving group.3 However, a problem exists in the simultaneous control of regio- and stereochemistry and only a few synthetically useful protocols are known.4 An elegant solution to these selectivity problems has emerged, and employs reagent-directing leaving groups (RGD),5 among which the ortho-diphenylphosphanylbenzoate group (o-DPPB) has proven particularly useful.6 These reactions occur with complete control of regio- and stereochemistry, including alkene geometry, for both cyclic and acyclic alcohol derivatives (Scheme 1). Stoichiometric amounts of readily available Grignard reagents are sufficient and the directing group can be recovered quantitatively. Starting from readily available enantiothermically pure allylic alcohol derivatives, perfect 1,3-chirality transfer with retention was observed for the formation of tertiary and quarternary carbon centers. Furthermore, the directing power of the o-DPPB function can be switched off by oxidation to the phosphate oxide, allowing a non-directed allylic substitution with opposite stereochemistry.7

However, if prochiral allylic alcohols are to be employed, the task of an enantioselective allylic substitution arises. In this case, chirality information would have to reside either in the reagent/catalyst employed or, alternatively, it may be part of the leaving group (Scheme 1). Pioneering work has been reported by Denmark et al., who employed chiral carbamate reagent-directing groups.8 Calò et al. have reported the use of chiral oxazoline systems.9

Because of the superior ability of the reagent-directing o-DPPB group for controlling regio- and stereochemistry of the allylic substitution, we decided to explore a similar but chiral RDG to control enantioselectivity upon allylic substitution with prochiral allylic alcohol derivatives. We envisioned the ortho-diphenylphosphanyl-ferrocene carboxylate (o-DPPF) as the ideal candidate since it shows similar geometry and donor properties compared to the o-DPPB function, and thus may offer similar benefits with respect to selectivity control of the allylic substitution with organocopper reagents (Scheme 1).

Results and Discussion

Allylic esters of the ortho-diphenylphosphanylferrocene carboxylic acid (1) (o-DPPFA)10 were prepared employing the Steglich esterification protocol.11 The corresponding racemic and enantiomerically pure (ee >99%) o-DPPF

Scheme 1 Directed allylic substitution of chiral and prochiral allylic substrates with achiral o-DPPB and planar chiral o-DPPF reagent-directing leaving groups (RDG).
Esters 9–15 were obtained as orange solids or oils in generally good yields (Table 1).

In a first set of experiments, optimal reaction conditions with respect to regioselectivity control (SN$_2^*$ versus SN$_2$) were examined starting from o-DPPF ester rac-9 (Table 2).

As a result, regioselectivity of the allylic substitution depends significantly on Grignard concentration and Grignard addition time. The lower the Grignard concentration and the slower the addition time, the higher the regioselectivity in favor of the SN$_2^*$ product, with best results for Grignard concentration of 0.1 M (n-BuMgX) to 0.025 M (MeMgI) and an addition time of two hours (Table 2, entries 4 and 7). These observations indicate that the regioselective directed SN$_2^*$-reaction pathway seems to proceed through an organocopper reagent rather than a cuprate species. This is in accord with previous observations from Bäckvall et al.$^{12}$ The nature of the copper(I) source employed was found to be of minor importance (Table 2, entries 9–12).

With these optimized conditions for a SN$_2^*$ regioselective directed allylic substitution in hand, we focused on asymmetric induction. Thus, enantiomerically pure o-DPPF ester (Rp)-9 was treated with n-BuMgBr and dependence of enantioselectivity on reaction temperature was studied first (Scheme 2, Table 3).

Optimal results were obtained at 0 °C which gave the known SN$_2^*$ product (S)-18 in a regioselectivity of 98:2 and an ee of 88% (Table 3, entry 2). Going either to higher (Table 3, entry 1) or lower temperatures (Table 3, entries 3 and 4) afforded lower selectivities.

Variation of the copper(I) source did not improve selectivities (Table 4). Noteworthy are the reactions with copper cyanide. In this case the allylic o-DPPF ester (Rp)-9 was added to the preformed lower order cyanocuprate. In the case of rapid addition (Table 4, entry 1) a low ee in favor of the opposite optical antipode (R)-18 was observed. Increasing the addition time to two hours (Table 4, entry 2) gave essentially racemic 18. These results indicate that in the case of lower order cyanocuprate a phosphanedirected reaction pathway is suppressed.

### Biographical Sketches

**Bernhard Breit**, born in 1966, studied chemistry at the University of Kaiserslautern where he obtained his doctorate in 1993 with Professor Regitz. After postdoctoral training with Professor Trost at Stanford University, Bernhard Breit worked in Marburg with Professor R. W. Hoffmann to obtain his habilitation. In 1998/99 he was as a Visiting Professor at Harvard University, Cambridge (USA), and from 1999 to 2001 he was Professor of Organic Chemistry at the University of Heidelberg. Since April 2001, he holds a chair of Organic Chemistry at the University of Freiburg.

His awards include the Steinhofer award, the Heinz-Maier-Leibnitz award (DFG), the ‘Dozenten award’ of the Fonds der Chemischen Industrie, the Alfried Krupp award and the Novartis European Young Investigator Award.

He is author and coauthor of 60 publications and 5 patents. His current research interests focus around catalysis and organic synthesis.

**Daniel Breuninger** was born in 1974 and studied chemistry at the University of Kaiserslautern (Germany). In 2000 he joined the group of Prof. Dr. Breit at the University of Heidelberg (Germany) and followed him in the next year to the University of Freiburg (Germany). In September 2004 he has finished his PhD thesis. His research is focused on the development of a chiral directing group and its application in metal-mediated and metal-catalyzed reactions.
The choice of solvent had a significant influence on reaction selectivity (Table 5). Thus, changing from diethyl ether to dichloromethane increased enantioselectivity significantly to an optimal ee of 95% (Table 5, entry 4).

Taking these optimized reaction conditions, transfer of other Grignard reagents was explored (Table 6). Whereas methyl- and isopropyl-Grignard could be added with good regio- and enantioselectivity (Table 6, entries 1 and 3), reaction with phenyl Grignard marks a synthetic limitation of this method.

A rationale which may account for the observed stereochemistry is depicted in Scheme 3. Thus, a reactive conformation in which the $\sigma^*$-orbital of the leaving group is aligned such as to overlap efficiently with the alkene $\pi$-system is most reasonable. Minimization of A$_{1,3}$ strain and an internal delivery of the copper nucleophile through phosphane coordination in accord with previous observations installs the $(S)$-absolute configuration in the substitution products 16, 18, and 20.

To see whether double bond geometry of the allyl electrophile has an influence on reaction selectivity, we studied allylic substitution with the (Z)-o-DPPF ester $(R_p)$-10 (Table 7). In all cases good regioselectivities were noted. However, enantioselectivity was significantly lower than for the corresponding (E)-o-DPPF ester $(R_p)$-9 and the opposite enantiomer was formed.

In order to study substrate scope, allylic substitution with cinnamyl derivatives $(S)p$-11–13 was examined (Table 8). In all cases, regioselectivities were lower compared to the cyclohexyl-substituted allylic systems. The same holds for enantioselectivity of these reactions. Neither a donor nor an acceptor substituent at the aromatic unit had a beneficial influence on selectivity parameters.

In a last set of experiments, we explored the potential of this methodology towards enantioselective construction of quarternary carbon centers. For this purpose, allylic...
substitutions of geraniol- and nerol-(Sp)-α-DPPF esters (Sp)-14 and (Sp)-15 were examined (Scheme 4).

In both cases, the Sb2′ products were formed with excellent regioselectivities of >98:2. Again, double bond geometry had a decisive influence on the stereochemical course of these reactions. Thus, although in moderate enantioselectivity, opposite optical antipodes of 30 were formed starting either from geraniol- or the nerol-(Sp)-α-DPPF ester 14, 15.

Table 2  Regioselectivity of Allylic Substitution with α-DPPF Ester rac-9 as a Function of Concentration, Grignard Reagent, and Copper Source

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu source</th>
<th>RMgX</th>
<th>Addition time</th>
<th>Equiv. RMgX</th>
<th>Sb2′:Sb2b</th>
<th>Yield (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>MeMgI (1.34 M)</td>
<td>5 min</td>
<td>1.1</td>
<td>0:100</td>
<td>ndd</td>
</tr>
<tr>
<td>2</td>
<td>CuBr·SMe2</td>
<td>MeMgI (1.25 M)</td>
<td>5 min</td>
<td>1.2</td>
<td>65:35</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>CuBr·SMe2</td>
<td>MeMgI (0.82 M)</td>
<td>2 h</td>
<td>1.2</td>
<td>87:13</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>CuBr·SMe2</td>
<td>MeMgI (0.025 M)</td>
<td>2 h</td>
<td>1.3</td>
<td>98:2</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>CuBr·SMe2</td>
<td>n-BuMgBr (0.025 M)</td>
<td>2 h</td>
<td>1.2</td>
<td>94:6</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>CuBr·SMe2</td>
<td>n-BuMgBr (0.36 M)</td>
<td>2 h</td>
<td>1.3</td>
<td>96:4</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>CuBr·SMe2</td>
<td>n-BuMgBr (0.11 M)</td>
<td>2 h</td>
<td>1.3</td>
<td>98:2</td>
<td>nd</td>
</tr>
<tr>
<td>8</td>
<td>CuBr·SMe2</td>
<td>i-PrMgBr (0.1 M)</td>
<td>2 h</td>
<td>1.3</td>
<td>90:10</td>
<td>82</td>
</tr>
<tr>
<td>9e</td>
<td>CuCN</td>
<td>n-BuMgBr</td>
<td>1 min</td>
<td>1.0</td>
<td>98:2</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td>CuBr</td>
<td>n-BuMgBr (0.1 M)</td>
<td>2 h</td>
<td>1.4</td>
<td>94:6</td>
<td>nd</td>
</tr>
<tr>
<td>11</td>
<td>CuBr/P(OEt)3</td>
<td>n-BuMgBr (0.025 M)</td>
<td>2 h</td>
<td>1.2</td>
<td>99:1</td>
<td>nd</td>
</tr>
<tr>
<td>12</td>
<td>CuBr/P(OEt)3</td>
<td>n-BuMgBr (0.1 M)</td>
<td>2 h</td>
<td>1.3</td>
<td>96:4</td>
<td>nd</td>
</tr>
</tbody>
</table>

a Reaction conditions: Grignard reagent was added via syringe during the specified addition time to a mixture of rac-9 and the copper(I)salt (0.5 equiv) in Et2O (0.01 M) at r.t. (ca. 24 °C).
b Determined by GC of reaction mixture (CPSil5CB).
c All reactions gave a quantitative conversion according to TLC analysis, indicated yield of isolated pure compound after flash chromatography is significantly lower due to product volatility; nd = not determined.
d Ca. 60% allylic alcohol were formed.
e To the preformed lower order cyanocuprate (1.0 equiv, 0.03 M in Et2O) was added rac-9 (0.03 M in Et2O) during 1 min.

Table 3  Temperature Dependence of Enantioselectivity and Regioselectivity of Allylic Substitution of α-DPPF Ester (Rp)-9 with n-BuMgBr

<table>
<thead>
<tr>
<th>Entry</th>
<th>n-BuMgBr</th>
<th>T (°C)</th>
<th>Sb2′:Sb2b</th>
<th>ee (%)e</th>
<th>Yield (%)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.031 M (1.2 equiv)</td>
<td>r.t.</td>
<td>98:2</td>
<td>85 (S)</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>0.023 M (1.2 equiv)</td>
<td>0</td>
<td>98:2</td>
<td>88 (S)</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>0.030 M (1.3 equiv)</td>
<td>–10</td>
<td>84:16</td>
<td>76 (S)</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>0.026 M (1.2 equiv)</td>
<td>–20</td>
<td>85:15</td>
<td>78 (S)</td>
<td>95</td>
</tr>
</tbody>
</table>

a Reaction conditions: n-BuMgBr in Et2O was added during 2 h to a solution of (Rp)-9 and CuBr·SMe2 (0.5 equiv) in Et2O (0.01 M) at the temperature indicated.
b Determined by GC(CPSil5CBA) of crude reaction mixture.
c Determined by chiral GC (G-TA).
d Indicated yield of isolated pure compound; nd = not determined; in all cases a quantitative conversion was reached, according to TLC analysis.

substitutions of geraniol- and nerol-(Sb)-α-DPPF esters (Sb)-14 and (Sb)-15 were examined (Scheme 4).
In conclusion, we have shown that employing the ortho-diphenylphosphanylferrrocene carboxylate (o-DPPF) system as a planar chiral reagent-directing leaving group enables enantioselective copper-mediated allylic substitution with Grignard reagents. Careful optimization of reaction parameters allowed for, in some cases, excellent regioselectivities and enantioselectivities up to 95% ee.

Reactions were performed in flame-dried glassware under argon (purity >99.998%). The solvents were dried by standard procedures, distilled, and stored under argon. PE refers to petroleum ether with boiling point range of 40–60 °C. Cy refers to cyclohexane. 1H, 13C NMR spectra: Varian Mercury 300 HFCP, Bruker AM 400, Bruker DRX 500, with tetramethylsilane (TMS), chloroform (CHCl₃) or benzene (C₆H₆) as internal standards (p = pseudo). 31P NMR spec-
tra: Varian Mercury 300 HFCp with 85% H3PO4 as external standard. Melting points: Melting point apparatus by Dr. Tottoli (Büchi), all temperatures quoted are uncorrected. Elemental analyses: VarioEL (Elementaranalysen GmbH). Mass spectrometry: Thermo Finnigan MAT 8200 and TSQ 7000. Flash chromatography: Silica gel 40–63 \( \mu \text{m} \), (230–400 mesh, Macherey-Nagel). The descriptors for planar chirality are based on the rules introduced by Schögl.13

### Preparation of \( \alpha \)-DPPF Esters 9–15; General Procedure

To a suspension of \( \alpha \)-DPPF \(^{10}\) at r.t. in CH2Cl2 was added successively the allylic alcohol, DCC and DMAP. The reaction mixture was stirred at r.t. until TLC showed complete consumption of starting material. Filtration of the reaction mixture through CH2Cl2-wetted celite, evaporation of the solvent, and purification of the crude product through flash chromatography gave the corresponding esters 9–15 in analytically pure form.

**rac-\( (E) \)-3-Cyclohexyl-2-propen-1-yl-2-(diphenylphosphanyl)ferrocene Carboxylate (rac-9)\)**

From rac-1\(^{10} \) (1.996 g, 4.82 mmol), \((E)\)-3-cyclohexyl-2-propenol (2)\(^{14} \) (0.817 g, 5.83 mmol), DCC (1.234 g, 5.98 mmol) and DMAP (0.601 g, 4.92 mmol) in CH2Cl2 (50 mL) after 48 h reaction time was obtained rac-\( \alpha \)-DPPF ester rac-9 [1.801 g, 70%, \( R \left( S_{ac} \right) \), \( R _ {f} = 0.07 \) (PE–EtOAc, 50:1)] as an orange foam; mp = 84 °C. Absolute configuration assigned in analogy to previous results. Contaminated with bicyclohexane.

### Table 7

<table>
<thead>
<tr>
<th>Entry(^{a})</th>
<th>RMgX</th>
<th>Addition time</th>
<th>( S_{ac} ):( S_{ac}^{2b} )</th>
<th>ee (( % ))(^{c})</th>
<th>Yield (( % ))(^{d})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>McMgI</td>
<td>0.5 equiv/h</td>
<td>96:4</td>
<td>40 (( R ))</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>( n )-BuMgBr</td>
<td>1 equiv/h</td>
<td>98:2</td>
<td>13 (( R ))</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>( i )-PrMgBr</td>
<td>1 equiv/h</td>
<td>97:3</td>
<td>58 (( R ))</td>
<td>89</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction conditions: 1.3 equiv Grignard (0.1 M in Et2O) was added to a solution of \( \alpha \)-DPPF-ester \( (R_{p})-10 \) and 0.5 equiv of CuBr·SMe2 in CH2Cl2 (0.01 M) at 0 °C.

\(^{b}d\) See footnotes Table 3.

### Table 8

<table>
<thead>
<tr>
<th>Entry(^{a})</th>
<th>R’</th>
<th>RMgX</th>
<th>( S_{ac}^{2b} ):( S_{ac} )</th>
<th>ee (( % ))(^{c})</th>
<th>Yield (( % ))(^{d})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>( n )-BuMgBr (1.2 equiv)</td>
<td>87:13</td>
<td>78 (( R ))(^{e})</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CyMgBr (1.3 equiv)</td>
<td>98:2</td>
<td>71 (( S ))(^{e})</td>
<td>&gt;100(^{f})</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>( n )-BuMgBr (1.2 equiv)</td>
<td>84:16</td>
<td>65 (( R ))(^{e})</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>( n )-BuMgBr (1.2 equiv)</td>
<td>94:6</td>
<td>68 (( R ))(^{e})</td>
<td>37</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction conditions: Grignard (0.1 M in Et2O) was added to a solution of \( \alpha \)-DPPF-ester \( (S_{p})-11-13 \) and 0.5 equiv of CuBr·SMe2 in CH2Cl2 (0.01 M) at 0 °C.

\(^{b}d\) See footnotes Table 3.

\(^{e}\) Absolute configuration assigned in analogy to previous results.

<table>
<thead>
<tr>
<th>Entry(^{a})</th>
<th>R’</th>
<th>RMgX</th>
<th>( S_{ac}^{2b} ):( S_{ac} )</th>
<th>ee (( % ))(^{c})</th>
<th>Yield (( % ))(^{d})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>( n )-BuMgBr (1.2 equiv)</td>
<td>87:13</td>
<td>78 (( R ))(^{e})</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CyMgBr (1.3 equiv)</td>
<td>98:2</td>
<td>71 (( S ))(^{e})</td>
<td>&gt;100(^{f})</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>( n )-BuMgBr (1.2 equiv)</td>
<td>84:16</td>
<td>65 (( R ))(^{e})</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>( n )-BuMgBr (1.2 equiv)</td>
<td>94:6</td>
<td>68 (( R ))(^{e})</td>
<td>37</td>
</tr>
</tbody>
</table>

\(^{f}\) Contaminated with bicyclohexane.

J = 12.3, 6.3, 1.1 Hz, OCH3), 5.07 (ddd, 1 H, J = 2.6, 1.4, 1.1 Hz, Cp-H), 5.43 (ddd, 1 H, J = 15.5, 6.3, 1.4 Hz, OCH3(CH=CH), 5.69 (dd, 1 H, J = 15.5, 6.6, 1.1 Hz, OCH3(CH=CH), 7.17–7.25 (m, 5 H, C5H5), 7.34–7.38 (m, 3 H, C5H5), 7.45–7.50 (m, 2 H, C6H5).

13C NMR (125 MHz, CDCl3): δ = 26.1 (2 C, C5H11), 26.2 (C5H11), 32.6 (d, 2 C, JCP = 2.4 Hz, C5H11), 46.4 (C5H11), 65.2 (OCH3), 71.1 (5 C, C5H5), 71.8 (CP-CH), 74.2 (CP-CH), 75.3 (d, JCP = 4.8 Hz, CP-C), 79.5 (d, JCP = 15.7 Hz, CP-C), 121.9 (OCH3(CH=CH), 128.0 (CH=CH), 128.2 (d, 2 C, JCP = 6.7 Hz, CH=Ph), 128.3 (d, 2 C, JCP = 7.3 Hz, CH=Ph), 129.1 (CH=Ph), 132.4 (d, 2 C, JCP = 19.4 Hz, CH=Ph), 135.1 (d, 2 C, JCP = 21.5 Hz, CH=Ph), 138.5 (d, JCP = 13.6 Hz, CH=Ph), 139.7 (d, JCP = 13.0 Hz, C=Ph), 141.7 (OCH3(CH=CH), 171.7 (d, JCP = 2.7 Hz, COOR).

31P NMR (121 MHz, CDCl3): δ = −18.12.

MS (EI, 70 eV): m/z (%) = 536 (46, [M+]1), 413 (100), 385 (86), 369 (23).

HPLC (Chiralcel-AD, heptane–i-PrOH 90:10, 25 °C, 0.5 mL/min, 244 nm): tR[(R)−9]: 10.49 min (50.4%), tR[(S)−9]: 12.65 min (49.6%).


**Scheme 4** Alkyl substitution of geraniol- and nerol-(R)-o-DPPF esters (S)−14 and (S)−15.
From \(C_6H_4\), 7.17–7.21 (m, 5 H, \(C_6H_5\)), 7.25 (d, 2 H, \(J_{1,2} = 1.4, 1.1\) Hz, \(Cp-H\)), 5.98 (dt, 1 H, \(J_{1,2} = 1.2\) Hz, \(Cp-H\)), 3.78 (s, 3 H, \(OCH_3\)), 4.20 (s, 5 H, \(C_5H_5\)), 4.42 (pt, 1 H, \(C\)), 114.0 (2 C, \(CH-PhOMe\)), 121.3 (OCH2, 6 mL) after 23 h reaction time was obtained \(\alpha\)-DPPF ester \(\langle S\rangle_{-1}^{13}\) (0.298 g, 91%) \(\delta_{\text{H}, \text{H}} = -116^\circ\) (c = 0.58, CHCl3).

**rac-\((E)-3-(p-Methoxyphenyl)-2-propen-1-yl\)-2-(diphenylphosphino)ferrocenecarboxylate \([\langle S\rangle_{-12}\])**

From rac-1 (0.435 g, 1.05 mmol), \((E)\)-p-methoxy-cinnamylalcohol \((S)_{16}\) (0.207 g, 1.26 mmol) and DMAP \((0.125, 1.05 \text{ mmol})\) in \(CH_2Cl_2\) \((10 \text{ mL})\) after 48 h reaction time was obtained \(\alpha\)-DPPF ester \(\langle S\rangle_{-12}^{14}\) (0.489 g, 85%, \(R_1 = 0.12\) (PE-\(\text{EtOAc}, 50:1\))) as an orange solid; mp = 75°C.

**rac-\((E)-3-(p-Bromophenyl)-2-propen-1-yl\)-2-(diphenylphosphino)ferrocenecarboxylate \([\langle S\rangle_{-13}\])**

From rac-7 (0.140 g, 0.85 mmol), DCC \((0.172 g, 0.83 \text{ mmol})\) and DMAP \((0.084, 0.69 \text{ mmol})\) in \(CH_2Cl_2\) \((10 \text{ mL})\) after 22 h reaction time was obtained \(\alpha\)-DPPF ester \(\langle S\rangle_{-13}^{14}\) (0.325 g, 83%; \(\delta_{\text{H}, \text{H}} = -106^\circ\) (c = 0.81, CHCl3)).

**rac-\((E)-3-(p-Bromophenyl)-2-propen-1-yl\)-2-(diphenylphosphino)ferrocenecarboxylate \((\text{rac-13})\)**

From rac-4th \((1.227 g, 2.96 \text{ mmol}), (E)-p-bromocinnamylalcohol \((S)_{16}\) (0.756 g, 3.55 mmol), DCC \((0.747 g, 3.55 \text{ mmol})\) and DMAP \((0.370, 2.96 \text{ mmol})\) in \(CH_2Cl_2\) (30 mL) after 48 h reaction time was obtained \(\alpha\)-DPPF ester \(\text{rac-13}\) (1.14 g, 63%, \(R_1 = 0.12\) (PE-\(\text{EtOAc, 50:1}\))) as an orange solid; mp = 157°C.

**rac-\((E)-3-(p-Methoxyphenyl)-2-propen-1-yl\)-2-(diphenylphosphino)ferrocenecarboxylate \((\text{rac-12})\)**

From rac-4th \((0.125 \text{ g}, 1.05 \text{ mmol})\) in \(CH_2Cl_2\) \((10 \text{ mL})\) after 48 h reaction time was obtained \(\alpha\)-DPPF ester \(\langle R\rangle_{-12}^{14}\) (0.58, \(CHCl_3)).

**rac-\((E)-3-(p-Bromophenyl)-2-propen-1-yl\)-2-(diphenylphosphino)ferrocenecarboxylate \((\text{rac-13})\)**

From rac-4th \((0.756 \text{ g}, 3.55 \text{ mmol}), (E)-p-bromocinnamylalcohol \((S)_{16}\) (0.370 g, 2.96 mmol) in \(CH_2Cl_2\) (30 mL) after 48 h reaction time was obtained \(\alpha\)-DPPF ester \(\text{rac-13}\) (1.14 g, 63%, \(R_1 = 0.12\) (PE-\(\text{EtOAc, 50:1}\))) as an orange solid; mp = 157°C.

**C6H4 = 7.3 Hz, CH-\(\text{CHPh}\)), 128.6 (2 C, CH-\(\text{CHPh}\)), 129.2 (CH-\(\text{CHPh}\)), 132.3 (d, 2 C, \(J_{1,2} = 18.9 \text{ Hz, CH-CHPh}\)), 133.9 (OCH2, 1H, \(OCH_2\)), 135.1 (d, 2 C, \(J_{1,2} = 20.4 \text{ Hz, CH-CHPh}\)), 136.6 (C-Ph), 138.3 (d, \(J_{1,2} = 13.6 \text{ Hz, C-PhPh})\), 139.6 (d, \(J_{1,2} = 12.6 \text{ Hz, C-PhPh})\), 171.2 (d, \(J_{1,2} = 2.9 \text{ Hz, COOR})\).

**HRMS:** \(m/z = 608.0203\); found: 608.0203.

**HRMS:** \(m/z = 608.0202\); found: 608.0203.

**rac-\((E)-3,7-Dimethylocta-2,6-dien-1-yl\)-2-(diphenylphosphino)ferrocenecarboxylate \((\text{rac-14})\)**

From rac-4th \((1.108 g, 2.67 \text{ mmol}), \text{geraniol} (1.048 g, 3.22 \text{ mmol})\), DCC \((0.657 g, 3.27 \text{ mmol})\) and DMAP \((0.330, 2.70 \text{ mmol})\) in \(CH_2Cl_2\) (27 mL) after 26 h reaction time was obtained \(\alpha\)-DPPF ester \(\text{rac-14}\) (0.746 g, 51%, \(R_1 = 0.17\) (PE-\(\text{EtOAc, 50:1}\))) as an orange-brown oil.

**HRMS:** \(m/z = 608.0202\); found: 608.0203.

---

*Synthesis 2005, No. 1, 147–157 © Thieme Stuttgart · New York*
Copper-Mediated Allylic Substitution Reactions with Grignard Reagents

General Procedure
To a stirred solution of the α-DPFF ester (9-15) (0.03 to 0.15 mmol) in the solvent indicated (0.01M, see Tables 2-8) was added the copper salt (0.5 equiv unless otherwise noted) and eventually the coligand. After 15 min, the Grignard reagent (1.0 to 1.4 equiv) was added in the specified time (a syringe pump was used for addition times above 5 min). After complete consumption of the starting ester (TLC control, normally directly after Grignard addition), the reaction was quenched with saturated NH₄Cl solution (20 mL/mmol ester) and 12.5% NH₄ solution (10 mL/mmol). After stirring for 5 min, the phases were separated and the aequous phase was extracted with Et₂O (2 × 40 mL/mmol). The combined organic phases were washed with brine (40 mL/mmol), dried over Na₂SO₄, and the solvent was removed carefully. To the residue was added pentane and the suspension was filtered through a pad of silica gel with pentane and after removing of the solvent, the ratio of the SN2 substitution products, which were not separable by column chromatography, were determined. Column chromatography (silica gel, pentane) gave the substitution products, which were not separable by column chromatography. The enantiomeric excess was determined by GC (G-TA).

3-Cyclohexyl-1-butene (16)
GC (G-TA, 30 °C isotherm, 130 kPa He): tᵣᵢ₈ [(α)D] = 39.5 min, tᵣᵢ₈ [(β)D] = 41.7 min.

(S)-[α]-3,3-Dimethyl-2,6-dien-1-yl-2-(diphenylphosphino)-ferrocene carboxylate [(S)-14]

From (S)-10 (0.337 g, 0.82 mmol), geraniol (7) (0.214 g, 1.39 mmol), DCC (0.207 g, 1.39 mmol) and DMAP (0.101 g, 0.83 mmol) in CH₂Cl₂ (8 mL) after 26 h reaction time was obtained α-DPFF ester (S)-14 [0.401 g, 89%]; Rᵣ [(α)D] = 0.18 (PE-ÉtoAc, 50:1) as an orange-brown oil; [α]D = −115° (c = 0.51, CHCl₃).

Anal. Caled for C₃₉H₃₅FeO₂P: C, 71.81; H, 6.41. Found: C, 71.81; H, 6.41.

(S)-[α]-2-Cyclohexyl-1-butene (17)

From (S)-10 (0.222 g, 0.54 mmol), nerole (8) (0.105 g, 0.68 mmol), DCC (0.131 g, 0.64 mmol) and DMAP (0.065 g, 0.53 mmol) in CH₂Cl₂ (6 mL) after 24 h reaction time was obtained α-DPFF ester (S)-15 [0.401 g, 89%, Rᵣ = 0.18 (PE-ÉtoAc, 50:1) as an orange-brown oil; [α]D = −115° (c = 0.51, CHCl₃).

Anal. Caled for C₃₉H₃₅FeO₂P: C, 71.81; H, 6.41.

Copper-Mediated Allylic Substitution with Grignard Reagents

4.46 (dd, 1 H, (CH₃)CH₂], 132.4 (d, 2 C, JCP = 19.4 Hz, CH₃Ph), 135.2 (d, 2 C, JCP = 21.5 Hz, CH₃Ph), 138.5 (d, JCP = 13.5 Hz, CPh), 139.7 (d, JCP = 12.8 Hz, CPh); 141.8 [CH=C(CH₃)₂], 171.3 (d, JCP = 2.6 Hz, COOR).

3H NMR (121 MHz, CDCl₃): δ = −15.73.

MS (EI, 70 eV); m/z (%) = 550 (63, [M⁺]), 413 (100), 385 (45), 369 (97), 304 (39), 293 (17), 275 (13), 229 (22), 215 (16), 186 (27), 170 (33), 69 (37).

HPLC (Chiracel-AD, heptane–PrOH 97:3, 20 °C, 0.8 mL/min, 250 mm): τᵣ [(R)D-14]: 8.07 min (49.7%), τᵣ [(S)D-14]: 10.31 min (50.3%).

4.46 (dd, 1 H, (CH₃)CH₂], 171.3 (d, JCP = 2.6 Hz, COOR).

51P NMR (121 MHz, CDCl₃): δ = −15.73.

MS (EI, 70 eV); m/z (%) = 550 (63, [M⁺]), 413 (100), 385 (45), 369 (97), 304 (39), 293 (17), 275 (13), 229 (22), 215 (16), 186 (27), 170 (33), 69 (37).

HPLC (Chiracel-AD, heptane–PrOH 97:3, 20 °C, 0.8 mL/min, 250 mm): τᵣ [(R)D-14]: 8.07 min (49.7%), τᵣ [(S)D-14]: 10.31 min (50.3%).

Enantioselective Copper-Mediated Allylic Substitution with Grignard Reagents

FEATURE ARTICLE
Enantioselective Copper-Mediated Allylic Substitution with Grignard Reagents

155

3-Cyclohexyl-3-phenyl-1-propene (22)

The analytical and spectroscopic data correspond to those reported previously.24

HRMS: m/z calcd for C_{13}H_{21}: 180.077; found: 180.1878.

(Ε)-1-Cyclohexyl-1-heptene (19)

The analytical and spectroscopic data correspond to those reported previously.23

HRMS: m/z calcd for C_{12}H_{20}: 174.1406; found: 174.1408.

(Ε)-1-Phenyl-1-heptene (25)

The analytical and spectroscopic data correspond to those reported previously.23

HRMS: m/z calcd for C_{15}H_{24}: 200.1140; found: 200.1151.

3-(p-Methoxyphenyl)-1-heptene (28)

The analytical and spectroscopic data correspond to those reported previously.24

HRMS: m/z calcd for C_{19}H_{22}O: 204.1514; found: 204.1514.

(Ε)-1-(p-Methoxyphenyl)-1-heptene (29)

The analytical and spectroscopic data correspond to those reported previously.24

3-(p-Bromophenyl)-1-heptene (30)

GC (CP-Chirasil-Dex CB, 130 °C isotherm, 135 kPa H2): \( t_R \) [\( \sim \)] 28: 30.6 min, \( t_R \) [\( + \)] - \( + \) 28: 31.5 min.

\[ [\alpha]_D^{20} = -11.4^\circ \quad (c = 0.28, \text{ CHCl}_3, \text{ ee} = 68\%). \]

\[ R_f = 0.62 (\text{Cy–EtOAc, } 10:1); \text{ colorless liquid.} \]

1H NMR (300 MHz, CDCl3): \( \delta = 0.86 \) (t, 3 H, \( J = 7.1 \mathrm{~Hz} \), \( CH_3 \)), 0.88 (s, 3 H, \( CH_3 \)), 1.06–1.15 (m, 2 H, \( CH_2 \)), 1.16–1.24 (m, 6 H, \( 3 \times CH_2 \)), 1.51 (s, 3 H, \( CH_3 \)), 1.60 (d, 3 H, \( J = 0.9 \mathrm{~Hz} \), \( CH_3 \)), 1.79 (dt, 2 H, \( J = 11.9, 6.2 \mathrm{~Hz} \), \( CH_2CH=CH_2 \)), 4.81 (dd, 1 H, \( J = 17.5, 1.5 \mathrm{~Hz} \), \( CH=CH_2 \)), 4.89 (dd, 1 H, \( J = 10.8, 1.5 \mathrm{~Hz} \), \( CH=CH_2 \)), 4.99–5.04 (m, 1 H, \( CH=C(CH_3)_2 \)), 5.62 (dd, 1 H, \( J = 17.5, 10.8 \mathrm{~Hz} \), \( CH=CH_2 \)).

13C NMR (125 MHz, CDCl3): \( \delta = 14.2 (CH_2) \), 17.6 (CH_3), 22.7 (CH_2CH=CH_2), 22.9 (CH_3), 23.6 (CH_3), 25.8 (CH_3), 26.3 (CH_3), 28.8 (CH_3), 111.3 (CH=CH_2), 125.2 (CH=CH_2), 131.0 (CH=CH_2), 148.4 (CH=CH_2).

The analytical and spectroscopic data correspond to those reported previously.25

MS (EI, 70 eV): \( m/z \) [\( \sim \)] 32: 194 (11, [M^+]), 192 (11), 184 (48), 182 (45), 116 (100), 103 (10), 89 (11), 63 (10), 50 (10), 41 (12).

 Acknowledgment

We thank the Fonds of the Chemical Industry and the Krupp Foundation (Krupp Award for young university teachers to BB) for financial support as well as M. Lutterbeck, S. Preuß for technical and Dr. R. Krüger and G. Fehrenbach for analytical assistance.

References


