Copper-Mediated and -Catalyzed *o*-DPPB-Directed Allylic Substitution

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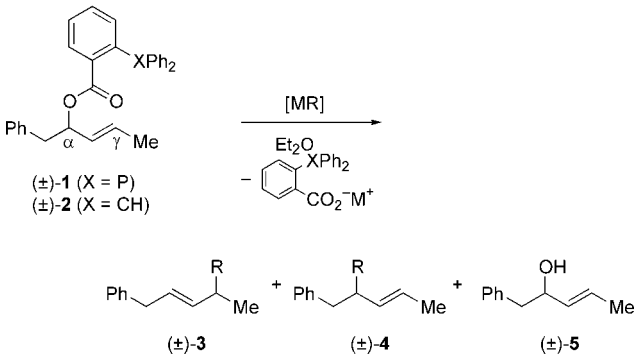
This paper is dedicated to Professor David A. Evans on the occasion of his 60th birthday

Abstract: Complete control of chemo-, regio- and stereoselectivity in the course of copper-catalyzed and -mediated allylic substitution could be obtained with the *ortho*-diphenylphosphanyl (*o*-DPPB) function as a reagent-directing leaving group. Complete chirality transfer by way of a *syn*-addition process has been achieved for cyclic and acyclic systems. Readily available Grignard reagents may be employed as nucleophiles and the directing *o*-DPPB group can be recovered quantitatively. The reaction requires neither cooling nor an excess of organometallic reagent.

Keywords: allylic substitution; asymmetric synthesis; organocopper reagents; synthetic methods

Synthetic methods which allow the stereoselective construction of a desired carbon skeleton in a predictable and reliable fashion are of great value to organic synthesis. In this respect allylic substitution with organocopper reagents is a synthetically appealing operation since hard nucleophiles such as alkyl- and aryl-type substituents may be introduced into an existing carbon skeleton. However, efficient control of regioselectivity, i.e., α (S_N2) versus γ (S_N2') attack is often a severe problem (see Scheme 1).[1] A solution to this problem might be a directing leaving group which may control the trajectory of the incoming copper nucleophile to occur as an exclusive γ-attack. Additionally, a directing leaving group may reverse the stereochemistry of allylic substitution to occur as a *syn*-addition in opposition to the standard *anti*-attack relative to the leaving group. Several leaving groups have been evaluated for this purpose, among which carbamates[2] and benzothiazoles[3] have proven to be useful. However, both systems suffer from several drawbacks. For instance, control over alkene geometry upon reaction of acyclic derivatives is often unsatisfactory. As a consequence, chirality transfer in acyclic allylic systems may be incomplete.[2] Frequently, an excess of organocopper reagent has to be used which is undesirable, in particular, if valuable organic residues are to be transferred. Additionally, the directing leaving group is generally irreversibly lost in the overall process.



Scheme 1.

We recently identified the *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB)-group as a multifunctional reagent-directing group.[4] Several late transition metal-catalyzed or -mediated processes such as hydroformylation,[5] rhodium-catalyzed domino processes,[6] palladium-catalyzed atropselective biaryl coupling[7] as well as conjugate addition of organocopper reagents[8] have been described. We now report on a new function of this group, namely its use as a reagent-directing leaving group for regio- and stereoselective allylic substitution with organocopper reagents.

Our study commenced with the allylic-*o*-DPPB ester (±)-**1**. This substrate was chosen since it is structurally not biased towards preference of either α- or γ-attack to give alkenes **3** and **4**, respectively.

In a first experiment, *o*-DPPB ester **1** was treated with two equivalents of dimethylcuprate at –20 °C

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Table 1: Results of allylic substitution of esters (±)-**1** and (±)-**2** with organocopper reagents.

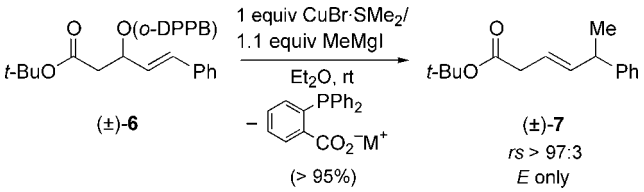
entry	equiv. [MR]	X =	T [°C]	t [h]	yield (%)[a]	ratio of **3**[b]:**4**:**5**
1	2 Me_2CuLi	P	–20	3	> 95	75:25:-
2	2 Me_2CuLi	P	–80	6	> 95	74:26:-
3	2 Me_2CuLi	CH	–20	3	> 95	78:22:–
4	2 Me(CN)CuLi	P	–20	65	> 95	95:5:–
5	**1 CuBr·SMe_2/1.1 MeMgI**	**P**	**rt**	**2 min**	**> 95**	**>99:<1:-**
6	1 CuBr·SMe_2/1.1 MeMgI	CH	rt	6	80[c]	42[e]:15:21
7	2 MeMgI	P	rt	12	> 95	–:–:>99
8	1 CuBr·SMe_2/1.1 BuMgCl	P	rt	2	98[d]	>99:<1:–
9	1 CuBr·SMe_2/1.1 *i*-PrMgCl	P	rt	2	84[d]	97:3:–
10	1 CuBr·SMe_2/1.1 PhMgBr	P	rt	2	94[b]	88:12:–

[a] GC yield.
[b] *E/Z* > 99:1.
[c] Conversion.
[d] Isolated yield after aqueous work-up and flash chromatography.
[e] The S_N2' product **3** was obtained as a *E/Z* mixture (64:36).

(Table 1, entry 1). A quantitative conversion was observed to give a 3:1 mixture of S_N2' product **3** and S_N2 product **4**. Decreasing the reaction temperature did not effect the regioselectivity (entry 2).

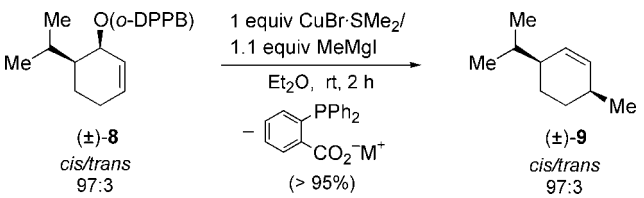
To test whether this result is due to a directing effect of the *o*-DPPB group the CH-derivative **2** was employed (entry 3). Thus, both benzoate functions should have the same steric demand whereas the phosphine-free derivative **2** should have lost its ability to coordinate the organocopper reagent. However, in both cases almost the same regioselectivity and reactivity were observed (entries 1 and 3). Hence, at least for the dimethylcuprate reagent a directing effect of the *o*-DPPB group may be excluded. We next switched to a lower order cyanocuprate which is known to provide an intrinsically higher S_N2' selectivity.[1] Accordingly, the γ-substitution product **3** was obtained in a 97:3 ratio (entry 4). However, reaction rate was rather low. The best result was obtained when we pretreated the *o*-DPPB-ester **1** with one equivalent of copper bromide · dimethyl sulfide.[9] Subsequent addition of just one equivalent of methyl Grignard reagent in ether provided even at room temperature within less than two minutes the S_N2' product exclusively with complete control of alkene geometry (entry 5). In a control experiment the CH-benzoate **2** was used. A significant decrease of chemo- and regioselectivity as well as *E/Z*-selectivity was found (entry 6). Furthermore the reaction is significantly slower in the absence of the phosphane function. Six hours were required to achieve a conversion of 80% whereas the reaction for *o*-DPPB derivative **1** was completed in less than two minutes under the same reaction conditions.[10] Hence, both observations, the differences in chemo-, regio- and diastereoselectivity as well as the significant rate acceleration underline the role of the *o*-DPPB group to function as a directing leaving group.

In addition to a methyl group, *n*-butyl, *iso*-propyl, and a phenyl substituent could be transferred with excellent levels of regioselectivity and with complete control of olefin geometry (*E:Z* > 99:1 in all cases, entries 8–10). The reaction is compatible with the presence of an ester group and can even enforce deconjugation as shown for the reaction with styrene derivative (±)-**6** to give *E*-alkene (±)-**7** in excellent yield and selectivity (Scheme 2). Notably, in all cases the *ortho*-diphenylphosphinobenzoic acid could be recovered in the work-up process almost quantitatively.



Scheme 2.

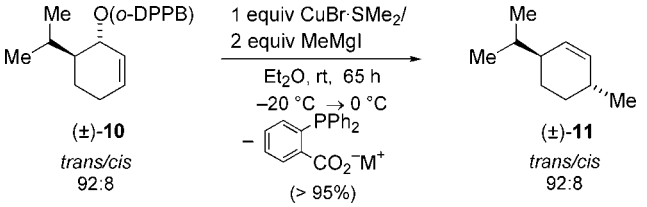
To probe the stereochemistry of the *o*-DPPB-directed allylic substitution we chose the *cis*- and *trans*-cyclohexenes (±)-**8** and (±)-**10** as model systems. In both cases a completely *syn*-selective nucleophile transfer was observed to give *cis*- and *trans*-menthene [(±)-**9**, (±)-**11**], respectively (Scheme 3 and Scheme 4).



Scheme 3.

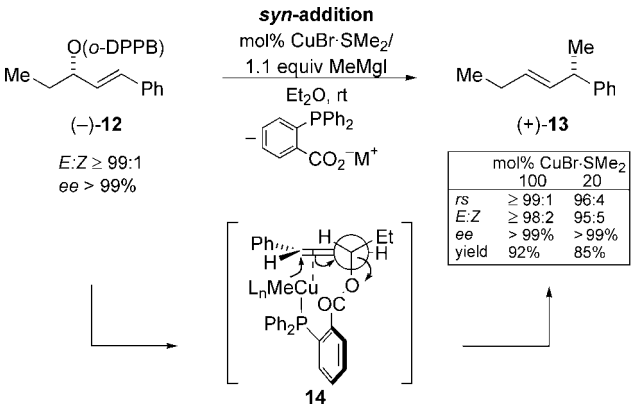
To explore chirality transfer in acyclic systems the enantiomerically pure allylic *o*-DPPB ester derivative (–)-**12** was selected.

The substitution reaction proceeded smoothly under standard conditions at room temperature to fur-



Scheme 4.

nish the *E*-alkene (+)-**13** in 92% isolated yield (regioselectivity > 99:1, Scheme 5). The enantiomeric purity of the product alkene (+)-**13** was determined by chiral GC to be > 99%.[11] Accordingly, the *o*-DPPB directed allylic substitution occurs also for acyclic systems with complete chirality transfer by way of a *syn*-addition process. The formation of the substitution product (+)-**13** is readily rationalized via reactive conformation **14** which should be favored based on steric and stereoelectronic arguments. Notably, the reaction can be run with substoichiometric amounts of copper salt (20 mol %) without significant loss of selectivity (Scheme 5).



Scheme 5.

In summary the copper-mediated (and -catalyzed) *o*-DPPB directed allylic substitution with Grignard nucleophiles occurs with complete control of regio- and stereochemistry as well as alkene geometry for both cyclic and acyclic allylic alcohol derivatives. Readily available Grignard reagents may be employed as nucleophiles and the directing *o*-DPPB group can be recovered quantitatively. The reaction requires neither cooling nor an excess of organometallic reagent and even catalytic amounts of copper may be sufficient.

Experimental Section

Representative Procedure: Synthesis of (S)-2-Phenyl-3-hexene (13)

To a solution of *o*-DPPB-ester **12** (565 mg, 1.25 mmol, 1.0 equiv.) [ee > 99% (determined at the stage of the allyl alcohol by chiral GC, Betadex™ 110) $[\alpha]_D^{20}$: –54°, *c* 1.9 in $CHCl_3$] in 25 mL of freshly dried diethyl ether (0.05 M) was added $CuBr{\cdot}SMe_2$ (257 mg, 1.25 mmol, 1.0 equiv., 99%) in one portion and the resulting yellow suspension was stirred for 5 minutes at room temperature. MeMgI (1.3 mL, 1.38 mmol, 1.1 equiv., 1.06 M solution in diethyl ether) was added dropwise within 5 minutes and the bright yellow suspension was stirred for further 2 hours at room temperature. The reaction was quenched by successive addition of a saturated aqueous NH_4Cl solution (8 mL) and an aqueous ammonia solution (12.5%, 10 mL) followed by the addition of pentane/diethyl ether (1:1, 10 mL). The mixture was stirred at rt for 10 min during which a yellow precipitate formed. The mixture was filtered and the residue washed with additional pentane/diethyl ether (5:1, 20 mL). The organic phase of the filtrate was separated and the aqueous phase was extracted with three further portions of diethyl ether (10 ml). The combined organic phases were washed with brine, dried ($MgSO_4$), and the solvent removed under vacuum. Flash chromatography (SiO_2, eluent pentane) furnished (*S*)-2-phenyl-3-hexene (**13**); yield: 184 mg (92%); $[\alpha]_D^{20}$: +10° (*c* 1.5, pentane); ee > 99% (GC, permethyl-β-cyclodextrin column).

Selected physical data of **13**: ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ = 0.98 (t, *J* = 7.4 Hz, 3 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 2.03 (m, 2 H), 3.42 (m_c, 1 H), 5.49 (dt, *J* = 15.2, 6.0 Hz, 1 H), 5.59 (dt, *J* = 15.4, 6.7 Hz, 1 H), 7.16–7.22 (m, 3 H), 7.28–7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ = 13.9, 21.6, 25.5, 42.2, 125.9, 127.2 (2 C), 128.3 (2 C), 130.8, 133.9, 146.6; HR-MS (EI): calcd. for $C_{12}H_{16}$: 160.1252, found 160.1238.

Recovery of the *ortho*-Diphenylphosphanylbenzoic Acid (*o*-DPPBA)

The yellow residue obtained in the filtration process above was dissolved in dichloromethane (20 mL), washed with water (10 mL), followed by addition of pH 4.75 buffer in methanol/water (1:1, 20 mL) and KCN (600 mg, 9.2 mmol) upon which the color of the organic phase changed from yellow to colorless. The phases were separated and the aqueous phase washed with three more portions of dichloromethane (10 mL each). The combined organic phases were washed with water (20 mL), dried ($MgSO_4$), and the solvent removed under vacuum to give *o*-DPPBA as a pale yellow solid; yield: 303 mg (85%).

Reaction Procedure for Employment of Catalytic Amounts of Copper(I) Bromide · Dimethyl Sulfide

To a solution of *o*-DPPB-ester **12** (276 mg, 0.61 mmol, ee >99%) in diethyl ether (12 mL) was added copper bromide · dimethyl sulfide (25.1 mg, 0.12 mmol) in one portion and the resulting yellow suspension was stirred for 5 min at room temperature. A 0.96 M solution of methylmagnesium iodide (0.70 mL, 0.67 mmol) was added within 5 min and the bright yellow suspension was stirred for further 3 h at room temperature. The reaction was quenched by successive addition of a saturated aqueous NH_4Cl-solution (7 mL) and an aqueous ammonia solution (12.5%, 4 mL) followed by the addition of diethyl ether (12 mL). The organic phase was separated and the aqueous phase was extracted with three further portions of diethyl ether (10 mL). The combined or-

ganic phases were washed with brine, dried ($MgSO_4$), and the solvent removed under vacuum. Column chromatography (SiO_2, eluent pentane 9:1) furnished (+)-**13**; yield: 83 mg (85%, ee >99%). Analytical GC (CP SIL 5CB, Chrompack; 40 °C, 2 min, 10 °C/min, 200 °C, 12 min): R_t[(+)-**13**] = 11.36 min (91%), (*Z*)-alkenic isomer, R_t = 11.12 min (5%) and regioisomer, (*E*)-1-phenyl-3-methyl-1-pentene R_t = 12.29 min (4%). Chiral GC (Permethyl-β-cyclodextrin, Chrompack; 65 °C): R_t[(+)-**13**] = 67.58 min.

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