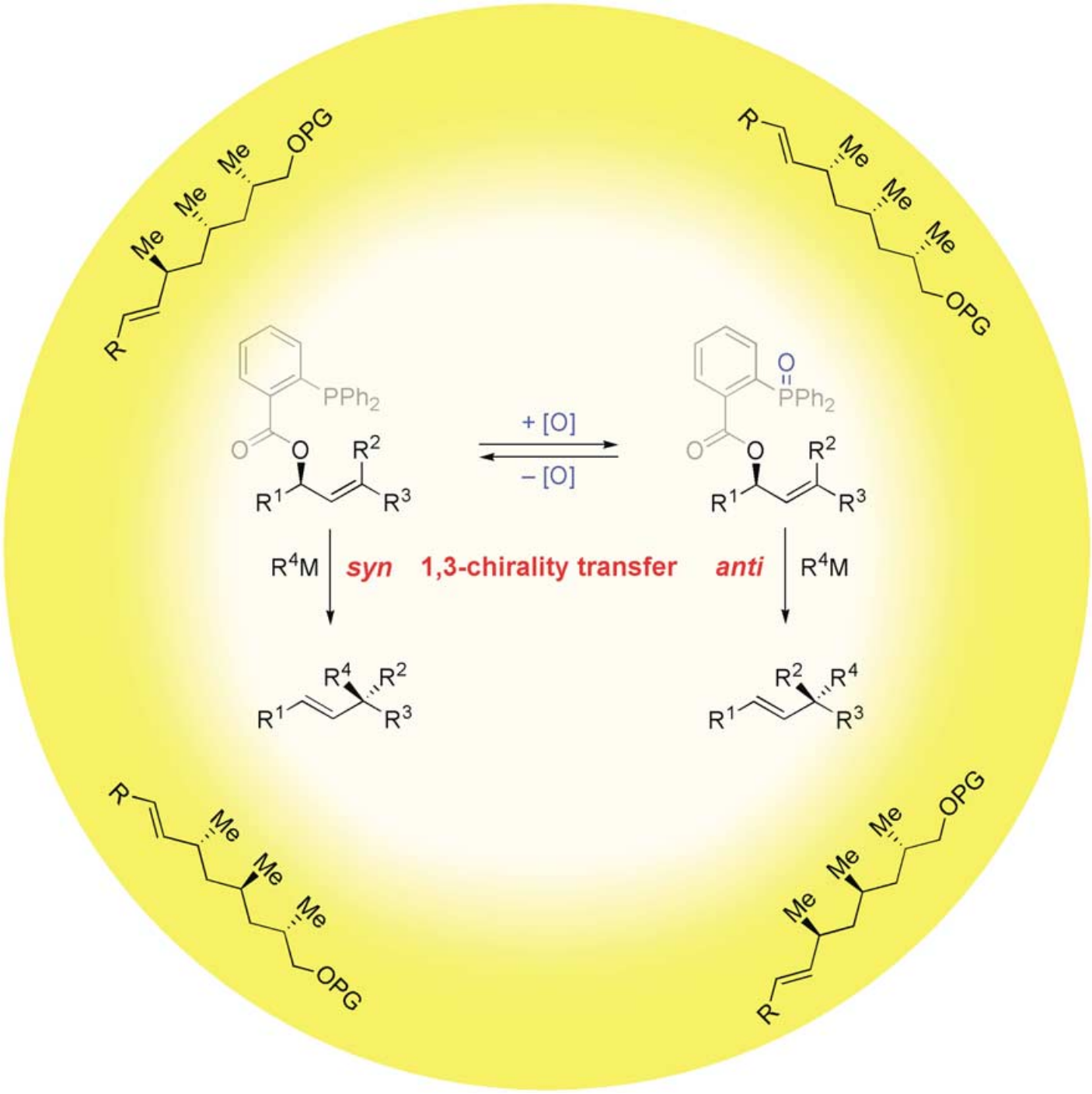
Communications



Oxidation of the directing leaving group in an S_N2' reaction with Grignard reagents causes a switch in the sense of the 1,3-chirality transfer from *syn* to *anti* substitution. The *syn*-directing effect is used for building up oligo(deoxypropionate)s diastereoselectively. For more information, see the Communications by B. Breit and co-workers on the following pages.

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Asymmetric Synthesis

Stereospecific and Stereodivergent Construction of Quaternary Carbon Centers through Switchable Directed/Nondirected Allylic Substitution**

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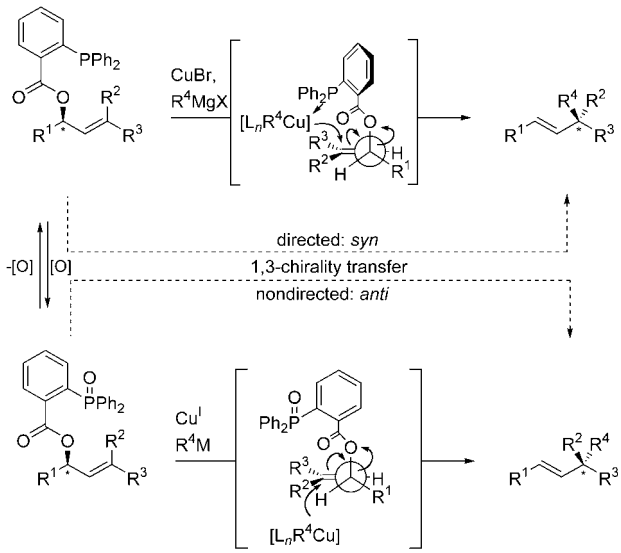
The enantioselective construction of quaternary stereogenic carbon centers is a challenge in organic synthesis. Much progress has been made with enantioselective catalytic methods, but still no general solution to this synthetic problem exists.[1] A reliable alternative strategy for the predictable installation of a quaternary stereocenter is 1,3-chirality transfer from a more readily accessible stereogenic center by a sigmatropic process, such as the Claisen rearrangement.[2] However, the nature of the sigmatropic process sets structural limitations on the type of carbon nucleophile that can be transferred. Allylic substitution with organometallic carbon nucleophiles could provide a more general solution if all aspects of selectivity could be controlled. Of particular interest is copper-mediated allylic substitution, as it allows the introduction of hard nucleophiles, such as alkyl, alkenyl, and aryl groups, into an existing carbon skeleton.[3] These reactions generally proceed by *anti* attack of the nucleophile with respect to the leaving group.[3,4] However, the simultaneous control of regio- and stereochemistry is a difficult problem to solve, and only a few successful examples are known.[5]

Progress has been made in this area with substrate-directed reactions in which reagent-directing leaving groups, such as carbamates[6] and benzothiazoles,[7] are used. However, control over the geometry of the double bond in the product is often unsatisfactory, so that the chirality transfer is incomplete.[3] Furthermore, in many cases an excess of the organometallic reagent is required, which is particularly undesirable if valuable organic residues are to be transferred. We recently found a solution to these problems by employing the *ortho*-diphenylphosphanylbenzoate group (*o*-DPPB) as a new reagent-directing leaving group. Copper-mediated and copper-catalyzed allylic substitution with only a stoichiometric amount of a Grignard reagent could be carried out with excellent chemo-, regio-, and stereoselectivity and with recovery of the directing group.[8]

We report herein on the regioselective, stereospecific, and stereodivergent construction of quaternary carbon stereocenters through *o*-DPPB-directed, copper-mediated allylic substitution with Grignard reagents. Furthermore, we show that the stereochemical outcome of the title reaction can be reversed through an oxidative on/off switch with regard to the directing power of the *o*-DPPB group. Thus, both enantiomers of the substitution product can be prepared from a single enantiomer of the substrate (Scheme 1).



Scheme 1. Concept of stereodivergent allylic substitution with organocopper reagents for the stereospecific construction of quaternary carbon centers by employing a switchable directing/nondirecting leaving group.

In a first series of experiments we studied the regioselectivity of the directed allylic substitution with respect to the formation of a quaternary carbon center. Thus, treatment of the secondary trisubstituted allylic *o*-DPPB derivative **1**[9] with $CuBr{\cdot}SMe_2$ (0.5 equiv)[10] and a methyl or *n*-butyl Grignard reagent (1.1 equiv)[11] provided the S_N2' substitution products **2** and **3**, respectively, with complete control of regioselectivity and double-bond geometry (Table 1, entries 1 and 2). Furthermore, the *o*-DPPB esters (*E*)-**4** and (*Z*)-**4**, derived from the primary trisubstituted allylic alcohols geraniol and nerol, respectively, underwent analogous transformations to give the products **5**–**7** of S_N2' substitution in excellent yields and with perfect regioselectivity, independent of the double-bond geometry in the starting material (Table 1, entries 3–6).

To study chirality transfer we chose the *o*-DPPB esters (−)-**8a** and (−)-**8b**, which are readily available from D-mannitol. The corresponding products of allylic substitution are equipped with appropriate functionalities for the flexible incorporation of the quaternary stereocenter into a desired carbon skeleton. The reaction of the *p*-methoxybenzyl (PMB) ether derivative (−)-**8a** with a range of Grignard reagents in the presence of $CuBr{\cdot}SMe_2$ (0.5 equiv) proceeded smoothly with excellent regio- and stereoselectivity (Scheme 2; Table 2,

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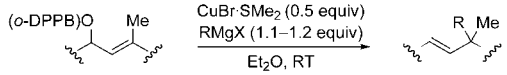
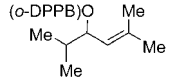
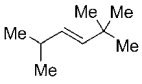
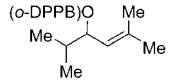
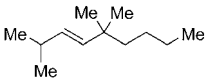
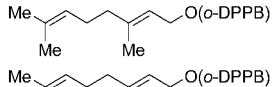
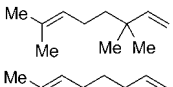
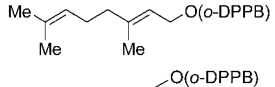
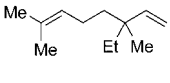
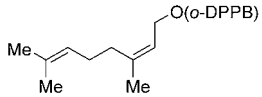
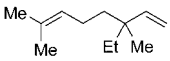
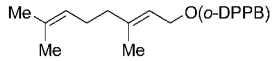
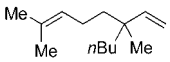
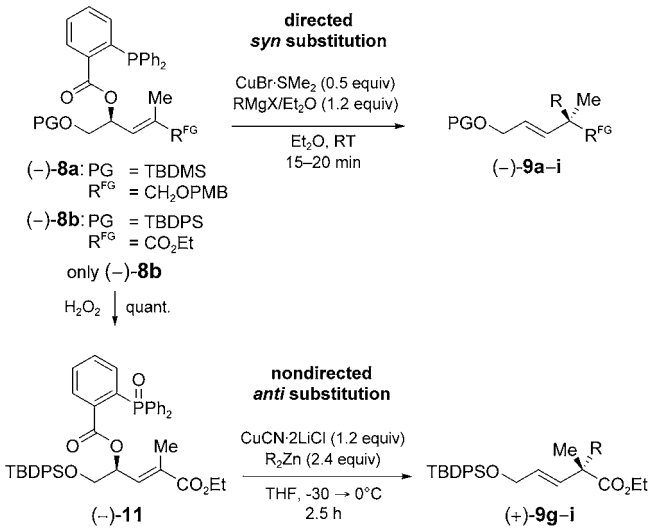
Table 1: Regioselective formation of quaternary carbon centers through *o*-DPPB-directed allylic substitution.[a]



Entry	*o*-DPPB ester[b]		RMgX (equiv)	Product		S_N2'/S_N2[c]	Yield [%][d]
1		**1**	MeMgI (1.1)		**2**	>99:1	68[e]
2		**1**	*n*BuMgBr (1.1)		**3**	99:1	99
3		(*E*)-**4**	MeMgI (1.2)		**5**	95:5	91
4		(*E*)-**4**	EtMgBr (1.2)		**6**	>98:2	80
5		(*Z*)-**4**	EtMgBr (1.2)		**6**	>98:2	95
6		(*E*)-**4**	*n*BuMgBr (1.2)		**7**	>99:1	87

[a] Reactions were performed in diethyl ether, c(*o*-DPPB ester) = 0.05 M. The Grignard reagent (0.51–1.23 M in diethyl ether) was added to the reaction mixture with a syringe pump over a period of 30 min. [b] Prepared from the corresponding allylic alcohol by an esterification protocol reported previously.[9] [c] Determined by GC (CPSil5CB, 30 m, 0.32 mm ID, Chrompack). [d] Yield of isolated product after distillation (entry 1) or chromatographic purification (entries 2–6). [e] The low yield is due to the volatility of the product.



Scheme 2. Stereospecific and stereodivergent construction of quaternary carbon centers through the switchable directed/nondirected allylic substitution of the acyclic substrates (−)-**8a**/**b** and (−)-**11** (see Table 2). PG = protecting group, PMB = *p*-methoxybenzyl, TBDMS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

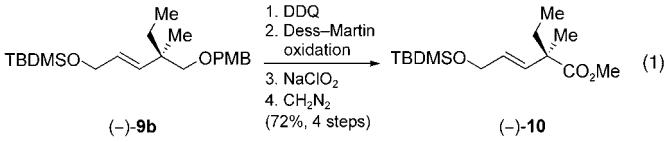
entries 1–4). Perfect 1,3-chirality transfer was observed in the construction of quaternary carbon centers (Table 2, entries 2–4). However, when a benzyl Grignard reagent was used the degree of chirality transfer was slightly lower (91%; Table 2, entry 5). The absolute configuration of the substitution products was determined upon the conversion of (−)-**9b** into the known ester (−)-**10** [Eq. (1); (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone)].[5b]

Table 2: Stereospecific and stereodivergent formation of quaternary carbon centers: acyclic substrates.[a]

Entry	Substrate[b] (*ee* [%])	R^2	S_N2'/S_N2[c]	E/Z[c]	Product (*ee* [%])[c]	CT[d] [%]	Yield[e] [%]
1	**8a** (94)	Me	>95:5	>95:5	**9a**	–	72
2	**8a** (94)	Et	>99:1	>99:1	(−)-**9b** (94)	100	86
3	**8a** (93)	*n*Bu	>99:1	>99:1	(−)-**9c** (93)	100	99
4	**8a** (93)	*i*Pr	>99:1	>99:1	(−)-**9d** (93)	100	89
5[f]	**8a** (93)	Bn	>99:1	>99:1	(−)-**9e** (85)	91	53
6	**8a** (92)	*t*Bu	14:86[g]	80:20[g]	**9f** (n.d.[h])	n.d.[h]	90
7	**8b** (>99)	Et	>99:1	>99:1	(−)-**9g** (98)	98	84
8	**8b** (>99)	*n*Bu	>99:1	>99:1	(−)-**9h** (97)	98	87
9	**8b** (>99)	*i*Pr	>99:1	>99:1	(−)-**9i** (97)	98	84
10	**11** (>99)	Et	>99:1	>99:1	(+)-**9g** (99)	100	85
11	**11** (>99)	*n*Bu	>98:2	>98:2	(+)-**9h** (99)	100	87
12[i]	**11** (>99)	*i*Pr	97:3[g]	>95:5	(+)-**9i** (>99)	100	94

[a] All reactions were performed in diethyl ether, c(*o*-DPPB ester) = 0.05 M. The Grignard reagent (0.76–1.23 M in diethyl ether) was added to the reaction mixture with a syringe pump over a period of 15–20 min. [b] Prepared from the corresponding allylic alcohol[12] by an esterification protocol reported previously.[9] The enantiomeric excess was determined by HPLC analysis of the corresponding allylic alcohol (Chiralpak AD (**8a**), Chiralcel OD-H (**8b**)). [c] Determined by ^{1}H NMR spectroscopy (entry 1) or HPLC analysis (entries 2, 3, 5, 7, 9: Chiralcel OD-H; entry 4: Chiralpak AD after removal of the TBDMS group; entries 9, 12: Chiralcel OD-H after removal of the TBDPS group). [d] The chirality transfer (CT) was calculated as CT = (*ee*(**9**)/*ee*(**8** or **11**)) × 100. [e] Yield of isolated product after chromatographic purification. [f] c(**8a**) = 0.01 M in diethyl ether; the Grignard reagent (0.07 M in diethyl ether) was added over a period of 90 min. [g] Product ratios were determined by ^{1}H NMR spectroscopy. [h] n.d. = not determined. [i] With 1-methyl-2-pyrrolidinone (NMP) as a cosolvent (one third of the total solvent volume).

Thus, as expected, the reaction proceeds through a *syn* substitution pathway with respect to the leaving group. The *o*-DPPB group acts as a directing leaving group through



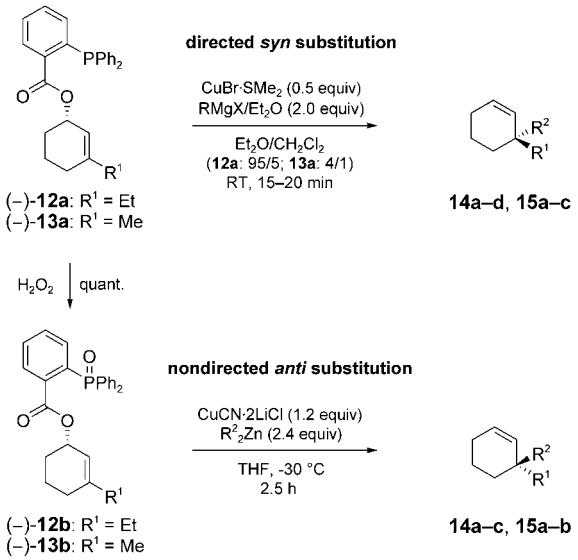
phosphane coordination of the organocopper reagent. A transition state that accounts for the observed stereochemistry is depicted in Scheme 1.

Next, allylic substitution of the enoate (−)-**8b** was examined. In this case the problem of thermodynamically unfavorable enoate deconjugation combines with a chemoselectivity issue arising from reactivity of the ethyl ester functionality toward the nucleophilic Grignard reagent.[3,5a,b] Interestingly, even in this case the directed allylic substitution of occurred with complete chemo-, regio-, and stereoselectivity and with excellent chirality transfer to give the substitution products (−)-**9g–i** (Table 2, entries 7–9).

To access the opposite enantiomers of the substitution products of the same allylic *o*-DPPB ester substrates the stereochemical course of the allylic substitution must be reversed. Instead of proceeding through a directed *syn* substitution pathway, the reaction should proceed through the nondirected *anti* attack of the nucleophile with respect to the leaving group. Thus, the directing power of the *o*-DPPB functionality would have to be turned off, for example, by oxidation of the phosphane group of the *o*-DPPB enoate (−)-**8b** to give the phosphane oxide (−)-**11**. The ability of the *o*-DPPB group to coordinate the copper reagent should thus be suppressed and the leaving-group ability of the benzoate group increased significantly.

Treatment of the allylic *o*-DPPB oxide ester (−)-**11** with dialkyl zinc reagents in the presence of CuCN·2 LiCl in THF furnished the *anti* S_N2' substitution products (+)-**9g–i** in good yields with perfect regioselectivity and excellent 1,3-*anti* chirality transfer.[13] However, when the *o*-DPPB ester (−)-**8b** was subjected to reaction conditions identical to those used in entries 10–12 of Table 2, allylic substitution did not occur even after warming the reaction mixture to room temperature and prolonged reaction time (24 h). Evidently the oxidation of the phosphane functionality to the phosphane oxide serves two purposes. First, it switches off the directing power of the phosphane group and thus suppresses the directed *syn* substitution pathway. Second, it enhances the leaving-group ability of the benzoate group to make nondirected *anti* substitution possible. This methodology is also applicable to cyclic substrates with similar efficiency. For example, stereodivergent directed/nondirected substitution of the six-membered-ring systems **12a**,**b** and **13a**,**b** is possible (Scheme 3; Table 3).

In conclusion, we have shown that the *o*-DPPB/*o*-DPPB oxide system can be used as a switchable directing/nondirecting leaving group in a copper-mediated allylic substitution reaction with Grignard and organozinc reagents for the regioselective, stereospecific, and stereodivergent construction of quaternary carbon centers. Thus, both enantiomers of the substitution product are readily available from one enantiomer of the substrate.



Scheme 3. Stereospecific and stereodivergent construction of quaternary carbon centers through the switchable directed/nondirected allylic substitution of the cyclic substrates (−)-**12a/b** and (−)-**13a/b** (see Table 3).

Table 3: Stereospecific and stereodivergent formation of quaternary carbon centers: cyclic substrates.

Entry	Substrate[a] (*ee* [%])	R	S_N2'/S_N2[b]	Product (*ee* [%])[b]	CT[c] [%]	Yield[d] [%]
1[e]	**12a** (97)	Me	99:1	(+)-**14a** (96)	99	>95
2[e]	**12a** (97)	*n*Bu	>99:1	(+)-**14b** (96)	99	>95
3[e]	**12a** (97)	*i*Pr	98:2	(−)-**14c** (96)	99	>95
4[e]	**12a** (97)	Ph	40:60	(+)-**14d** (92)	95	>95
5[f]	**13a** (94)	Et	96:4	(−)-**14a** (91)	97	>95
6[f]	**13a** (94)	*n*Bu	98:2	(+)-**15a** (94)	100	>95
7[f]	**13a** (94)	*i*Pr	96:4	(−)-**15b** (91)	97	>95
8[f]	**13a** (94)	Ph	41:59	(+)-**15c** (82)	87	>95
9[g]	**12b** (97)	Me	99:1	(−)-**14a** (93)	96	>95
10[g]	**12b** (97)	*n*Bu	>99:1	(−)-**14b** (96)	99	>95
11[g]	**12b** (97)	*i*Pr	97:3	(+)-**14c** (94)	97	>95
12[g]	**13b** (94)	Et	>99:1	(+)-**14a** (93)	99	>95
13[g]	**13b** (94)	*n*Bu	99:1	(−)-**15a** (94)	100	>95
14[g]	**13b** (94)	*i*Pr	99:1	(+)-**15b** (93)	99	>95

[a] Prepared from the corresponding allylic alcohol following an esterification protocol reported previously.[9] The enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H (**12a**), Chiralcel OD-H (**13a**)). [b] Determined by ^{1}H NMR spectroscopy and GC analysis (Supelco Beta Dex 110 (**14a**,**14d**,**15c**), C.E.I. G-TA (**14b**,**14c**,**15a**,**15b**)). [c] The chirality transfer (CT) was calculated as CT = (*ee*(**14**)/*ee*(**12**)) × 100. [d] Yield was determined by GC. [e] The Cu-complexed *o*-DPPB esters were added in diethyl ether/dichloromethane (95:5, c = 0.01 M) to the Grignard reagent (0.05 M in diethyl ether) by using a syringe pump (6 mL h^{-1}). [f] As for [e], but diethyl ether/dichloromethane (4:1, *c* = 0.01 M). [g] The oxidized *o*-DPPB esters (*c* = 0.07 M in THF) were added to the zinc–copper reagents (*c* = 1.00 M in THF) at a rate of 12 mL h^{-1}.

Experimental Section

Synthesis of (−)-**9h** (*syn* substitution): $CuBr{\cdot}SMe_2$ (11.9 mg, 0.058 mmol) was added to a solution of freshly purified (−)-**8b** (82 mg, 0.117 mmol, >99% *ee*) in diethyl ether (2.3 mL), and the mixture was stirred for a further 5 min at room temperature. *n*BuMgBr (0.11 mL, 0.140 mmol, 1.23 M solution in diethyl ether)

was added to the resulting yellow solution over a period of 20 min by using a syringe pump. When the addition of the Grignard reagent was complete, the reaction mixture was quenched by adding a saturated aqueous solution of NH_4Cl (2.5 mL), followed by diethyl ether (10 mL) and an aqueous solution of NH_3 (12.5%, 1 mL). This mixture was extracted with diethyl ether (3 × 20 mL). The combined ethereal phases were washed with water (10 mL), then brine (10 mL), and dried ($MgSO_4$). The solvent was then removed in vacuo. Flash chromatography of the residue on silica with petroleum ether (60–70)/diethyl ether (95:5) yielded analytically pure (−)-**9h** (45 mg, 85%, $S_N2'/S_N2 > 99:1$, $E/Z > 99:1$, >97% *ee*) as a colorless oil. HPLC (Chiralcel OD-H, 15°C, *n*-heptane, 0.8 mL min^{-1}, 227 nm): t_R ((−)-**9h**): 20.01 min (98.7%), t_R ((+)-**9h**): 21.90 min (1.3%); $[\alpha]_D^{22} = -3.7$ ($c = 1.75$, $CHCl_3$); ^{1}H NMR (400.136 MHz, $CDCl_3$, TMS): $\delta = 0.89$ (t, 3H, $J = 7.3$ Hz, CH_3), 1.06 (s, 9H, 3 × CH_3), 1.23 (t, 3H, $J = 7.3$ Hz, CH_3), 1.24 (s, 3H, CH_3), 1.28 (m, 4H, 2 × CH_2), 1.53 (m, 1H, CH_2), 1.67 (m, 1H, CH_2), 4.10 (m, 1H, CH_2), 4.13 (m, 1H, CH_2), 4.22 (dd, 2H, $J = 5.5$, 1.7 Hz, CH_2), 5.58 (m, 1H, CH), 5.90 (dt, 1H, $J = 15.9$, 1.7 Hz, CH), 7.39 (m, 6H, Ar-H), 7.68 ppm (m, 4H, Ar-H); ^{13}C NMR (100.624 MHz, $CDCl_3$): $\delta = 14.0$, 14.2, 19.2, 21.0, 23.1, 26.8 (3 × C), 26.8, 39.2, 47.6, 60.5, 64.5, 127.6 (4 × C), 127.6, 129.6 (2 × C), 133.9, 134.2 (2 × C), 135.6 (4 × C), 176.0 ppm; elemental analysis (%) calcd for $C_{28}H_{40}O_3Si$ (452.70): C 74.29, H 9.01; found: C 74.38, H 8.91.

Synthesis of (+)-**9h** (*anti* substitution): A freshly prepared solution of CuCN·2 LiCl in THF (52 μL, 0.052 mmol, 1M; a mixture of the two salts was dried for 2 h at 120°C in vacuo (oil pump) prior to use) was cooled to −30°C and diluted with additional THF (0.5 mL). A solution of nBu$_2$Zn in heptane (0.1 mL, 0.1 mmol, 1.0M) was added dropwise, and the resulting colorless solution was stirred for a further 10 min at −30°C. A solution of (−)-**11** (31 mg, 0.043 mmol, >99% *ee*) in THF (1 mL) was added over a period of 5 min. The resulting colorless solution was warmed to 0°C over 2.5 h, during which time a beige suspension formed (quantitative conversion by TLC). The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (2 mL), followed by diethyl ether (20 mL) and an aqueous solution of NH_3 (12.5%, 0.5 mL). This mixture was extracted with diethyl ether (3 × 10 mL). The combined ethereal phases were washed with water (10 mL), then brine (10 mL), and dried ($MgSO_4$). The solvent was removed in vacuo. Flash chromatography of the residue on silica with petroleum ether (60–70)/ethyl acetate (95:5) yielded pure (+)-**9h** (17 mg, 87%, $S_N2'/S_N2 > 99:1$, $E/Z > 98:2$, >99% *ee*) as a colorless oil. HPLC (Chiralcel OD-H, 15°C, *n*-heptane, 0.5 mL min^{-1}, 227 nm): t_R ((−)-**9h**): 20.01 min (0.5%), t_R ((+)-**9h**): 21.90 min (99.5%); $[\alpha]_D^{20} = +9.1$ ($c = 0.87$, $CHCl_3$).

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