$\beta = 95.38(3)^\circ$, $V = 2323.9(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 3.469$ Mg m^{-3}, $F(000) = 2240$, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $\mu(Mo_{K\alpha}) = 5.116$ mm^{-1}, $T = 298$ K. Of 11197 reflections collected in the range $2.1 \le 2\theta \le 53.1^\circ$ using the $\theta - 2\theta$ scan mode, 5132 were independent. Lorentzian polarization and empirical absorption corrections ($T_{min} = 0.252$, $T_{max} = 0.317$) were applied, and the structure solved and refined against F^2 using SHELX86 and SHELXL93 (G. M. Sheldrick, Universität Göttingen) with 5131 reflections (all unique reflections except for one with very negative F^2). All atoms were refined anisotropically. $R_1 = 0.058$, $wR_2 = 0.063$ for 121 parameters; max./min. residual electron density: 1.444/ − 0.924 e Å^{-3}. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666 (Frau S. Höhler-Schlimm); e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-406839.

[14] K.-H.Lii, P. F.Shin, T.-M. Chen, *Inorg. Chem.* **1993**, *32*, 4373-4377.

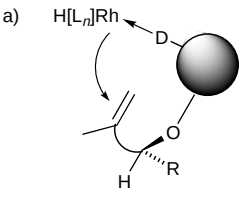
[15] I. D.Brown, D.Altermatt, *Acta Crystallogr. Sect. B* **1985**, *41*, 244 – 247.

ortho-Diphenylphosphanylbenzoyl-Directed Cuprate Addition to Acyclic Enoates**

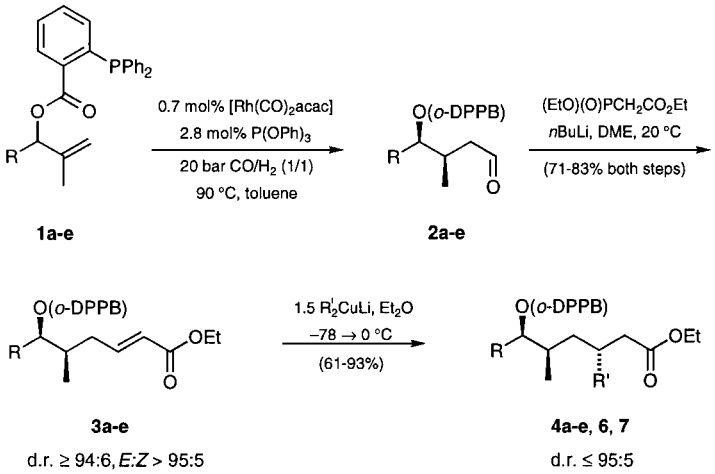
Bernhard Breit*

Reactions for constructing carbon skeletons, which lead to the formation of new stereogenic centers, are efficient transformations in organic synthesis. The control of stereoselectivity in such a process can be effected by either the reagent or the substrate. However, the latter is particularly difficult to achieve for acyclic substrates because of their structural flexibility. To overcome this problem, one has to make more efficient use of the chirality information inherent in the substrate. This can be achieved with the aid of a catalyst-directing group, which has been used successfully to control stereoselectivity in the rhodium-catalyzed hydroformylation of acyclic olefins (Scheme 1).[1] We report here that *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB), the catalyst-directing group succesfully used in the hydroformylation reactions, can be employed in a subsequent step as a reagent-directing group for the diastereoselective addition of Gilman cuprates to α,β-unsaturated enoates (Scheme 1).

Enoates **3** were chosen as the test substrates, because a stereoselective 1,4-addition of an organometallic reagent that transfers a methyl group would provide the structural building blocks found in biologically important natural products of the polyketide class (e.g. the antitumor agent dictyostatin 1 and the ionophor calcimycin).[2, 3] Enoates **3** were obtained by *o*-DPPB-directed diastereoselective hydroformylation followed by Horner – Wadsworth – Emmons (HWE) olefination of the crude hydroformylation products (**2** → **3**) in good yields (71 – 83 %), diastereoselectivities (*syn*:*anti* ≥ 94:6), and *E*/*Z* selectivities (> 95:5).



Scheme 1. Working hypothesis for the *o*-DPPB group (shown schematically as a sphere; D = donor) a) as a catalyst-directing group and b) with the examples of hydroformylation and conjugated addition of cuprates.



Treatment of **3a** with 1.5 equivalents of lithium dimethyl cuprate provided the 1,4-addition product **4a** (93 %) in a diastereomer ratio of 95:5 (Table 1, entry 1).[4] To determine the relative configuration, **4a** was transformed into the δ-lactone **5** by standard reactions (Scheme 2). A 2D NOESY NMR experiment with **5** confirmed the axial position of the proton at C3 as well as the methyl group at C5, that is, an *anti* relationship between the two 1,3-positioned methyl groups of the acyclic 1,4-addition product **4a**.

This reaction is not restricted to the transfer of a methyl group. Therefore, the addition of lithium di-*n*-butyl cuprate also proceeded with excellent diastereoselectivity (→*anti*-**6**, d.r. > 95:5, entry 2). In the case of lithium divinyl cuprate the diastereoselectivity was lower (→*anti*-**7**, d.r. = 80:20, entry 3).

With regard to the preparation of important building blocks of polyketide natural products, the addition of dimethyl cuprate is the most important reaction. Combining stereoselective *o*-DPPB-directed hydroformylation, HWE olefination, and stereoselective *o*-DPPB-directed cuprate addition provided access to acyclic building blocks with up to four stereogenic centers (→**4b** – **e**, entries 4 – 7). The 1,4-addition product **4b** is a potential C13 – C20 building block of the ionophor calcimycin, since it has the correct relative configuration at the four stereogenic centers. In addition, **4e** possesses the correct absolute configuration of this polyketide (entries 4 and 7).[3]

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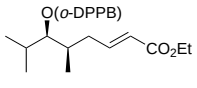
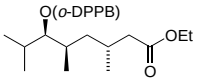
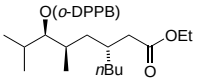
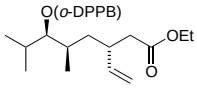
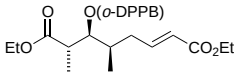
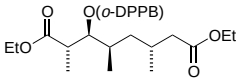
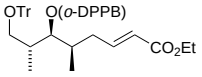
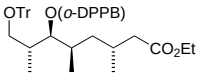
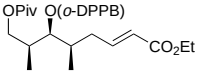
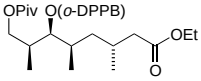
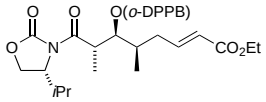
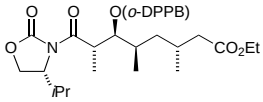
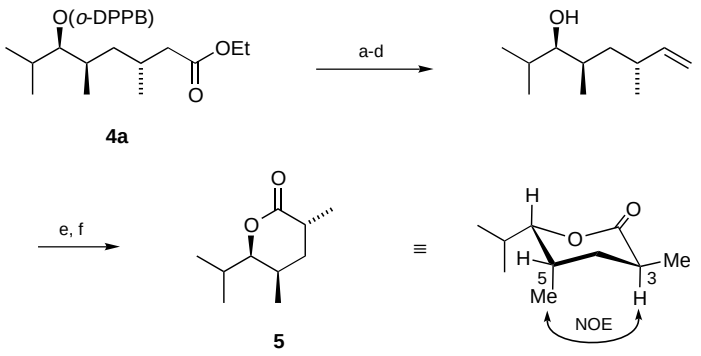
Table 1. Results of the diastereoselective conjugate addition of Gilman cuprates to enoates **3**.

Entry	Enoate	Major diastereomer[a]	Yield [%][b]	d.r. (*anti*:*syn*)[c]
1	 **3a**	 **4a**	93	95:5
2	**3a**	 **6**	68	95:5
3	**3a**	 **7**	61	80:20
4	 **3b**	 **4b**	68	95:5
5	 **3c**	 **4c**	71	86:14
6	 **3d**	 **4d**	60	85:15
7	 (−)-**3e**	 (−)-**4e**	75	95:5

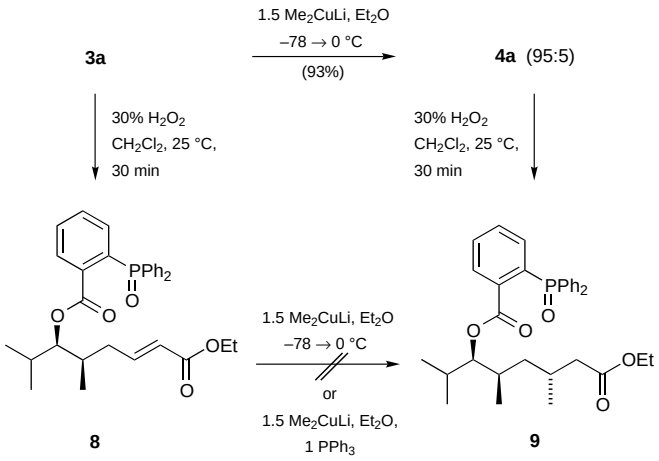
[a] The cuprate additions were performed according to the experimental procedure described for **3a**. Tr = Ph_3C, Piv = $(H_3C)_3CCO$.[b] After purification by flash chromatography. [c] Determined from ^1H NMR spectra of the crude product.

Even though the *o*-DPPB group represents an intrinsically coordinating functionality, it has not yet been proven that it is actually the origin of the observed diastereoselectivity.[5] An experiment which could give further mechanistic insight should be cuprate addition to enoate **8**, which differs from **3a** only by oxidation of the phosphane functionality to a phosphane oxide. This should suppress the ability of the *o*-DPPB group to coordinate to a cuprate. If the *o*-DPPB group does not play a significant role in controlling diastereoselectivity, one should also observe diastereoselectivity with derivative **8**. For that reason compounds **3a** and **8** were subjected to identical reaction conditions. Whereas the phosphane **3a** yielded the 1,4-addition product **4a** in 93% yield and with a diastereomer ratio of 95:5, the phosphane oxide **8** gave only unselective decomposition products besides recovered starting material.[6] Evidently, the phosphane functionality of the *o*-DPPB group is essential for a successful addition of dimethyl cuprate to the enoates **3**. However, the importance of the intramolecular attachment of the phosphane is still unclear.[7]

To address this issue, the phosphane oxide **8** was again treated with dimethyl cuprate under the identical conditions used above with one exception: the addition of one equivalent of triphenylphosphane as an external ligand.



Scheme 2. Determination of the relative configuration of **4a** by transformation into the δ-lactone **5**: a) $LiAlH_4$ (3 equiv), Et_2O, 0 → 25 °C, 2 h (94%); b) TsCl (1.1 equiv), pyridine (4 equiv), CH_2Cl_2 (0.2 M), 25 °C (72%); c) *o*-$NO_2C_6H_4SeCN$ (1.1 equiv), $NaBH_4$ (1.2 equiv), DMF, 25 °C, 6 h (100%); d) 30% H_2O_2 (10 equiv), THF, 3 h (96%); e) O_3, CH_2Cl_2, −78 °C, then PPh_3 (1.1 equiv), −78 → 25 °C (99%); f) PCC on Al_2O_3 (2 equiv), CH_2Cl_2, 36 h (70%).



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Again, besides recovered starting material, only unspecified decomposition products were found. Not even a trace of the expected 1,4-addition product **9**, which was prepared independently by oxidation of **4a**, could be identified by NMR spectroscopy.

These results indicate that stereoselective cuprate addition to enoates **3** proceeds by an intramolecular transfer of the cuprate to one of the two diastereotopic enoate faces that is mediated by the *o*-DPPB group. Thus, the *o*-DPPB group controls reactivity as well as stereoselectivity. In addition to the already known ability of the *o*-DPPB group to act as catalyst-directing group, this system has also the potential to act as an organocuprate-directing functionality.

Experimental Section

3a→**4a** (entry 1 in Table 1): To a solution of lithium dimethylcuprate—prepared from CuI (143 mg, 0.75 mmol) and a 1.11M solution of methyl lithium (1.35 mL, 1.5 mmol) in Et_2O at $-5\,^{\circ}C$—in Et_2O (5 mL) was added dropwise a solution of **3a** (251 mg, 0.5 mmol) in Et_2O (2.5 mL). The mixture was stirred for 1 h at $-78\,^{\circ}C$, the cold bath removed, and the mixture allowed to warm to $0\,^{\circ}C$ within 15 min. The reaction mixture was stirred for another 75 min at $0\,^{\circ}C$ and then quenched by adding a saturated solution of aqueous NH_4Cl (2.5 mL). The mixture was diluted with *tert*-butyl methyl ether (25 mL) and 15% aqueous NH_3 (20 mL). The mixture was shaken vigorously until both phases were homogenous. The aqueous phase was separated and extracted with *tert*-butyl methyl ether ($2\times$ 10 mL). The combined organic phases were dried over Na_2SO_4, and the solvent removed in vacuo. NMR spectroscopic analysis of this crude product revealed a diastereomer ratio of 95:5. Flash chromatography with petroleum ether/*tert*-butyl methyl ether furnished 241 mg of **4a** (93%) as a colorless, highly viscous oil.[8]

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[1] a) B. Breit, *Angew. Chem.* **1996**, *108*, 3021 – 3023; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2835 – 2837; b) B. Breit, *Liebigs Ann.* **1997**, 1841 – 1851; c) B. Breit in *Organic Synthesis via Organometallics* (Eds.: G. Helmchen, J. Dibo, D. Flubacher, B. Wiese), Vieweg, Braunschweig, **1997**, pp. 139 – 146; d) B. Breit, *Chem. Commun.* **1997**, 591 – 592.

[2] G. R. Pettit, Z. A. Cichacz, F. Gao, M. R. Boyd, J. M. Schmidt, *J. Chem. Soc. Chem. Commun.* **1994**, 1111 – 1112.

[3] a) M. O. Chaney, P. V. Demarco, N. D. Jones, J. L. Occolowitz, *J. Am. Chem. Soc.* **1974**, *96*, 1932 – 1933; b) D. A. Evans, C. E. Sacks, W. A. Kleschick, T. R. Taber, *ibid.* **1979**, *101*, 6789 – 6791.

[4] The addition of higher order cuprates to structurally similar acyclic enoates having a methyl-substituted stereocenter in the δ-position proceeded in a stereorandom fashion: B. H. Lipshutz, *Tetrahedron Lett.* **1983**, *24*, 127 – 130.

[5] The ability of phosphanes to coordinate to Gilman cuprates is known: a) X-ray crystal structure analysis of $[Cu(fluorenyl)_2(PPh_3)]^-[Li(thf)_4]^+$: A. J. Edwards, M. A. Paver, P. R. Raithby, M.-A. Rennie, C. A. Russell, D. S. Wright, *Organometallics* **1994**, *13*, 4967 – 4972; b) NMR investigations of $[LiI\cdot n Bu_2Cu(Pn Bu_3)Li]$: J. S. Filippo, Jr., *Inorg. Chem.* **1978**, *17*, 275 – 283.

[6] The addition of Gilman cuprates to enoates is generally not a synthetically useful reaction. Alternative reaction pathways such as 1,2-addition are often preferred. See ref. [4] and G. H. Posner, *Org. React.* **1972**, *19*, 1 – 113. For more recent reviews on organocuprate chemistry, see B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 135 – 631; N. Krause, A. Gerold, *Angew. Chem.* **1997**, *109*, 194 – 213; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186 – 204.

[7] The addition of PPh_3 to the Gilman cuprate Ph_2CuLi was claimed to increase the reactivity and yield of a 1,4-addition: C. Jallabert, H. Riviere, P. W. Tang, *J. Organomet. Chem.* **1976**, *104*, 1 – 8.

[8] Selected physical data for **4a**: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.7$ (m, 12H, $4CH_3$), 1.0 (m, 1H), 1.1 (m, 4H), 1.7 – 2.1 (m, 5H), 4.0 (q, $J =$ 7.2 Hz, 2H, OCH_2), 4.7 (dd, $J = 7.2$, 5.0 Hz, 1H, HCO), 6.8 (m, 1H, ArH), 7.2 – 7.3 (m, 12H, ArH), 8.0 (m, 1H, ArH); ^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 13.51$, 14.23, 17.98, 19.05, 19.30, 27.62, 29.45, 31.80, 40.54, 42.62, 59.99, 82.80, 128.05, 128.35 (d, $J_{C,P} = 7.2$ Hz, 4C), 129.45 (2C), 130.45, 131.76, 133.90 (d, $J_{C,P} = 20.8$ Hz, 2C), 134.0 (d, $J_{C,P} = 21.1$ Hz, 2C), 134.21 (the signal for one *ipso* aryl C atom, expected at $\delta = 134$ as a doublet, is hidden by the signals at $\delta = 133.90$ and 134.21), 138.21 (d, $J_{C,P} = 12.2$ Hz, 2C), 141.15 (d, $J_{C,P} = 28.3$ Hz), 166.30 (d, $J_{C,P} = 2.6$ Hz), 172.78; ^{31}P NMR (81.015 MHz, $CDCl_3$): $\delta = -2.8$; elemental analysis calcd for $C_{32}H_{39}O_4P$ ($M_r = 518.6$): C 74.11, H 7.58; found: C 74.08, H 7.63.

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