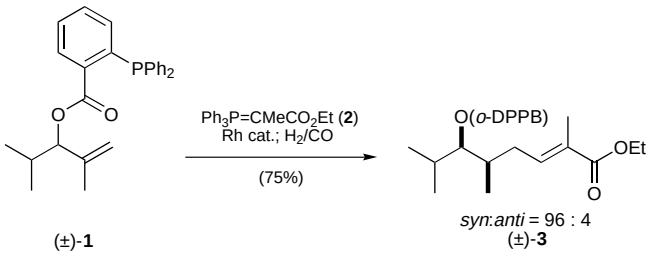
Domino Hydroformylation-Wittig Reactions**

Bernhard Breit* and Stephan K. Zahn

Efficient organic synthetic transformations are those capable of combining any two given complex building blocks in a convergent synthesis. An important example is the Wittig olefination, a reliable operation for forming carbon–carbon double bonds.[1] This reaction requires the generation of an aldehyde as a coupling partner, which is typically realized via a redox functional group interconversion or a deprotection. However, according to a definition by Hendrickson only those steps that elaborate the framework of the desired target are deemed synthetically efficient.[2] Those framework constructing reactions that simultanously provide a new stereogenic center in a selective manner are, according to Corey, even more efficient.[3] Hence, a reaction in agreement with these efficiency criteria would be a merged stereoselective hydroformylation, Wittig reaction process. Herein we report the first domino hydroformylation–Wittig as well as the first domino hydroformylation-Wittig-hydrogenation process with both methallyl and homomethallyl alcohols as alkenic substrates.[4]

When the methallyl-*o*-DPPB ester (±)-**1** (*o*-DPPB = *ortho*-diphenylphosphanylbenzene) was subjected to hydroformylation conditions in the presence of 1.1 equivalents of the stabilized disubstituted Wittig ylide **2** the 1,6-functionalized trisubstituted alkene (±)-**3** was isolated in good yield and diastereoselectivity (*syn*:*anti* = 96:4; Scheme 1).[5–7] As we have shown previously, diastereoselectivity in the course of the hydroformylation reaction is controlled by the substrate-bound, catalyst-directing *o*-DPPB group.[8, 9] The intrinsic *trans* selectivity of the Wittig olefination when using stabilized

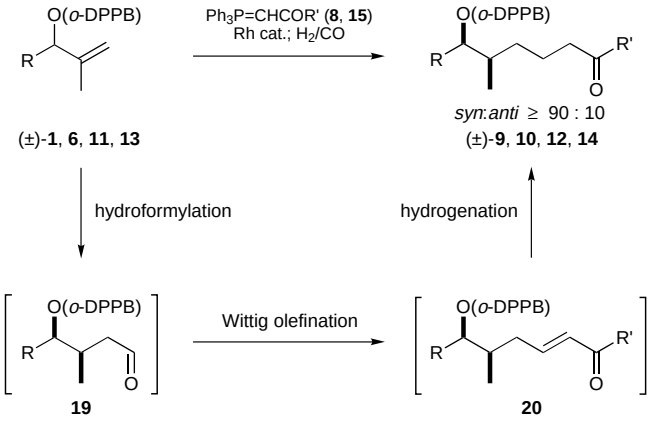


Scheme 1. Reaction conditions: 1.1 equiv $Ph_3P{=}CMeCO_2Et$ (**2**), 0.7 mol% $[Rh(H)(CO)(PPh_3)_3]$, toluene, 90 °C, 48 h, 20 bar H_2/CO (1/1).

ylides dictates the *E*-olefin geometry. Hence, this process allows the stereoselective formation of a trisubstituted double bond and the formation of a carbon–carbon single bond in a single operational step. In addition, a new stereogenic center is formed in the acyclic system with high levels of stereoselectivity.

When the disubstituted acetyl Wittig ylide **4** was used, the trisubstitued α,β-unsaturated ketone (±)-**5** was obtained in good yield and diastereoselectivity (Table 1, entry 2). The presence of a second methyl group bearing a stereocenter within the starting *o*-DPPB ester substrate (±)-**6** (Piv = pivaloyl, $(H_3C)_3CCO$) enabled the construction of a building block with three consecutive stereogenic centers (entry 3). However, a limitation of this domino reaction was set by the basicity of the Wittig ylide employed. Nonstabilized ylides lead to inactivation of the rhodium catalyst.

Interestingly, when the mono-substituted stabilized Wittig ylide **8** was used, the saturated derivatives (±)-**9**, (±)-**10**, (±)-**12**, and (±)-**14** were obtained as single reaction products in satisfactory to good yields (Scheme 2) and with diastereoselectivities ranging from 9:1 (entry 6) up to >98:2 (entry 7).



Scheme 2. Reaction conditions: 1.5 equiv $Ph_3P{=}CHCOR'$ (**8** or **15**), 0.7 mol% $[Rh(H)(CO)(PPh_3)_3]$, toluene, 90 °C, 48 h, 20 bar H_2/CO (1/1).

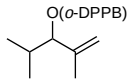
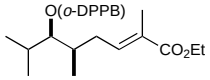
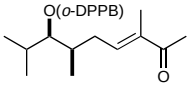
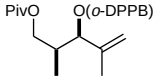
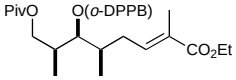
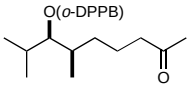
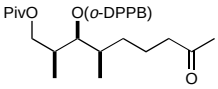
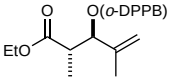
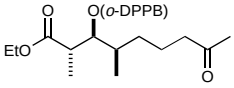
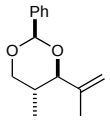
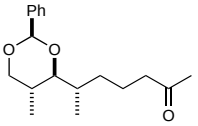
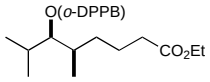
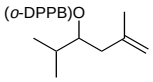
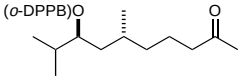
The apparent mechanism of this sequential transformation consists of three separate steps. First *o*-DPPB-directed stereoselective hydroformylation provides the aldehyde **19**,[8] which should react immediately with the Wittig ylide present to form the corresponding α,β-unsaturated carbonyl derivative **20**. Rhodium-catalyzed hydrogenation of this alkene concludes the sequence of events, and affords the saturated ketones (±)-**9**, (±)-**10**, (±)-**12**, and (±)-**14**.[7] The reaction could be used for the construction of the all-*syn*, the *anti*–*syn* and the all-*anti* stereotriad sequences that are known as central building blocks of polyketide natural products.[10] The 1,2-asymmetric induction was controlled in all those reactions within the hydroformylation step by making use of either the substrate-bound, catalyst-directing *o*-DPPB group (entries 4–6),[7] or by making use of substrate control through conformational constraints (entry 7).[11] In addition to the acetyl-substituted Wittig ylide **8**, the ester substituted ylide **15** could be employed. However, the yield of the corresponding saturated ester product (±)-**18** was low, presumably as a result of oligomer formation (entry 8). The reaction could also be applied to a homomethallyl-*o*-DPPB ester ((±)-**17**; Scheme 3). The substrate-bound, catalyst-directing *o*-DPPB group allowed the control of the diastereoselectivity by

[*] Priv.-Doz. Dr. B. Breit, Dipl.-Chem. S. K. Zahn
Fachbereich Chemie der Universität
Hans-Meerwein Strasse, D-35043 Marburg (Germany)
Fax: (+49) 6421-28-8917
E-mail: breit@ps1515.chemie.uni-marburg.de

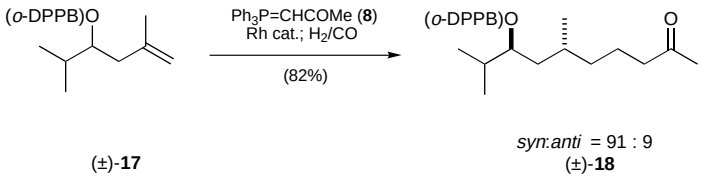
[**] This work was supported by the Fonds der Chemischen Industrie (fellowship to S.K.Z.), the Deutsche Forschungsgemeinschaft (SFB 260), and the Otto Röhm Gedächtnisstiftung. We thank Prof. R. W. Hoffmann for his continuous support as well as BASF AG and Degussa AG for their gift of chemicals.

  1433-7851/99/3807-0969 $ 17.50+.50/0

Table 1. Diastereoselective domino hydroformylation-Wittig and domino hydroformylation-Wittig-hydrogenation reactions.

Entry[a]	Alkene		Ylide	Major diastereomer[7]		Yield[b] [%]	d.r. (*syn*:*anti*)[c]
1		(±)-**1**	$Ph_3P{=}CMeCO_2Et$ **2**		(±)-**3**	75	96:4
2		(±)-**1**	$Ph_3P{=}CMeCOMe$ **4**		(±)-**5**	78	92:8
3		(±)-**6**	**2**		(±)-**7**	60	92:8
4		(±)-**1**	$Ph_3P{=}CHCOMe$ **8**		(±)-**9**	70	92:8
5		(±)-**6**	**8**		(±)-**10**	68	92:8
6		(±)-**11**	**8**		(±)-**12**	60	90:10
7		(±)-**13**	**8**		(±)-**14**	78[d]	> 98:2
8		(±)-**1**	$Ph_3P{=}CHCO_2Et$ **15**		(±)-**16**	36	92:8
9		(±)-**17**	**8**		(±)-**18**	82	91:9

[a] See ref. [5, 6] for a representative procedure and physical data for compounds (±)-**3** and (±)-**9**. [b] Yield of isolated product after column chromatography. [c] Determined by NMR spectroscopic analysis of the crude reaction mixture. [d] Based on 77% conversion (24h at 60 °C).



Scheme 3. Reaction conditions: 1.5 equiv $Ph_3P{=}CHCOMe$ (**8**) 0.7 mol% $[Rh(H)(CO)(PPh_3)_3]$, toluene, 50 °C, 4 d, 20 bar H_2/CO (1/1).

making efficient use of 1,3-asymmetric induction.[9] Thus, the 1,7-functionalized *anti*-ketone (±)-**18** was obtained in good yield and diastereoselectivity (entry 9).

Hence, this sequential transformation allows in a single operational step the formation of two carbon–carbon single bonds, with concomitant generation of a new stereogenic center with high levels of acyclic stereocontrol. This reaction may potentially be used to couple any two given complex building blocks in the context of a convergent synthetic strategy.

Received: October 22, 1998 [Z12559IE]
German version: *Angew. Chem.* **1999**, *111*, 1022–1024

Keywords: asymmetric synthesis · domino reactions · hydroformylations · synthetic methods · Wittig reactions

[1] a) A. Maercker, *Org. React.* **1965**, *14*, 270–490; b) M. Schlosser, *Top. Stereochem.* **1970**, *5*, 1–30; c) W. S. Wadsworth, Jr., *Org. React.* **1977**, *25*, 73–253; d) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927; e) H. J. Bestmann, O. Vostrowsky, *Top. Curr. Chem.* **1983**, *109*, 85–163; f) K. C. Nicolaou, M. W. Härter, J. L. Gunzer, A. Nadin, *Liebigs Ann.* **1997**, 1283–1301.

[2] a) J. B. Hendrickson, *J. Am. Chem. Soc.* **1975**, *97*, 5784–5800; b) J. B. Hendrickson, *J. Am. Chem. Soc.* **1977**, *99*, 5439–5450; c) J. B. Hendrickson, *Angew. Chem.* **1990**, *102*, 1328–1338; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1286–1295.

[3] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York **1989**, Chap. 4, pp. 47–57.

[4] For the concept of domino reactions in organic synthesis, see a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; c) T. L. Ho, *Tandem Organic Reactions*, Wiley, New York, **1992**; d) H. M. R. Hoffmann, *Angew. Chem.* **1992**, *104*, 1361–1363; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1332–1334.

[5] Representative procedure for the preparation of ester (±)-**3**: To a solution of $[RhH(CO)(PPh_3)_3]$ (6.4 mg, 7×10^{-3} mmol, 0.7 mol%) in toluene (3 mL) at 20 °C (exclusion of air and moisture), was added subsequently (±)-**1** (402 mg, 1.0 mmol) and ylide **2** (399 mg,

  1433-7851/99/3807-0970 $ 17.50+.50/0

1.1 mmol), and the solution stirred for 5 min. The resulting solution was transferred by cannula with rinsing (toluene, 2 mL) into a carefully evacuated and argon filled stainless-steel autoclave. The autoclave was heated to 90 °C and subsequently pressurized with H_2/CO (1/1, 20 bar). After stirring the mixture for 48 h at this temperature the autoclave was cooled rapidly to 20 °C and depressurized. The reaction solution was filtered through a small pad of silica with *tert*-butyl methyl ether (50 mL). After evaporation of the solvent the crude product was analyzed by NMR spectroscopy to determine the diastereomer ratio (96:4). Subsequent column chromatography on silica (solvent: petrolether/*tert*-butyl methyl ether, 9/1) provided the unsaturated ester (±)-**3** (391 mg, 0.75 mmol) as a highly viscous oil.

[6] All compounds were characterized by ^{1}H, ^{13}C, ^{31}P NMR spectroscopies and elemental analysis. Selected physical data for (±)-**3**: ^{1}H NMR (300.133 MHz, $CDCl_3$): $\delta = 0.66 - 0.75$ (m, 9H, $3CH_3$), 1.14 (t, $J = 7.1$ Hz, 3H, CH_3CH_2), 1.61 (s, 3H, CH_3), 1.73 – 2.01 (m, 4H), 4.03 (q, $J = 7.1$ Hz, 2H, CH_2), 4.72 (dd, $J = 7.6$ Hz, 3.7 Hz, 1H), 6.58 (m_c, 1H, CH-olefin), 6.79 (m_c, 1H, ArH), 7.11 – 7.16 (m, 11H, ArH), 7.23 (m_c, 1H, ArH), 7.99 (m_c, 1H, ArH); ^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 12.21$, 13.34, 13.91, 17.93, 18.84, 29.38, 32.71, 34.28, 59.96, 81.87, 127.76, 128.01 (d, $J_{C,P} = 7.1$ Hz, 2C), 128.08 (d, $J_{C,P} = 7.2$ Hz, 2C), 128.25 (2C), 128.52, 130.10, 130.81 (2C), 133.53 (d, $J_{C,P} = 20.8$ Hz, 2C), 133.66 (d, $J_{C,P} = 21.0$ Hz, 2C), 133.93, 137.78 (d, $J_{C,P} = 12.5$ Hz), 137.81 (d, $J_{C,P} = 11.9$ Hz), 139.75 , 140.88 (d, $J_{C,P} = 28.2$ Hz), 165.92, 167.60; ^{31}P NMR (81.015 MHz, $CDCl_3$): $\delta = -2.9$; elemental analysis calcd for $C_{32}H_{37}O_4P$ (516.62): C 74.49, H 7.22; found: C 74.61, H 7.34. Selected physical data for (±)-**9**: ^{1}H NMR (300.133 MHz, $CDCl_3$): $\delta = 0.67 - 0.78$ (m, 9H, $3CH_3$), 0.97 (m, 1H, CH), 1.08 (m, 1H, CH), 1.43 (m, 2H, CH_2), 1.65 (m, 1H, CH), 1.80 (m, 1H, CH), 1.97 (s, 3H, CH_3), 2.10 – 2.20 (m, 2H, CH_2), 4.72 (dd, $J = 7.8$ Hz, 4.1 Hz, 1H), 6.82 (m_c, 1H, ArH), 7.10 – 7.20 (m, 11H, ArH), 7.26 (m_c, 1H, ArH), 8.01 (m_c, 1H, ArH); ^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 13.40$, 18.08, 18.88, 21.04, 26.61, 29.20, 32.84, 34.01, 43.42, 81.55, 124.91, 127.76, 128.04 (d, $J_{C,P} = 6.8$ Hz, 2C), 128.12 (d, $J_{C,P} = 5.7$ Hz, 2C), 128.62, 130.08, 131.47 (2C), 133.52 (d, $J_{C,P} = 20.8$ Hz, 2C), 133.68 (d, $J_{C,P} = 21.0$ Hz, 2C), 133.88, 137.63 (d, $J_{C,P} = 10.3$ Hz), 137.96 (d, $J_{C,P} = 11.8$ Hz), 140.77 (d, $J_{C,P} = 27.9$ Hz), 165.97, 208.44; ^{31}P NMR (81.015 MHz, $CDCl_3$): $\delta = -2.9$; elemental analysis calcd for $C_{30}H_{35}O_3P$ (474.58): C 75.93, H 7.43; found: C 75.77, H 7.57.

[7] The relative configuration of the domino reaction products was determined at the aldeyde stage, since the stereochemistry-determining step is the hydroformylation.[8, 9, 11] This was confirmed by stepwise transformation of the known aldehyde (±)-**19** derived from olefin (±)-**1**[8] into both the domino hydroformylation-Wittig product (±)-**20** ($Ph_3P{=}CHCOMe$, CH_2Cl_2, RT, 2 d, 80 %) and the domino hydroformylation-wittig-hydrogenation product (±)-**9** (0.7 mol % [Rh(H)(CO)(PPh_3)$_3$], H_2 (20 bar), toluene, 60 °C, 24 h, 62 %).

[8] 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.

[9] a) B. Breit, *Chem. Commun.* **1997**, 591 – 592; b) B. Breit, *Eur. J. Org. Chem.* **1998**, 1123 – 1134.

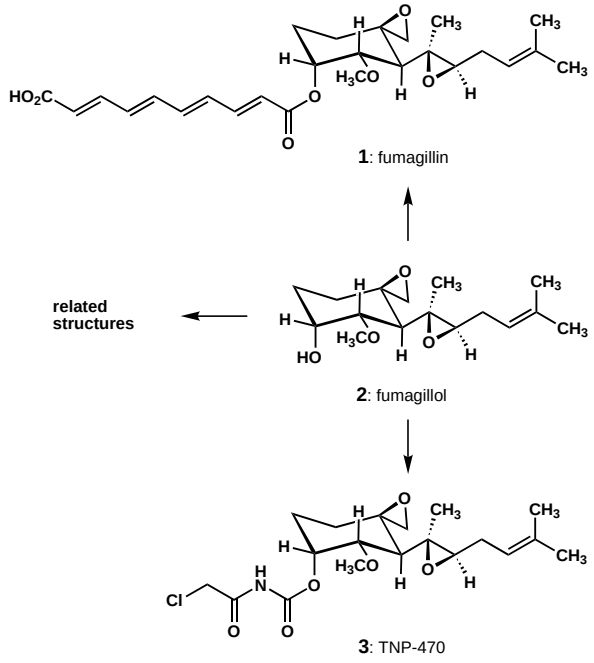
[10] R. W. Hoffmann, *Angew. Chem.* **1987**, *99*, 503 – 517; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 489 – 503.

[11] B. Breit, S. K. Zahn, *Tetrahedron Lett.* **1998**, *39*, 1901 – 1904.

A Concise Synthesis of Fumagillol**

David A. Vosburg, Sven Weiler, and Erik J. Sorensen*

Fifty years ago Hanson and Eble reported that cultures of the fungus *Aspergillus fumigatus* inhibited *Staphylococcus aureus* 209 bacteriophage.[1] The active constituent was named fumagillin, and was soon renowned for its potent antiparasitic properties.[2] The meritorious studies of Tarbell and co-workers yielded insight into the chemical behavior of fumagillin and a hypothesis about its constitution.[3] An X-ray crystallographic analysis confirmed the outcome of the chemical degradation campaign and thus established the structures of fumagillin (**1**) and its saponification product fumagillol (**2**).[4] Each substance is distinguished by two



epoxide functions, one of which is highly reactive, and six contiguous stereocenters. Fumagillin presented itself as an attractive objective for research in organic synthesis because of its novel structure and utility as an amebicide.[5] In a landmark paper in 1972 Corey and Snider described their elegant studies that culminated in the first chemical synthesis of this natural product.[6, 7]

Interest in the biological properties of fumagillin experienced a renaissance when Judah Folkman and his group discovered that **1** and its semi-synthetic derivative TNP-470

[*] Prof. Dr. E. J. Sorensen, D. A. Vosburg, Dr. S. Weiler
The Skaggs Institute for Chemical Biology
and Department of Chemistry
The Scripps Research Institute, 10550 North Torrey Pines Road
La Jolla, California 92037 (USA)
Fax: (+1) 619-784-2798
E-mail: sorensen@scripps.edu

[**] We thank Drs. D. H. Huang and L. B. Pasternack for NMR spectroscopic assistance, and Dr. G. Siuzdak for mass spectrometric assistance. This work was generously supported by The Skaggs Institute for Chemical Biology and by a predoctoral fellowship from the National Science Foundation to D.A.V.