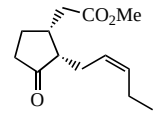
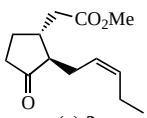
Industrial Synthesis of (+)-*cis*-Methyl Dihydrojasmonate by Enantioselective Catalytic Hydrogenation; Identification of the Precatalyst [Ru((−)-Me-DuPHOS)(H)-(η^6-1,3,5-cyclooctatriene)](BF$_4$)**

Daniel A. Dobbs, Koenraad P. M. Vanhessche, Eric Brazi, Valentin Rautenstrauch,* Jean-Yves Lenoir, Jean-Pierre Genêt,* Jason Wiles, and Steven H. Bergens

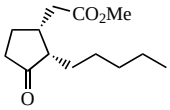
The jasmonoids, (+)-*cis*-jasmonic acid and its derivatives, have numerous phytobiological activities,[1] and in particular the methyl ester (+)-*cis*-methyl jasmonate[2] (+)-**1** also has an odor[3] that is greatly appreciated in perfumery.[4] The study of the jasmonoids began in 1962, when a near-equilibrium mixture of (−)-*trans*-methyl jasmonate (−)-**2** (main component, see below) and (+)-**1** was isolated from jasmine oil and



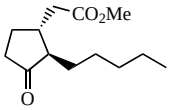
(+)-**1**



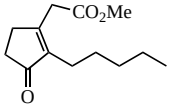
(−)-**2**



(+)-**3**



(−)-**4**



5

identified.[5] The connectivities within (+)-**1** and (−)-**2** were established by hydrogenation to the corresponding methyl dihydrojasmonates (+)-**3** and (−)-**4** and by comparison with a synthetic mixture of (±)-**3** and (±)-**4**. Subsequent work established the relative and absolute configurations, the biosynthesis, the biological activities, and, in particular, that only the unstable (+)-*cis*-jasmonic acid and its derivatives are biologically active.[1] Acid- and base-catalyzed epimerization at C(2) of the *cis* isomers is facile and the resulting *trans* isomers are thermodynamically favored. The equilibrium between (+)-**1** and (−)-**2** and that between (+)-**3** and (−)-**4** thus favors the *trans* isomers (−)-**2** and (−)-**4** by about 95:5 at ambient temperature.

Numerous syntheses of methyl jasmonates have been reported; early syntheses targeted (±)-**2**[2, 5c] and later work (±)-**1** and (+)-**1**.[6] To date, all reported syntheses of (±)-**1** and (+)-**1** are still at the laboratory scale and only the racemic equilibrium mixture is produced industrially but on a relatively small scale.

Since the early 1970s, Firmenich has commercialized the corresponding racemic, near-equilibrium mixture of methyl dihydrojasmonates[5b] under the trade name Hedione (approximately 10% (±)-**3**, 90% (±)-**4**) and this is now an important, large volume perfumery chemical.[4] Dihydrojasmonic acids and methyl dihydrojasmonates have since also been identified as natural products that have some biological activities.[7] These fragmentary data for the dihydro series, plus the possible analogy to the jasmonoids suggested that (+)-*cis*-methyl dihydrojasmonate (+)-**3**, the dihydro derivative of (+)-**1**, might be the only component of Hedione that has an odor. To investigate the olfactory properties, all four stereoisomers were prepared on a small scale.[8] Evaluation by our perfumer colleagues established that (+)-**3** is indeed the only stereoisomer that has an odor but the presence of the other three modifies the odor of (+)-**3** and also affects the performance of a perfume in which the mixture is used. One is constrained to use equilibrium mixtures in many applications because of rapid epimerization but it was found that one can use (+)-**3** and avoid equilibration in fine perfumery and thereby achieve a striking "radiance" of the perfume. To develop an industrial synthesis of (+)-**3** was therefore a desirable and challenging goal.[9]

In principle, the most direct route to (+)-**3** was enantioselective catalytic hydrogenation of the vinylogous β-oxoester **5**.[10] The *syn* addition of H_2 across the C=C bond would generate the required *cis* geometry and neutral conditions might avoid epimerization. As expected, all attempts to use known chiral catalysts to hydrogenate **5** failed. A new, more electrophilic, coordinatively unsaturated catalyst system that would react with the tetrasubstituted C=C bond in **5** was required.

We found that the treatment of equimolar solutions of [Ru(1,2:5,6-η-cod)(η^3-methallyl)$_2$] **6**[11] (cod = 1,5-cyclooctadiene) and various chiral diphosphane ligands (P–P) in CH_2Cl_2 with one equivalent of $HBF_4 \cdot Et_2O$[12] and a catalytic amount of $BF_3 \cdot Et_2O$ at ambient temperature for about 30 min generates mixtures containing precatalysts that can be used directly for the hydrogenation of **5** (0.01 M solutions of **5** in CH_2Cl_2, nominal precatalyst loading 1–3 mol%, ambient temperature, 30–100 bar). This process is derived from procedures that were developed by one of us[13] and in parallel by Heiser et al.[14] These groups treated **6** with approximately two equivalents of acids that contain coordinating conjugate bases (HCl, HBr, HI, and CF_3CO_2H, respectively). Both

[*] Dr. V. Rautenstrauch, Dr. D. A. Dobbs, Dr. K. P. M. Vanhessche, Dr. E. Brazi
Firmenich SA, Corporate R&D Division
P.O. Box 239, 1211 Geneva 8 (Switzerland)
Fax: (+41) 22-780-33-34
E-mail: valentin.rautenstrauch@firmenich.com
Prof. J.-P. Genêt, Dr. J.-Y. Lenoir
Laboratoire de Synthèse Organique
Ecole Nationale Supérieure de Chimie de Paris
11, rue Pierre et Marie Curie, 75231 Paris Cédex 05 (France)
Fax: (+33) 1-44-07-10-62
E-mail: genet@ext.jussieu.fr
J. Wiles, Prof. S. H. Bergens
Department of Chemistry
University of Alberta
Edmonton, AB, T6G 2G2 (Canada)

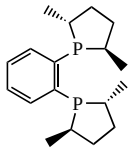
[**] We are much indebted to R. Challand and Y. Kirschmann (Firmenich) for skillful and exacting experimental work throughout the project. We thank W. Thommen, R. Brauchli, F. Delavenay, and C. Hottelier (Firmenich), and G. Bigam, G. Aarts, and Dr. T. Nakashima (University of Alberta) for the NMR investigations, Dr. R. McDonald (University of Alberta) for the X-ray structure determination of (−)-**7**·HBF$_4$, and Dr. F. Spindler (Novartis) for providing us with a series of JOSIPHOS-type ligands.

  0570-0833/00/3911-1992 $ 17.50+.50/0

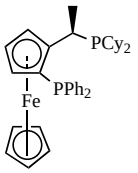
methallyl groups are abstracted on protonation and added P–P displaces the cod ligand to generate precatalysts "$[\{Ru(P\text{–}P)X_2\}_n]$" ($n = 2$, 3) and $[Ru(P\text{–}P)(CF_3CO_2)_2]$, respectively.

On attempting to generate cationic, and hence more electrophilic, coordinatively unsaturated catalysts, we instead used both an acid ($HBF_4 \cdot Et_2O$, soluble in many organic solvents) with a weakly coordinating conjugate base (BF_4^-), and a weakly coordinating, aprotic reaction medium (CH_2Cl_2). Note that the known, direct reaction between **6** and P–P, which leads to the species $[Ru(P\text{–}P)(\eta^3\text{-methallyl})_2]$,[13a,b] is negligibly slow under the conditions of our process and that catalytic amounts of $BF_3 \cdot Et_2O$ are required, although the exact role of the $BF_3 \cdot Et_2O$ is unclear.

The most active and enantioselective chiral diphospane P–P ligands among the 40 we screened were (–)-Me-DuPHOS (–)-**7**,[15] (–)-JOSIPHOS (–)-**8**,[16] (Cy = cyclohexyl) and the JOSIPHOS-derivative (–)-**9** with *p*-CF_3-phenyl groups instead of the phenyl groups in **8**.[17] Electron-rich



(–)-**7**

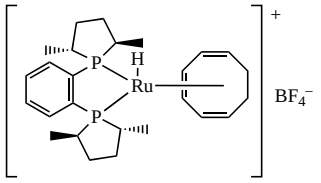


(–)-**8**

P–P ligands containing dialkylphosphane groups are required for high activity. Use of P–P ligands with two diphenylphosphane groups produced precatalysts with poor activities. Use of (+)-(BINAP)[18] resulted in low activity and *ee* (enantiomer ratio (e.r.): (+)-**3**:(–)-**3** = 71:29 (GC[6l])). Our best enantioselectivities were modest but acceptable for our purposes (e.r.: (+)-**3**:(–)-**3** = 88:12 with (–)-**9**, 82:18 with (–)-**7**, and 75:25 with (–)-**8**). The *cis* selectivities were mostly very good throughout the series of ligands surveyed and excellent (+)-**3**:(–)-**4** ≥ 99:1 (GC)) with (–)-**7**, (–)-**8**, and (–)-**9**. The traces of the *trans* isomer (–)-**4** we detect are likely due to epimerization.

Optimization of the (–)-Me-DuPHOS (–)-**7** based process revealed that there are no substantial solvent effects and it can be run in almost neat substrate, **5**. In contrast, the (–)-JOSIPHOS (–)-**8** process requires a solvent. Use of a suitable solvent not only speeds up the hydrogenation but also increases the enantioselectivity. For example, the slow reaction without solvent leads to a final e.r. (+)-**3**:(–)-**3** of 79:21 (30 °C, 90 bar) but the reaction rate increases six fold and the e.r. increases to 94:6 when four volumes of *tert*-butyl methyl ether relative to **5** are added. We report final e.r. values for complete conversion because the product (+)-**3** itself gives a solvent effect at the high concentrations we use, so that its e.r. increases in the course of the reaction. For both processes, the kinetics are, up to ≈ 90% conversion, close to zero order in substrate **5**. Typical, readily obtainable turnover numbers using either ligand are about 2000 at 25 °C and 90 bar, with turnover frequencies between 100 and 200 h^{-1}.

Using (–)-**7** as a model ligand, the reaction generating the precatalysts was monitored by NMR spectroscopy in CD_2Cl_2. The species that forms immediately upon treatment of the mixture of **6** and (–)-**7** with $HBF_4 \cdot Et_2O$ and $BF_3 \cdot Et_2O$ is the phosphonium salt (–)-**7** · HBF_4. Its identity was confirmed by preparing it separately.[19] The reaction between **6** and (–)-**7** · HBF_4 in the presence of $BF_3 \cdot Et_2O$ first gives an intermediate **10** that transforms slowly into a stable precatalyst **11**.



11

Compound **11** can be conveniently isolated when the reaction is run in a CH_2Cl_2/MeOAc solvent mixture, from which **11** precipitates as a yellow crystalline solid. It is even more convenient to treat separately prepared crystalline, (–)-**7** · HBF_4[19] with **6** and $BF_3 \cdot Et_2O$ in neat MeOAc (see the Experimental Section), which avoids the need to measure out one equivalent of $HBF_4 \cdot Et_2O$. Both procedures give **11** in about 65% yield and it remains stable for months at –30 °C under argon. This is the first use of a protiophosphonium salt of a chiral P–P ligand to prepare a precatalyst.

The identity of $[Ru((-)\text{-Me-DuPHOS})(H)(\eta^6\text{-cot})](BF_4)$ **11** (cot = 1,3,5-cyclooctatriene) was ascertained from multinuclear one- and two-dimensional NMR spectroscopy and mass spectrometry (see the Experimental Section) and the solid-state structure was later determined by X-ray diffraction.[20] A second, minor product that formed is a $[Ru((-)\text{-Me-DuPHOS})(H)(\eta^4\text{-cod}')](BF_4)$ **12** (cod′ = 1,3-cyclooctadiene), which was identified later.[20] This minor product can be separated by recrystallization but that is normally not necessary as it is just as good a precatalyst as **11**. By analogy to work reported by one of us,[21] we suggest that **10**, which is only observed in solution,[22] is $[Ru\{(-)\text{-Me-DuPHOS})(1\text{-}3{:}5,6\text{-}\eta\text{-}C_8H_{11})\}(sol)](BF_4)$ (C_8H_{11} = 2,5-cyclooctadienyl; sol = Et_2O, CH_2Cl_2). If so, **10** could be generated through protolytic cleavage of a methallyl group from **6** (to generate isobutene), coordination of (–)-**7**, allylic C–H activation at the cod ligand, and release of a second isobutene moiety. Loss of a solvent molecule from **10** with allylic activation from 1-3:5,6-η-C_8H_{11} would generate **11**.

Crystalline **11** and **10**, generated in solution, can both be used for the hydrogenation of **5**, which shows that they have similar reactivities to H_2 to generate the same active catalyst. Exposure to H_2 brings about the hydrogenation of the cot and C_8H_{11} ligands (to generate cyclooctane); the nature of the resulting, extremely electrophilic catalyst "$[Ru((-)\text{-Me-DuPHOS})(H)(sol)](BF_4)$" is explored in detail in another paper.[20]

Monitoring the reaction by NMR spectroscopy shows, that when the same kind of process is applied to (–)-JOSIPHOS (–)-**8**, several compounds are formed and only a minor component, a $[Ru((-)\text{-JOSIPHOS})(H)(\eta^6\text{-cot})](BF_4)$ **13** is

  0570-0833/00/3911-1993 $ 17.50+.50/0

identified. It seems that all the components of this mixture react with H_2 under catalytic conditions to generate the same catalyst, because the activity of the mixture about equals that of pure **13** generated by another route.[20]

Experimental Section

All operations were carried out in a glove box (under Ar; <1 ppm O_2 and H_2O) at ambient temperature unless indicated otherwise. NMR tubes were sealed under Ar and spectra were measured in CD_2Cl_2 at 300 K.

(−)-**7**·2 HBF_4: To a stirred solution of (−)-**7** (4.00 g, 13.06 mmol) in CH_2Cl_2 (25 mL) was added $HBF_4 \cdot Et_2O$[12] (3910 μL, 4.652 g, 28.73 mmol). The reaction mixture was stirred for 10 min and the solvent was removed in vacuo.[12] Addition of Et_2O (250 mL) precipitated a white powder, which was filtered, washed with Et_2O (5 × 60 mL), and dried in vacuo. Yield: 6.169 g (12.80 mmol, 98 %).

(−)-**7**·HBF_4: (−)-**7** (3.922 g, 12.80 mmol) and (−)-**7**·2 HBF_4 (6.169 g, 12.80 mmol) were dissolved in CH_2Cl_2 (115 mL) and the solution was stirred for 10 min. The solvent was removed in vacuo and addition of Et_2O (750 mL) precipitated a white powder, which was filtered, washed with Et_2O (2 × 200 mL), and dried in vacuo. Yield: 4.793 g (12.16 mmol, 95 %).

11: To a stirred solution of (−)-**7**·HBF_4 (1.182 g, 3.00 mmol) in MeOAc (75 mL) was added first **6** (0.958 g, 3.00 mmol) and, upon its dissolution, $BF_3 \cdot Et_2O$ (380 μL, 0.426 g, 3.00 mmol). The reaction mixture was stirred for 24 h and then maintained at −30 °C for 80 h without stirring. A bright yellow, crystalline precipitate formed, which was collected by filtration, rapidly washed with MeOAc (2 × 5 mL), and dried in vacuo. Yield: 1.190 g[23] (1.979 mmol, 66 %). ^{1}H NMR (400.1 MHz): $\delta = -9.97$ (1 H, br. t, $J_{PH} = 26.0$ Hz), 0.70 (3 H, dd, $J = 6.9$, 15.3 Hz), 0.93 (3 H, dd, $J = 7.4$, 16.2 Hz), 1.14 (3 H, dd, $J = 7.4$, 18.2 Hz), 1.33 (3 H, dd, $J = 6.9$, 17.2 Hz), 1.30 (1 H, m), 1.42 – 1.86 (5 H, m), 2.13 – 2.59 (8 H, m), 2.71 (2 H, m), 5.24 (1 H, br. t, $J = 7.9$ Hz), 5.38 (1 H, br. q, $J = 8.4$ Hz), 5.62 (2 H, m), 6.30 (1 H, dd, $J = 6.4$, 8.9 Hz), 6.57 (1 H, t, $J = 8.4$ Hz), 7.57 (4 H, m); ^{13}C{^{1}H} NMR (100.5 MHz): $\delta = 12.6$, 14.4 (s, CH_3), 16.2, 18.3 (d, $J_{PC} = 6.4$ Hz, CH_3), 32.0, 34.8, 35.9, 36.4, 37.4, 37.5 (s, CH_2), 39.9 (d, $J_{PC} = 25.7$ Hz, CH), 40.9 (d, $J_{PC} = 33.7$ Hz, CH), 44.4 (d, $J_{PC} = 16.1$ Hz, CH), 44.7 (d, $J_{PC} = 6.4$ Hz, CH), 94.1, 94.3, 96.1, 99.1, 101.0, 102.3, 131.0, 131.3 (s, CH), 131.4 (d, $J_{PC} = 17.7$ Hz, CH), 132.0 (d, $J_{PC} = 14.5$ Hz, CH), the signal for C (m) was too weak; ^{31}P NMR (161.9 MHz): $\delta = 84.9$, 87.5 (d, $J_{PP} = 20.3$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -152.4$; MS (desorption – CI using NH_3 as the reagent gas): isotopic cluster for $[C_{26}H_{39}P_2Ru]^+$ around *m/z* 515.

Received: December 27, 1999 [Z 14471]

[1] a) Reviews: T. K. Sarkar, B. K. Ghorai, *J. Indian Chem. Soc.* **1999**, *76*, 693 – 706; b) F. Schröder, *Angew. Chem.* **1998**, *110*, 1271 – 1274; *Angew. Chem. Int. Ed.* **1998**, *37*, 1213 – 1216; c) M. H. Beale, J. L. Ward, *Nat. Prod. Rep.* **1998**, 433 – 548; d) G. Sembdner, P. Parthier, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **1993**, *44*, 569 – 589; e) M. Hamberg, H. W. Gardner, *Biochem. Biophys. Acta* **1992**, *1165*, 1 – 18. See also: f) W. Boland, J. Hopke, J. Donath, J. Nüske, F. Bublitz, *Angew. Chem.* **1995**, *107*, 1715 – 1717; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1600 – 1602.

[2] Compound (−)-**2** was at first thought to be the primary natural product and responsible for the odor, and therefore named methyl jasmonate. Later, (+)-**1** was found to be both the primary product and the biologically active and odorant compound, and named methyl epijasmonate. For simplicity, we name as follows: (+)-*cis*-methyl jasmonate (+)-**1**, (−)-*trans*-methyl jasmonate (−)-**2**, (+)-*cis*-methyl dihydrojasmonate (+)-**3**, (−)-*trans*-methyl dihydrojasmonate (−)-**4**.

[3] T. E. Acree, R. Nishida, H. Fukami, *J. Agric. Food Chem.* **1985**, *33*, 425 – 427; R. Nishida, T. E. Acree, H. Fukami, *Agric. Biol. Chem.* **1985**, *49*, 769 – 772.

[4] G. Ohloff, *Scent and Fragrances*, Springer, Berlin, **1994**, pp. 151 – 154; G. Fráter, J. A. Bajgrowicz, P. Kraft, *Tetrahedron* **1998**, *54*, 7633 – 7703.

[5] a) E. Demole, E. Lederer, D. Mercier, *Helv. Chim. Acta* **1962**, *45*, 675 – 685; b) E. Demole, E. Lederer, D. Mercier, *Helv. Chim. Acta* **1962**, *45*, 685 – 692; c) E. Demole, M. Stoll, *Helv. Chim. Acta* **1962**, *45*, 692 – 703. For an important early review, see: d) E. Demole in *Fragrance Chemistry* (Ed.: E. T. Theimer), Academic Press, New York, **1982**, pp. 349 – 396.

[6] Reviews[1a, 5d]; (±)-**1**: a) M. Sannigrahi, D. L. Mayhew, D. L. J. Clive, *J. Org. Chem.* **1999**, *64*, 2776 – 2788; b) T. K. Sarkar, B. K. Ghorai, S. K. Nandy, B. Mukherjee, A. Banerji, *J. Org. Chem.* **1997**, *62*, 6006 – 6011; c) T. K. Sarkar, B. K. Ghorai, A. Banerji, *Tetrahedron Lett.* **1994**, *35*, 6907 – 6909; d) G. Stork, O. Ouerfelli, *New J. Chem.* **1992**, *16*, 95 – 98; e) T. Kitahara, Y. Warita, M. Abe, M. Seya, Y. Takagi, K. Mori, *Agric. Biol. Chem.* **1991**, *55*, 1013 – 1017; f) L. Crombie, K. M. Mistry, *J. Chem. Soc. Perkin 1* **1991**, 1981 – 1991; g) H. Seto, H. Yoshioka, *Chem. Lett.* **1990**, 1797 – 1800; h) L. Crombie, K. M. Mistry, *J. Chem. Soc. Chem. Commun.* **1988**, 539 – 540; i) T. Kitahara, K. Miura, Y. Warita, Y. Takagi, K. Mori, *Agric. Biol. Chem.* **1987**, *51*, 1129 – 1133; j) R. V. Stevens, N. Hrib, *Tetrahedron Lett.* **1981**, *22*, 4791 – 4794; k) H. Tanaka, S. Torii, *J. Org. Chem.* **1975**, *40*, 462 – 465. (+)-**1**: l) C. Fehr, J. Galindo, *Angew. Chem.* **2000**, *112*, 581 – 585; *Angew. Chem. Int. Ed.* **2000**, *39*, 569 – 573; m) T. K. Sarkar, B. Mukherjee, S. K. Gosh, *Tetrahedron* **1998**, *54*, 3243 – 3254; n) G. J. Roth, S. Kirschbaum, H. J. Bestmann, *Synlett* **1997**, 618 – 620; o) H. Stadtmüller, A. Vaupel, C. E. Tucker, T. Stüdemann, P. Knochel, *Chem. Eur. J.* **1996**, *2*, 1204 – 1220; p) H. Stadtmüller, P. Knochel, *Synlett* **1995**, 463 – 464; q) T. Kitahara, T. Nishi, K. Mori, *Tetrahedron* **1991**, *47*, 6999 – 7006; r) G. Helmchen, A. Goeke, G. Lauer, M. Urmann, J. Fries, *Angew. Chem.* **1990**, *102*, 1079 – 1080; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1024 – 1025; s) K. Weinges, U. Lernhardt, *Liebigs Ann. Chem.* **1990**, 751 – 754.

[7] O. Miersch, R. Kramell, B. Parthier, C. Wasternack, *Phytochemistry* **1999**, *50*, 353 – 361; M. C. S. Cano, E. G. Plaza, R. G. Muñoz, A. G. Benavente, *J. Essent. Oil Res.* **1998**, *10*, 67 – 69; A. S. C. Sing, J. Barbier, J. Smadja, *J. Nat.* **1997**, *9*, 8 – 16; G. Buchbauer, L. Jirovetz, V. K. Kaul, *J. Essent. Oil Res.* **1995**, *7*, 5 – 9; O. Miersch, G. Sembdner, K. Schreiber, *Phytochemistry* **1989**, *28*, 339 – 340; O. Miersch, A. Preiss, G. Sembdner, K. Schreiber, *Phytochemistry* **1987**, *26*, 1037 – 1039; W. Renold, R. Näf-Müller, U. Keller, B. Willhalm, G. Ohloff, *Helv. Chim. Acta* **1974**, *57*, 1301 – 1308.

[8] V. Rautenstrauch, J.-J. Riedhauser (Firmenich SA), WO 9600206, **1996** [*Chem. Abstr.* **1996**, *124*, 232126c]. Reduction of (±)-**3** with L-selectride and saponification gives (±)-all-*cis*-dihydrocucurbic acid (R. Kaiser, D. Lamparsky, *Tetrahedron Lett.* **1974**, *38*, 3413 – 3416). Resolution with (+)- and (−)-1-phenylethylamine, oxidation with pyridinium chlorochromate/NaOAc, and esterification with CH_2N_2 gives (+)-**3** and (−)-**3**. Epimerization with a catalytic amount of KNH_2 in liquid NH_3 at −75 °C gives (−)-**4** and (+)-**4**.

[9] The following patents cover the work described herein: V. Rautenstrauch, J.-P. Genêt, J.-Y. Lenoir (Firmenich SA), WO 9718894, **1997** [*Chem. Abstr.* **1997**, *127*, 83071p]; D. A. Dobbs, K. P. M. Vanhessche, V. Rautenstrauch (Firmenich SA), WO 9852687, **1998** [*Chem. Abstr.* **1999**, *130*, 40076p]. An alternative approach to (+)-**3** (and (+)-**1**) that does not involve catalytic hydrogenation was also developed at Firmenich.[6]

[10] P. Oberhänsli (Givaudan SA), DO 2008833, **1969** [*Chem. Abstr.* **1970**, *73*, 109364e].

[11] M. O. Albers, E. Singleton, J. E. Yates, *Inorg. Synth.* **1989**, *26*, 249 – 258.

[12] $HBF_4 \cdot Et_2O$, prepared by adding one equivalent of anhydrous HF to $BF_3 \cdot Et_2O$ (K. Hafner, A. Stephan, C. Bernhard, *Liebigs Ann. Chem.* **1961**, *650*, 42 – 62), is often designated as a 54 wt % solution of HBF_4 in Et_2O and is volatile (the components HF and $BF_3 \cdot Et_2O$ probably codistill).

[13] a) J.-P. Genêt, S. Mallart, C. Pinel, S. Juge, J. A. Laffitte, *Tetrahedron: Asymmetry* **1991**, *2*, 43 – 46; b) J.-P. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, M. C. Caño De Andrade, J. A. Laffitte, *Tetrahedron: Asymmetry* **1994**, *5*, 665 – 674; c) J.-P. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, L. Bischoff, M. C. Caño De Andrade, S. Darses, C. Galopin, J. A. Laffitte, *Tetrahedron: Asymmetry* **1994**, *5*, 675 – 690; d) J.-P. Genêt, *Acros Chimica Acta* **1994**, *1*, 1 – 8; e) J.-P. Genêt, V. Ratovelomanana-Vidal, M. C. Caño De Andrade, X. Pfister, P. Guerreiro, J.-Y. Lenoir, *Tetrahedron Lett.* **1995**, *36*, 4801 – 4804; f) C. Girard, J.-P. Genêt, M. Bulliard, *Eur. J. Org. Chem.* **1999**, 2937 – 2942.

[14] B. Heiser, E. A. Broger, Y. Crameri, *Tetrahedron: Asymmetry* **1991**, *2*, 51 – 62.

  0570-0833/00/3911-1994 $ 17.50+.50/0

[15] (−)-Me-DuPHOS (−)-**7** = (−)-1,2-bis((2*R*,5*R*)2,5-dimethylphospholanyl)benzene; M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125 – 10138.
[16] (−)-JOSIPHOS (−)-**8** = (−)-(*R*-(1)-[(*S*)-2-(diphenylphosphanyl)ferrocenyl]ethyldicyclohexylphosphane; A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062 – 4066.
[17] (−)-**9** = (−)-(*R*)-(1)-[(*S*)-2-(di(4-trifluoromethylphenyl)phosphanyl)-ferrocenyl]ethyldicyclohexylphosphane; F. Spindler (Ciba-Geigy AG), EP 646590, **1995** [*Chem. Abstr.* **1995**, *123*, 112416e].
[18] (+)-(*R*)-BINAP = (+)-(*R*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; A. Myashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932 – 7934.
[19] Treatment of (−)-**7** in Et_2O with 1 equiv. $HBF_4 \cdot Et_2O$ precipitates (−)-**7** · HBF_4 but generation and isolation of (−)-**7** · $2HBF_4$ by reaction with excess $HBF_4 \cdot Et_2O$, and comproportionation with 1 equiv. (−)-**7** (see Experimental Section) is somewhat more convenient. Both salts can be isolated as analytically pure, crystalline solids. The solid-state structure of (−)-**7** · HBF_4 was determined by X-ray diffraction. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-138771. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[20] K. P. M. Vanhessche, D. A. Dobbs, V. Rautenstrauch, J. Wiles, S. H. Bergens, unpublished results.
[21] J. A. Wiles, C. E. Lee, R. McDonald, S. H. Bergens, *Organometallics* **1996**, *15*, 3782 – 3784.
[22] ^{31}P NMR (161.9 MHz, CD_2Cl_2, 300 K): $\delta = 79.2$, 86.2 (d, $J_{PP} = 30.5$ Hz).
[23] This quality still contains ~5% of **12**, as determined by ^{31}P NMR.

Constant Selectivity Relationships of Addition Reactions of Carbanions**

Roland Lucius and Herbert Mayr*

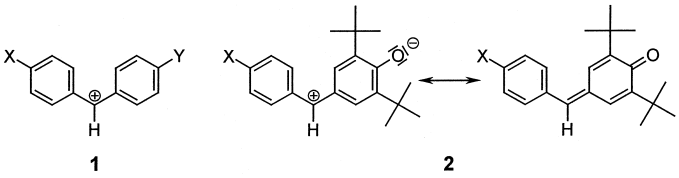
Dedicated to Professor Rolf Saalfrank on the occasion of his 60th birthday

Reactions of carbocations and related electrophiles with uncharged nucleophiles obey the linear free-energy relationship given in [Eq. (1)], where E = electrophilicity parameter, N = nucleophilicity parameter, and s = nucleophile-specific slope parameter.[1]

$$\log k\ (20\,^{\circ}C) = s(N + E) \qquad (1)$$

Since the slope parameter s is usually close to unity, it may be neglected for qualitative considerations, so that in practice reactions will be sufficiently fast at 20 °C if $(N + E) > -5$. Since the change of polarity is small in the rate-determining step of these ion – molecule reactions, the solvent effects on reaction rates are also small and can, to a first approximation, be neglected.[1c]

For the development of reactivity scales for uncharged nucleophiles, the benzhydryl cations **1** proved to be extraordinarily suitable reference electrophiles since their electrophilicities can be altered by almost 20 orders of magnitude by varying the substituents X and Y but the steric situation at the reactive site remains constant. Benzhydryl cations with amino groups in the *p*-position are the weakest reference electrophiles used so far to characterize the nucleophilicities of silyl enol ethers,[2] silyl ketene acetals,[2] and enamines.[3] In order to perform kinetic investigations with still stronger nucleophiles, a further reduction of the electrophilicity of benzhydryl cations is necessary, which may be achieved be employing the strong electron donor O^- at the position X or Y of compound **1**. Thus, the quinone methides **2** represent uncharged analogues of the benzhydryl cations **1**, which again allows a variation of electrophilicity under a constant steric situation. Richard et al.,[4] have already reported that quinone methides behave as highly resonance-stabilized carbocations.



The quinone methides **2a – d** are accessible through a Mannich-type reaction from 2,6-di-*tert*-butylphenol in a one-pot procedure.[5] For the determination of the reaction rates, the potassium[6] or tetra-*n*-butylammonium[7] salts of the carbanions **3** were dissolved in DMSO. After addition of 0.02 to 0.2 equivalents of **2**, the change in their UV/Vis absorbance between $\lambda = 200 - 600$ nm was monitored with a diode-array spectrometer,[8a] and featuring a fiber-optic immersion probe.[8b] The pseudo first-order rate constants, $k_{1\psi}$, determined from the exponential decay of the absorbance at the absorption maximum, were divided by the carbanion concentration to yield the concentration-independent rate constant k [Eq. (2)], to prove that second-order kinetics are present.

$$-d[\mathbf{2}]/dt = k[\mathbf{2}][\mathbf{3}] = k_{1\psi}[\mathbf{2}] \qquad k = k_{1\psi}/[\mathbf{3}] \qquad (2)$$

The observation of isosbestic points (Figure 1) excludes long-lived intermediates, and one can assume the simple mechanism outlined in Scheme 1.

[*] Prof. Dr. H. Mayr, Dipl.-Ing. R. Lucius
Department Chemie
Ludwig-Maximilians-Universität München
Butenandtstrasse 5 – 13 (Haus F), 81377 München (Germany)
Fax: (+49) 89-2180-7717
E-mail: hmy@cup.uni-muenchen.de

[**] We thank Dipl.-Chem. R. Loos for the investigation of **3g** and the Fonds der Chemischen Industrie for financial support.