work including a low-temperature structure determination will be needed to establish whether or not there is a correlation between central and external geometries for this molecule. Other systems containing probable proton tunneling groups such as NH_3 will also be suitable candidates for this purpose.

Received: July 7, 1997 [Z10644IE]
German version: *Angew. Chem.* **1997**, *109*, 331–334

Keywords: carboxylato complexes • chromium • Jahn–Teller distortion • neutron scattering • packing effects

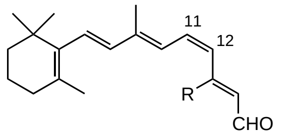
[1] T. Murao, *Phys. Lett. A* **1974**, *49*, 33.
[2] C. E. Anson, S. K. arapKoske, U. A. Jayasooriya, R. D. Cannon, *Spectrochim. Acta A* **1992**, *48*, 151.
[3] See for example: U. A. Jayasooriya, R. D. Cannon, R. P. White, G. J. Kearley, *Angew. Chem.* **1989**, *101*, 923; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 930; U. A. Jayasooriya, R. D. Cannon, R. P. White, J. A. Stride, R. Grinter, G. J. Kearley, *J. Chem. Phys.* **1993**, *98*, 9303; R. D. Cannon, U. A. Jayasooriya, R. Wu, S. K. arapKoske, J. A. Stride, O. F. Nielsen, R. P. White, G. J. Kearley, D. Summerfield, *J. Am. Chem. Soc.* **1994**, *116*, 11869.
[4] C. J. Simmons, B. J. Hathaway, K. Amornjarusiri, B. D. Santarsiero, A. Clearfield, *J. Am. Chem. Soc.* **1987**, *109*, 1047.
[5] S. K. Bollen, N. Chaisa-ard, E. Karu, R. P. White, R. D. Cannon, U. A. Jayasooriya, C. J. Carlile, S. T. Robertson, U. Steigenberger, J. Tomkinson, *Spectrochim. Acta A* **1990**, *46*, 911.
[6] *Spectrochim Acta A* **1992**, *48*, 379ff.
[7] M. K. Johnson, D. B. Powell, R. D. Cannon, *Spectrochim. Acta A* **1981**, *37*, 995.
[8] S. C. Chang, G. A. Jeffrey, *Acta Crystallogr. Sect. B* **1970**, *26*, 673.
[9] M. Sorai, M. Tachiki, H. Suga, S. Seki, *J. Phys. Soc. Jpn.* **1971**, *30*, 750; K. J. Schenk, H. U. Gudel, *Inorg. Chem.* **1982**, *21*, 2253.
[10] C. E. Anson, J. P. Bourke, R. D. Cannon, U. A. Jayasooriya, M. Molinier, A. K. Powell, *Inorg. Chem.*, submitted.
[11] A. Heidemann, S. Clough, P. P. McDonald, A. J. Horsewill, K. Neumaier, *Z. Phys. B* **1985**, *58*, 141; F. Fillaux, C. J. Carlile, *Chem. Phys. Lett.* **1989**, *162*, 188; A. Prager, A. Heidemann, W. Hausler, *Z. Phys. B* **1986**, *64*, 447; G. J. Kearley, H. Blank, J. K. Cockcroft, *J. Chem. Phys.* **1987**, *86*, 5989; H. Blank, G. J. Kearley, *ibid.* **1987**, *87*, 6809.
[12] S. Clough, A. Heidemann, A. J. Horsewill, M. N. J. Paley, *Z. Phys. B* **1984**, *55*, 1.
[13] J. P. Bourke, R. D. Cannon, R. Grinter, U. A. Jayasooriya, *Spectrochim. Acta A* **1993**, *49*, 685.
[14] The detailed fitting procedure was as follows. On the basis of the observed spectra the coupling scheme referred to in the text was adopted. This gave the energy level scheme shown in Figure 2, and four bands with transition probabilities in the ratio 1:2:2:4. These were assigned as one low-energy transition (not observed), two overlapping transitions (band B), and a fourth transition (band C). Diagonalization of the Hamiltonian matrix within a refinement cycle allowed V and W to be adjusted to give a best fit to the observed transitions; the relative intensities are constrained to the calculated ratios. This gave $V = 62$ meV and $W = 21$ meV, and the energies listed in Table 1.

Stereocontrolled Synthesis of (11*Z*)-Retinal and Its Analogues[**]

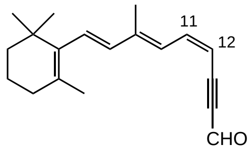
Jun'ichi Uenishi,[*] Reiko Kawahama, Osamu Yonemitsu, Akimori Wada, and Masayoshi Ito

(11*Z*)-Retinal is a key chromophore in the visual system of the retina, which assembles with an apo-protein (opsin) to form rhodopsin.[1] When rhodopsin is exposed to photons, it is promoted to an excited state which induces a bleaching process by an enzymatic cascade. Thus, the signal is delivered to the brain through synaps, and vision is possible.[2] Although part of this mechanism was previously revealed, many unexplained interactions still remain for the visual pigments, and, in particular, the mode of action for sensing color has yet to be clarified. To study such a mechanism, pure (11*Z*)-retinal and its analogues are highly desired.[3] However, the stereoselective synthesis of pure (11*Z*)-retinals has been difficult, since they are unstable towards light, heat, acids, and bases; isomerization, condensation, or polymerization are promoted. Although a number of syntheses of (11*Z*)-retinal and its analogues have appeared, all required a separation of the stereoisomers at a certain stage.[3] The synthetic problem is largely due to the lack of a reliable method for controlling the (*Z*)-alkenyl unit at the C11 position in the conjugated pentaene system.

Since we succeeded in synthesizing conjugated polyenes bearing a (*Z*)-alkenyl component,[4] (11*Z*)-retinal was a natural target for our polyene syntheses. Furthermore, this synthetic method is able to supply a number of (11*Z*)-retinal derivatives in a stereochemically pure form. Here we describe the first strictly stereocontrolled synthesis of (11*Z*)-retinal (**1**) and its analogues **2** and **3**.



1 R = CH_3
2 R = H



3

Scheme 1 summarizes the retrosynthesis of the (11*Z*)-retinals. Cleavage of the C12–C13 bond gives rise to the important and flexible intermediate **5**, which couples with an appropriate alkenylboronic acid or alkyne by Pd-catalyzed cross-coupling reactions to afford **1**, **2**, and **3** with retention of

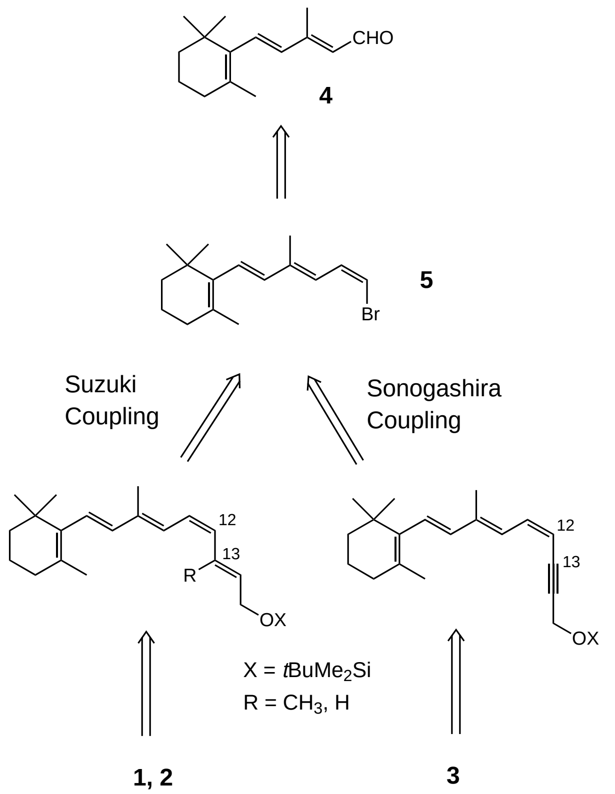
---

[*] Prof. Dr. J. Uenishi, Prof. Dr. O. Yonemitsu, Dr. R. Kawahama
Department of Chemistry, Faculty of Science
Okayama University of Science
Ridaicho, Okayama 700 (Japan)
Fax: Int. code + (81) 86254-2891
E-mail: juenishi@chem.ous.ac.jp

Prof. Dr. A. Wada, Prof. Dr. M. Ito
Kobe Pharmaceutical University, Kobe (Japan)

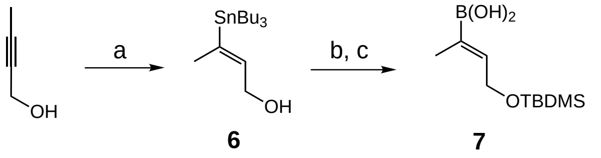
[**] This work was supported by the Grant-in-Aid for Scientific research on Priority Area No. 08245101 from the Ministry of Education, Science, Sports and Culture of the Japanese Goverment, and a Special Grant for Cooperative Research administered by the Japan Private School Promotion Foundation.

the geometries. It is important that this coupling is conducted very mildly without isomerization of the (11*Z*)-double bond in the conjugated pentaene. The key intermediate **5** can be obtained in geometrically pure form from the known aldehyde **4**[5] by the method we developed.[4]



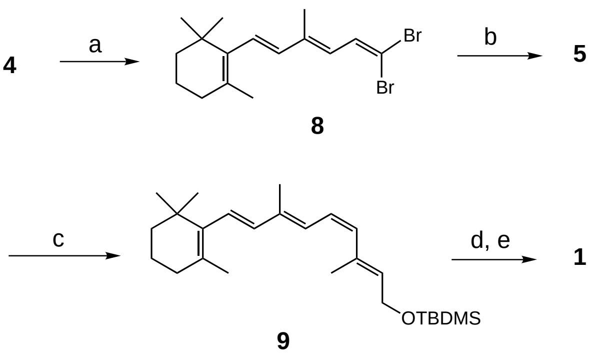
Scheme 1. Retrosynthesis of **1**–**3**; X = protecting group.

The synthesis of **1** requires the coupling partner **7**, which corresponds to the C13–C15 carbon chain; the synthesis of **7** is described in Scheme 2. A regio- and stereoselective addition of the tributylstannyl cuprate[6] to 2-butyn-1-ol gave (*E*)-3-tributylstannyl-2-buten-1-ol (**6**) in 83 % yield.[7] Protection of the primary alcohol group of **6** with *t*BuMe$_2$SiCl (TBDMSCl) afforded the corresponding silyl ether in 93 % yield. The tributylstannyl group was substituted with boronic acid in the three steps by the standard method:[8] 1) treatment of the alkenylstannane by alkenyllithium with BuLi, 2) quenching of the resulting alkenyllithium with triisopropyl boronate, and 3) hydrolysis of the boronate to boronic acid. The sequence gave **7** in 57 % yield based on 2-butyn-1-ol.



Scheme 2. Synthesis of alkenylboronic acid **7**. a) $(Bu_3Sn)_2CuCNLi_2$, MeOH, THF, −10 °C; b) TBDMSCl, KH, THF, RT; c) 1. BuLi, THF, −78 °C; 2. $B(O\mathit{i}Pr)_3$; 3. aq HCl.

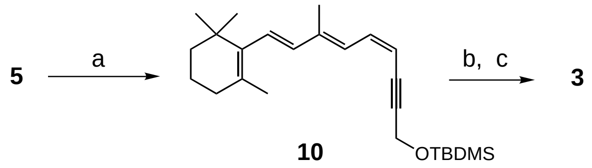
The construction of **1** from **4** is shown in Scheme 3. Aldehyde **4** was dibromomethylenylated at 0 °C with carbon tetrabromide and triphenylphosphane in dichloromethane[9] to afford **8** in 88 % yield.[10] Stereoselective hydrogenolysis of **8** with tributyltin hydride in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ proceeded very cleanly to give **5** in 86 % yield exclusively. This is an unstable molecule which decomposed easily upon exposure to light or acid. However, if kept in frozen benzene in the presence of a small amount of triphenylphosphane at −20 °C, **5** can be stored for one month. The Suzuki coupling of **5** with **7** was carried out in THF at room temperature in the presence of a catalytic amount of $[Pd(PPh_3)_4]$, Ag_2CO_3, and an aqueous solution of KOH to give **9** in 77 % yield with retention of configuration. Removal of the silyl ether protecting group of **9** with tetrabutylammonium fluoride and successive oxidation with $BaMnO_4$ furnished isomerically pure **1** (85 % yield over two steps). The spectroscopic data was in accordance with those reported for (11*Z*)-retinal.[11]



Scheme 3. Synthesis of **1**. a) CBr_4, PPh_3, CH_2Cl_2, 0 °C; b) cat. $[Pd(PPh_3)_4]$, Bu_3SnH, C_6H_6, RT; c) **7**, cat. $[Pd(PPh_3)_4]$, KOH, Ag_2CO_3, THF, RT; d) Bu_4NF, THF, RT; e) $BaMnO_4$, CH_2Cl_2, RT.

In the same manner as described for **1**, 13-demethyl-(11*Z*)-retinal (**2**) was obtained in 58 % yield from **5**. Coupling of **5** with (*E*)-3-(*tert*-butyldimethylsilyl)oxy-1-propenyl-1-boronic acid[12] (90 %, based on the recovery of **5**) followed by removal of the silyl ether protecting group (85 %) and oxidation of the alcohol (76 %) afforded **2** without the formation of any other stereoisomers.[13]

Palladium-catalyzed cross-coupling of **5** with O-protected propargyl alcohol introduced a C13 alkynyl component to form **3** instead of the *E*-ethenyl functionality in **1**. Scheme 4 depicts the synthesis of **3**. Intermediate **5** was coupled with



Scheme 4. Synthesis of **3**. a) *tert*-Butyldimethylsilyl propargyl ether, cat. $[Pd(PPh_3)_4]$, cat. CuI, $\mathit{i}Pr_2NH$, C_6H_6, RT; b) Bu_4NF, THF, RT; c) $BaMnO_4$, CH_2Cl_2, RT.

tert-butyldimethylsilyl propargyl ether in the presence of [Pd(PPh_3)$_4$] (5 mol %), CuI, and diisopropylamine in benzene under the standard Sonogashira conditions[14] to give **10** in 88 % yield. The reaction proceeded without isomerization of the (11*Z*)-double bond. After the TBDMS group was quantitatively removed with Bu_4NF, the primary alcohol obtained was oxidized with $BaMnO_4$ to give **3** (68 % yield over two steps).[15]

We have demonstrated an efficient and concise synthesis of geometrically pure (11*Z*)-retinals, in which a construction of the conjugated pentaene system involving the (*Z*)-alkenyl unit is achieved. (11*Z*)-Retinals prepared by this method exhibit perfect purity in their geometry. An advantage of this method is that it can be used to prepare a wide range of (11*Z*)-retinals and thus offers a further development in the research of vision.

Experimental Section

8: PPh_3 (1.92 g, 7.32 mmol) was added all at once to an ice-cooled, stirred solution of **4** (400 mg, 1.83 mmol) and CBr_4 (912 mg, 2.75 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 5 min at the same temperature and then purified by column chromatography (silica gel, hexane) to give a mixture of **8** and retroionylidene bromide (638 mg, 8.8:1 ratio) in a combined yield of 98%. Oil; $R_f = 0.62$ (hexane); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.03$ (6H, s), 1.44 – 1.50 (2H, m), 1.57 – 1.66 (2H, m), 1.71 (3H, d, $J = 0.9$ Hz), 1.91 (3H, d, $J = 1.2$ Hz), 2.01 (2H, br t, $J = 6.2$ Hz), 6.01 (1H, d, $J = 10.9$ Hz), 6.13 (1H, d, $J = 16.1$ Hz), 6.33 (1H, dd, $J = 16.1$, 0.8 Hz), 7.27 (1H, d, $J = 10.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.5$, 19.2, 21.7, 28.9 (2C), 33.1, 34.2, 39.6, 90.7, 125.7, 129.6, 130.0, 133.6, 136.8, 137.6, 139.5; MS (70 eV): *m/z* (%): 376 (M^+, 52), 374 (M^+, 100), 372 (M^+, 50), 361 (19), 359 (34), 357 (20), 295 (11), 293 (11), 214 (29), 199 (38); HR-MS calcd for $C_{16}H_{22}Br_2$ (M^+): 376.0047, 374.0068, 372.0088; found: 376.0043, 374.0089, 372.0089.

5: A solution of Bu_3SnH (0.84 mmol, 2.27 mL, 0.37 M in benzene) was added to a mixture of **8** (298 mg, 0.8 mmol) and [Pd(PPh_3)$_4$] (37 mg, 0.032 mmol) in benzene (5.7 mL) at room temperature. The mixture was stirred for 20 min, diluted with hexane (30 mL), washed with water (2 mL) and brine (2 mL), and dried over $MgSO_4$. The extract was concentrated under reduced pressure below 10°C and purified by column chromatography (alumina, hexane) to give **5** (203 mg) in 86 % yield. After addition of PPh_3 (30 mg), the mixture was frozen in benzene at −20°C for storage. Oil; $R_f = 0.59$ (hexane); UV (hexane): $\lambda_{max} = 301$, 239 nm; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.03$ (6H, s), 1.44 – 1.49 (2H, m), 1.57 – 1.67 (2H, m), 1.72 (3H, d, $J = 0.8$ Hz), 1.94 (3H, d, $J = 1.0$ Hz), 2.02 (2H, br t, $J = 6.2$ Hz), 6.18 (1H, d, $J = 16.2$ Hz), 6.20 (1H, d, $J = 7.1$ Hz), 6.30 (1H, d, $J = 16.2$ Hz), 6.33 (1H, d, $J = 11.0$ Hz), 6.98 (1H, dd, $J = 11.0$, 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.3$, 19.2, 21.7, 28.9 (2C), 33.0, 34.2, 39.6, 108.2, 124.8, 128.9 (2C), 129.8, 137.2, 137.6, 139.7; MS (70 eV): *m/z* (%): 296 (M^+, 85), 294 (M^+, 99), 281 (21), 279 (18), 215 (100), 199 (35); HR-MS calcd for $C_{16}H_{23}Br$ (M^+): 296.0963, 294.0983; found: 296.0958, 294.0979.

9: [Pd(PPh_3)$_4$] (42 mg, 0.036 mmol), an aqueous solution of KOH (7.2 mL, 2 N), and Ag_2CO_3 (398 mg, 1.44 mmol) were successively added at room temperature to a mixture of **5** (104 mg, 0.36 mmol) and **7** (268 mg, 0.88 mmol) in degassed THF (2.6 mL). The reaction mixture was stirred for 3 h at the same temperature, diluted with 10% ether in hexane (40 mL), washed with water (3 × 5 mL) and brine (5 mL), and dried over $MgSO_4$. The organic extract was condensed under reduced pressure below 10°C, and the oily residue purified by column chromatography (silica gel, diethyl ether/hexane, 2/98) to give **9** (111 mg) in 77 % yield. The material is very light-sensitive, and should be handled in the dark. Oil; $R_f = 0.18$ (hexane); UV (hexane): $\lambda_{max} = 322$, 236 nm; ^1H NMR (300 MHz, C_6D_6): $\delta = 0.08$ (6H, s), 0.99 (9H, s), 1.11 (6H, s), 1.44 – 1.51 (2H, m), 1.54 – 1.63 (2H, m), 1.73 (3H, s), 1.76 (3H, d, $J = 0.8$ Hz), 1.85 (3H, d, $J = 1.1$ Hz), 1.95 (2H, br t, $J = 6.2$ Hz), 4.26 (2H, d, $J = 6.6$ Hz), 5.88 (1H, t, $J = 6.6$ Hz), 5.90 (1H, d, $J = 11.8$ Hz), 6.28 (1H, d, $J = 16.0$ Hz), 6.38 (1H, d, $J = 16.0$ Hz), 6.38 (1H, dd, $J = 12.0$, 11.8 Hz), 6.88 (1H, d, $J = 12.0$ Hz); ^{13}C NMR (75 MHz, C_6D_6): $\delta = -5.0$, 12.3, 17.2, 18.4, 19.7, 21.9, 26.1 (2C), 29.1, 33.2, 34.5, 39.9, 60.4, 125.2, 127.0, 127.4, 129.1, 132.4, 133.4, 134.3, 136.8, 138.3, 138.9; MS (70 eV): *m/z* (%): 400 (M^+, 100), 385 (9), 343 (8), 269 (8), 254 (12), 199 (9); HR-MS calcd for $C_{26}H_{44}OSi$ (M^+): 400.3162; found: 400.3167.

10: A mixture of **5** (100 mg, 0.34 mmol), *tert*-butyldimethylsilyl propargyl ether (115 mg, 0.68 mmol), diisopropylamine (95 µL, 0.68 mmol), [Pd(PPh_3)$_4$] (20 mg, 0.017 mmol), and CuI (6.5 mg, 0.034 mmol) in degassed benzene (3.4 mL) was stirred at room temperature for 30 min. The reaction mixture was diluted with hexane and washed with water (2 mL × 2) and brine (2 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure below 10°C. The crude mixture was purified by column chromatography (silica gel, diethyl ether/hexane, 2/98) to give **10** (115 mg) in 88 % yield. The material is very light-sensitive, and should be handled in the dark. Oil; $R_f = 0.17$ (hexane); UV (hexane): $\lambda_{max} = 324$, 252 nm; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.15$ (6H, s), 0.93 (9H, s), 1.03 (6H, s), 1.44 – 1.49 (2H, m), 1.57 – 1.66 (2H, m), 1.72 (3H, d, $J = 0.9$ Hz), 1.95 (3H, d, $J = 0.9$ Hz), 2.02 (2H, br t, $J = 6.0$ Hz), 4.53 (2H, d, $J = 2.5$ Hz), 5.46 (1H, d, $J = 10.6$ Hz), 6.17 (1H, d, $J = 16.0$ Hz), 6.27 (1H, d, $J = 16.0$ Hz), 6.56 (1H, d, $J = 12.1$ Hz), 6.76 (1H, dd, $J = 12.1$, 10.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.0$, 12.7, 18.3, 19.2, 21.7, 25.9 (2C), 28.9, 33.1, 34.2, 39.6, 52.5, 82.6, 95.2, 107.6, 126.9, 128.7, 129.8, 136.2, 137.4, 137.7, 139.1; MS (70 eV): *m/z* (%): 384 (M^+, 31), 369 (3), 327 (2), 149 (100); HR-MS calcd for $C_{25}H_{40}OSi$ (M^+): 384.2849; found: 384.2838.

Received: August 5, 1997 [Z 10782 IE]
German version: *Angew. Chem.* **1998**, *110*, 334 – 336

Keywords: alkenes · bioorganic chemistry · cross-coupling · palladium · retinoids

---

[1] R. R. Birge, *Annu. Rev. Biophys. Bioeng.* **1981**, *10*, 315 – 354; J. E. Dowling, *The Retina*, Harvard University Press, Cambridge, **1987**.

[2] K. Nakanishi, R. Crouch, *Isr. J. Chem.* **1995**, *35*, 235 – 272; R. R. Rando, *Angew. Chem.* **1990**, *102*, 507 – 526; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 461 – 480; J. C. Saari, *The Retinoids, Biology, Chemistry and Medicine*, 2nd ed. (Eds.: M. B. Sporn, A. B. Roberts, D. S. Goodmann), Raven, New York, **1994**, chap. 9, pp. 351 – 395.

[3] Reviews: R. S. H. Liu, A. E. Asato, *Tetrahedron* **1984**, *40*, 1931 – 1969; M. Dawson, P. D. Hobbs, *The Retinoids, Biology, Chemistry and Medicine*, 2nd ed. (Eds.: M. B. Sporn, A. B. Roberts, D. S. Goodmann), Raven, New York, **1994**, chap. 2, pp. 5 – 178; recent synthesis of (11*Z*)-retinals: B. Borhan, R. Kunz, A. Y. Wang, K. Nakanishi, N. Bojkova, K. Yoshihara, *J. Am. Chem. Soc.* **1997**, *119*, 5758 – 5759; A. Wada, Y. Tanaka, N. Fujioka, M. Ito, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2049 – 2052, and references therein.

[4] J. Uenishi, R. Kawahama, O. Yonemitsu, J. Tsuji, *J. Org. Chem.* **1996**, *61*, 5716 – 5717; J. Uenishi, R. Kawahama, Y. Shiga, O. Yonemitsu, J. Tsuji, *Tetrahedron Lett.* **1996**, *37*, 6759 – 6762.

[5] R. W. Dugger, C. H. Heathcock, *Syn. Commun.* **1980**, *10*, 509 – 515; J. A. Pardoen, P. P. Mulder, E. M. M. van Den Berg, J. Lugtenburg, *Can. J. Chem.* **1985**, *63*, 1431 – 1435; A. Wada, S. Hiraishi, M. Ito, *Chem. Pharm. Bull.* **1994**, *42*, 757 – 759.

[6] J.-F. Betzer, J. Ardisson, J. -Y. Lallemand, A. Pancrazi, *Tetrahedron Lett.* **1997**, *38*, 2279 – 2282.

[7] **6**: Oil; $R_f = 0.21$ (EtOAc/hexane, 1/9); IR (neat): $\tilde{\nu} = 3326$ cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.86 - 0.93$ (15H, m), 1.24 – 1.38 (6H, m), 1.41 – 1.55 (6H, m), 1.70 (1H, br s), 1.88 (3H, s), 4.26 (2H, d, $J = 6.0$ Hz), 5.75 (1H, tq, $J = 6.0$, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.0$, 13.6, 19.3, 27.3, 29.1, 58.8, 139.3, 142.3.

[8] H. C. Brown, T. E. Cole, *Organometallics* **1983**, *2*, 1316 – 1319.

[9] F. Ramirez, N. B. Desai, N. McKelvie, *J. Am. Chem. Soc.* **1962**, *84*, 1745 – 1747.

[10] This yield was determined by ^1H NMR spectroscopy for a mixture of **8** and the unseparable by-product 10-bromo-3,5,7,9-tetraene (retroionylidene bromide), which results from direct bromination of **4** under the reaction conditions. However, the by-product decomposed easily within several hours at room temperature.

[11] Y. Katsuta, M. Sakai, M. Ito, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2185 – 2192.

[12] (*E*)-1-[3-(*tert*-Butyldimethylsilyl)oxy-1-propenyl]-1,3,2-benzodioxaborole could be used instead of the boronic acid for this reaction.

[13] **2**: Oil; $R_f = 0.34$ (EtOAc/hexane, 5/95); IR (KBr): $\tilde{\nu} = 1677, 1580\ \text{cm}^{-1}$; UV (EtOH): $\lambda_{max} = 379, 243$ nm; ^{1}H NMR (300 MHz, C_6D_6): $\delta = 1.11$ (6H, s), 1.44–1.50 (2H, m), 1.53–1.63 (2H, m), 1.72 (3H, s), 1.76 (3H, d, $J = 1.0$ Hz), 1.95 (2H, br t, $J = 6.5$ Hz), 5.79 (1H, m), 6.01 (1H, dd, $J = 15.1, 7.7$ Hz), 6.27 (1H, d, $J = 16.1$ Hz), 6.35–6.47 (3H, m), 7.12 (1H, dd, $J = 15.1, 12.0$ Hz), 9.42 (1H, d, $J = 7.7$ Hz); ^{13}C NMR (75 MHz, C_6D_6): $\delta = 12.4$, 19.6, 21.9, 29.1 (2C), 33.3, 34.5, 39.8, 124.8, 126.2, 130.1, 130.4, 132.2, 133.8, 137.9, 138.0, 141.0, 144.8, 192.2; FAB-MS: *m*/*z*: 271 (M^++H); HR-MS calcd for $C_{19}H_{27}O$ (M^++H): 271.2062; found: 271.2068.

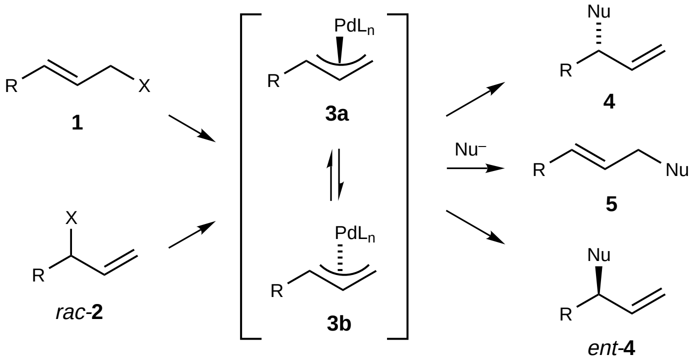
[14] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467–4470.

[15] **3**: Oil; $R_f = 0.23$ (EtOAc/hexane, 15/85); IR (KBr): $\tilde{\nu} = 2160, 1659, 1584\ \text{cm}^{-1}$; UV (EtOH): $\lambda_{max} = 370, 252$ nm; ^{1}H NMR (300 MHz, C_6D_6): $\delta = 1.04$ (6H, s), 1.35–1.45 (2H, m), 1.50–1.60 (2H, m), 1.61 (3H, s), 1.63 (3H, s), 1.89 (2H, br t, $J = 6.5$ Hz), 5.16 (1H, d, $J = 10.5$ Hz), 6.20 (1H, d, $J = 16.0$ Hz), 6.36 (1H, br d, $J = 16.0$ Hz), 6.62 (1H, dd, $J = 12.1, 10.5$ Hz), 6.78 (1H, d, $J = 12.1$ Hz), 8.91 (1H, d, $J = 1.2$ Hz); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 15.6$, 19.6, 21.8, 29.1 (2C), 33.2, 34.5, 39.8, 91.9, 96.5, 104.6, 127.0, 130.8, 131.4, 137.6, 137.7, 142.9, 143.1, 175.4; MS (70 eV): *m*/*z* (%): 268 (M^+); HR-MS calcd for $C_{19}H_{24}O$ (M^+): 268.1826; found: 268.1814.

New Ligands for Regio- and Enantiocontrol in Pd-Catalyzed Allylic Alkylations

Roger Prétôt and Andreas Pfaltz*

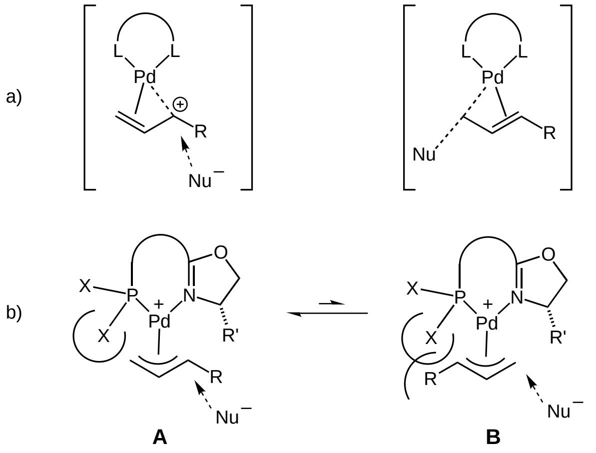
During the last few years dramatic progress has been made in the enantiocontrol of palladium-catalyzed allylic alkylations. New chiral ligands have been developed which can induce impressive levels of enantioselectivity in reactions with stabilized carbanions and various N-, O-, and S-nucleophiles.[1] However, the lack of regiocontrol is often a problem. For example, monosubstituted allylic substrates such as **1** and **2** (R = aryl) generally react predominantly at the unsubstituted allyl terminus (Scheme 1).[2] Consequently, the achiral, linear product **5** is formed rather than the chiral, branched isomer **4** or its enantiomer *ent*-**4**, which are the preferred products for applications in asymmetric synthesis. Although predominant formation of the branched isomers has been observed with achiral catalysts derived from other metals[3] (most notably W and Ir), the development of enantioselective catalysts for this class of substrate remains a challenge.



Scheme 1. Pd-catalyzed allylic alkylations generally produce the same products, regardless of whether substrate **1** or **2** is employed.

In 1995 we reported on the conversion of (*E*)-3-aryl-2-propenylphosphates **1** (R = aryl, X = OP(O)(OEt)$_2$) into chiral malonic acid derivatives **4** (Nu = CH(CO$_2$Me)$_2$).[4] High enantiomeric excesses and moderate to good regioselectivities were achieved with a tungsten catalyst prepared from the chiral (phosphanyloaryl)dihydrooxazole ligand **6a**[5] (see Scheme 3). The corresponding (*Z*) isomers and racemic substrates **2**, on the other hand, afford low enantioselectivities, in contrast with analogous Pd-catalyzed reactions, which generally proceed via rapidly equilibrating allyl intermediates and, therefore, in most cases give identical results with these three types of substrates.

Here we describe a new class of palladium catalysts that afford good enantio- and regioselectivities with both achiral and racemic aryl-substituted substrates **1** and **2**. The design of these catalysts was based on the following considerations: 1) Nucleophilic attack by an S$_N$2-type process should take place preferentially at the less substituted allyl terminus, whereas the opposite regioselectivity would be expected in an S$_N$1-like reaction via a cationic transition state (Scheme 2a).



Scheme 2. Nucleophilic attack in the Pd-catalyzed allylic alkylation. a) Transition states in S$_N$1- (left) and S$_N$2-like (right) processes. b) Steric encumbrance introduced by bulky substituents X on the P atom of the ligand favors attack of the substituted allyl terminus.

In order to enhance the S$_N$1 character, we decided to introduce electronegative substituents at the coordinating P atom that render the Pd center more electrophilic. 2) Steric factors affecting the equilibrium between allyl intermediates **A** and **B** also can play an important role (Scheme 2b). Bulky groups at the P atom are expected to destabilize isomer **B** as well as the transition states of the reaction pathways leading from **B** to the corresponding substitution products. Therefore, a pathway via **A** should be preferred and, assuming that nucleophilic attack at the allyl terminus *trans* to the Pd–P

---

[*] Prof. Dr. A. Pfaltz, Dipl.-Chem. R. Prétôt
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr (Germany)
Fax: Int. code + (49) 208-306 2992
E-mail: pfaltz@mpi-muelheim.mpg.de