Tetrahedron Letters, Vol.31, No.48, pp 6995-6998, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

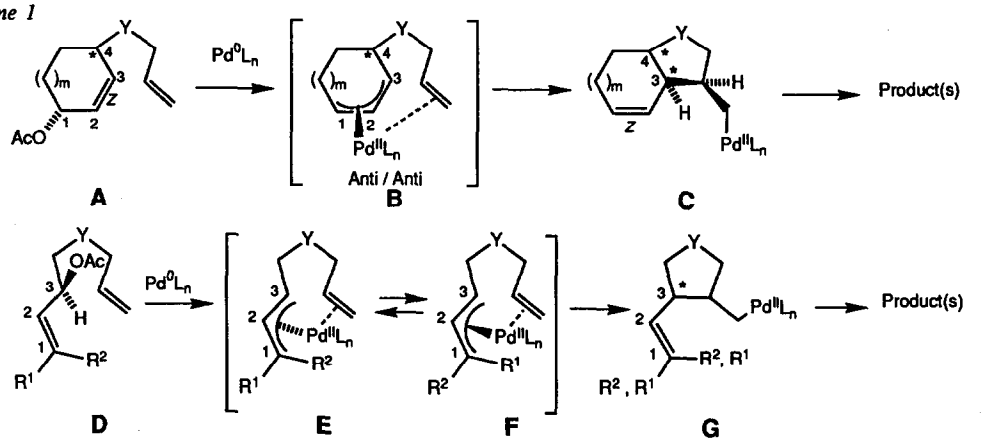
PALLADIUM CATALYZED CYCLIZATIONS OF ENANTIOMERICALLY PURE ACYCLIC 4-ACETOXY-2,8-NONADIENES: EFFICIENT CHIRALITY TRANSFER

Wolfgang Oppolzer*, Timothy N. Birkinshaw and Gérald Bernardinelli
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

Abstract: *S*-4-Acetoxy-6-aza-2,8-nonadienes 9 and 11 were subjected to Pd(0)-catalyzed cyclizations. The *S,E*-acetate 9 gave exclusively *S,E*-pyrrolidine 12, whereas the antipodal product *R,E*-12 was formed from the *S,Z*-precursor 11 (Scheme 3). X-ray-diffraction analysis of tartrate 13 served to assign the absolute configuration of 12.

1-Acetoxy-2-cycloalkenes A having an olefinic chain attached to C(4) were shown to undergo palladium catalyzed cyclizations A → B → C with clean transfer of chirality from C(1) in A to C(3) in C (Scheme 1). [1]

Scheme 1

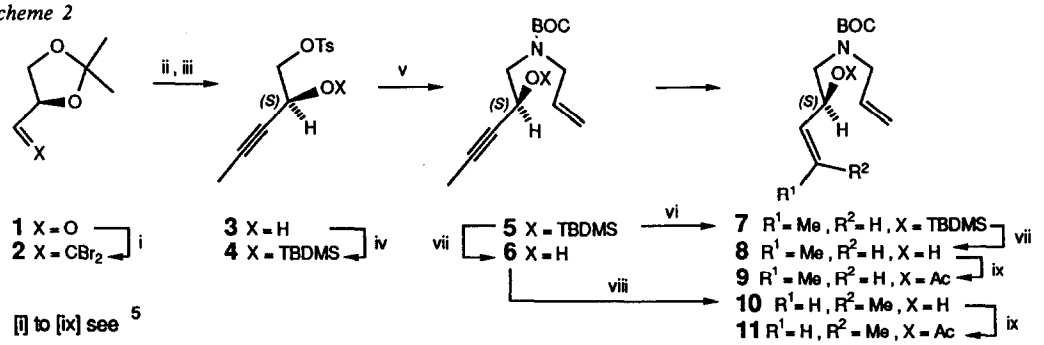


The observed overall topicity implies conventional displacement of the acetate group by Pd(0) with inversion [2] in first step A → B; more notably, the alkene moiety attacks the allylpalladium unit *cis* relative to the metal (suprafacially) in step B → C. [1].

On extending this stereospecific tandem oxidative addition/allylation to acyclic substrates the conformational mobility of acyclic allylpalladium species [3] has to be taken into account. For example, with regard to cyclizations D → G it was interesting to elucidate the extent to which the equilibrium E ⇌ F affects the stereochemical outcome.

E and *Z* acetoxydienes 9 [4] and 11 [4], both having the *S* configuration at the oxygenated center, were selectively prepared in high stereochemical purity starting from *R*-2,3-*O*-isopropylideneglyceraldehyde 1 (Scheme 2). [5,6]

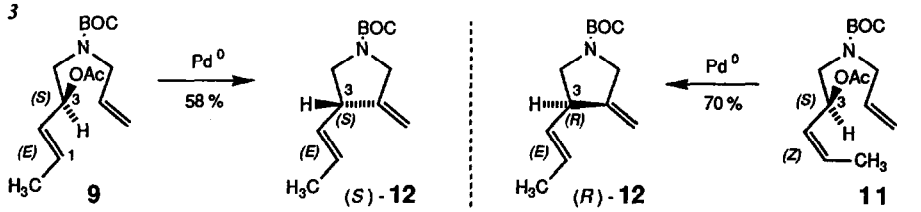
Scheme 2



This approach to 9 and 11 diverges at the stage of acetylene 5 [4] which on reduction with sodium in ammonia provided *E*-alkene 7. [4] Desilylation of 5 and hydrogenation of acetylenic alcohol 6 [4] in the presence of *Lindlar* catalyst furnished *Z*-alkene 10. [4] The *E*- and *Z*-intermediates 7 and 10 were purified by chromatography on $AgNO_3$-pretreated silica gel and then converted into the key precursors *S,E*-acetate 9 and *S,Z*-acetate 11.

The results of our cyclization studies are summarized in Scheme 3.

Scheme 3

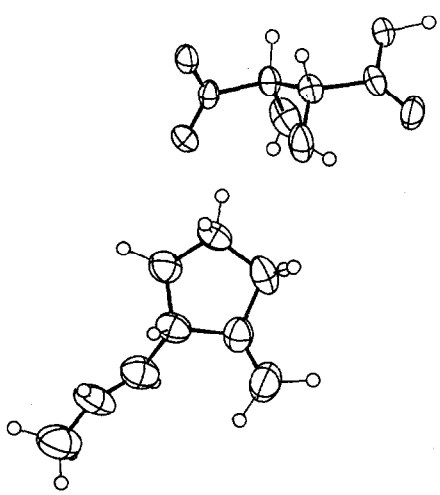


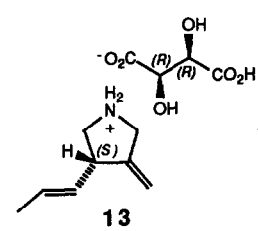
Heating a 0.2 M solution of acetate 9 (*e.e.* = 98.6%, *E/Z* = 99.6:0.4) [7] in acetic acid together with 1 mol% of $Pd(PPh_3)$ under N_2 at 70°C for 3 h, shaking of the mixture with aq. $NaHCO_3/Et_2O$, workup and flash chromatography (FC) afforded *E*-propenylpyrrolidine *S*-12 [4] (58% yield) as the only isolable product. *N*-deprotection of *S*-12 (TFA, r.t., 1 h), *N*-acylation with the acid chloride prepared from *R*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid and GC analysis (*Carbowax 20* capillary column) of the resulting *Mosher* derivative [8a] revealed that cyclization product *S*-12 is enantiomerically pure within the limits of detection (>96% *e.e.*).

Subjecting the acetoxydiene 11 (*e.e.* = 98.6%, *E/Z* = 1.3:98.7) [7] to the same Pd-catalyzed cyclization conditions provided the antipodal *E*-propenyl-substituted pyrrolidine *R*-12 [4] (70% yield). GC-analysis of its *Mosher* derivative [8a] (from *S*(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid) showed for *R*-12 an enantiomeric excess of >96%.

To assign the absolute configuration of the cyclization products 12 the (-)-pyrrolidine obtained from *S,E*-acetoxydiene 9 was converted into the crystalline tartrate 13 (1) TFA, MeOH; 2) aq. K_2CO_3; 3) *R,R*-tartaric acid, EtOH). X-ray diffraction analysis of recrystallized salt 13 [9] (MeOH/*i*PrOH, m.p. 136-137.5°C) (Figure 1) proved unambiguously the *S*-configuration of the pyrrolidinium cation (considering the *R,R*-configuration of the tartrate anion).

Figure 1: X-ray diffraction analysis of tartrate 13

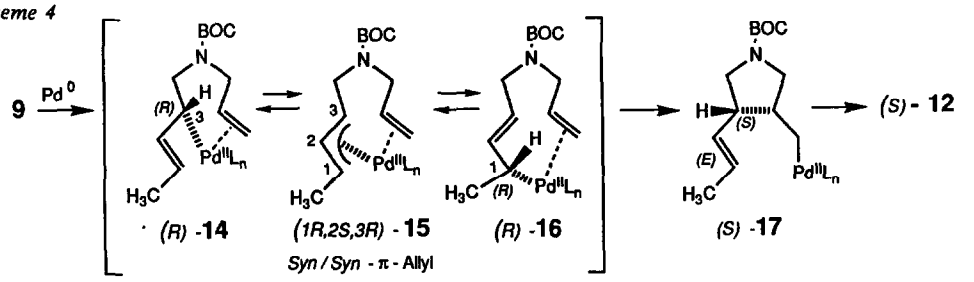




13

It thus follows that *S,E*-acetoxydiene 9 gives pyrrolidine *S*-12 with net inversion at C(3) and retention of the olefinic *E*-configuration. This result can be easily explained (Scheme 4).

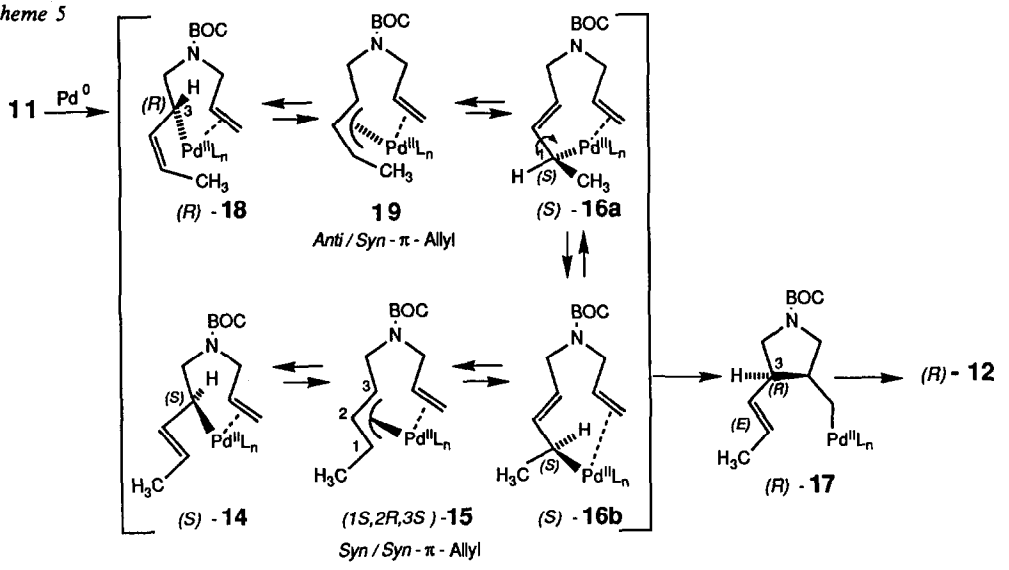
Scheme 4



Displacement of the acetate group in 9 by palladium(0) proceeds with inversion to afford the conformationally stable *syn/syn*-π-allyl complex 1*R*,2*S*,3*R*-15. Subsequent allylpalladium/olefin insertion occurs *cis* relative to the palladium [1] giving cyclized alkylpalladium species *S*-17. β-Elimination of *S*-17 yields the isolated product *S*-12.

On the other hand, net retention at C(3) coupled with complete *Z* → *E*-isomerization was observed on analogous cyclization of the *S*,*Z*-acetoxydiene 11. The overall topicity 11 → *R*-12 apparently reflects the conformational mobility of the initially formed *anti/syn*-π-allyl complex 19 (Scheme 5) which isomerizes *via the* σ-allylpalladium conformers *S*-16a ⇌ *S*-16b giving the more stable *syn/syn*-π-allyl isomer 1*S*,2*R*,3*S*-15. [2]

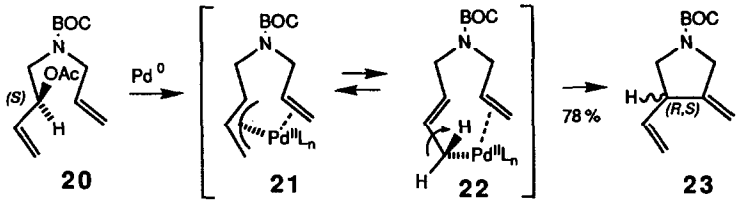
Scheme 5



This π–σ–π rearrangement thus produces the π-allyl intermediate 15 which is antipodal to the one formed more directly from the *S*,*E*-dienylacetate 9 (*c.f.*, Scheme 4). The observed high stereoselectivity of the overall transformation 11 → *R*-12 leads to the conclusion that the *anti*→*syn* isomerization 19 → 1*S*,2*R*,3*S*-15 is significantly faster than the succeeding allylpalladium/alkene insertion.

It was, therefore, not surprising that the terminally non-substituted, enantiomerically pure 3-acetoxy-1.7-octadiene 20 [4,10] yielded only racemic product 23 [4] under similar Pd-catalyzed cyclization conditions (Scheme 6).

Scheme 6



Nonetheless, excellent chirality transfer can be expected on palladium catalyzed intramolecular alkene additions to open-chain 1,3-disubstituted allylacetates as exemplified here by the enantiodivergent transformations 5 → *S*-12 and 5 → *R*-12.

Acknowledgements: Financial support of this work by the *Swiss National Science Foundation, Sandoz Ltd.*, Basel and *Givaudan SA*, Vernier, is gratefully acknowledged. We thank *The Royal Society*, London for a European Fellowship to T.N.B. We are grateful to Mr. *J.P. Saulnier*, Mr. *A. Pinto* and Mrs. *C. Clément* for NMR and MS measurements.

REFERENCES AND NOTES

1) W. Oppolzer, J.-M. Gaudin, T.N. Birkinshaw, *Tetrahedron Lett.* 1988, *29*, 4705. W. Oppolzer, T.H. Keller, M. Bedoya-Zurita, C. Stone, *ibid.*, 1989, *30*, 5883. Review on catalytic "palladium-ene type cyclizations": W. Oppolzer, *Angew. Chem.* 1989, *101*, 39; *Angew. Chem. Int. Ed. Engl.* 1989, *28*, 38.

2) 'Principles and Applications of Organotransition Metal Chemistry', Eds. J.P. Collman, L.S. Hegedus, J.R. Norton, R.G. Finke, University Science Books, Mill Valley, California, 1987, p. 881.

3) Pd(0)-catalyzed reactions of acyclic 1,3-disubstituted 1-acyloxy-2-alkenes with malonate anions proceeding with high chirality transfer and concomitant *Z* → *E* isomerization have been previously observed and attributed to a relatively fast π-σ-π rearrangement of *anti/syn*- to *syn/syn* π-allylpalladium intermediates: B.M. Trost, T.P. Klun, *J. Am. Chem. Soc.* 1981, *103*, 1864; T. Hayashi, A. Yamamoto, T. Hagihara, *J. Org. Chem.* 1986, *51*, 723; M. Uemura, T. Minami, K. Hirotsu, Y. Hayashi, *ibid.*, 1989, *54*, 469. Similar *Z* → *E* isomerizations accompany the stereospecific Pd(0)-catalyzed hydrogenolysis of alkenyloxiranes with formic acid: M. Oshima, H. Yamazaki, I. Shimizu, M. Nisar, J. Tsuji, *J. Am. Chem. Soc.* 1989, *111*, 6280.

4) All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS. $[\alpha]_D$ values, ($CHCl_3$, c = g/100 ml) = 5: +53.3° (1.41, 28°C); 9: +29.5° (1.15, 20°C); 11: -2.65° (1.13, 20°C); *S*-12: -37.6° (0.55, 20°C); *R*-12: +35.7° (0.79, 20°C); 20: +10.2° (1.27, 25°C).

5) *Stereodivergent preparation of acetoxydienes* 9 *and* 11 *from R-2,3-O-isopropylideneglyceraldehyde* 1: [i] PPh_3 (2.2 equiv), CBr_4 (1.1 equiv), CH_2Cl_2, 0°C; addition of 1 (prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (Fluka) [6], 1 equiv), -78°C; 30 min, -78°C; MeOH, Na_2CO_3, -78°C → r.t.; FC (63% yield). [ii] Addition of MeLi in Et_2O (2 equiv) to 2 (1 equiv), THF, -78°C; 1 h, -78°C; 1 h, r.t.; addition of MeI (1.2 equiv), 3 h, r.t.; workup; MeOH, *p*-TsOH (cat.), 16 h r.t.; FC, crystallization (65% yield, m.p. 71-73°C). [iii] resulting diol (1 equiv), TsCl (1.2 equiv), pyridine/CH_2Cl_2 (9:5), 0°C, 10 h; r.t., 13 h; FC (58% yield). [iv] 3 (1 equiv), TBDMS chloride (1.2 equiv), imidazole (2.7 equiv), DMF, r,t,, 3 h; FC (94% yield). [v] 4 (1 equiv), allylamine (excess), 50°C, 40 h, evaporation; $(BOC)_2O$ (1.2 equiv), r.t., 1 h; FC (86% yield). [vi] 5 (1 equiv), Na metal (16 equiv), NH_3, -78°C, 45 min; FC on $AgNO_3$-impregnated SiO_2 (63% yield). [vii] Silylether (1 equiv), $Bu_4N^+F^-$ (1.25 equiv), THF, r.t., 1-2 h; FC (87-90% yield). [viii] 6, *Lindlar* catalyst, quinoline, THF, stirring under H_2 (1 atm), 4 h; FC on $AgNO_3$-impregnated SiO_2 (75% yield). [ix] Alcohol (1 equiv), Ac_2O/pyridine (3:4, excess), DMAP (cat.), CH_2Cl_2, r.t., 16 h; FC (96% yield).

6) Review on 2,3-*O*-isopropylideneglyceraldehyde: J. Jurczak, S. Pikul, T. Bauer, *Tetrahedron*, 1986, *42*, 447.

7) *E*/*Z*-ratios of acetoxydienes 9 and 11 determined by capillary GC (OV-1). Enantiomeric excess values of 9 and 11 determined by HPLC (*Merck Hibar Lichrosorb* 5μ, hexane/THF 97:3) of the esters prepared either from *E*-alcohol 8 and *R*-α-methoxyphenylacetic acid [8b] or from *Z*-alcohol 10 and *S*-α-methoxyphenylacetic acid, [8b] respectively.

8) a) J.A. Dale, H.S. Mosher, *J. Am. Chem. Soc.* 1973, *95*, 512; b) *Idem, ibid.*, 1968, *90*, 3732.

9) Crystallographic data have been deposited at the *Cambridge Data Centre*. Structure factors may be obtained from one of us (G.B.). *Philips PW 1100 diffractometer (MoKα)*. The structure was solved by a direct method (*Multan-87*) and refined by least square analyses. The crystals of tartrate 13 are monoclinic, a = 7.2192 (12), b = 8.5015 (12), c = 11.558 (2) Å; $P2_1$, Z = 2; d_c = 1.29 g. cm^{-3}; $F(000)$ = 292. R = 0.060, (ωR = 0.043; ω = $1/\sigma^2$(Fo)) for 932 observed reflections [|Fo| ≥ 4σ (Fo)].

10) Acetoxyoctadiene 20 was prepared from 1 *via* Wittig reaction [6] followed by acetal cleavage, monotosylation, amination with allylamine, *N*-protection and *O*-acetylation using analogous reaction conditions as described in 5.

(Received in Germany 18 September 1990)