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SYNTHESIS OF NITROGEN- OR OXYGEN- CONTAINING RING SYSTEMS BY PALLADIUM-CATALYZED INTRAMOLECULAR OLEFIN ALLYLATIONS [1)]

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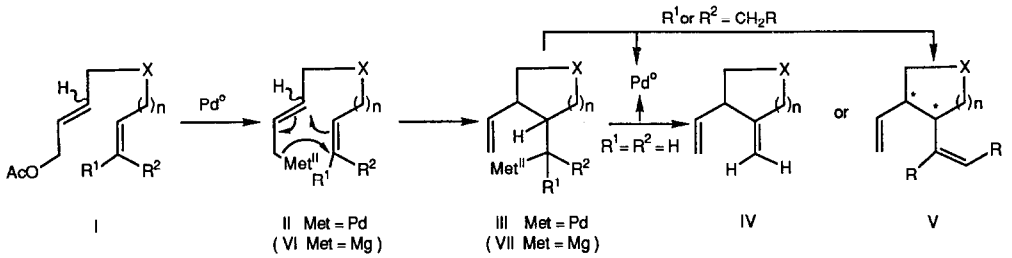
Abstract: $Pd(PPh_3)_4$-catalyzed cyclizations of *N*-allyl(crotyl, or 3-butenyl),*N*-butenyloxy derivatives and of an allyl(2-butenyloxy) ether give pyrrolidines, piperidines and a tetrahydrofuran in good yields. Hexahydroindoles and octahydroquinolines are thus obtained from the corresponding *N*-(2- or 3-butenyl),*N*-(4-acetoxy-2-cyclohexenyl) amides with excellent stereocontrol.

Pd(0)-catalyzed cyclizations of 1-acetoxy-2,7(8)-dienes I, X = $C(SO_2Ar)_2$ or $C(COOMe)_2$, n = 1 (n = 2) provide a variety of five-(six-) membered carbocyclic systems (Scheme 1) [2)]. For example, annelated cyclo- pentenes, -hexenes and -heptenes were obtained in a highly stereospecific manner when the allylacetate unit was part of a ring [3)].

Scheme 1



We also hoped that the formal palladium-"ene" step II → III would be compatible with the presence of heteroatoms X = N,O etc., in advantageous contrast to the corresponding magnesium-ene process VI → VII [4)]. The results reported below confirm our expectations.

Heating acetoxydienyl amides (-amine) 1 [5,6)] with 0.05 equiv of $Pd(PPh_3)_4$ in acetic acid at 80° smoothly furnished 3-methylene-4-vinylpyrrolidines 5 [5)] (Scheme 2, Table).

Scheme 2

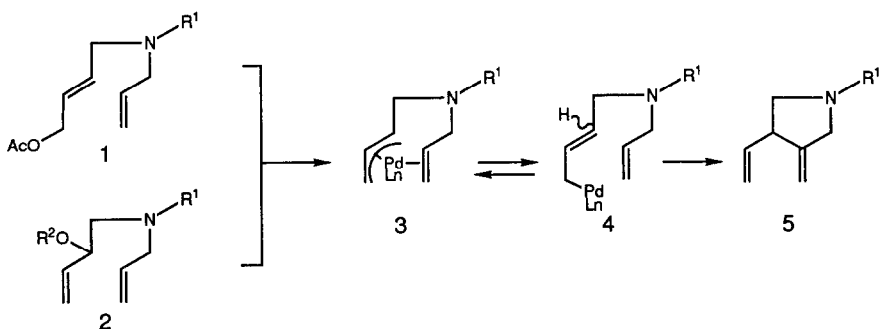


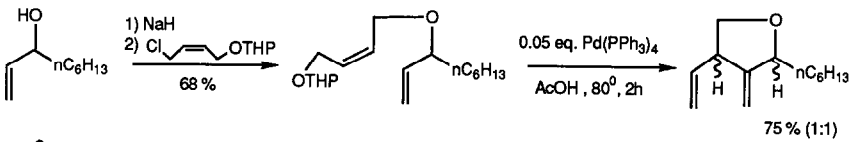
Table: *Pd(0)-Catalyzed Cyclizations (in AcOH, 80°):* 1 → 5, 2 → 5.

Entry	Series	Starting Material	R^1	R^2	$Pd(PPh_3)_4$ equiv.	Reaction Time h	Yield % of 5
1	**a**	1	CH_2Ph	-	0.05	3.0	72
2	**b**	1	$COOCH_2Ph$	-	0.05	1.0	69
3	**c**	1	SO_2pMePh	-	0.05	0.5	72
4	**d**	2	C(O)Ph	C(O)Ph	0.05	0.5	81
5	**e**	2	SO_2pMePh	H	0.07	3.5	78

Since dienylamides 1b and 1c (*Entries 2,3*) cyclized faster than the benzylamine 1a (*Entry 1*) we focused our attention on *N*-acylated substrates. Allyloxy derivatives 2 [5,7] (*Entries 4,5*), notably the free allylic alcohol 2e, also gave pyrrolidines 5 under similar reaction conditions, presumably *via* the same allyl-Pd intermediates 3 and 4 [8].

Scheme 3 illustrates the analogous formation of a tetrahydrofuran.

Scheme 3

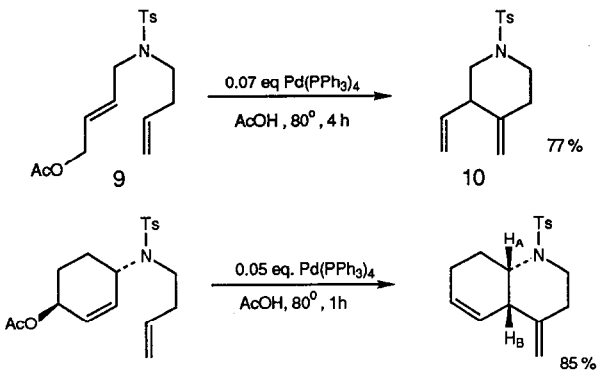


6 7 8

The ether 7 [5], readily available [9] from secondary allylic alcohol 6, gave 8 [5] in 75% yield as a 1:1- *cis/trans*- mixture. It is worth noting that the oxidative addition of Pd(0) to 7 proceeds with selective substitution of the allylic acetal whereas the allylic ether moiety remains intact.

Similar transformations of the homologous acetoxydienes 9 [5] → 10 [5] and 11 [5,10] → 12 [5] illustrate the applicability of this method for syntheses of mono- and poly-cyclic piperidines

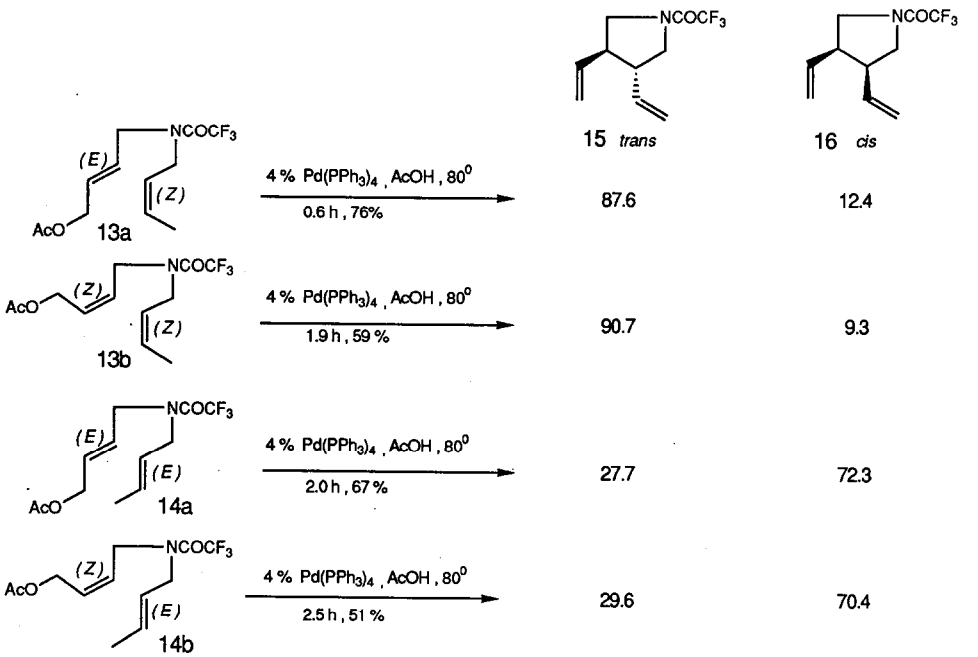
Scheme 4



9 10 11 12 J_{AB} = 5.5 Hz

Pd(0)- catalyzed transformations of *(E,Z), (Z,Z), (E,E), (Z,E)*- *N*-trifluoroacetamides 13 [5,11] and 14 [5,11] into 3,4-divinylpyrrolidines 15 [5,12] and 16 [5,12] (Scheme 5) exemplify the insertion of a terminally methyl- substituted olefinic bond into the allylpalladium unit (II → III, R^1 = H, R^2 = CH_3; R^1 = $\sim\!CH_3$, R^2 = H) followed by the β-elimination of a methyl- hydrogen atom (→ V, R = H); furthermore, they provide stereochemical information on the palladium-"ene" step II → III.

Scheme 5

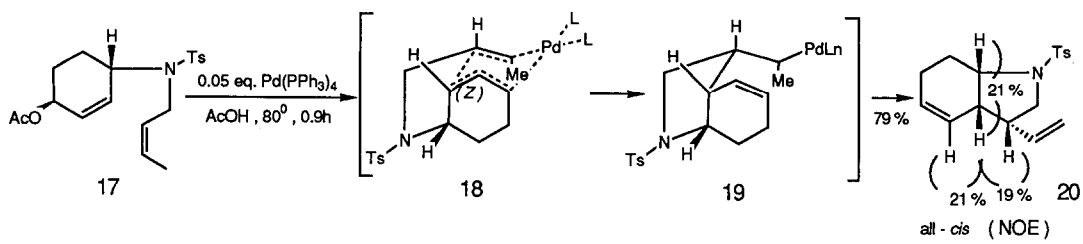


Heating dienes 13a or 13b, containing a *(Z)*-enophile, with 4% $Pd(PPh_3)_4$ in AcOH at 80° for 50 to 110 min gave in each case a ~8:1- mixture of pyrrolidines 15 and 16. Monitoring the cyclizations of 13 and 14 (GC) shows the reaction rates to decrease in the order 13a > 13b > 14a > 14b. After 7 - 9% conversion of 13a (1 min) and 13b (10 min) product ratios 15/16 = 86:14 and 88:12, respectively, were observed. Under identical reaction conditions *(E)*-crotylamides 14a and 14b furnished approximatively constant product ratios 15/16 = ~1:3 *i.e.* in favor of the thermodynamically less stable *cis*-pyrrolidine 16. Hence, the observed *trans/cis*- product ratios are largely kinetically controlled and independent of the allylacetate configuration, consistent with a *(Z)/(E)*-allylpalladium equilibration prior to insertion II → III [13].

The "enophile" configuration, however, is more relevant since the *(Z)*-isomers 13 were converted preferentially to the *trans*-product 15, whereas the *(E)*-isomers 14 afforded (less selectively) *cis*-substituted 16 as the main product [14].

In contrast, if the *(Z)*-configuration of an allylpalladium species II, n = 1 is enforced by incorporation into a ring only *cis*-substituted insertion products III were expected irrespective of the enophile configuration [13].

Scheme 6



Indeed, Pd(0)- catalyzed cyclization of acetoxycyclohexenylamide 17 [5,10] gave exclusively 3-vinylhexahydroindole 20 [5], assigned the all-*cis*-stereochemistry based on *NOE*-measurements.

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REFERENCES AND NOTES

1) Presented in part (W.O.) at the Annual Spring Meeting of the Swiss Chemical Society, Geneva, March 1988.

2) W.Oppolzer, J.-M.Gaudin, *Helv. Chim. Acta* 1987, *70*, 1477; W.Oppolzer, *Pure & Appl. Chem.* 1988, *60*, 39.

3) W.Oppolzer, J.-M.Gaudin, T.N.Birkinshaw, submitted to *Tetrahedron Lett.*.

4) Attempts to cyclize VI, Met^{II} = MgBr, X = NTs, n = 1, $R^1 = R^2$ = H, gave (after aq. workup) only *N*-allyl,*N*-toluenesulfonamide, presumably *via* elimination of 1,3-butadiene: W.Oppolzer, W.Pachinger unpublished work.

5) All isolated intermediates and products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS.

6) Dienes 1 were readily obtained by alkylation of either *N*-allyl,*N*-benzylamine with (4-acetoxy-2-butenyl)methyl carbonate ref.2) [1.1 equiv, $Pd(PPh_3)_4$ (0.05 equiv), THF, RT, 3h, → 1a, 81%], or deprotonated (NaH, 0°, DMF) *N*-allylamides with 1-acetoxy-4-chloro-2-butene (DMF, 0°), prepared according to: J.Collonge, G.Poilane *Bull. Soc. Chim. Fr.* 1955, 953.

7) Allyloxy derivatives 2 were obtained by treating *N*-allylbenzylcarbamate with NaH (1.2 equiv, DMF, RT, 1h) followed by 3,4-epoxy-1-butene (3 equiv, DMF, RT, 13h), hydrolysis/decarboxylation of the resulting *N*-allyl-5-vinyl-2-oxazolidone (8N KOH, 5 equiv, MeOH, reflux, 16 h) to give *N*-allyl-*N*-(2-hydroxy-3-butenyl)amine which was acylated [PhCOCl (3 equiv), Py (4 equiv), DMAP (0.1 equiv), CH_2Cl_2, RT, 1.5 h → 2d], [TsCl (2.4 equiv), Py (3 equiv), CH_2Cl_2, 0°, 1.5 h → 2e].

8) Direct π-allylpalladium/olefin insertion of 3 cannot be excluded.

9) *(Z)*-1-chloro-4-(*O*-tetrahydropyranyl)-2-butene: P.Deslongchamps, S.Lamothe, H.-S.Lin, *Can. J. Chem.* 1987, *65*, 1298.

10) Dienes 11 (68%) and 17 (67%) were obtained by successive treatment of the corresponding *N*-butenyltoluenesufonamide with NaH (1.1 equiv, DMF, RT, 1h) and *cis*- 1-acetoxy-4-chloro-2-cyclohexene (1.1 equiv, DMF, 100°, 1h) prepared according to: J.-E.Bäckvall, J.E.Nyström, R.E.Nordberg, *J. Am. Chem. Soc.* 1985, *107*, 3676.

11) Stereochemically pure *(E,Z)*- *(Z,Z)*-, *(E,E)*- and *(Z,E)*- acetoxydienes 13 and 14 were prepared by alkylations of the sodium salts (NaH, DMF, 0°) of pure *(Z)*- and *(E)*-*N*-crotyltrifluoracetamides with either *(E)*-1-bromo-4-acetoxy-2-butene [obtained from methyl 4-bromocrotonate: i) DIBAL (2 equiv), PhMe, -78° → RT; ii) Ac_2O, DMAP cat., 16 h],(DMF, 0°, 2h → 13a, 14a, 73-78%) or with *(Z)*-1-chloro-4-acetoxy-2-butene [ref. 6)] (DMF, RT, 5h, → 13b, 14b, 70-74%). Crotylamines (purified by crystallization of their hydrochlorides): *(Z)*: M.G.Ettlinger, J.E.Hodgkins, *J. Am. Chem. Soc.* 1955, *77*, 1831; *(E)*: J.D.Roberts, R.H.Mazur, *ibid.* 1951, *73*, 2509.

12) *Trans*- and *cis*-products 15 and 16 were assigned by comparing the chemical shifts of the ^{13}C-NMR-signals of C(3,4) of the *N*-toluenesulfonamides prepared from 15: δ= 48.46 ppm and from 16: δ = 46.35 ppm. For ^{13}C-NMR- studies of 3,4-diethyl-1-methylpyrrolidine showing the C(3,4)-signals of the *trans*- isomer downfield from those of the *cis*- isomer: D.G.Hawthorne, S.R.Johns, R.I.Willing, *Aust. J. Chem.* 1976, *29*, 315.

13) We assume that the cyclizations of 13a, 13b, 14a and 14b proceed *via* the corresponding *(E)*-allylpalladium intermediates II as indicated by the reaction rate differences of 13b < 13a, and 14b < 14a and, more clearly, by the *(Z)/(E)*-isomerizations 13b → 13a and 14b → 14a, observed by GC- and ^{1}H-NMR-analysis of recovered dienes after partial cyclizations of 13b and 14b. Cyclization of 13b to (*trans*) 15 *via* a *(Z)*-allyl-Pd/olefin insertion II → *trans*-III is also unlikely since it implies a strained chair-like transition state. A strained transition state would also disfavor the formation of *trans*-III, n = 1 by insertion of an *anti*-disposed olefinic chain into a π-allyl-Pd species.

14) Inspection of molecular models presuming a chair-like metallo-ene transition state shows repulsion of a Pd-ligand with an "equatorial" enophile-methyl substituent to disfavor the transformations 13 → 16 and 14 → 15.

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